

Inheritable Genetic Modification and a Brave New World:

Did Huxley Have It Wrong?

by MARK FRANKEL

Blurb

In the fall of 2000, the American Association for the Advancement of Science called on science to slow down. In a report it issued on inheritable genetic modification, AAAS took the position that no genetic modifications affecting the germ line, whether intentional or inadvertent, should be undertaken until the technology's safety, efficacy, and social implications had been subject to widespread public discussion. Further, said AAAS, there should be no work on inheritable genetic modification until a system of public oversight was in place that exercised authority over research in both the public and private sectors.¹

Yet only six months after the report was released, a fertility clinic reported “the first case of human germline modification resulting in normal healthy children.”² The work was done through the transfer of ooplasm, which surrounds the nucleus of the egg and is essential for it to thrive, from donor eggs into the eggs of women who have experienced recurring implantation failure—fertilization occurs, but the resulting embryo will not implant in their uterus. An inadvertent consequence of this procedure was that

mitochondrial DNA found in the ooplasm of the donated material was introduced into the recipient eggs.

The clinic reported that the technique had “led to the birth of 30 babies worldwide.” The clinic also reported that both the donated mitochondrial DNA and that of the birth mother were found in all the cells of those babies born by this method—a modification of the children's genome, since they inherited mitochondrial DNA from two mothers. Presumably, they will pass this inherited DNA on to their offspring. The report was met with ethical disapproval in some quarters of the United States,³ and the British reminded us that the procedure would be illegal in the United Kingdom.⁴

In his 1932 book, *Brave New World*, Aldous Huxley led us to believe that when it came to our genes and reproductive futures, our worst nightmare was government involvement in procreative activities and a society that devalued individual decisionmaking. But as we begin the twenty-first century, the greater danger, I believe, is a highly individualized marketplace fueled by an entrepreneurial spirit and the free choice of large numbers of parents that could lead us down a path, albeit incrementally, toward a society that abandons the lottery of evolution in favor of intentional genetic modification. The dis-

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coveries of genetics will not be imposed on us. Rather, they will be sold to us by the market as something we cannot live without.

State of the Art

By inheritable genetic modification, or IGM, I mean interventions capable of modifying genes that are transmitted to offspring and to generations beyond. IGM includes interventions made early enough in embryonic development to have global effects—that is, to affect all of one's cells—as well as any interventions targeted at the reproductive cells—sperm and ova—or their precursor stem cells. It encompasses modifications both of nuclear and of extra-nuclear genomes, and modifications that are inadvertent side effects of other, deliberate genetic interventions (of, for example, somatic cell gene transfer). The only criterion is that the modification be inheritable.

What can one say about the promise and the risks of IGM? Some light might be shed on this question by work on somatic cell gene transfer, which is designed to treat or eliminate disease through genetic intervention only in the person receiving treatment. There are different technical approaches to such gene transfer. In “gene augmentation or addition,” new genetic material is inserted into the body in order to take over the function of a faulty gene. The offending genes are not removed; instead, their adverse effects are masked by the new material. In “gene correction,” a normal gene segment is swapped for the segment with the defect. Yet another approach is “gene repair,” in which a normal fragment of DNA is introduced into a cell and the cell's own DNA repair machinery permanently corrects the faulty DNA sequence.⁵ None of these interventions is easy to do; nor is it clear that any of them will do what we want them to do—restore health to the person treated. Despite considerable investment by the government and

by the private sector, the reported successes have been very rare.⁶

Somatic cell gene transfer came under fire following the death in 1999 of Jesse Gelsinger, who was enrolled in a clinical trial that involved the insertion of genetic material.⁷ A review of the “latest developments in somatic gene transfer technology” concluded that “it is not easy to assess exactly all these risk factors. . . . A number of complex issues must be addressed to evaluate the probability of having adverse effects in patients related to the treatment, and to establish the extent of the possible harm that patients may sustain.”⁸

A very recent incident has highlighted other possible harms to patients. In October 2002, researchers reported that a child treated successfully with gene therapy in France for an ordinarily fatal immune deficiency disease had developed a form of leukemia, and that there was persuasive evidence that the treatment was a major contributing factor.⁹ In January 2003, another child was discovered to have developed leukemia.

