Human Inheritable Genetic Modifications

Assessing Scientific, Ethical, Religious, and Policy Issues

Prepared by the
American Association for the Advancement of Science

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Introduction

This report assesses the scientific prospects for inducing controlled inheritable genetic changes in human beings and explores the ethical, religious, and social implications of developing and introducing technologies that would change the genetic inheritance of future generations. The analysis leads to a set of recommendations as to whether and how to proceed. The report is based on the deliberations of a working group of eminent scientists, ethicists, theologians, and policy analysts convened by the American Association for the Advancement of Science (AAAS) and further analysis by project staff.

Rapid breakthroughs in genetic research, spurred by the Human Genome Project, advances in molecular biology, and new reproductive technologies, have advanced our understanding of how we might approach genetic interventions as possible remedies for diseases caused by genetic disorders, particularly for those caused by abnormalities in single genes. Limitations of current medical therapies to treat diseases with a genetic component have led to efforts to develop techniques for treating diseases at the molecular level, by altering a person's cells. To date, most of the research and clinical resources related to gene therapy have been invested in developing techniques for targeting nonreproductive body cells. Somatic gene therapies designed to treat or eliminate disease are intended to affect only the individuals receiving treatment. Very recently, researchers announced credible successes in improving patient health through gene therapy,[1] perhaps signaling that years of research are about to bear fruit.

[1] Mark A. Kay, Catherine S. Manno, Margaret V. Ragni, Peter J. Larson, Linda B. Couto, Alan McClelland, Bertil Glader, Amy J. Chew, Shing J Tai, Roland W. Herzog, Valder Arruda, Fred Johnson, Ciaran Scallan, Erik Skarsgard, Alan W. Flake, Katherine A. High, "Evidence for Gene Transfer and Expression of Factor IX in Haemophilia B Patients Treated with an AAV Vector," *Nature Genetics* (2000) 24: 257-261, and Marina Cavazzana-Calvo, Salima Hacein-Bey, Geneviève de Saint Basile, Fabian Gross, Eric Yvon, Patrick Nusbaum, Françoise Selz, Christophe Hue, Stéphanie Certain, Jean-Laurent Casanova, Philippe Bousso, Françoise Le Deist, and

Recent advances in animal research are also raising the possibility that we will eventually have the technical capacity to modify genes that are transmitted to future generations.[2] This report uses the term inheritable genetic modification (IGM) to refer to any biomedical intervention that can be expected to modify the genome that a person can transfer to his or her offspring. One form of IGM would be to treat the germ or reproductive cells that develop into the egg or sperm of a developing organism and transmit its heritable characteristics. Another form of germ line therapy would be to modify the gametes (sperm and egg cells) or the cells from which they are derived. Still other technologies under development, such as the insertion of artificial chromosomes, would also introduce inheritable genetic changes.

Greater knowledge of genetics is also making it possible to contemplate genetic interventions not only to treat or eliminate diseases but also to "enhance" normal human characteristics beyond what is necessary to sustain or restore good health. Examples would be efforts to improve height or intelligence or to intervene to change certain characteristics, such as the color of one's eyes or hair.[3] Such interventions could be attempted through either somatic modification or IGM.

Alain Fischer, "Gene Therapy of Human Severe Combined Immunodeficiency (SCID) - X1 Disease," *Science* (2000) 288: 669-672.

[2] Two such advances were published this year. In one instance, scientists developed a method for cloning large animals (sheep) in which they can target a gene into a particular location or remove specific genes. While the process is not efficient at this stage of research, it is proof of principle that such genetic manipulations can be done in a way that would make them more predictable than current methods of altering animals' genes. See K.J. McCreath, J. Howcroft, K.H.S. Campbell, A. Coleman, A. E. Schnieke, and A. J. Kind, "Production of Gene-Targeted Sheep By Nuclear Transfer from Cultured Somatic Cells," *Nature* (June 29, 2000) 405:1066-1069. In the second instance, researchers reported that they were able to make artificial chromosomes pass through three generations of mice and remain active. See Deborah O. Co, *et al*., *Chromosome Research* (2000) 8: 183-191.

[3] See Erik Parens, ed. *Enhancing Human Traits: Ethical and Social Implications* (Washington, DC.: Georgetown University Press, 1998), particularly the essay by Eric T. Juengst, "What Does Enhancement Mean?" pp. 29-47 in that volume.

What reasons do advocates give for developing and applying this technology? In theory, modifying the genes that are transmitted to future generations would have several advantages over somatic cell gene therapy. Inheritable genetic modifications offer the possibility of preventing the inheritance of some genetically based diseases within families rather than repeating somatic therapy generation after generation. Some scientists and ethicists argue that germ line intervention is medically necessary to prevent certain classes of disorders because there are situations where screening and selection procedures will not be applicable, such as when both parents have the same mutation.[4] Because germ line intervention would influence the earliest stage of human development, it also offers the potential for preventing irreversible damage attributable to defective genes before it occurs. Over a long period of time, germ line gene modification could be used to decrease the incidence of certain inherited diseases in the human gene pool currently causing great suffering.[5] By contrast, because somatic cell gene therapy treats only the affected individuals, it could not be used to decrease the incidence of diseases in the same way.

However, there are significant technical obstacles, as yet unresolved, to developing scientific procedures appropriate to inheritable genetic applications. Because these interventions would be transmitted to the progeny of the person treated, there would need to be compelling scientific evidence that these procedures are safe and effective; for those techniques that add foreign material, their stability across generations would need to be determined, based initially on molecular and animal studies, before proceeding with germ line interventions in humans. It is not yet possible to meet these standards. Nor is it possible to predict when we will be able to do so.

IGM also raises profound ethical, theological, and policy issues that need to be thoroughly discussed and evaluated. Efforts to modify

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[4] Burke K. Zimmerman, "Human Germ Line Therapy: The Case for Its Development and Use," *The Journal of Medicine and Philosophy* (1991) 16: 597.

[5] See, for example, LeRoy Walters and Julie Gage Palmer, *The Ethics of Human Gene Therapy* (New York and Oxford: Oxford University Press, 1997), pp. 62-63.

genes that are transmitted to future generations have the potential to bring about not only a medical, but also a social revolution, for they offer us the power to mold our children in a variety of novel ways. These techniques could give us extraordinary control over biological properties and personality traits that we currently consider essential to our humanness. Even with the technical ability to proceed, we would still need to determine whether these procedures offer a theologically, socially, and ethically acceptable alternative to other technologies under development to treat genetic diseases. Do we have the wisdom, ethical commitment, and public policies necessary to apply these technologies in a manner that is equitable, just, and respectful of human dignity?

The potential magnitude of these interventions makes it very important to improve societal awareness of the technical possibilities, give careful consideration to the implications of their use, and design a process for sustained public discussion before proceeding. Informed public discussion will require an understanding of the scientific possibilities and risks, as well as the pressing moral concerns this technology raises.

The furor over the possibility of cloning human beings through the application of the somatic cell nuclear transfer technology used to clone the lamb Dolly and subsequently other mammals underscores the importance of undertaking a serious examination of the scientific, ethical, religious, and policy implications of new technologies in advance of scientific breakthroughs. As the media coverage and public reaction to the Roslin Institute's work on mammalian cloning showed, it is far more difficult to have an informed and unemotional public discussion after a scientific discovery is announced than before it becomes a reality.

Scientists and ethicists have called attention to the need for scientific and ethical discussions related to inheritable human genetic interventions for nearly thirty years. As early as 1972, a few scientists warned that prospective somatic cell gene therapy would carry a risk of inadvertently altering germ cells as well as their targeted so-

matic cells.[6] In 1982, a Presidential Commission declared that "especially close scrutiny is appropriate for any procedure that would create inheritable genetic changes."[7]

To date, however, there has been little sustained public consideration of this topic.[8] While the science is advancing rapidly, our understanding of the ethical, religious, and policy implications has not kept pace. Typically, our society proceeds in a "reactionary mode," scrambling to match our values and policy to scientific developments. But with a scientific advance that raises profound issues related to the possibilities of modifying our genetic futures it is important to plan ahead, to decide whether and how to proceed with its development, and to give direction to this technology through rigorous analysis and public dialogue.

To facilitate public deliberations about IGM, two programs within AAAS – the Scientific Freedom, Responsibility and Law Program and the Program of Dialogue on Science, Ethics, and Religion – coorganized a two-and-a-half-year project assessing scientific, ethical, theological, and policy issues related to inheritable genetic modification (IGM). Our goal was to formulate recommendations as to what, if any, types of applications should be encouraged and what safeguards should be instituted. Building on a forum on human germ line issues cosponsored by the two programs in September 1997,[9] the

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[6] Theodore Friedmann and Richard Robin, "Gene Therapy for Human Genetic Disease?" *Science* (1972) 175: 952.

[7] President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research, *Splicing Life: The Social and Ethical Issues of Genetic Engineering with Human Beings* (Washington, D.C.: U.S. Govemment Printing Office, November 1982), p. 3.

[8] There have been a few efforts to stimulate debate. In March 1998 a symposium entitled "Engineering the Human Germline" was held at UCLA. A publication was issued based on the symposium presentations. See Gregory Stock and John Campbell, eds., *Engineering the Human Germline: An Exploration of the Science and Ethics of Altering the Genes We Pass on to Our Children* (Oxford and New York: Oxford University Press, 2000). Also see, David B. Resnik, Holly B.Steinkraus, and Pamela J. Langer, *Human Germline Gene Therapy: Scientific, Moral and Political Issues* (Austin, Texas: R. G. Landes Companys, 1999).

[9] See, http://www.aaas.org/spp/dspp/sfrl/projects/glforum.htm.

project convened a working group of scientists, ethicists, theologians, and policy analysts to develop a series of recommendations. Much of the work was conducted in two subgroups, each of which was broadly multidisciplinary in composition. The first subgroup examined the feasibility of various kinds of human germ line applications, the risks involved, the appropriate scope and limits of germ line research and applications on human subjects, and consent issues. The second subgroup considered the social, ethical, and theological implications of IGM. The working groups met together to formulate findings and craft public policy recommendations. Members of the two working groups are identified in Appendix A.

Major Findings, Concerns, and Recommendations

A majority of the project's working group members endorses the following findings, concerns, and recommendations.

Findings

- The working group concluded that IGM cannot presently be carried out safely and responsibly on humans. Current methods for somatic gene transfer are inefficient and unreliable because they involve addition of DNA to cells rather than correcting or replacing a mutated gene with a normal one. They are inappropriate for human germ line therapy because they cannot be shown to be safe and effective. A requirement for IGM, therefore, is the development of reliable gene correction or replacement techniques.

- With current gene addition technologies, iatrogenic genetic damage could occur as a result of the unintended germ line side effects of somatic cell therapy. These problems seem at least as great as the harmful genetic damage that might arise from intentional germ line transfers. Therefore, attention must also be given to the accompanying side effects of somatic cell therapies already in use or planned.

- The working group identified few scenarios where there was no alternative to IGM for couples to minimize the prospect that their offspring will have a specific genetic disorder. The further development of somatic cell gene transfer, moreover, will offer more options for treating one's offspring.

- Guided by the theologians – mainline Protestant, Catholic, and Jewish traditions – and ethicists on the working group, the group concluded that religious and ethical evaluations of IGM will depend on the nature of the technology, its impact on human nature, the level of safety and efficacy, and whether IGM is used for therapeutic or enhancement purposes. Ethical considerations related to the social effects of IGM, particularly its implications

for social justice**,** will play a major role in shaping the attitudes of religious communities.

- To date, the private sector has played a prominent role in the funding of somatic cell genetic research, raising questions about the influence of commercial interests on the conduct of researchers and on the scope and direction of the research. Similar questions are likely to surface if IGM research and applications go forward.

Concerns

- The ability of IGM to shape the genetic inheritance of future generations raises major ethical concerns. IGM might change attitudes toward the human person, the nature of human reproduction, and parent-child relationships. IGM could exacerbate prejudice against persons with disabilities. The introduction of IGM in a society with differential access to health care would pose significant justice issues and could introduce new, or magnify existing, inequalities.

- IGM for enhancement purposes is particularly problematic. Enhancement applications designed to produce improvements in human form or function could widen the gap between the "haves" and the "have nots" to an unprecedented extent. Efforts to improve the inherited genome of persons might commodify human reproduction and foster attempts to have "perfect" children by "correcting" their genomes. Some types of enhancement applications might lead to the imposition of harmful conceptions of normality. The dilemma is that IGM techniques developed for therapeutic purposes are likely to be suitable for enhancement applications as well. Thus, going forward with IGM to treat disease or disability will make it difficult to avoid use of such interventions for enhancement purposes even when this use is considered ethically unacceptable.

Recommendations

- Even in advance of a decision about whether to proceed with IGM as traditionally understood as gene transfer in reproductive cells, a public body should be assigned responsibility to monitor and oversee research and developments in IGM, more broadly conceptualized as any technique aimed at modifying the genes that a person can transmit to his or her offspring. Some interventions that fall within the scope of the working group's definition of IGM are already taking place without the oversight that we believe is necessary.

- It is important to promote extensive public education and discussion to ascertain societal attitudes about proceeding with IGM and to develop a meaningful process for making decisions about the future of this technology. These efforts should be informed by an understanding of the relevant science, involve an extended discussion of the cultural, religious, and ethical concerns associated with IGM, and be as open and inclusive as possible. International consultation on these matters should also be encouraged.

- If a societal decision is made to proceed with IGM, a comprehensive oversight mechanism should be put in place with authority to regulate IGM applications in both the public and private sectors. Such a mechanism would help to promote public safety, develop guidelines for the use of IGM, ensure adequate public participation in policy decisions regarding IGM, and address concerns about commercial influence and conflicts of interest.

- Any protocol for somatic cell transfer in which inheritable modifications are reasonably foreseeable should not proceed without assessing the short- and long-term risks and without proper public oversight.

- Before IGM can proceed, there should be a means in place for assessing the short- and long-term risks and benefits of such interventions. Society must decide how much evidence of safety,

efficacy, and moral acceptance will be required before allowing human clinical trials or IGM applications.

- At this time, the investment of public funds in support of the clinical development of technologies for IGM is not warranted. However, basic research should proceed in molecular and cellular biology and in animals that is relevant to the feasibility and effects of germ line modification.

