POLICY FORUM: GENE TECHNOLOGY

Genetic Enhancement in Humans

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Dramatic advances in gene transfer technology since the early 1980s have prompted consideration of its use in humans to enhance phenotypic traits. The notion that genetic modification could confer special advantages on an individual has generated excitement. Controversial issues surround this prospect, however. A practical concern is determining how to ensure equal access to such advanced medical technologies. There has also been speculation that genetic enhancement might affect human evolution, and philosophical objections have been raised, based on the belief that to intervene in such fundamental biological processes is to "play God." Although such philosophical questions cannot be resolved through data analysis, we nevertheless have the tools in hand to objectively assess our state of progress. We can also assess the impact that promulgation of such technology might have on human evolution and formulate sensible guidelines for developing policies governing human genetic enhancements.

Defining genetic enhancement

Some experts have argued that "enhancement" can have different meanings depending on the circumstances. For example, when a disease is common, the risk for developing the disorder may be considered the norm, and genetic alleviation of that risk might be regarded as a form of enhancement (*1*). This kind of semantic gamesmanship is misleading. The obvious public concern does not relate to improvement of traits for alleviation of deficiencies or reduction of disease risk, but to augmentation of functions that without intervention would be considered entirely normal. To raise the athletic capabilities of a schoolyard basketball player to those of a professional or to confer the talents of Chopin on a typical college music professor is the sort of genetic enhancement that many find troublesome. The experts in the gene transfer field should acknowledge the distinction in order to avoid causing public distrust and undermining the deliberative process.

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Another important distinction is that between genetic changes that are heritable and those that cannot be genetically transmitted. At the present time, gene transfer approaches that involve the early embryo are far more effective than somatic cell gene therapy methodologies. Embryo gene transfer affords the opportunity to transform most or all cells of the organism and thus overcomes the inefficient transformation that plagues somatic cell gene transfer protocols. Moreover, the commonly used approaches to embryo gene insertion—pronuclear microinjection (*2*) and transfection of embryonic stem cells (*3*)—are associated with stable, high expression of donor DNA. Typically, however, genetic changes introduced into the embryo extend to the gametes and are heritable.

Scenarios can be constructed wherein introduced genes could be deleted from germ cells or early embryos derived from the treated individual. For example, transferred genes could reside on artificial chromosomes that could be deleted by activating a recombinase that induced recombination of the chromosome ends (*1*). Such approaches, however, are currently only speculative. Germline gene transfer has already succeeded in several animal species. Because of this and the general belief that voluntary abstention from germline modification in humans is unlikely, a candid discussion of genetic enhancement must include the possibility that changes introduced will be transmitted to offspring.

The state of the art

Animal experiments thus far have attempted to improve what are intuitively regarded as "simple" traits such as growth rate or muscle mass. Efforts to genetically improve the growth of swine have involved insertion of transgenes encoding growth hormone (*4, 5*). Nevertheless, despite the fact that growth hormone transgenes are expressed well in swine, increased growth does not occur (*4, 5*). Although the transgenic animals fortuitously have less body fat (*5*), these unexpected benefits cannot be extrapolated to human clinical protocols. Before a human embryo is treated with recombinant DNA, we must know exactly what we are doing.

Another spectacular failed attempt at enhancement resulted from efforts to increase muscle mass in cattle. When expressed in mice, the avian c-*ski* gene, the cellular counterpart of the retroviral *v-ski* oncogene, induced massive muscle hypertrophy (*6*). This prompted efforts to produce cattle expressing a c-*ski* transgene. When gene transfer was accomplished, the transgenic calf initially exhibited muscle hypertrophy, but muscle degeneration and wasting soon followed. Unable to stand, the debilitated animal was killed (*7*).