IGM poses even greater uncertainties related to risk because the interventions would be passed on to the progeny of those treated. Thus we need compelling evidence that the procedures are safe. [OK?] But as the AAAS report concluded, that evidentiary standard cannot yet be met.¹⁰ How do we assess whether, for example, in future generations a gene necessary for healthy development will be accidentally turned off, or a gene that contributes to a certain type of cancer turned on? In a provocative article published earlier this year, one scientist claims that genomic researchers have underestimated, if not ignored, a phenomenon known as “alternative splicing,” which involves the formation of new combinations of gene sequences containing the building blocks of life—proteins—each of them different from the unspliced original and each capable of being inherited. This raises questions about the predictability of the inheritability of traits based solely on

DNA, leaving the author to warn that “any artificially altered genetic system . . . must sooner or later give rise to unintended, potentially disastrous, consequences.”¹¹ Yet how would one design and execute a protocol that enabled us to make such a determination, since many of the effects from IGM may not show up for generations? Other, even more compelling questions relate to how society would assess the potential benefits and risks of a successful germ line intervention in the context of various social and ethical considerations.

Although we have much to learn about applying IGM techniques to humans, researchers have established proof of principle in animals, where foreign genes introduced into mice have been transmitted and expressed for at least three generations.¹² Moreover, recent advances in stem cell and cloning research, which were reported after completion of the AAAS study, will likely provide more options for doing IGM.¹³ As knowledge of human genetics grows in the years ahead, the technical obstacles may fall by the wayside sooner than we expect. To what uses, then, might IGM be put? One would be to target IGM toward the alleviation or elimination of genetic diseases. The other would be to enhance human traits.

A Return to Normalcy

In principle, IGM would have the benefit of preventing the inheritance of genetic diseases in families rather than treating it every time it appears, generation after generation. And by targeting either germ cells or the embryo, IGM could intervene before a condition occurs—before it causes irreversible damage. Some possible health-related uses: transferring ooplasmic mitochondrial DNA to avoid potentially lethal diseases and problems with repeated miscarriages that are caused by faulty mitochondrial DNA; treating sperm or sperm stem cells to help men overcome infertility caused by a genetic mutation; and treating gametes or early-

stage embryos [RIGHT?] to allow couples in which both partners share a recessively inherited disorder to have a genetically-related child free of the disease. All of these cases, it should be pointed out, are relatively rare, and all of them require some form of assisted reproduction.

There already exist, however, other, better-tested techniques to avoid passing on mutant genes. These include genetic screening and counseling, prenatal diagnosis and abortion, egg or sperm donation, and adoption either of a child or an embryo. Another technique, known as pre-implantation genetic diagnosis, combines in vitro fertilization (IVF) with pre-implantation diagnosis and selection of embryos. Individual cells are removed from an embryo, fertilized outside the body, and tested for the presence of genetic mutations (to the extent that tests are available). Embryos without known mutations are then implanted in the woman via IVF. This approach could have wide application, although it would not work in those cases where both parents have identical versions of the same mutant gene.

With these techniques available, and in light of the enormous difficulties associated with determining risks, why bother with IGM? The answer lies in its possible use for genetic enhancement.

Beyond Normalcy

It is this prospect, I believe, that generates the most excitement over IGM, and the most uneasiness. I will argue enhancement applications more than medical uses determine the scope, direction, pace, and acceptance of IGM in the United States. And it will be the market and free choice, not government, that pushes it along. But I am getting ahead of myself.

By “genetic enhancement” I mean improving human traits that without intervention would be within the range of what is commonly regarded as normal, or improving them be-

yond what is needed to maintain or restore good health. Examples could include increasing height, improving intelligence, altering behavior, or changing eye color, all of which have been shown to have some underlying genetic connection. IGM offers the promise that genes associated with characteristics found to be undesirable (or less desirable) could be replaced by those linked to desired traits.

There are promises and perils associated with genetic enhancement. On the one hand, we know that some people are born more “genetically fit” than others, giving them certain advantages. The promise of enhancing the capabilities of those who are genetically less fortunate is an exciting and noble prospect for some people. And by increasing, for example, the intelligence of individuals, all of society may gain from the knowledge they generate or from the better choices they make in the course of their lives. [OK?]

On the other hand, genetic enhancement could also lead us to devalue various social and environmental factors that influence human development in concert with genes. There might be less appreciation for productive social interaction in a classroom, for example, or for the hard work traditionally required to become a successful professional. These conventional methods of enhancement may have some intrinsic value that could never be duplicated by a genetic intervention. In fact, a preoccupation with genetic enhancement may place too much emphasis on the genes and ultimately prevent us from solving problems that are really embedded in the structure of our society.