- Human trials of inheritable genetic changes should not be initiated until techniques are developed that meet agreed upon standards for safety and efficacy. In the case of the addition of foreign genetic material, the precise molecular change or the changes in the altered genome should be proven with molecular certainty, probably at the sequence level, to ascertain that no other changes have occurred. Furthermore, the functional effects of the designed alteration should be characterized over multiple generations to preclude slowly-developing genetic damage and the emergence of an iatrogenic genetic defect. In the case in which attempts at IGM involve precise correction of the mutant sequence and no addition of foreign material, human trials should not begin before it can be proven at the full genome sequence that only the intended genetic change, limited to only the intended site, has occurred. If it is shown at the full genome sequence level that the sequence of a functionally normal genome has been restored, there will likely be no need for multigeneration evaluation.

- The role of market forces in shaping the future of IGM research and applications should be carefully assessed to ensure that adequate attention is paid to public priorities and sensibilities.

- Existing conflict of interest guidelines governing research should be reviewed and, where appropriate, amended and vigorously enforced to address the increasing role of commercial interests in genetics research. The guidelines should specify when a financial interest in a commercial IGM venture is grounds for precluding an investigator's direct participation in a clinical trial supported by that company. They should require that investiga-

tors disclose any financial interests in the research during the informed consent process, and should prohibit researchers with a direct financial interest in a study's outcome from participating in that study's selection of patients, the informed consent process, or the direction of the study.

Defining Inheritable Genetic Modification

This report generally uses the terminology "inheritable genetic modification" rather than the more common "germ line" interventions.[10] It does so because the traditional distinction between somatic and germ line changes does not cover the full range of developing scientific technologies that open the possibility of creating inheritable genetic changes. Gene transfer into germ line cells constitutes the paradigm class of interventions able to shape the genes of offspring. Nevertheless, other technologies, techniques, and interventions can also introduce inheritable genetic changes. One example is the micromanipulation techniques already in use that make it possible to compensate for mitochondrial genetic diseases, either through inserting segments of healthy mitochondria or placing the nucleus in a substitute egg (in vitro ovum nuclear transplantation).[11]

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[10] For a more in depth discussion of the definitional issues, see Eric Juengst and Erik Parens, "Germ Line Dancing: Definitional Considerations for Policy Makers," in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

[11] In 1997, there was a report of the birth of a child following transfer of donor egg cytoplasm into a recipient egg taken from a woman who experienced poor embryo development and failed implantation. The baby inherited the mitochondrial genes from the donor cytoplasm and will likely produce offspring who will also inherit those genes. Although the main purpose of the intervention was to revitalize an egg, the transfer of mitochondrial genes in this case is an example of germ line modification. See Jacques Cohen, Richard Scott, Tim Schimmel, Jacob Levron, and Steen Willadsen, "Birth of Infant after Transfer of Anucleate Donor Oocyte Cytoplasm into Recipient Eggs," *Lancet* (1997) 350: 186-87. Also see Donald S. Rubenstein, David C. Thomasma, Eric A. Schon, and Michael J. Zinaman, "Germ-Line Therapy to Cure Mitochondrial Disease and Ethics of In Vitro Ovum Nuclear Transplantation," *Cambridge Quarterly of Healthcare Ethics* (1995) 4: 316-39.

So may other new technologies, as, for example, the introduction of inheritable artificial chromosomes that could engineer human embryos without the need for any gene transfer intervention at all.

The term "modification" also seems preferable to the more commonly used "therapy." Somatic cell gene therapy generally refers to medical procedures that use DNA in the therapeutic treatment of a patient's disease. It was originally used to describe the transfer of a normal gene into a cell of a subject with a defective gene in an attempt to restore cell function. With recent technological advances, gene therapy now includes a wider range of treatments. In IGM, in contrast, while the immediate subject of the procedure is the patient, the ultimate subject is his/her progeny. The exception will be those rare cases in which somatic cell interventions done at a very early stage of development, such as *in utero* transfer, also result in inadvertent germ line changes.

A second reason why the term "modification" seems preferable is that potential germ line interventions may not necessarily be used for therapeutic purposes. For reasons discussed below, germ line transfers are just as likely, perhaps even more likely, to be used for enhancement purposes as to treat disease or disability. Enhancement is a term referring to biomedical interventions intended to improve human performance, functioning, or appearance beyond that which is necessary to sustain or restore good health.[12] Examples of potential IGM modifications aimed at enhancement would be inserting additional copies of a growth hormone gene to try to attain additional height or altering the efficiency of gene expression related to cognitive abilities in an effort to increase memory.

IGM, as used in this report, refers to the technologies, techniques and interventions that are capable of modifying the set of genes that a subject has available to transmit to his or her offspring. IGM includes all interventions made early enough in embryonic or fetal development to have global affects and interventions later in life that affect the gametes' precursor tissues, as well as the sperm and ova themselves. IGM encompasses inheritable modifications regardless of whether the intervention modifies nuclear or extra-nuclear ge-

[12] Eric T. Juengst, "What Does Enhancement Mean," p. 9.

nomes, whether the intervention relies on molecular genetic or other technical strategies, and even whether the modification is a side effect or the central purpose of the intervention.

The kinds of interventions that fall within the scope of the definition of IGM are those that raise the following core issues:

- They are interventions that hold out the prospect of increasing our control over the specific hereditary traits of the next generation and beyond if they succeed;

- They are interventions that make inheritable changes in the genes of surviving offspring, rather than interventions that simply select among offspring on the basis of their naturally inherited genes;

- They are interventions associated with scientific research, i.e., biomedical interventions, rather than social practices;

- They pose the risk of creating iatrogenic and other genetic harms.

Therapeutic Need

Clear therapeutic need should be the primary criterion for proceeding with IGM, given the investment of resources that would be required to develop effective techniques for germ line intervention and concerns about safety. Yet, the working group could identify few instances where IGM would be needed. There are currently several alternative approaches available that will help parents avoid passing on defective genes to their offspring. These include genetic screening and counseling, prenatal diagnosis, and abortion, preimplantation diagnosis and embryo selection, gamete donation, and adoption. In the future, *in utero* somatic gene therapy and gene therapy on patients after birth are likely to offer effective means for correcting defects.

The use of IGM should be weighed for effectiveness, safety, efficiency, and social acceptance against these other means, but it is

likely that modifying the germ line will carry with it greater uncertainty regarding outcomes. Moreover, at least initially and in most cases, IGM will still require prenatal diagnosis with the prospect of selective abortion to prevent the birth of seriously impaired children.

It has been suggested that IGM first be tried for the treatment of male infertility or disorders transmitted by the male through modifying sperm, or spermatogonia, the stem cell precursor of fully matured spermatocytes.[13] A specific mutation has been identified that leads to infertility in males.[14] Correction of this mutation in spermatagonia cells would presumably lead to motile sperm that could be used for *in vitro* fertilization. While there is already an alternative way to treat infertility in the male that can result in a genetically-related child, intracytoplasmic sperm injection, or ICSI, this procedure has the disadvantage of passing on the infertility gene to the next generation.

There are several advantages to targeting infertility in males: (1) correction of the defect only requires altering the spermatagonia, without the need for systemic application; (2) successful correction would result in motile sperm that could be analyzed for any mutations prior to fertilization; and (3) a high efficiency of mutation correction would not be needed since only a limited number of sperm would be required for *in vitro* fertilization. Given the narrow application of this approach, the possibility of checking for mutations before creating an embryo, and the relatively low efficacy required, the working group also believed that this form of IGM could be a useful place to start. Nevertheless, it is not yet technically feasible to proceed with this use of IGM, and the working group did not believe that a major effort to develop IGM technologies for this purpose is warranted at this time.

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[13] Kenneth W. Culver, "Gene Repair, Genomics and Human Germ line Modification," in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).
[14] *Ibid.*

Efficacy of Different Approaches to IGM

After many years of frustration in producing techniques for efficient gene transfer of somatic cell-based gene therapy, clinical scientists have recently published credible evidence for the therapeutic benefit of gene transfer techniques to patients with two diseases: hemophilia B and X-linked immunodeficiency.[15] The development of effective gene delivery techniques at the somatic cell level raises the inevitable question of the technical potential and the desirability of genetic modification to affect subsequent generations for either disease prevention or enhancement purposes. For such applications to become feasible would require solutions to a number of technical problems and questions, including the identification of the target cell, the nature and efficiency of the gene delivery methods, determination of both the short-term safety and long-term disease prevention or enhancement effects as well as the long-range developmental implications of the added genes.

In principle, genes and other foreign genetic elements might be introduced into the germ line of an organism by genetic modification of the gametes themselves, by genetic modification of the fertilized egg, or by gene transfer into the cells of an early embryo in a way that allows gene transfer into the developing gametes. There are several serious technical impediments, however, to safe and effective successful transfer of foreign genetic material into the human germ line through all of these approaches. One major obstacle is the limited capacity of most transfer methods that concentrate on replacement of the coding function of a gene unaccompanied by its full complement of regulatory genetic elements to ensure appropriate levels, timing, or distribution of gene expression. The development of new transfer techniques, such as artificial chromosomes, may partially overcome this obstacle, but may generate other problems associated with the presence of excessive amounts of some sequences and the uncertain effects of creating too many chromosome segments compared to the normal genotype.

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[15] Mark A. Kay, *et.al*, "Evidence for Gene Transfer and Expression of Factor IX in Haemophilia B Patients Treated with an AAV Vector," and Marina Cavazzana-Calvo, et. al, "Gene Therapy of Human Severe Combined Immunodeficiency (SCID) - X1 Disease."

Current methods of IGM in animals include introduction of foreign genes into the germ line by gene transfer into a fertilized egg.[16] Since the foreign gene is introduced into an embryo at its earliest stage of development (the fertilized egg), all the cells of the developing animal, including the reproductive cells, will contain the newly introduced gene, although gene expression will vary from one tissue to another. This is the basis for the now standard methods for producing animals that express foreign genes stably and permanently ("transgenic" animals). Unfortunately, even in the best hands, the methods are highly inefficient and produce offspring ("founder" animals) that express the foreign genetic material to variable extents in various tissues. Those founders with distribution of the foreign gene in the appropriate tissues must subsequently be bred to produce a transgenic animal line with the desirable properties. Such breeding programs would obviously not be ethically permissible in human studies.

An interesting new approach to the production of transgenic animals has recently been reported that may provide a means of providing very large amounts of genetic information to the germ line of mice in the form of independently replicating artificial chromosomes.[17] A study reports for the first time the introduction of an extra, artificially constructed chromosome to transgenic mice and its subsequent transmission to progeny mice. Obviously, it will be necessary to determine the long-term developmental effects of producing a state of aneuploidy (an abnormal number of chromosomes) in an animal. While artificial chromosomes in theory may permit the inclusion of large amounts of the necessary regulatory sequences to accompany a desired new genetic function in transgenic animals, such a manipulation could be accompanied by some genetic and developmental damage. There are no known states of aneuploidy in the human that are free of detectable, and in most cases very severe, genetic and developmental abnormalities.

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[16] Jon W. Gordon and Frank H. Ruddle, "Gene Transfer into Mouse Embryos: Production of Transgenic Mice by Pronuclear Injection," *Methods in Enzymology* (1983) 101: 411-432.

[17] See Deborah O. Co, *et al*., *Chromosome Research* (2000) 8: 183-191.

Genetic modification is also currently practiced in animals by introducing a gene or other genetic element into cells derived from mammalian embryos or early fetuses that are "toti-potential" and that can develop on their own into an entirely new organism under the appropriate conditions.[18] Such "stem cells" can be grown indefinitely in the laboratory, genetically modified by established gene transfer methods, and then introduced into an early embryo in a way that allows the modified cells to contribute to all tissues of the developing animal, including the germ cells. Since animals born after this manipulation contain mixtures of unmodified and modified cells, they are "chimeric" and, like the transgenic animals described above, must be bred to establish animal lines that are entirely derived from the genetically modified stem cells. The imperfect efficiency of gene transfer that is tolerable in animal studies would not be acceptable for humans. Nor would it be acceptable in humans as it is in animal studies to eliminate damaged offspring in unsuccessful experiments, the requirement for breeding the genetically modified founder and chimeric animals. Only with the eventual development of specific targeted chemical correction of mutations would these unwanted effects be averted, thereby making IGM potentially safe and therefore feasible. The potential for safe and feasible modification, however, does not resolve the difficult questions of how and in what time scale the results of initial IGM studies involving gene transfer could possibly be tested.

Studies in the mouse have proven that the introduction of foreign genes into the mammalian germ line can result in the correction or prevention of genetic disease in progeny of treated animals. While there is less experience with similar transgenic studies in other mammals, it seems likely that prevention of genetic disease would be just as feasible in other species. The impressive results in the mouse have come through the production of transgenic animals in which normal copies of genes are introduced into a fertilized mouse egg in a way that allows stable and heritable insertion of the foreign gene into the genome of the fertilized egg with subsequent permanent and stable gene expression. When transgenic mice carrying such foreign

[18] James A. Thomson and Jon S. Odorico, "Human Embryonic Stem Cell and Embryonic Germ Cell Lines," *Trends in Biotechnology* (2000) 18: 53-57.

genes are identified and bred, subsequent generations of those founder mice can express the new gene stably and permanently and thereby can prevent or correct a genetic defect. Examples of such stable prevention of genetic disease in the mouse include correction of the genetic defects responsible for growth hormone deficiency in dwarfism, degenerative neurological diseases such the Lesch-Nyhan and "shiverer" defects, and genetic causes of atherosclerosis in the mouse, among many others. In such transgenic animals, the original mutant gene remains in place but its function is complemented by the product of the new gene that has been inserted into the genome.

Nevertheless, there are a number of important features of the transgenic technology in its present form that makes it inapplicable for human IGM. The transgene methodology is exceedingly inefficient, and produces animals possessing the desired traits with an efficiency, at best, of only several percent. Founder transgenic mice that demonstrate inadequate distribution or incorrect expression of the added gene or that are damaged by the procedure are generally destroyed. Such a technology is obviously not appropriate for humans.