Another complication is that the technology developed for therapeutic purposes will be the same as that used for enhancement. So while we might approve of IGM for medical treatment, its availability will likely promote creeping enhancement applications as well. For example, scientists are now testing the use of [OK?] gene

transfer to strengthen the muscles of children with muscular dystrophy, but the same technique could be used to increase an athlete’s strength and endurance. An even more revealing example concerns the use of Human Growth Hormone, or HGH, which is genetically engineered to supplement natural growth hormone. While originally approved to treat children deficient in natural growth hormone, it could be used to make normal children taller, and indeed one newspaper has reported that some parents have requested HGH for children within the normal height range for their age because they want to improve their chances in competitive basketball.¹⁴

Further complicating matters is that distinguishing between treatment and enhancement may get increasingly difficult. The line where one ends and the other begins may become blurred as our experience with IGM expands. Hence, interventions which now give us pause may become more acceptable in the future. Surveys have shown that 40 to 45 percent of Americans approve of using genetic technologies to bolster their children’s physical and mental traits.¹⁵ I suspect that as more people get used to the idea, it will become even more appealing. Americans already avail themselves of cosmetic surgery to make them look better, drugs to make them more alert, and herbs to promote sexual performance. And we expect and praise parents for doing all that they can to enhance their children’s well-being; it is “the natural expression of parental affection.”¹⁶ For many Americans, IGM will merely be seen as a logical extension of what is commonplace throughout America today, and it will be increasingly difficult to draw a clear line between the use of genetics for therapeutic purposes and its use for other ends.

Yet enhancement by genetics is also qualitatively different from enhancement by other means. Existing methods of enhancement, from pharmacology to advanced music lessons,

are aimed at the current generation of adults and children. They are not biologically intrusive in a manner that will significantly shape our evolutionary course. Inheritable genetic enhancement would have long-term effects on persons yet to be born. Thus we have little, if any, precedent for this way of using IGM. We would be venturing into unknown territory, but without any sense of where the boundaries should lie, much less with an understanding of what it means to cross such boundaries.

To Market, To Market

There are good reasons to believe that market forces are more likely than other factors to determine the path we take on IGM. Science in general is increasingly valued for its commercial promise, and some recent developments reinforce the specific connection between genetics and the market. In the case of somatic cell gene transfer research, the focus of the field has shifted from rare genetic disorders, now viewed as offering limited profits, to more common ailments that promise greater financial gain. As one observer of the field noted, “The whole concept of gene therapy for genetic diseases doesn’t fit the business model.”¹⁷ Another foresees movement in the direction of “the most profitable human conditions because there is even [MARK: is “even” right? Perhaps we should replace with ellipses.] far more money to be made in curing baldness and wrinkles than there ever will be in cancer of HIV/AIDS.”¹⁸

To some extent, that is what is occurring now. For example, the president of Anticancer, Inc., a San Diego company working on a genetic cure for baldness, has publicly stated that FDA approval will be sought for marketing the product for hair regrowth in cancer patients who become permanently bald due to chemotherapy, but that once such approval is granted, the product will be marketed to all those experiencing baldness.¹⁹ The experience so far with somatic cell

gene transfer suggests that, if left to its own, IGM is likely to follow the push and pull of the market, as applications for treating disease are either limited or more efficiently handled by other means, as Americans become more accustomed to the notion of enhancement, and as businesses offer commercially attractive products.

Genetics and Reproduction

Advances in reproductive technology have given thousands of infertile couples the chance to have a child. But merging these advances with those in genetics promises to extend choices beyond whether and when to have a child to what sort of child to have. Greater knowledge of genetics now enables people considering pregnancy to use new reproductive technologies to ensure [OK?] that their child has a certain genetic makeup.

Until very recently, that typically meant avoiding a genetically related disease that could be passed on. For example, in 2001 doctors reported on the use of PGD to identify human embryos that lacked a specific cancer-causing gene mutation. They implanted only embryos without the disease gene into a woman’s uterus, and she gave birth to a baby free of the cancer syndrome that runs in the father’s family.²⁰ It was also announced in early 2002 that the same procedure had been used to help a woman who has the gene for early-onset Alzheimer’s disease have a baby free of that mutation.²¹

But the technology has now gone well beyond that limited purpose. Two years ago in the United States, IVF and PGD were used to produce a child whose genetic make-up made possible a life-saving treatment for an older sister. Several embryos were created and tested to ensure that they were genetically similar to the older sister yet lacked mutant gene that had given the sister a fatal disease. The result was a healthy baby boy, from whom umbilical cord cells were suc-

cessfully used to treat his sister.²² Within days of the story appearing in the popular press, authorities in England received more than a dozen requests for approval to undergo the same procedure. In response, the British government subsequently approved use of a pre-implantation technique that detects a range of genetic abnormalities,²³ and earlier this year a British couple gave birth to a baby born with a desired genetic characteristic—cells capable of saving her older sibling from leukemia.²⁴

Who among us would not want to avoid passing on mutant genes to future children or help existing children overcome serious diseases? What these examples show is a willingness on the part of people to select future children for specific genetic traits. A technique that was originally created to help people screen *out* certain characteristics has crept in a different direction, now enabling people to screen *in* desirable characteristics. For now, the latter has been for the noble purpose of saving the lives of exiting children. But where does one draw the line? Should we screen out for short stature? Or screen in for eye color?