Genetically altered “stem cells” can also be used to create animals with permanent new genetic properties in subsequent generations. Early mammalian embryos and fetuses contain cells that have the capacity to develop completely on their own into fully formed living progeny. Such cells include the so-called “embryonic stem cells” (ES) derived from the interior of early embryos or embryonic germinal ridge cells (EG) from early fetuses. Embryonic stem cells or embryonic germinal ridge cells have been isolated not only from mouse embryos but also from a number of other mammals, including humans. They can be grown indefinitely in the laboratory, modified by introduction of foreign genes via standard gene transfer methods, and finally re-introduced into an early embryo in a way that allows them to be incorporated into the tissues of resulting offspring, including the reproductive tissues. Since the ES and EG cells appear mixed in various amounts with original cells of the embryo, the resulting animals are chimeras of unmodified and modified cells. In order to establish lines of animals derived entirely from the genetically modified ES or EG cells and that contain no unmodified cells, it is necessary to identify and breed animals among the chimeras that

contain reproductive cells derived from the modified ES or EG cells. However, despite the difficulties, at least one animal study has shown that ES cells can be used as carriers of therapeutic genes.[19]

Current methods do not allow safe and controlled application of this stem cell germ line modification in humans. As with transgenic animals, the efficiency of production of chimeric animals with stem cells is low and the degree with which the genetically altered stem cells become part of the developing embryo is highly unpredictable. Only by identifying the chimeras that contain the desired gene in the reproductive cells and by breeding them can animals be created with stable new genetic properties that can be passed to later generations. Therefore, until methods are developed by which the incorporation of the stem cells can be made very highly efficient or, at least, more predictable, the best that one might achieve is a progeny animal with uncontrolled and unpredictable mixtures of defective and corrected cells, a situation obviously not appropriate for human application.

Gene transfer into eggs or sperm is not yet feasible. Germ line modification might most easily be approached by introducing foreign therapeutic genes directly into the reproductive cells - ova and sperm. Sperm would be an attractive possibility since they are so readily available. While progress has been made toward gene transfer into cultured cells that can be transplanted into the testis and produce mature sperm, there have been no published demonstrations of gene transfer into fully mature sperm themselves. Several studies have reported *in vivo* gene transfer into mouse spermatocytes through physical methods of gene transfer, and a recent unpublished study has also shown gene transfer into mouse spermatocytes after virus vector delivery to the blood of adult mice. In neither kind of study has gene transmission been demonstrated to offspring. No similar studies have been reported in female animals as a route of gene transfer to the eggs. Of course, human egg cells can also be obtained by moderately invasive methods already used commonly

[19] Sara Benedetti, Barbara Pirola, Bianca Pollo, Lorenzo Magrassi, Maria Grazia Bruzzone, Dorotea Rigamonti, Rossella Galli, Silvia Selleri, Francesco Di Meco, Claudio De Fraja, Angelo Vescovi, Elena Cattaneo, and Gaetano Finocchiaro, "Gene Therapy Of Experimental Brain Tumors Using Neural Progenitor Cells," *Nature Medicine* (2000) 6: 447-450.

for *in vitro* fertilization (IVF) methods. While no studies have yet been reported on the genetic modification of such cells, it is likely that relatively simple gene transfer methods would eventually be capable of stable gene transfer into isolated single egg cells and that such cells could then readily be fertilized and used to produce progeny.

Several mouse studies have recently been reported in which sperm have been used as vehicles for carrying foreign genes into eggs and for expressing new genes in progeny animals. While these studies are in very preliminary stages and are not yet confirmed, it seems possible that this technology will permit relatively efficient and simple gene transfer into eggs in the context of IVF.

The development of mammalian cloning has provided still another method for stably introducing foreign, potentially therapeutic genes into descendents of a specific individual, not by initial introduction of a new genetic element into the germ line but rather by nuclear transfer. Cloning has been carried out successfully in animal systems including sheep, mice, pig, cows and others.[20] The donor nucleus can be genetically modified by any one of the methods for gene transfer prior to transfer into the enucleated oocyte, thereby producing a clone that expresses a specific new function that can then be transmitted through generations by the usual methods of sexual reproduction.[21]

While cloning successes are accelerating in a number of mammalian species, including mice, sheep, cows and others, major technical problems remain that must be overcome before cloning procedure can safely be applied to humans. The efficiency of successful cloning continues to be low, with efficiencies of only one in several

[20] Ian Wilmut, Angelina E. Scnieke, Jim McWhir, Alexander J. Kind, and Keith H.S. Campbell, "Viable Offspring Derived from Fetal and Adult Mammalian Cells," *Nature* (1997) 385: 810-813.

[21] Angelika E. Schnieke, Alexander J. Kind, William A. Ritchie, Karen Mycock, Angela R. Scott, Marjorie Ritchie, Ian Wilmut, Alan Colman, Keith H. S. Campbell, "Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts," *Science* (1997) 278: 2130-2133.

hundred attempts in large animals such as sheep and cows. The derivation of the donor nucleus from a somatic cell implies the possible transfer to the cloned progeny of whatever genetic damage had accumulated in the donor cell prior to transfer, possibly pre-destining cloned animals to increased susceptibility to age-related disorders such as cancer and degenerative disease. Furthermore, the replication potential of cells in the cloned animals has yet to be fully characterized and may be altered by age-related changes in the telomeres - regions of the chromosomes that seem to serve as clocks that keep track of the number of divisions that a cell line has undergone. Early studies suggested, for instance, that cells of the cloned sheep Dolly contained somewhat shortened telomeres, implying that her cells had a reduced number of replications available to them. More recent and still unpublished studies in cows have not confirmed that finding.[22] Obviously it will be some time before the properties of donor nuclei and cloned animals will be well enough understood to permit studies in humans.

However, the cloning technology is now well enough established to have been combined recently with targeted gene delivery to develop a powerful new approach to IGM through a simplified and more controllable production of "transgenic" animals.[23] The method combined the use of sequence-specific gene targeting vectors to introduce potentially therapeutic genetic changes into fetal sheep fibroblasts followed by nuclear transfer into enucleated sheep oocytes by now-established mammalian cloning methods. Although the efficiency in this initial study of production of viable animals by this procedure was low, it did result in the live birth of genetically modified and apparently healthy sheep containing and expressing the added genetic elements. The approach has the advantage of obviating the need for ES or EG "stem" cells, and therefore avoiding the difficulties associated with the need to produce and breed chimeric animals. The method proves that genetically modified "transgenic" animals can indeed be produced through a cloning approach, using genetically targeted somatic cells rather than ES or EG cells, and

[22] Rick Weiss, "Dolly's Premature Aging Not Evident in Cloned Cows," *The Washington Post*, (April 28, 2000), p. A3.
[23] See Kenneth J. McCreath, *et al.*, *Nature* (June 29, 2000) 405:1066-1069.

thereby potentially lowers some of the technical barriers standing in the way of human application.

Several of the methods described above involve addition of foreign genes in ways that do not correct the genetic defect in the cells, but simply add new genes to provide the function that the mutant gene is unable to provide. Potentially important new gene therapy techniques are in very earliest phases of development. They are not intended to add new genes to cells without modifying or removing the endogenous defective genes but rather to carry out a very precise correction of the sequence error in the mutant gene.[24] These methods take advantage of precise, sequence-specific mechanisms that human and other mammalian cells have to alter gene sequences as part of mechanisms for correcting DNA damage and deleterious mutations. These "repair" mechanisms operate by processes of "mismatch repair" and "homologous recombination" that excise or chemically correct mutant sequences during the alignment of DNA strands containing normal and mutated sequences. The repair mechanisms recognize that one strand has undergone a sequence change that prevents proper alignment of the bases with the correct original sequence. The resulting repair mechanisms lead to the correction of the mutated sequence and the "replacement" of the mutant gene with a normal sequence. The result is the disappearance of the mutant base and its replacement with the proper base reconstituting the normal sequence. The advantage of this approach for correction of disease-related genes would be, at best, a specific replacement of abnormal sequence with the correct sequence identical to the wild-type sequence at that site and no trace of the disease-causing gene. At worst, since the gene modification is envisioned to be specific for the target site, failure to correct the defect or inefficiency of the correction would pose no added risks of further genetic damage.

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[24] Betsy T. Kren, Paramita Bandyopadhyay, and Clifford J. Steer, "In Vivo Site-directed Mutagenesis of the Factor IX Gene by Chimeric RNA/DNA Oligonucleotides," *Nature Medicine* (1998) 4: 285-290 and Kenneth W. Culver, Wang-Ting Hsieh, Yentram Huyen, Vivian Chen, Jilan Liu, Yuri Khripine, and Alexander Khorlin, "Correction of Chromosomal Point Mutations in Human Cells with Bifunctional Oligonucleotides," *Nature Biotechnology* (1999) 17: 989-993.

All the methods described are susceptible to uncertainty and error. In biomedicine, as well as in all other forms of scientific research, one must be aware of technical problems and unexpected adverse results in initial studies so that one can design appropriate modifications in subsequent experiments.

Safety Issues

Members of the working group concluded that it is not now possible to undertake IGM safely and responsibly. For IGM technologies to meet safety standards, there must be evidence that the procedures used do not cause unacceptable short-term or long-term consequences either for the treated individual or succeeding generations of offspring. This means that an altered embryo must be able to transit all human developments without a mishap due to the induced intervention. And for those techniques that add foreign material, there must be multigenerational data showing that the modification or improvement of a specific genetically determined trait is stable and effective and does not interfere with the functioning of other genes.

The need for high safety standards reflects several considerations. IGM has the potential to shape the genetic future of not only a single individual but of multiple descendants across generations. Since IGM would affect the embryo at the earliest stage of development, such interventions are likely to have far more systemic effects than conventional medical therapies or even somatic gene transfers.

There are other factors that also support establishing stringent standards. Most of the patients involved in somatic gene trials are desperately ill and do not have an alternative means of treatment. In contrast, as noted earlier, there are other reproductive options for couples who wish to minimize the chance that their offspring will have a specific genetic abnormality.

At the present time the hazards of IGM are largely unknown and unpredictable. We do not have sufficient biological knowledge and understanding of the human genome to predict the long-term risks from genetically engineering human cells. Manipulating the germ line might generate harmful interactions between inserted or modi-

fied genes and other genes in the recipient genome that would have untoward and unanticipated side effects in children. An inadvertently introduced error might in some circumstances become a permanent part of a child's genetic legacy and might affect generations to come. In addition, the elimination of certain disease-linked genes might also remove some beneficial effects of having those genes.

Scientists have not yet developed vectors that deliver genes to the intended locations within the cell or the means of assuring proper gene expression over time. Genetic information that is inserted in the wrong place in the genome is not subject to normal control and evolution. Genes that are expressed in the wrong tissues, or wrong developmental stage, or at the wrong levels may have deleterious effects on the proper functioning of a cell, tissue, or organ. Leaving the defective gene in place also raises the possibility that the disease might reappear in future generations. Because gene addition techniques introduce viruses and other matter into cells, they also add to the risk of iatrogenic harms.

Thus a central requirement for IGM is the development of new technologies that replace deleterious genes by homologous recombination or some other method of gene replacement or correction rather than by gene addition. Gene replacement would minimize the potential for iatrogenic harms and increase the probability of appropriate gene expression across generations of offspring.[25]

Another requirement before conducting human trials of IGM involving gene addition is to obtain multigenerational data on which to make determinations of safety and efficacy. As noted, it is possible that some risks from the intervention would not manifest themselves for generations. Experience with somatic cell gene therapy will help clarify the long-term risks from genetically engineering human cells, but will not be able to show multigenerational effects. Animal research, particularly on non-human primates, will be a valuable

[25] See, Theodore Friedmann, "Approaches to Gene Transfer to the Mammalian Germ Line," and Kenneth Culver, "Gene Repair, Genomics, and Human Germ Line Modification," in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

source of data, but will not be conclusive for assessing IGM effects on human subjects. Tracing gene transfers that have inadvertent germ line effects could be a source of some data, but the yield would be limited because such effects are likely to be haphazard and not well controlled. Moreover, the techniques now used for somatic gene transfer will not necessarily be those used in the future for IGM. Even if these data are available though, it could take another sixty or eighty years to have any multigenerational data. As a society, we must begin to consider how much evidence of safety and efficacy will be required before permitting either human clinical trials or non-medical applications.

The risks of such research and problems associated with gathering sufficient data to examine their effects in the treated subject were recently highlighted in an "informal" proposal presented to the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) in fall 1998. Preliminary discussion was sought by researchers seeking to correct genetic defects in a fetus before birth. The scientists pointed out that there is a "distinct possibility" that the experiment could cause inadvertent changes in the fetus's germ line cells,[26] leading to genetic alteration, including possible genetic mutations, that could be transmitted to that fetus's future children. At a previous meeting of the RAC, officials of the Food and Drug Administration (FDA) had expressed concern about the "potential risk for inadvertent germ line intervention" based on animal studies that had in some cases found that material distributed by vectors was detected in the animal's reproductive organs.[27] Both FDA and RAC participants at the meeting noted the need for "more

[26] Cover letter submitted by Dr. W. French Anderson to the NIH Office of Recombinant DNA Activities on July 31, 1998 accompanying two "pre-protocols" for *in utero* gene transfer. The pre-protocols were intended to provide a context for the identification of the scientific, safety, ethical, legal, and social issues raised by *in utero* gene transfer. During the September 24-25, 1998 meeting of RAC, members and other invited experts initiated a public dialogue on *in utero* gene transfer research as a first step in identifying the substantive public policy issues. Dr. Anderson was a member of the AAAS working group.

[27] Minutes from the Recombinant DNA Advisory Committee Meeting, December 15-16, 1997, *Human Gene Therapy* (1998) 9: 1658.

rigorous experimental data…to assure that there are no untoward effects on the germ line."[28]

For the reasons outlined above, many members of the working group, including several of the scientists, question whether we will ever have enough confidence in the safety of IGM to proceed to clinical use. This assessment led some to conclude that it would never be scientifically and ethically appropriate to begin human applications until we can surmount this problem.

Inadvertent Germ Line Modifications

Current regulating mechanisms seek to prevent inadvertent germ line modifications. The document "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects" (Points to Consider), prepared by the NIH Recombinant DNA Advisory Committee (RAC), states that "RAC will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell transfer." [29] The one exception was RAC's recent consideration of the proposal to correct genetic defects in a fetus before birth described above, which could lead to inadvertent changes in the fetus's germ line cells. However, the scientists were seeking an informed discussion of the issues, not authorization to proceed.[30]

Despite these precautions, it is very likely that some of the somatic transfer trials authorized by RAC have had unintentional or secondary impacts on the germ line. It is difficult to know, however, because to-date data ascertaining the incidence of such effects, as for example through autopsies of research subjects who have died, have not been routinely collected.

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[28] *Ibid*., p. 1659.

[29] NIH Guidelines for Research Involving Recombinant DNA Molecules, Appendix M., "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects," (Points to Consider), *Federal Register* (April 27, 1995) 60: 20737; or http://www4.od.nih.gov/oba/guidelines.html.

[30] Cover letter submitted by Dr. W. French Anderson to the NIH Office of Recombinant DNA Activities on July 31, 1998.

As somatic gene therapy trials proceed, it is likely that some of the new technologies and approaches may increase the likelihood of secondary germ line modifications. *In utero* gene transfer, which has the potential benefit of correcting genetic deficiencies before they produce serious adverse consequences, raises the possibility of inadvertent gene transfer to the germ line. It is also possible that gene correction techniques currently under development may produce secondary germ line changes.

The possibility of genetic problems occurring as a result of the unintended germ line side-effects of somatic cell therapy seem at least as great or greater than those that might arise from intentional IGM. Presumably, if researchers were conducting intentional IGM they would be using methods designed to cause the least possible genetic disruption in germ cells. Further, if they were using *in vitro* embryos, they would attempt to monitor the effects of the genetic manipulation before they implanted an embryo. With intentional IGM, there would be at least some safeguards for minimizing the possibility that a person would be born with iatrogenic genetic damage. The same cannot be said of an inadvertent germ line modification.

Thus, the working group concluded that any somatic genetic therapy applications where there is a reasonably foreseeable possibility of IGM should not proceed at this time. There is first a need for further scientific analysis to assess short- and long- term risks and public discussion to determine the extent to which there is support for going forward with secondary germ line changes.

Religious Perspectives on IGM

Among the world's religious traditions, there is a widely shared presumption in favor of healing. Most faiths endorse medicine in some form as a highly valued human action. This support often includes the explicit recognition that medicine sometimes treats disease by altering nature in some respect, for example, by interfering with the natural course of a pathogen.

Yet, the religious traditions represented in the project also share a deep uneasiness regarding actions that might alter human nature or affect human relationships. Such a cautionary approach has marked the responses of religious commentators to nearly every medical advance, and IGM is no exception.

In the 1990s, when religious scholars began to comment on the underlying principle of somatic cell gene therapy, they generally offered approval on the grounds that gene therapy is a reasonable extension of medicine and remains rooted in the presumption in favor of healing. Certain concerns were raised, but these were not uniquely religious or theological. They had to do with issues of safety, involvement of children, or justice in access to the therapy.[31]

Alterations that would affect the genetic inheritance of future generations have elicited a more cautious response. Positions of religious bodies on the appropriateness of intergenerational genetic interventions have ranged from the studied and intentional silence on the matter in a National Council of Churches statement[32] to various documents that have significant reservations about undertaking germ line intervention.[33] It is also relevant to note that Jeremy Rifkin, a social activist and critic of genetic engineering, obtained support from the chief officers of most major Protestant denominations and several Roman Catholic bishops for a 1983 position paper opposing all "efforts to engineer specific genetic traits into the germline of the human species." The document was released with "a call upon Congress to prohibit genetic engineering of the human germline cells."[34]

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[31] Audrey R. Chapman, *Unprecedented Choices: Religious Ethics at the Frontiers of Science* (Minneapolis: Fortress, 1999), pp. 67-68.

[32] National Council of Churches of Christ in the U.S.A., "Genetic Science for Human Benefit," adopted by the Governing Board May 22, 1986.

[33] The strongest example of this latter category is a 1992 Methodist statement. See United Methodist Church, *Book of Discipline of the United Methodist Church* (Nashville, TN: United Methodist Publishing House, 1992), pp. 97-98.

[34] This document is quoted in Roger Lincoln Shinn, *The New Genetics: Challenges for Science, Faith and Politics* (Wakefield, R.I. and London: Moyer Bell, 1996), p. 125.

This categorical opposition did not, however, mirror the official policies adopted by these communions.

The official position of most religious communities that have a relevant policy are better characterized as expressing caution rather than categorical rejection of IGM. In many of these policy statements the distinction between the acceptability of somatic cell therapy and the problematic nature of germ line therapies appears to be made primarily on the grounds of safety rather than intrinsic theological or ethical objection to germ line per se. Many of the documents advocate a temporary moratorium rather than a permanent ban so as to assure safety and provide ample time for ethical reflection to guide scientists and society.[35]

Our working group identified the following religious concerns in respect to IGM:

The Status of the Human Embryo

Religious traditions vary quite considerably in their views on the status of the human embryo and on the question of whether the embryo is to be regarded as a fully human person from the moment of conception. The fabrication of microscopic embryos entirely outside the womb from extracted gametes, separate from conjugal relationships, introduces unique quandaries unimagined in the canonical texts that govern religio-legal responses in many religious traditions. In the Jewish and Muslim traditions, for example, embryos created *in vitro* may not technically even be considered to be human. According to these traditions, all embryos, both those created as a result of sexual relationships and those brought into existence through IVF techniques, may be regarded as "like water" for the first 40 days of conception; such embryos are not considered to be "ensouled."[36] Many liberal Christian communities share a developmental view of

[35] See, for example, the World Council of Churches, *Biotechnology: Its Challenge to the Churches and the World* (Geneva: WCC, 1989), p. 14

[36] Laurie Zoloth-Dorfman, "Ethics of the Eighth Day: Jewish Perspective on Human Germ Line Interventions," in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

the human embryo: it is accorded respect, regarded with dignity, but only gradually considered to have the full standing of a human person as the pregnancy progresses and it achieves the ability to live independently.[37]

In contrast, it is the official position of several major churches and the personal belief of many Christians, as well as adherents of some other traditions, that the human embryo is to be regarded as a human person from conception. This belief implies that the embryo is never to be treated as an object of experiment or research and then to be discarded. This concern bears upon some but not all strategies and techniques that may be used in the development and clinical application of germ line modifications. IGM would, for example, be permissible in the Roman Catholic tradition, as long as the procedure was clearly therapeutic; did not directly or indirectly destroy or injure the human intellect or will, or otherwise impair their respective functions; and did not involve *in vitro* fertilization, experimentation on embryos, their destruction in the course of developing the therapy, or the externalization of the embryos during the course of the therapy.[38]

Respect for Human Finitude

Many religions understand humans as limited not only by their ability to understand and comprehend fully, but also by the human creaturely condition, driven by needs, temptations, passion, and the fear of death. Religious thinkers tend to share the suspicion that human beings exaggerate their knowledge of and their ability to control

[37] For a discussion of the theological basis of developmental perspectives, see Karen Lebacqz, Michael M. Mendiola, Ted Peters, Ernlé W.D. Young, and Laurie Zoloth-Dorfman, "Research with Human Embryonic Stem Cells: Ethical Implications," *The Hastings Center Report* (1999) 29: 31-36.

[38] Father Albert Moraczewski, "The Catholic Church's Moral Tradition and Germ Line Genetic Intervention," in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming); Working Party of the Catholic Bishops Joint Committee on Bioethical Issues, *Genetic Intervention on Human Subjects* (London: Catholic Bishops Joint Committee on Bioethical Issues, 1996), p. 31.

nature through technology. Some traditions, notably some Christian denominations, also suggest that human beings routinely deceive themselves by thinking that they know more than they do or that they can predict the future more clearly than they can in fact, or that such predictions are free from self-serving bias. Linked to the concern that enthusiasm for science might blind us to its deleterious effects, many in the religious community worry that the temptation for power or dominance might confound the ability to use technology for beneficial purposes.

Like many other technologies, our ability to foresee the full consequences of going forward with IGM will be partial at best. Hence, there is concern among religious thinkers that our enthusiasm for this technology and its benefits will tend to downplay the limits of our ability to know the effects of our acts and to proceed responsibly.

Social Justice

Many religious traditions have a commitment to social and economic justice and are concerned about the existing unequal access to health care. For people of faith this inequality violates the belief that the benefits of creation, including those that come in part from human effort, are to be widely shared. This makes many within the religious community particularly sensitive to the issue of equity in access to IGM. There is concern that the technology will enable us to enhance offspring in socially desirable and competitive ways, thereby further privileging the wealthy and powerful by securing the position of their offspring against competition.[39]

The Relationship between Parents and Children

Religious traditions tend to emphasize the relational dimension of human life. In part, this is a challenge to what is sometimes viewed as the excessive individualism of secular culture. More

[39] A recent statement dealing with this issue is the "Resolution Opposing Experimental Research for and the Act of Genetic Engineering," voted by the 38th Annual Conference Session of the United Methodist Youth Fellowship of the North Carolina Conference of the United Methodist Church, July 23, 1999.

deeply, this is grounded in a view of the world, articulated differently across the religions, but which sees value in structures and relationships such as the family. Like the concern of some secular ethicists, religious thinkers have worried that too great a readiness to attempt to control the genetic inheritance of our offspring will undermine the value and meaning of the parent-child relationship. Simply put, the intrusion of technology, even if very well intended, could reduce the child to an artifact, a product of technological design, at least in the mind of the child or of his or her parents. Parents would become designers, whose will to have a certain kind of child is etched into the genetic code of their offspring. This is not to glorify the fragile imperfections of nature but to ask a critical question: should we use our technology to alter the relationship so that parents and children become designers and product? This concern becomes all the more urgent if parents ever attempt to modify or enhance traits that are socially desirable or competitively advantageous.

Ethical Analysis: Intrinsic Considerations

There are additional ethical considerations that must be taken into account before attempting IGM. The first is whether there are fundamental reasons that such interventions are, in principle, morally impermissible. The second is the social and moral impact these technologies will have on the human community. Based on the analysis presented below, the working group concluded that if concerns about the safety and reliability of such modifications and their likely deleterious social and justice impact can be addressed, there would seem to be no reason to regard such interventions as morally prohibited in principle.

The value of genes

Some analysts maintain that human genes have a special significance and value because they are biologically essential to our existence as human beings. Others argue that our genes distinguish us from one another as individuals and are at the core of our humanness. Some persons holding these positions draw the conclusion that

the special status of genes precludes intervening in the germ line to modify human genes.[40]

While acknowledging that human genes have special significance and value, the working group disagreed that the status of genes precludes undertaking IGM. Much like other body parts, genes have a derivative value and worth. In recognition of this special derivative worth, we refuse to sell human organs and certain other body parts or to mistreat human bodies after death, but this does not require us to consider bodies or body parts as sacrosanct and untouchable. Quite the contrary, just because our genes bear such special importance for our functioning as human beings, it is ethically important to ensure that they perform appropriately. Moreover, it can be argued that if we had the technical ability to do so, without seriously damaging our own well-being and values important to our society, we may even have an obligation to repair genes both in those who are currently alive and in our progeny as well.

Impact on the human gene pool

Some analysts have argued that future generations have a right to inherit an unmodified human gene pool because the gene pool represents their "genetic patrimony," a resource to which all people have equal claim as the "common heritage" of our species.[41] A corollary claim, made for example in a resolution adopted by the Parliamentary Assembly of the Council of Europe, is that individuals have a right to a genetic heritage that has not been tampered with artificially, except in circumstances that have been recognized as fully compatible with respect for human rights.[42]

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[40] Audrey R. Chapman, *Unprecedented Choices: Religious Ethics at the Frontiers of Science*, pp. 153-156, provides examples of this perspective.

[41] See, for example, Emmanuel Agius, "Germ-line Cells: Our Responsibilities for Future Generations," in Salvino Busuttil, Emmanuel Agius, Peter Serracino Inglott, and Tony Macelli, eds., *Our Responsibilities Towards Future Generations* (Valletta, Malta: Foundation for International Studies, 1990), pp. 133-143.

[42] Parliamentary Assembly, Council of Europe, "Recommendation 934 on Genetic Engineering, " adopted January 26, 1982, in *Texts Adopted by the*

The working group did not accept these claims. Strictly speaking, while individual humans have germ line cells and germ cell lineages, the human species does not have a "germ line" in the genealogical sense. The human gene pool is a heuristic abstraction, not a natural object, and lacks a material referent in nature. Individuals inherit a specific set of genes derived from their parents. Thus from a biomedical perspective, there is no intergeneration "human germ line" that could serve as an asset to the future. [43]

While it is important to ensure that future generations have fair access to the benefits of human genetic research, it is conceptually mistaken to interpret the human gene pool as an "endowment" accumulated by the wise investments of natural selection over which we now have stewardship. [44] The evolutionary process that controls the allelic content of the human gene pool is an unmanaged and unmanageable one. The human gene pool is not a stable given, but has been in flux over the course of human history.

It is also doubtful that IGM would have a serious impact on the gene pool. The number of carriers of recessive alleles related to monogenic impairments is far greater than the number of homozygotes with the diseases. Therefore, if we treat the latter with IGM, we would eliminate only a miniscule percentage of the carriers and would not have a major effect on the gene pool. [45]

Lack of consent by future generations

Some analysts argue that it is wrong in principle to change the genetic makeup of future individuals through germ line interventions

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Assembly, 33rd Ordinary Session, Third Part, January 25-29, 1982 (Strasbourg: the Council, 1982).

[43] Eric T. Juengst, "Should We Treat the Human Germ-Line as a Global Human Resource?' in Emmanuel Aguis and Salvino Busuttil, eds., *Germ-Line Intervention and our Responsibilities to Future Generations* (Great Britain: Kluwer Academic Publishers, 1998), pp. 88-89.

[44] *Ibid*., pp. 85-93.

[45] Bernard Davis, "Germ-line Gene Therapy: Evolutionary and Moral Considerations," *Human Gene Therapy* (1992) 3: 361-365.

because we cannot obtain their consent.[46] It should be noted though that the topic of intergenerational ethics is itself controversial, with philosophers and ethicists disagreeing on the nature and basis of obligations to future generations.[47]

The working group acknowledged that we have an intergenerational responsibility to guard the interests of future persons who are currently voiceless in this respect, but it took issue with those who claim that this obligation precludes IGM. If we do have responsibilities to our descendants, our obligations undoubtedly encompass efforts to make life better for our children and subsequent descendants. This could include eliminating deleterious genes and thereby improving the health of future generations.

Ethical Analysis: Contextual Considerations and Societal Impact

Like all technologies, IGM will not be undertaken in the abstract. If we go forward with human applications, these genetic alterations will be conducted through some series of procedures, on particular subjects, for specific purposes, and in concrete social, economic, and cultural contexts. All of these contextual factors will contribute to its impact on society.