Poised to help meet, if not fuel, parents’ desire to make their offspring healthier, and perhaps prettier, smarter, and more athletic as well, is a cottage industry that has sprung up in the past two decades in assisted reproductive technology. What began as an effort by fertility clinics to help infertile couples have a child is now a growth industry offering a range of services no longer confined to the infertile.

Some infertility clinics are offering couples the opportunity for “family balancing” via techniques that can virtually assure parents a child of a particular sex.²⁵ The idea is to use PGD to distinguish between embryos with the Y chromosome and those lacking it, and then implant the “right” embryo or embryos. In October 1999, in a statement declaring that the use of solely for sex selection “should be discouraged,”²⁶ the Amer-

ican Society for Reproductive Medicine said, “Those who argue that offering parental choices of sex selection is taking a major step toward ‘designing’ offspring present concerns that are not unreasonable in a highly technologic culture.”²⁷ Web sites have sprung up where persons can market their gametes and couples can assess the height, weight, hair and eye color, education, and musical and athletic abilities of potential suppliers of eggs or sperm.²⁸ Some egg donors “are becoming shrewd businesswomen, asking top dollar for their high IQs or good looks.”²⁹ And all this is occurring in an industry where there are strong economic interests in expanding services under the banner of enhancing consumer choice, and where choice is reinforced by the very high value that our society places on reproductive freedom.³⁰ It will be difficult to overcome the resistance of consumers to any effort to restrict their access to such technologies.

The market is now poised to take advantage of the increasing power of genetic technology, producing financial profit for some and giving parents the “best product” for their money. In the vernacular of the marketplace, people are not parents; they are consumers, and distinctions long recognized between reproduction and production begin to fade.

Whither Policy?

For society, deciding the fate of IGM will be among the most profound decisions it ever faces. Former Senator Daniel Moynihan once remarked that while it was important in the development of civilization for someone to have invented the wheel, it was equally important that soon thereafter someone invent the brake. We must balance our scientific efforts with a better understanding of where they are leading. Not all social values are well served by the push and pull of commerce. Individual decisions regarding the use of these genetic technologies may be personally beneficial, but they may not lead us toward a so-

cially desirable outcome. In the meantime, the larger moral and social climate can be changed in ways that make applying the brakes difficult.

An editorial in the *St. Louis Post-Dispatch* articulated the problem nicely:

private entities tend to be profit driven—which should be the last consideration in how we alter the human race. . . . [T]he . . . critical question is whether government should set rules for both public and private genetic manipulation of the species. If there continues to be no public oversight of the private entities, there will be nothing to stop fertility clinics from offering whatever genetic manipulation becomes possible and marketable.³¹

So what do we do? The 2000 AAAS report recommended several steps that remain important. Most important among them was that no IGM, whether involving intentional or “reasonably foreseeable” inadvertent transmission, should go forward at this time. In a subsequent article appearing in *Science* following the report by the fertility clinic of mitochondria DNA transmission, my co-author and I stressed the urgency of moving more quickly to put in place a system of public oversight with authority over IGM efforts in both the public and private sectors.³² Accompanying this oversight mechanism should be a national public dialogue on whether and, if it is deemed acceptable, how such research and its applications should proceed.

These proposals are premised not on a belief that IGM should never be tried, but that it must pass the test of public discourse, undergo rigorous assessment of its potential impacts, and receive explicit public approval. [OK?] There should be no backdoors, whether due to gaps in public policy or an aggressive marketplace, through which IGM inches its way into our lives. These technologies are highly seductive, and we could easily

get used to them without fully considering their consequences.

In the book *Future Shock*, Alvin Toffler wrote that the future arrives too soon and in the wrong order. If the future occurred in the right order, we could understand changes before they happened, rather than after, and could better prepare. That is not, of course, the way it works. But the future is not fixed, either. The question with regard to IGM is whether we will shape it or be shaped by it.

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