The working group identified a series of problems related to these contextual considerations. The implications for equity and justice are of particular concern. Some of these issues derive from contingent and variable factors, like the existing system of health care finance, which may be more equitable at some point in the future. Others are more ingrained, such as attitudes toward human beings in general and children in particular. These are less accessible to alteration through public policy initiatives. Many, but not all members of the working group, drew the conclusion that these con-

[46] Marc Lappé, "Ethical Issues in Manipulating the Human Germ Line," *Journal of Medicine and Philosophy* (1991) 16: 621-639.

[47] See, for example, Pilar Ossosio, "Inheritable Genetic Modifications - Do We Owe Them to Our Children?" in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

textual factors, singly and jointly, indicate that we are not currently at a point where we should allow the development and use of IGM.

Inequities in access to genetic therapies

Unless there are major changes in the health care system in this country, there will likely be a lack of equity in access to IGM.[48] This reflects a number of factors: the absence of universal health insurance, patterns of inequalities in access to health care in this country, a projected scarcity in the availability of genetic services relative to demand, and the role of market forces in the development of such genetic interventions. At least initially, access will undoubtedly also be limited by the need for considerable knowledge and sophistication to take advantage of such a complex technology.

Current inequalities in access to medical care seem likely to operate with respect to genetic services. At present some one-sixth of the population, approximately 44 million people, lacks health insurance, and many other persons have forms of insurance that offer insufficient coverage. Minorities are far more likely to be uninsured than whites: about one-third of Hispanics and one-quarter of blacks lack health insurance as compared to about one-eighth of whites.[49] Moreover, various studies have shown that minorities with insurance are more likely to have only minimal or basic coverage and to suffer from various forms of "therapeutic discrimination" that limit access to a wide variety of procedures and therapies.[50]

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[48] See, for example, Audrey R. Chapman, "Justice Implications of Germ Line Modifications, " in Audrey R. Chapman and Mark S. Frankel eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

[49] Herbert Nickens, "Health Services for Minority Populations," in Thomas H. Murray, Mark A. Rothstein, and Robert F. Murray, Jr., eds., *The Human Genome Project and the Future of Health Care,* (Bloomington and Indianapolis: Indiana University Press, 1996), p.70.

[50] Marilyn A. Winkleby, "Accelerating Cardiovascular Rick Factor Change in Ethnic Minority and Low Socioeconomic Groups," *Annals of Epidemiology* (1997) 7: 5196-5103; George A. Kaplan and Julian E. Keil, "Socioeconomic Factors and Cardiovascular Disease: A Review of the Literature," *Circulation* (1993) 88: 1973-1998.

IGM most likely would be available only to those with expensive private insurance or sufficient wealth to purchase it. At a minimum, most private insurers are likely to delay agreeing to reimburse policy holders for these genetic services until their efficacy and safety are clearly demonstrated. Another likely impediment to the accessibility of IGM is the refusal of most health insurers to pay for high technology reproductive services like *in vitro* fertilization (IVF) that are likely to be a necessary means of delivery of IGM.

Health insurance policies rarely cover anything considered to be nontherapeutic. This would of course apply to enhancement modifications. While it remains to be seen how costly these techniques would be, their development by the private sector on a for-profit basis means that they are likely to be beyond the means of many citizens, making them available only to a narrow, wealthy segment of society.[51]

To make techniques for IGM available in a system based on the ability to pay would be very problematic, even if they were employed on a small scale. It would add inherited advantages to all the benefits of nurture and education already enjoyed by the affluent, and constitute one more brick in the wall dividing "haves" from "have nots." Therefore, the working group concluded that reform of the health care system to make IGM available on a more equitable basis constituted an important ethical consideration.

Some members of the working group also held the view that as long as we cannot or do not provide basic health care to all members of our society we should not invest in the development of expensive new technologies like IGM. Others would go further and argue that it is pointless to talk about any kind of just distribution of genetic technologies unless and until all persons have access to adequate nutrition, potable water, sanitation, and basic vaccinations. However, other members countered that the world is full of inequalities in health care, but we do not restrict research and use of promising medical technologies.

[51] It has been estimated that current techniques of somatic gene therapy cost at least $100,000 per year per patient. On this point, see LeRoy Walters and Julie Gage-Palmer, *The Ethics of Human Gene Therapy*, p. 53.

Reinforce or increase existing discrimination

The working group was concerned that as long as Americans still discriminate unfairly on the basis of physical appearance, ancestry, or abilities, the introduction of IGM would pose some risk of exacerbating social prejudices. This is particularly a problem in a country, like our own, which has a long and disturbing history of drawing sharp distinctions among citizens on the basis of race and ethnicity and where many persons harbor beliefs in biological determinism. It is important to remember the ways in which past attempts to use reproductive interventions to improve the genetic prospects of future generations have reinforced and exacerbated social injustices against the poorer, less powerful, and more stigmatized amongst us.[52] IGM may increase prejudice against persons with disabilities. This is yet another reason that the development and introduction of IGM techniques should provoke concern, scrutiny, and caution, especially since the culture of prejudice is less susceptible to remedy by direct public policy initiatives.

Challenges to equality

As early as 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research raised the concern that human germ line therapy could create enormous social injustices.[53] Subsequently, other analysts have warned that the genetic revolution will pose unprecedented challenges to equal opportunity, particularly in a society such as ours with unequal access to genetic services.[54]

The working group acknowledged that IGM would not create new problems of inequity, but anticipated that it could significantly magnify inequalities already rooted in American culture. IGM would

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[52] Troy Duster, *Backdoor to Eugenics* (New York, Routledge, 1990).

[53] President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research, *Splicing Life*, p. 67.

[54] Thomas H. Murray, "Introduction: The Human Genome Project and Access to Health Care," in Thomas H. Murray, Mark A. Rothstein, and Robert F. Murray, Jr., *The Human Genome Project and the Future of Health Care*, p. ix.

have a cumulative impact; the advantages and enhancements of one generation would be passed on to their progeny. Many members of the working group were very concerned that unequal access to IGM technologies would mean that those persons who can already provide the best "environments" for their children would also be able to purchase the best "natures." Thus, those who had preferential access to life's material goods would be able to purchase genetic improvements for their children and their children's descendants, and thereby become doubly advantaged. How much of an advantage this would confer and thereby contribute to inequality would depend, of course, on the types of modifications that will become possible.

Commercialization and commodification

Some ethicists and religious thinkers fear that human germ line manipulation would accelerate tendencies to commodify children and evaluate them according to standards of quality control.[55] In the existing market-based system of financing health care and related research, the patient is thought of in economic terms as the consumer and the health care provider as a seller of services on the open market. All manner of judgments, including decisions about medical treatment, are made in terms of cost-benefit analysis, functionality, and productivity. In such circumstances, the pull of commerce is very powerful, and it will be difficult to erect barriers to prevent the wholesale treatment of genetic intervention as simply one more commodity in the marketplace, a type of commercial service aimed at delivering the product of a desirable baby to the parent as consumer.

Members of the working group found merit in these concerns about commodification. Obviously, IGM will not constitute the source of the attitudes that make science and medicine just one more form of concentrated social power or turn parenting into an exercise

[55] See, for example, Cynthia Cohen, "Creating Tomorrow's Children: The Right to Reproduce and Oversight of Germ Line Interventions," and Sondra Wheeler, "Parental Liberty and the Right of Access to Germ Line Intervention," in Audrey R. Chapman and Mark S. Frankel eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

of power over offspring for the sake of the satisfaction of parental desires. But it might well exacerbate such attitudes by providing parents with a powerful tool, which, when combined with the natural parental desire to enhance the quality of life of their children, will fuel further research and development of IGM that will require society to confront its uneasiness over commodification. If competitive parents keen for "success" for their offspring were to undertake to design the most advantageous genome for their offspring, this would undermine our ethical ideal of unconditional acceptance of children, no matter what their abilities and traits. This would constitute a further corruption of parenting and of human relationships in general.

Ethically Appropriate Applications of IGM: Therapy versus Enhancement

Like somatic cell interventions, IGM offers the possibility of genetic enhancements, genetic alterations intended to improve what are already "normal" genes. Modifying a complex normal trait will require far more sophisticated knowledge than we currently have about how genetic factors contribute to their development. It will also necessitate developing the technical ability to manipulate several different genes in concert with one another.

One of the reasons why a distinction is made between therapeutic and enhancement germ line intervention is the fear that the ability to discard unwanted traits and improve wanted characteristics will lead to a form of eugenics. First used by Francis Galton around the turn of the century, eugenics, meaning "good birth," became a movement in the early part of the 20th century with the goal of weeding out what proponents believed were the "bad" traits of society and promoting "good" ones. Negative eugenics sought to discourage breeding among those considered to be socially inferior, including the so-called feeble minded, criminals, and the incurably mentally ill. Prominent scientists in the United States, such as Charles Davenport, the director of the Cold Spring Harbor Laboratory, were proponents of eugenics principles. By the late 1920s, 28 states in this country had passed laws allowing for compulsory sterilization of undesirables, and such concerns contributed to the promulgation of restrictive immigration policies. It has been estimated

that 30,000 people were sterilized on eugenic grounds in the United States by 1939, many against their will and most while incarcerated in prisons or mental institutions. Similar laws were adopted in many European countries. On both sides of the Atlantic these laws were often only formally repealed or declared unconstitutional in the past thirty years.[56] Nazism, which went well beyond these measures by officially sanctioning both compulsory sterilization of patients and the killing of members of "inferior" races, is the most horrendous example of eugenics as a state policy.

The literature on enhancement poses the prospect that it will become increasingly difficult to differentiate between prevention and enhancement in genetic medical interventions. It is contended that in the absence of an objective definition for "normal" state, the meaning of what is considered normal will likely shift. The result could be that interventions now appearing to be radical will become acceptable in the future.[57] Similarly, interventions that currently are classified as enhancements may eventually become categorized as therapeutic.

Another theme is that enhancement applications of IGM, especially if this technology is heavily promoted by commercial developments, would tend to encourage affluent parents to attempt to "improve" their future children's genomes so as to endow them with various advantages. Some ethicists express a concern that this dynamic may promote something analogous to a kind of "soft eugenics," a "kinder, gentler program to 'perfect' human individuals by 'correcting' their genomes" in conformity to specific societal norms or to an identified "economically successful genotype."[58]

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[56] Arthur J. Dyck, "Eugenics in Historical and Ethical Perspective," in John F. Kilner, Rebecca D. Pentz, and Frank E. Young, eds., *Genetic Ethics: Do the Ends Justify the Genes?* (Grand Rapids: William B. Eerdmans Publishing Co., 1997), pp. 25-39.

[57] Gregory Fowler, Eric T. Juengst, and Burke K. Zimmerman, "Germ-Line Gene Therapy and the Clinical Ethics of Medical Genetics," *Theoretical Medicine* (1989) 10: 151-65.

[58] Roger Lincoln Shinn, *The New Genetics*, pp. 140-141.

Other ethicists have raised the concern that enhancement technologies might lead to the imposition of harmful or skewed conceptions of normality and concomitantly what constitutes improvement of human traits. Some scientists and ethicists have seen dangers in the effort to define a normal human genome precisely because it also implies that deviations from the normal sequence would be considered abnormal or undesirable. Others have pointed out the tendency of individuals and societies to seek to impose their own standards and cultural particularities on the world.[59] IGM used for enhancement purposes would reflect and embody the values held by those sponsoring and having access to the technology who could then shape the genetic inheritance of future generations.

Would applications of IGM constitute a form of eugenics? The working group concluded that, with the qualifications noted earlier, the use of IGM to prevent and treat clear-cut diseases in future generations is ethically justifiable and does not constitute a form of eugenics. There were far stronger reservations about undertaking IGM for enhancement purposes.

While acknowledging that there will be difficult borderline cases, the working group believed that it would be possible to distinguish between IGM applications for therapy and enhancement. It strongly recommended that IGM should be used only for cases which are clearly therapeutic. And many members would add the further qualification that IGM should be pursued only when other treatment options are unavailable.

Most members also had fundamental misgivings about undertaking genetic interventions intended to enhance the traits of future generations. For at least some of the members of the working group, enhancement applications of IGM bordered on a form of "soft eugenics." Some members proposed that we should avoid inadver-

[59] For a recounting of these discussions, see Roger Lincoln Shinn, *The New Genetics: Challenges for Science, Faith, and Politics*, pp. 97-102, and Anita Silvers, "A Fatal Attraction to Normalizing: Treating Disabilities as Deviations from 'Species-Typical' Functioning," in Erik Parens, ed., *Enhancing Human Traits*, pp. 95-123.

tently redefining our humanness unless and until we have consciously decided that it would be ethically acceptable to do so.

Nevertheless, the working group recognized that there is a fundamental dilemma in trying to draw a line between the acceptability of IGM for therapeutic purposes and the inappropriateness of using it for purposes of enhancement. The technology for therapy and enhancement procedures is basically the same. Thus, developing the applications to correct defective alleles is likely to promote creeping enhancement applications as well. For example, the ability to correct the genes responsible for Alzheimer's disease would mean that it might also be possible to enhance memory as well.

In theory, genetic enhancement could be accomplished through either somatic or germ line intervention. Whether or not the latter will start us down a slippery slope toward enhancements, the desire to undertake enhancements will most likely favor IGM over somatic technology. Genetic enhancements are likely to require altering several genes that work in concert with each other. Such genetic interventions are likely to be more effective when conducted early in the development of the embryo or on the fetus *in utero*, although this remains to be demonstrated. In many, perhaps most instances, such early intervention would result in alteration of the germ line whether or not it was intended.[60] The very considerable expense involved might incline parents to try to get the most for their investment, again favoring the IGM option. Medical centers offering somatic gene therapies appear less likely than IVF clinics to promote germ line enhancements or to encourage prospective parents to maximize their investment in reproductive services.[61]

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[60] Maxwell J. Mehlman and Jeffrey R. Botkin, *Access to the Genome: The Challenge to Equality* (Washington, D.C.: Georgetown University Press, 1998), p. 34.

[61] See Mark S. Frankel and Michele S. Garfinkel, "To Market, To Market: The Effects of Commerce on Germ Line Intervention," in Audrey R. Chapman and Mark S. Frankel eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

Reproductive Rights

It has been argued that parents have the right to reproduce and to choose whatever means available, consistent with the availability of technology and avoidance of harm to others, in order to attempt to ensure a normal pregnancy and healthy baby.[62] Reproductive autonomy is understood as the individual's right to freedom from interference or constraint in the exercise of his/her reproductive capacity, including the right to make choices about conception, contraception, and termination of pregnancy. Advances in genetics and reproductive medicine promise to extend this range of choice. If safe and effective IGM is developed, it would enable parents not only to select the genes of their children, but also to influence the inheritance of their children's progeny.

Is the right to reproduce a global right that includes the right to apply IGM and other forms of "quality control" technologies to select and control the genetic makeup of future offspring? The working group concluded that individuals and couples are not entitled to proceed unimpeded to use these technologies to control the genes of future children in almost any way that they choose. While many legal commentators agree that decisions about whether to have children are deeply significant and should be given considerable scope, it is questionable as to whether the right to reproduce extends to the use of inheritable genetic modifications.[63]

The working group did not believe that parental authority over children would insulate parental decisions about the use of IGM from state control. In law, as in morality, the comprehensive liberty that parents enjoy in the care and rearing of their children is intended to provide the family with the means to nurture children into adulthood. When parents fall significantly below social standards of ade-

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[62] John A. Robertson, *Children of Choice: Freedom of Choice and the New Reproductive Technologies* (Princeton: Princeton University Press, 1994).

[63] See Cynthia B. Cohen, "Creating Tomorrow's Children: The Right to Reproduce and Oversight of Germ Line Interventions," in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

quacy in the fulfillment of their responsibilities toward their children, their parental authority can be legally terminated.[64]

The working group concluded that the power to select the genetic constitution and selective characteristics of our descendants raises important ethical and social issues that are legitimate subjects of public regulation. By extension, government has the authority and responsibility to develop reasonable regulations covering the use of IGM in order to protect the interests of children as well as core values of the community.

Balancing Scientific Freedom and Responsibility

People recognize the enormous power of expert knowledge and the influence it can have on their lives. All of us look to scientists and physicians for authoritative answers to complex and serious problems of the day. And as a society, we have quite readily invested in the education and training of scientists, in research on important health and social issues, and in the infrastructure essential for sustaining scientific research. Nevertheless, recent history is replete with examples of increasing apprehension on the part of Americans about the effects of science, especially in the biomedical arena, on their lives. As a result, the extent of social controls over science has grown during the past several decades, as society tries to balance its faith in free scientific inquiry with broader social values.[65]

As we observe in this report, IGM is likely to generate both high hopes and uneasiness. Currently, it is the policy of the federal government not to "entertain proposals for germ line alterations."[66] This

[64] See Sondra Wheeler, "Parental Liberty and the Right of Access to Germ Line Intervention," in Audrey R. Chapman and Mark S. Frankel, eds., *Human Genetic Modifications Across Generations: Assessing Scientific, Ethical, Religious, and Policy Issues* (forthcoming).

[65] David H. Guston, *Between Politics and Science* (United Kingdom: Cambridge University Press, 2000).

[66] NIH Guidelines for Research Involving Recombinant DNA Molecules, Appendix M., "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects."

is not a policy of proscription; there is no explicit ban on such research. Rather, it is a policy that takes the view that it is premature on scientific and ethical grounds to proceed with IGM. Presumably, if these conditions were to change appreciably, the government would reconsider the policy. Certainly, change will not occur without allowing research to proceed at some level, concurrent with appropriate oversight and a society-wide dialogue on the moral questions surrounding IGM.

This policy imposes a heavy responsibility on scientists and their institutions, whether academic or commercial. "Scientific freedom…is an acquired right, generally approved by society as necessary for the advancement of knowledge from which society may benefit."[67] But "scientific freedom and responsibility are basically inseparable."[68] Society expects scientists to pursue research within the constraints of established social controls, such as those to protect the rights and welfare of human subjects, and according to the norms and ethical traditions of the scientific community. To act responsibly, therefore, with respect to IGM means not engaging in such research until public regulatory mechanisms are in place to review proposals, while also supporting educational efforts to help scientists and the public consider the broader implications of the research.

Effective Public Oversight

If IGM is to be pursued, an effective system of public oversight must first be in place. There are four reasons for this:

- Public Safety. As indicated by somatic gene modification experiments, we must be vigilant to protect the safety of those participating in experimental studies. This is even more critical with IGM research since the well being of future children will be affected. Concern for public safety is heightened by the intense commercial interest in genetics research and potential applications, where pressures for quick results—and profits—have led

[67] AAAS Committee on Scientific Freedom and Responsibility, *Scientific Freedom and Responsibility* (Washington, DC: American Association for the Advancement of Science, 1975), p. 5.
[68] *Ibid.*

to claims that a rush to clinical trials has outstripped our understanding of the basic science involved.[69]

- Social Values. While the private sector can contribute valuable resources in developing IGM, the public interest requires the promotion of broad social values, such as freedom of scientific inquiry, assurances that people in need will have access to benefits derived from research, and that decisions on the uses of IGM will be openly vetted in the arena of public discourse. Effective public involvement will help to ensure that the scope and direction of IGM research reflect adequate attention to public priorities.

- Transparency. A system of oversight that promotes openness and the sharing of scientific data and findings is more likely to produce better science and expose unacceptable practices than a system biased toward secrecy. For IGM to progress, researchers must have ready access to data and experience from other studies to build on. Access will also help them spot trends that may have implications for the safety of patients enrolled in related studies. But as recent experience in many fields of science, including somatic gene research, over the past decade indicates, the influence of commerce has created incentives for investigators and companies supporting them to keep secret anything that reflects poorly on their progress.[70] This is not an environment in which science best flourishes or that inspires public confidence.

- Public Confidence. If the public does not trust a system of oversight to protect human subjects or to preserve and promote important social values, then research will not, and should not, go forward. Recent events associated with somatic gene experiments have raised public doubts about the cogency of scientists' claims regarding the promise of such research and about the ability of current oversight mechanisms to offer adequate safeguards for experimental subjects.

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[69] Eliot Marshall, "Gene Therapy's Growing Pains," *Science* (1995) 269: 1050-55. The claim was voiced by former NIH director, Harold Varmus.

[70] Rick Weiss, "Gene Therapy Firms Resist Publicity," *The Washington Post* (December 11, 1999), p. A2.

Current Status of Oversight

Experience with somatic gene therapy research raises serious doubts that society is adequately prepared to proceed with IGM research in the absence of more effective public oversight. An array of bodies now oversee and regulate somatic gene research, including Institutional Review Boards, bio-safety committees, the Office for Protection from Research Risks (recently renamed the Office of Human Research Protection) in the Department of Health and Human Services, the FDA, and the NIH's RAC. However, recent disclosures of deficiencies with informed consent procedures,[71] the lack of full disclosure of serious adverse outcomes,[72] charges of financial conflicts of interest among researchers in the field, [73] and at least one death in a clinical trial resulting from the application of a direct attempt at gene therapy[74] have thrown the adequacy of this system of oversight into serious question. Subsequent investigations by the government, including the U. S. Congress, revealed a number of disturbing features of the current system of oversight, leading one U.S. Senator to remark that "our oversight system is failing."[75]

A lack of coordination between the NIH and FDA and the way researchers perceive their reporting responsibilities to each agency have undoubtedly hampered existing oversight efforts. Federal regulations require gene therapy researchers to report all adverse events, no matter what the severity, to both the FDA and NIH. The NIH requirement is for immediate reporting, while the FDA has several categories of events with different reporting times. Many researchers appear to have been confused by these differing require-

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[71] Eliot Marshall, "FDA Halts All Gene Therapy Trials at Penn," *Science* (2000) 282: 565-66.

[72] Rick Weiss, "Gene Therapy Firms Resist Publicity."

[73] Deborah Nelson and Rick Weiss, "Gene Research Moves Toward Secrecy," *The Washington Post* (November 3, 1999), p. A1.

[74] Jeffrey Brainard, "Citing Patient Deaths, Key Senator Urges Better Oversight of Gene-Therapy Trials," *The Chronicle of Higher Education* (February 3, 2000), or http://www.chronicle.com/daily/2000/02/2000020301n.htm

[75] *Ibid.* The remarks were made by Senator Bill Frist, Chair of the Senate Subcommittee on Public Health, at a February 2, 2000 hearing of the Subcommittee.

ments, claiming that they did not know that they were supposed to notify NIH as well as FDA.[76] This is not a trivial matter, since the RAC's review of reports of adverse events is an open and public process, while the FDA is required by statute to conduct its review in private. To complicate matters further, the FDA has been criticized for not routinely communicating reports of adverse events that it receives to NIH.[77] Congress and the responsible federal agencies have responded to these problems in recent months. Legislation was introduced in Congress to tighten up the supervision of federally-funded somatic gene clinical trials.[78] Both NIH and FDA issued a clarification in fall 1999 to institutions, companies and researchers engaged in gene therapy research making clear the latter's reporting responsibilities,[79] and the RAC has recently recommended a plan that would harmonize the reporting requirements of NIH and FDA.[80] It remains to be seen how effective these steps will be.

In addition to inadequacies in the regulatory function of the current oversight system, there has not been adequate public consideration of the scope and direction of gene therapy research, much of which is driven by the private sector. The result is that the focus of the field has moved away from severe and rare genetic disorders to more common ailments, in part because of the greater health impact of these diseases and in part because of the potential of greater profits. There are those who believe that, without additional public deliberation, there will continue to be movement in the direction of treat-

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[76] Theodore Friedmann, "Principles for Human Gene Therapy Studies," *Science* (2000) 287: 2163 and 2165.

[77] Paul Smaglik, "NIH Tightens Up Monitoring Of Gene-Therapy Mishaps," *Nature* (2000) 404: 5.

[78] Paul Smaglik, "Congress Gets Tough with Gene Therapy," *Nature (*2000) 403: 583-84.

[79] Letter from Amy Patterson, Director of the NIH Office of Recombinant DNA Activities, to federally funded institutions (November 22, 1999); Letter from Kathryn C. Zoon, Director of the FDA Center for Biologics Evaluation and Research, to gene therapy IND sponsors and principal investigators (November 5, 1999).

[80] Advisory Committee to the Director, Working Group on NIH Oversight of Clinical Gene Transfer Research. "Enhancing the Protection of Human Subjects in Gene Transfer Research at the National Institutes of Health," July 12, 2000; see http://www.nih.gov/about/director/07122000.htm.

ing non-medical conditions, for example, baldness or hair color, where far more money can be made than in treating disease.[81] There has not been sufficient public discourse devoted to identifying public priorities for somatic gene therapy research. This is not surprising given that there is only a single mechanism in place to coordinate such deliberations, the RAC, which only a few years ago had its mandate and scope of authority dramatically curtailed. More public involvement will be needed in setting priorities for IGM research lest we cede by default the future direction of such research to the private sector.

If IGM were to become widely available, consumer access, whether for medical or non-medical applications, would likely be through clinics such as those that now offer a range of assisted reproductive technologies to couples. These *in vitro* fertilization (IVF) clinics have prospered during the past decade with increasing consumer demand for access to new technologies that offer infertile couples the hope for a genetically-related baby. And IVF clinics are eager to meet those demands by offering a range of services, including, for example, treatments to allow post-menopausal women to bear children and for couples to achieve "family balancing" via techniques that increase the odds of having a child of a particular sex.[82] The industry is virtually unregulated, however, leaving couples to fend for themselves in a highly competitive environment, where due to "aggressive marketing of services by 300-plus clinics…the risks and concerns over the use of the techniques have been all but ignored."[83] This had led to an industry where couples seeking the "best genes money can buy" have precipitated bidding wars over certain donors,[84] where advertising by some clinics has been called

[81] Michael S. Langan, "Prohibit Unethical 'Enhancement' Gene Therapy," statement delivered at NIH Gene Policy Conference, Bethesda, MD, September 11, 1997.
[82] Rick Weiss, "Va. Clinic Develops System for Choosing Sex of Babies," *The Washington Post* (September 10, 1998), p. A1.
[83] Robert H. Blank, "IVF and the Internet," *Politics and the Life Sciences* (1999) 18: 119.
[84] Lisa Gerson, "Human Harvest," *Boston Magazine* (May 1999), or http://www.bostonmagazine.com/highlights/humanharvest.shtml.

questionable, if not deceptive,[85] where the process of informed consent used by some clinics has been described as "seriously deficient,"[86] and where allegations of negligence have led to law suits against IVF clinics and practitioners.[87] The working group was concerned about the absence of effective public oversight for this commercial sector and worried that IGM technologies would become another "off-the-shelf" product that the industry will promote to attract customers.

A Framework for Oversight

Although there are major technical obstacles to developing human IGM in the responsible ways that we have recommended, it is possible that at some time in the future scientific advances will make it feasible to undertake IGM. Even prior to that, improvements in non-human IGM research may make it tempting to apply the techniques to humans in the absence of the precautionary approach that we propose, thereby presenting us with a policy decision about how to proceed. In the interest of ensuring that society is prepared for such developments, the working group recommended that a system of oversight be in place before human IGM research or applications are permitted.

A system of oversight should be established at the national level, with authority over human IGM activities in both the public and private sectors; it should balance the value of scientific freedom against an assessment of the effects of pursuing IGM research; it should be independent of the sources of funding for IGM research or applications; and it should pre-empt any state or local laws that would contradict its ability to fulfill its mandate. The oversight system would be responsible for:

- Promoting a national conversation (and encourage international participation as well) on the acceptability of IGM for therapeutic

[85] Robert H. Blank, "IVF and the Internet," pp. 119-22.
[86] New York State Task Force on Life and the Law, *Assisted Reproductive Technologies: Analysis and Recommendations for Public Policy*, April 1998, p. 230.
[87] *Ibid*., p. 292.

and enhancement applications, and under what conditions human research and application could proceed. This public dialogue should be informed by our best understanding of the relevant science; it should involve an extended discussion of the cultural, religious, and ethical concerns associated with IGM; and it should be as open and inclusive as possible so that the values of all citizens can be carefully considered and weighed by all relevant policymaking bodies.

- Designing a mechanism for assessing the risks and benefits, including ethical, religious, and social implications, associated with human IGM, and weighing that assessment against alternative means to achieve similar goals. As a society we must be prepared to consider how much evidence of safety, efficacy, and ethical acceptance will be required before endorsing either human clinical trials or applications outside an experimental protocol.

- Encouraging a national effort to develop guidelines to govern the use of IGM.

- Developing guidelines for managing conflicts of interest among IGM researchers and funders.

- Serving as a national repository for all data generated by IGM-related research and applications in animals or humans. Data from animal studies using IGM and from the use of other methods to modify the genome (e.g., somatic gene modification (including inadvertent effects), embryo preimplantation) may help to improve our understanding of the strengths and weaknesses of the various methods used to alter the germ line.

Once these steps have been taken and if a decision is made to proceed with human IGM, oversight should include:

- Independent scientific and ethical review of all IGM protocols or procedures in the public and private sectors, whether for therapeutic or enhancement purposes, as well as of somatic gene

transfer experiments where inadvertent inheritable modifications may reasonably be foreseen.

- Procedures for monitoring the use of IGM in both public and private sectors to ensure that guidelines are followed.

IGM raises two types of concerns. One, that the techniques will succeed, raising questions about the moral and policy implications of increased genetic control; and two, that they may inflict unanticipated genetic harms on future generations or produce unforeseen evolutionary effects on the human genome. The proposed system of oversight, and we include public involvement in this effort, must consider both types of concerns, and we offer several "points to consider" during deliberations on these matters. These points should not be considered fixed, but rather should be subject to periodic review in order to take into account advances in knowledge and technology and changes in social mores. They should aim to produce guidance on the following:

- Applying the assessment of benefits and risks to the use of IGM in particular cases.

- Designing a plan to maximize access to relevant data produced by all IGM research and applications, with proper consideration of patient confidentiality and the protection of proprietary data. Public safety and the advancement of knowledge should weigh heavily when determining what data should be made public and the timing of the release.

- Selecting subjects to participate in IGM research.

- Developing an appropriate consent process for IGM research.

- Identifying the parameters of appropriate public-private partnerships.

- Providing just access to approved uses of IGM for those without the means to obtain them.

An Intermediate Step

Although the working group does not recommend proceeding with IGM in humans at this time, recognizing that various techniques with IGM implications are now in use, such as the micromanipulation techniques intended to compensate for mitochondrial genetic diseases (*in vitro* ovum nuclear transplantation), or are proposed that could have the effect of modifying the human germ line, we counsel an intermediate step. This step is justified in order to ensure that such interventions are as effective and safe as possible. Our recommendations include the following:

- Basic research at the cellular and animal level related to the effects of germ line modification should be encouraged. This is consistent with the long-standing tradition of scientific freedom and reflects an understanding that to foreclose such research could rob us of unexpected discoveries that might inform progress in other areas of medical research as well as in IGM research.

- Data collection on the effects of germ line interventions should be a high priority. A uniform system of reporting such data should be established, and researchers should be required to incorporate into their protocols provisions for transferring data into a data bank administered by a national oversight body.

- Using the data collected through the reporting system and data bank we recommend, studies should also be supported to design ways to help us evaluate and decide when human IGM research should proceed. How can we assess the short- and long-term effects of IGM? How much evidence of safety and efficacy should we require before going forward? How can we gather that evidence in a way that is consistent with our obligations to human subjects and their future children?

- There should be widespread public discussions to gather information about people's understanding and concerns related to IGM. We have not yet had this kind of civic discourse in the United States, and it is not too early to begin to take the pulse of

America on what, if any, germ line research applications would be acceptable. It is essential that these discussions raise the level of public understanding of the science associated with IGM. Scientists must be prepared to communicate the results of their research in ways that are understandable to a diverse audience and are realistic in their appraisal of the promise and feasibility of IGM. The dialogue should aim to clear up misunderstandings and avoid false expectations, not perpetuate them.

- To help implement the above recommendations, there must be an oversight mechanism in place that can review these procedures already taking place that affect genetic inheritance as well as the prospect of IGMs. While we are not proposing the more elaborate system that was described above - it is neither justified by the extent of the ongoing research that would be covered nor the cost of establishing such a system - it is clear to us that this intermediate step needs to include a body that can assume a leadership role in establishing public confidence in a process that will track efficacy and ensure as much as possible the safety of research participants.

- This body should be independent of the sources of funding for the research.[88] (This requirement would preclude the current RAC from fulfilling this role. Nevertheless, we acknowledge the ongoing evaluation of the role that RAC should play in its oversight of somatic gene therapy, and we hope that these discussions can inform the development of an oversight mechanism for IGM.)

- This body should review and approve all protocols for somatic gene research in both the public and private sectors where inad-

[88] This is consistent with the recent decision by the U.S. Department of Health and Human Services to elevate its office to protect human research subjects into the Office of the Secretary to "remove the potential conflict of interest that existed because [it] has been part of the NIH, which finances some of the research the office has overseen." See Jeffrey Brainard, "Physician Is Called Top Candidate to Head Unit that Oversees Human Subjects Research," *The Chronicle of Higher Education* (May 17, 2000), or at http://chronicle.com/daily/2000/05/2000051703n.htm.

vertent germ line alterations may occur as well as protocols for other studies that could alter the germ line more directly (e.g., IVONT, somatic cell nuclear transfer). Until this system of oversight is in place, no research or clinical applications involving humans should proceed that have the direct or indirect potential to cause inheritable modifications.

- In addition to reviewing non-human evidence of efficacy and safety, the review should encompass the plans proposed by investigators or others to document any germ line intervention and to transfer data to the data bank that we recommend be established.

Conclusion

This report has emphasized that inheritable genetic modification cannot be carried out safely and responsibly on humans utilizing current methods for somatic gene transfer. At some point in the future scientists could develop more reliable genetic technologies that replace harmful mutations or correct them. Even if we have the technical ability to proceed, however, we would need to determine whether IGM would offer a socially, ethically, and theologically acceptable alternative to other technologies in prospect of development to prevent or correct damage attributable to mutated genes.

As described in this report, IGM might some day offer us the power to shape our children and generations beyond in ways not now possible, giving us extraordinary control over biological and behavioral features that contribute to our humanness. The working group concluded that the prospect of shaping the genetic inheritance of future generations raises major ethical and religious concerns. IGM for enhancement purposes has particularly problematical implications.

One of the challenges posed by IGM stressed in this report is the need for public education and public discussion to determine whether, and if so, how to proceed with developing IGM for human use. Ideally, these efforts should be informed by an understanding of the relevant science, involve an extended discussion of the cultural, religious, and ethical concerns associated with IGM, and be as open

and inclusive as possible. Until then, no research or applications that could cause inheritable modifications in humans should go forward.

The AAAS working group did not address the strategies and structures that would be required to construct and sustain such dialogue over time. We acknowledge, however, the critical importance of designing mechanisms that are open to all voices that wish to be heard and that can be expected to improve public understanding of what is at stake in proceeding with IGM. We encourage others to join with us in considering how best to begin and sustain such a national (and international) conversation.

We hope this report will be a useful contribution to those public conversations. The future is not fixed. It is critical that we understand the possibilities that lie ahead so that we can make informed and reasoned choices about the future.

*Glossary**

Allele. One of two or more alternative forms of a gene.

Aneuploidy. The presence of an irregular number of chromosomes, typically involving the absence of a chromosome (monosomy) or the presence of an additional copy of a chromosome (trisomy).

Artificial chromosomes. Recombinant DNA molecules that contain all the elements that enable them to replicate and be carried stably during cell division as independent chromosome-like structures. Artificial chromosomes may be engineered to carry therapeutic genes.

Basic research. Fundamental theoretical or experimental investigation to advance scientific knowledge, where immediate practical application is not the primary consideration.

Biological determinism. The view that development of an organism is determined solely by genetic factors.

Blastocyst. A preimplantation embryo consisting of 30-150 cells.

Chimera. An organism containing cells of different genotypes.

Chromosome. The structure in an organism that contains the entire genetic information of the organism, usually in the form of a condensed complex of DNA and specialized proteins.

Cloning. Refers to both molecules of DNA and to entire organisms. In the case of DNA molecules, cloning refers to the use of recombinant DNA methods to produce many copies of a starting molecule. In the case of organisms, it refers to the production of an organism

*****This glossary was compiled and edited with the assistance of: Jason Borenstein, Theodore Friedmann, Rachel Gray, Bhavani Pathak, and Sheryl Wallin.

with the identical nuclear genetic complement of another organism, usually by transfer of a donor nucleus into the egg cell of a recipient organism.

Deoxyribonucleic acid (DNA). The double-stranded molecule encoding the total genetic information of most organisms, consisting of four oligonucleotide bases strung along a sugar-phosphate backbone.

Embryo. An organism at the earliest stages of development. In the case of humans, generally is limited to the period before the end of the third month.

Embryonic germinal ridge cells (EG). Germ cell precursors which have migrated to a thickened ridge of tissue on the developing embryo known as the gonadal ridge region, where they will proceed to differentiate into either male or female cells. EG cells have the capacity to produce all or most all of the cell types of a mature organism and hence may be considered pluri-potential and possibly toti-potential.

Embryonic stem cells (ES). Cells in the blastocyst that can give rise to an embryo.

Endogenous gene. One of the naturally occurring genes in an organism, in contrast to a foreign "transgene" that has been transferred into the recipient genome.

Enucleated oocyte. The result of removal of the nucleus and therefore all the nuclear genes from an unfertilized, haploid oocyte that contained the maternal chromosomes.

Eugenics. The branch of science that deals with the improvement of the genetic quality of a species.

Extra-nuclear genome. Genetic material located outside of a cell's nucleus. Usually refers to the mitochondrial genes.

Founder organisms. Organisms that determine the genetic composition of a population.

Gamete. A haploid reproductive cell, either a sperm or oocyte.

Gene. A segment of DNA that encodes one or more functional products, such as proteins or RNA molecules.

Gene addition. The process by which foreign genetic information is added to a genome, as opposed to methods that permit exact exchange of genetic elements or modification of the nucleotide sequence.

Gene pool. The complete set of genetic information in a population; the gene pool includes all alleles present in the population.

Gene transfer. The introduction of foreign genetic material into a cell, often with the help of vectors such as viruses or lipid-DNA complexes.

Genetic code. Nucleotide triplets within the DNA sequence that specify different amino acid products.

Genetic enhancement. The use of gene transfer technology for non-disease-related purposes.

Genome. The complete set of genetic information of an individual.

Genotype. Genetic constitution of a cell or organism.

Germ cells. The reproductive cells of an organism, i.e., the sperm and egg cells.

Germ line. The cell lineage consisting of cells capable of contributing genetic material to subsequent generations.

Germ line intervention. The transfer of genetic material into germ line cells.

Haploid. Refers to a cell containing half the full complement of chromosomes of an organism, such as sperm cells and oocytes. Fer-

tilization results in the re-establishment of the normal full number of chromosomes.

Homologous recombination. A process by which the nucleotides of two or more nucleic acid molecules become aligned by base pairing and exchange elements of their sequences.

Homozygosity. The state in which the two alleles of a gene at a specific locus are identical.

Human Genome Project. An international collaborative effort to determine the sequence and location of all genes within the human genome.

Iatrogenic. Pertaining to an abnormal state or condition produced inadvertently in a patient by medical treatment.

Inheritable genetic modification (IGM). The induction of genetic changes capable of being inherited by an organism's offspring.

Intracytoplasmic sperm injection (ICSI). A micromanipulation procedure involving the insertion of a single sperm directly into the cytoplasm of a mature egg.

In utero. Accomplished within the uterus.

In vitro. Refers to processes outside a living cell or organism, as in a test tube.

In vitro ovum nuclear transplantation (IVONT). A process by which a nucleus is transferred from an adult cell to an enucleated egg, outside of a living organism.

In vivo. Accomplished within a living organism.

Micromanipulation techniques. Techniques used to dissect, vivisect, isolate, and manipulate microscopic materials.

Mitochondria. Specialized cellular substructures that are the principal energy producers for cells. They contain DNA that is inherited exclusively through the maternal lineage. Mitochondrial DNA is present in enucleated oocytes and constitutes the genetic difference between cloned organisms.

Monogenic traits. Normal or pathological genetic properties that are determined by alleles at a single genetic locus.

Mutation. A change in the wild type sequence or organization at a locus that produces a new, often pathological function.

Nuclear genome. Genetic information contained within a cell's nucleus.

Nucleus. The membrane-bound substructure within a cell that contains chromosomes.

Oocyte. A female sex cell that undergoes meiosis to give rise to a mature egg or ovum.

Plasmid. Extrachromosomal, circular, double-stranded DNA molecules, occurring naturally in some organisms such as bacteria and yeast, that can be used as vectors for transferring genes from one cell to another.

Polygenic disease. A genetic disorder resulting from the combined effects of more than one gene.

Reproductive cells. Germ cells, such as sperm cells or ovum.

Ribonucleic acid (RNA). A single-stranded nucleic acid that plays a central role in protein synthesis and gene regulation, consisting of the four oligonucleotide bases attached to a sugar-phosphate backbone. RNA contains ribose, in contrast to the deoxyribose in DNA.

Somatic cell. Any cell within the body that is not part of the germ line.

Somatic cell nuclear transfer. Cloning mechanism accomplished via the transfer of a somatic cell nucleus into the cytoplasm of an enucleated egg cell; mechanism used to produce the cloned sheep 'Dolly'.

Somatic gene therapy. Non-inheritable genetic changes induced in somatic cells in order to treat genetically-based diseases.

Telomere. The structure at the tips of all mammalian chromosomes, consisting of repeated oligonucleotide sequences. The length of the repeat elements is a partial measure of the number of replications a cell has undergone and partly determines the replicating potential of cells.

Transgene. Any cloned gene that has been introduced into a cell.

Transgenic organism. An organism that contains a foreign genetic element added to its genome.

Toti-potential cells. Cells such as embryonic stem (ES) and embryonic germinal ridge (EG) cells that are able to give rise to all tissue types found in a fully developed organism.

Vector. Any agent such as a virus, liposome, DNA-protein complex or artificial chromosome used to act as a vehicle to transfer genes into cells.

Wild Type. The naturally-occurring genotype or phenotype for a given organism.

Appendix A

WORKING GROUP MEMBERS

W. FRENCH ANDERSON, M.D., is the Director of the Gene Therapy Laboratories at the University of Southern California (USC) Keck School of Medicine, where he also serves as Professor of Biochemistry and Pediatrics, a Full Member of the Norris Comprehensive Cancer Center, and Program Coordinator for Gene Therapy in the Institute of Genetic Medicine. Before joining the USC faculty in 1992, he was Chief of the Molecular Hematology Branch at the National Heart, Lung and Blood Institute at the National Institutes of Health (NIH), and was also Chairman of the Department of Medicine and Physiology in the NIH Graduate Program. Dr. Anderson received a bachelor's degree from Harvard College (1958), an M.A. from Trinity College, Cambridge University (1960), an M.D. from Harvard Medical School (1963), and also holds two honorary degrees. For his work in pioneering gene therapy he has won several awards, including the King Faisal International Prize in Medicine in 1994. Dr. Anderson also headed the team that carried out the first approved human gene therapy clinical protocol.

R. MICHAEL BLAESE, M.D., has been Chief Scientific Officer and Head of Human Therapeutics of ValiGen, Corp. (formerly Kimeragen) since 1999. Before joining Kimeragen, he was a senior investigator at the National Institutes of Health for 33 years, most recently as Chief of the Clinical Gene Therapy Branch at the National Human Genome Research Institute. In the mid-80's, Blaese partnered with W. French Anderson at the NIH in a collaboration that ultimately resulted in the first clinical trial in 1990 of gene therapy for the treatment of an inherited disease. His research program at the NIH developed the fundamental technology leading to clinical trials of gene therapy for such disorders as genetic immunodeficiency, malignant melanoma, brain cancer, AIDS and metabolic blindness. He is a member of the Association of American Physicians, a Fellow of the AAAS, and an elected member of the Board of Directors of the American Society of Gene Therapy.

CYNTHIA B. COHEN, Ph.D., J.D., is a Senior Research Fellow at the Kennedy Institute of Ethics at Georgetown University in Washington, D.C. and an adjunct associate at The Hastings Center in Garrison, NY. She was formerly executive director of the National Advisory Board on Ethics in Reproduction and chair of the Philosophy Department at the University of Denver. She has also chaired several bioethics committees for the Episcopal Church. Her publications include *New Ways of Making Babies* and *Wrestling with the Future: Our Genes and Our Choices* as well as several articles on the right to reproduce, germ line interventions, and the commodification of the human body.

RONALD COLE-TURNER, Ph.D., is the H. Parker Sharp Professor of Theology and Ethics at Pittsburgh Theological Seminary, a position that relates theology and ethics to developments in science and technology. He holds an M.Div. and a Ph.D. from Princeton Theological Seminary. Professor Cole-Turner is the author of *The New Genesis: Theology and the Genetic Revolution* (1993), co-author (with Brent Waters) of *Pastoral Genetics: Theology and Care at the Beginning of Life* (1996), and editor of *Human Cloning: Religious Responses* (1997).

ROBERT COOK-DEEGAN, M.D., directs the National Cancer Policy Board, Institute of Medicine (IOM) and Commission on Life Sciences (National Academy of Sciences). He is also a Robert Wood Johnson Health Policy Investigator at the Kennedy Institute of Ethics, Georgetown University, where he is writing a primer on how national policy decisions are made about health research. From 1991-94, he directed IOM's Division of Biobehavioral Sciences and Mental Disorders. He worked for the National Center for Human Genome Research 1989-90, after serving as Acting Executive Director of the Biomedical Ethics Advisory Committee of the U.S. Congress 1988-1989. Dr. Cook-Deegan received his bachelor's degree in 1975 from Harvard College, and his M.D. from the University of Colorado in 1979. He is the author of *The Gene Wars: Science, Politics, and the Human Genome*.

KENNETH W. CULVER. M.D., is an Executive Director in the Pharmacogenetics Department at Novartis Pharmaceuticals Corporation in East Hanover, New Jersey. At Novartis, Dr. Culver is primarily responsible for integration of pharmacogenetics studies throughout clinical research and development. Prior to joining Novartis, Dr. Culver was Vice President of Gene Repair Research at Codon Pharmaceuticals, Inc., and previously a Senior Clinical Investigator at the National Institutes of Health. He was one of a team of scientists who pioneered the first clinical applications of gene therapy to immunodeficiency disorders and cancer. He graduated from the University of Iowa College of Medicine. Subsequently, he completed his internship and residency in Pediatrics and a fellowship in Pediatric immunology at the University of California, San Francisco.

TROY DUSTER, Ph.D., currently holds the position of Chancellor's Professor of Sociology and Director of the American Cultures Center at the University of California, Berkeley. He is also Professor of Sociology at New York University and a member of the Institute for the History of the Production of Knowledge at NYU. He served on the Committee on Social and Ethical Impact of Advances in Biomedicine, Institute of Medicine. From 1996-98, he served as chair of the joint NIH/DOE advisory committee on Ethical, Legal and Social Issues in the Human Genome Project *(The ELSI Working Group)*. His books and monographs include *Cultural Perspectives on Biological Knowledge* (co-edited with Karen Garrett, 1984), and *Backdoor to Eugenics* (Routledge, 1990), a book on the social implications of the new technologies in molecular biology. He received his Ph.D. in sociology from Northwestern University in 1962.

CHRISTOPHER EVANS, Ph.D., D.Sc., is Professor of Orthopaedic Surgery at Harvard Medical School and Director of the Center for Molecular Orthopaedics, which he founded in 1999. Dr. Evans is the Principal Investigator on the world's first arthritis gene therapy clinical trial, and an expert on the use of gene therapy to treat non-lethal diseases. Dr. Evans obtained a B.Sc. in Genetics & Microbiology, a Ph.D. in Biochemistry, and a D.Sc. degree from the University of Wales, Great Britain. After a period of post-doctoral research in the Department of Molecular Biology at the Free University of

Brussels, Belgium, he came to the U.S. as an Assistant Professor in the Department of Orthopaedic Surgery of the University of Pittsburgh School of Medicine, where in 1993 he became the inaugural Mankin Professor of Orthopaedic Surgery and Professor of Molecular Genetics and Biochemistry. While at the University of Pittsburgh, he obtained an M.A. in the History & Philosophy of Science. Dr. Evans's research has been recognized by a number of awards, including the Kappa Delta Award of the American Academy of Orthopaedic Surgeons.

JOHN C. FLETCHER, Ph.D., is Professor Emeritus of Biomedical Ethics and Internal Medicine at the University of Virginia (UVA) School of Medicine. He served as Kornfeld Professor of Biomedical Ethics and Director of UVA's center for Biomedical Ethics from 1987 to his retirement in 1997. Dr. Fletcher founded and directed the Bioethics Program of the Warren G. Magnuson Clinical Center, National Institutes of Health (NIH), 1977-87. He is completing a book with Dorothy C. Wertz based on an international survey of medical geneticists and counselors in thirty-seven nations.

THEODORE FRIEDMANN. M.D., received his A.B. and M.D. degrees from the University of Pennsylvania (1956 and 1960) and a Master's degree from the University of Oxford (1995). He is currently Professor of Pediatrics and Whitehill Professor of Biomedical Ethics at the University of California, San Diego (UCSD) and director of the UCSD Program in Human Gene Therapy. Dr. Friedmann received his clinical training in Pediatrics at the Children's Hospital in Boston and did postdoctoral fellowships at the University of Cambridge, the National Institutes of Health and the Salk Institute in La Jolla, CA. Along with Richard Roblin, he published what is considered by many to be the first description of the need for gene therapy for human disease. He has also published *The Development of Human Gene Therapy* as well as a summary of recent public policy difficulties and developments, "Principles for Human Gene Therapy Studies"(*Science* 287: 2163-2165, 2000).

ERIC T. JUENGST, Ph.D., is an Associate Professor of Biomedical Ethics at the Case Western Reserve University School of Medicine, Cleveland. He received his B.S. in Biology from the University of the South (1978) and his Ph.D. in Philosophy from Georgetown University (1985). He has taught medical ethics and the philosophy of science on the faculties of the medical schools of the University of California, San Francisco and Penn State University. In addition, he served as the first Chief of the Ethical, Legal and Social Implications Branch of the National Center for Human Genome Research at the NIH from 1990-94. He is currently the principal investigator of a NIH-funded research project anticipating the social policy issues that will be raised by the availability of genetic enhancement techniques. He serves on the Bioethics Committee of the March of Dimes, the U.S. Recombinant DNA Advisory Committee, the DNA Advisory Board of the FBI, and the editorial boards of several journals.

FATHER ALBERT S. MORACZEWSKI, O.P., Ph.D., S.T.M., currently is President Emeritus of the National Catholic Bioethics Center. In his present capacity Fr. Albert is also Distinguished Scholar in residence and Senior Consultant. Besides numerous articles in scientific and theological journals, Fr. Albert edited two books on genetics: *Genetic Counseling, The Church, and the Law* (with G. Atkinson, 1980) and *Genetic Medicine and Engineering: Ethical and Social Dimensions* (1983). In addition, he has also published several chapters and articles relevant to genetics, e.g.,"The Human Genome Project and the Catholic Church," in *International Journal of Bioethics*, 1992; "The Church and the Restructuring of Man," in *Emerging Issues in Biomedical Policy*, Volume III, Medicine Unbound: the Human Body and the Limits of Medical Intervention, R.H. Blank and A.L. Bonnicksen, eds., 1994.

ROBERT F. MURRAY JR., M.D., M.S., F.A.C.M.G., F.A.C.P., is Professor of Pediatrics and Medicine, College of Medicine, Howard University, and Chief of the Division of Medical Genetics, Department of Pediatrics and Child Health. Dr. Murray also serves as Chairman of the Graduate Department of Genetics and Human Genetics and as Professor of Genetics and Human Genetics in the Graduate School of Arts and Sciences. Dr. Murray received his M.D. degree from the University of Rochester School of Medicine

and Dentistry, in Rochester, NY, in 1958 and the Master of Genetics Degree in 1968 from the University of Washington, in Seattle. He is a fellow of AAAS and a member of the Institute of Medicine, National Academy of Sciences.

PILAR N. OSSORIO, Ph.D., J.D., received her Ph.D. in Microbiology and Immunology from Stanford University and her J.D. from the University of California at Berkeley. She is assistant professor of Law and Medical Ethics at the University of Wisconsin-Madison, and associate director of the Center for the Study of Race and Ethnicity in Medicine.

JULIE GAGE PALMER, J.D., is an attorney specializing in genetics and medical ethics. She is the author of several articles on gene therapy and co-author with LeRoy Walters of *The Ethics of Human Gene Therapy*. She is currently Counsel at Hopkins & Sutter in Chicago, Illinois. Beginning in 2001, she will teach Law, Science, and Medicine at the University of Chicago Law School. She received her law degree from the University of Michigan Law School and her A.B. from Harvard University, with a special concentration in ethics and biology.

ERIK PARENS, Ph.D., is the Associate for Philosophical Studies at The Hastings Center, a bioethics think tank in Garrison, NY. In 1988 he received his Ph.D. from The University of Chicago's Committee on Social Thought. Dr. Parens has published on many aspects of the new genetics, from genetic testing in managed care settings, to the prospect of genetic enhancement, to research on embryonic stem cells.

BONNIE STEINBOCK, Ph.D., is Professor and Chair of the Department of Philosophy at the State University of New York at Albany, with joint appointments in Public Policy and Public Health. A Fellow of The Hastings Center in Garrison, NY, she is author of over 50 articles in bioethics and a book, *Life Before Birth: The Moral and Legal Status of Embryos and Fetuses*. She has been a member of several working groups in the U.S. and Europe on issues in genetics and reproduction, and is currently writing a book entitled *Rethinking Reproduction*.

GLADYS B. WHITE, Ph.D., R.N., is a bioethicist and a nurse. She is currently the director of the Center for Ethics and Human Rights of the American Nurses Association and Adjunct Professor of Liberal Studies at Georgetown University, Washington, D.C. She is the former Executive Director of the National Advisory Board on Ethics in Reproduction and a study director and policy analyst of the former Office of Technology Assessment of the U.S. Congress. She received her Ph.D. in philosophy with concentrations in ethics and bioethics from Georgetown University and degrees in nursing from Catholic University of America and Duke University. Her research interests include reproductive technologies, genetics and biotechnology issues.

SONDRA WHEELER, Ph.D., was educated at Wesleyan University (B.A., 1979) and Yale University (Ph.D., 1992.) She teaches at Wesley Theological Seminary in Washington D.C., where she is the Martha Ashby Carr Professor of Christian Ethics. She works in biblical ethics, the history of theological ethics, and the virtue tradition as well as bioethics. She is the author of *Wealth as Peril and Obligation: The New Testament on Possessions, Stewards of Life: Bioethics and Pastoral Care*, and a variety of lectures and articles in biomedical ethics, as well as book sections and articles in other area of ethics.

LAURIE ZOLOTH, Ph.D., is Associate Professor of Social Ethics and Jewish Philosophy and Chair of the Jewish Studies Program in the College of Humanities at San Francisco State University. She is on the national board of the American Society for Bioethics and Humanities and is a member of the advisory committee for the Program of Dialogue on Science, Ethics and Religion (AAAS). Dr. Zoloth is also a member of the Geron Ethics Advisory Board. Her most recent book is *Health Care and the Ethics of Encounter: A Jewish Discussion of Social Justice*, and she is co-editor with Dena S. Davis of *Notes from a Narrow Ridge: Religion and Bioethics.*

Appendix B

PROJECT STAFF

AUDREY R. CHAPMAN, M.Div., Ph.D., serves as Director of two AAAS Programs, the Dialogue on Science, Ethics, and Religion and Science and Human Rights. She is trained both as a social scientist and a religious ethicist. She is the author or editor of 14 books, including *Unprecedented Choices: Religious Ethics at the Frontiers of Genetic Science* (September 1999) and *Perspectives on Genetic Patenting: Religion, Science, and Industry in Dialogue* (January 1999). Dr. Chapman is also an author of *Stem Cell Research and Applications: Monitoring the Frontiers of Biomedical Research*, a report by AAAS and the Institute for Civil Society.

MARK S. FRANKEL, Ph.D., is Director of the Scientific Freedom, Responsibility and Law Program at the American Association for the Advancement of Science (AAAS), where he develops and manages the Association's science, ethics and law activities. He is editor of the Association's quarterly publication, *Professional Ethics Report*, a AAAS Fellow, and has published extensively on the ethical and legal implications of advances in biomedicine. He is also an author of *Stem Cell Research and Applications: Monitoring the Frontiers of Biomedical Research*, a report by AAAS and the Institute for Civil Society.

RACHEL J. GRAY, M.A., is a Program Associate for the Scientific Freedom, Responsibility and Law Program at the American Association for the Advancement of Science and is a contributing editor to *Professional Ethics Report*. She received her M.A. in Biomedical Ethics in 1998 from Case Western Reserve University, Ohio, and a B.A. in Law with Honours in 1997 from Carleton University, Canada. Before joining AAAS, she researched and worked on topic areas including research ethics, genetics, and xenotransplantation.