Why did these enhancement experiments fail? For clues, it is useful to compare modern-day gene transfer technology with the more traditional approach to genetic engineering: selective breeding. Selective breeding maximizes the reproductive efficiency of individuals that exhibit desired characteristics. The selection strategy is oblivious to the number of genes responsible for generating the phenotype. Swine selected for rapid growth may consume more food, produce more growth hormone, respond more briskly to endogenous growth hormone, divert proteins toward somatic growth, and possess skeletal anatomy that allows the animal to tolerate increased weight. Dozens or perhaps hundreds of genes may influence these traits, but in selective breeding, favorable alleles at all loci can simultaneously be selected. In contrast, gene transfer selects one relevant locus and attempts to improve it in isolation. It is little wonder that this approach, albeit potentially powerful and efficient, is more chancy, and has, despite more than 10 years of effort, failed to yield even one unequivocal success. Greater success has been achieved in genetic enhancement of plants, which are more easily manipulated genetically and reproductively; for example, see (*8*).

Given the inherent limitations of the gene transfer approach to enhancement, discussion of extending such procedures to humans is scientifically unjustified. We clearly do not yet understand how to accomplish controlled genetic modification of even simple phenotypes. Where more complex traits such as intelligence are concerned, we have no idea what to do, and in fact we may never be able to use gene transfer for enhancement of such phenotypes. A useful way to appreciate the daunting task of manipulating intelligence through gene transfer is by considering the fact that a single cerebellar Purkinje cell may possess more synapses than the total number of genes in the human genome. There are tens of millions of Purkinje cells in the cerebellum, and these cells are involved in only one aspect of brain function: motor coordination. The genome on-

ly provides a blueprint for formation of the brain; the finer details of assembly and intellectual development are beyond direct genetic control and must perforce be subject to innumerable stochastic and environmental influences.

Genetic engineering and human evolution

Some have suggested that genetic enhancement and related reproductive technologies now give us the power to control human evolution. This solemn pronouncement is totally without scientific foundation. The evolution of the human species may be understood as a nonrandom change in allelic frequencies resulting from selective pressure. The change progresses over generations because individuals with specific patterns of alleles are favored reproductively. If new alleles were introduced by gene transfer, the impact on the species would be negligible. Every month worldwide approximately 11 million babies are born. The addition of one genetically modified individual could not significantly affect gene frequencies. Moreover, if the "enhanced" individual had his or her first child at the age of 20, then 2,640,000,000 unengineered children would be born during the interval between the birth and procreation of the gene recipient. Even if 1000 successful gene transfers were performed per year, a number not likely to be achieved in the foreseeable future, those newborns would constitute only 1/132,000 of all live births. Thus, any effort to enhance the human species experimentally would be swamped by the random attempts of Mother Nature.

Finally, there is no certainty that genetically enhanced individuals would have greater biological fitness, as measured by reproductive success. A genius or great athlete who has no children has no biological fitness as defined in evolutionary theory. For these reasons, neither gene transfer nor any of the other emerging reproductive technologies will ever have a significant impact on human evolution.

Developing policy

If we accept the notion that genetic enhancement is not practicable in the near future, what policies should we develop concerning the use of such technology? The decision to undertake any form of invasive medical intervention immediately renders the treatment subject a patient who has a right to informed consent as well as to protection from unjustifiably dangerous medical manipulation. Our inability to predict the consequences of an attempt at genetic enhancement makes informed consent impossible, and current knowledge from animal experiments tells us that embryo gene transfer is unsafe: The common approach of pronuclear microinjection is characterized by random integration of donor DNA, a lack of control of the number of gene copies inserted, significant rearrangements of host genetic material, and a 5 to 10% frequency of insertional mutagenesis (*9*). Homologous recombination (*10*) in embryonic stem cells overcomes many of these shortcomings, but human embryonic stem cell transfection would necessarily be followed by nuclear transfer into enucleated oocytes. Because nuclear transfer in at least two animal models is associated with a low birth rate and a very high rate of late pregnancy loss or newborn death (*11*), this procedure is also unsafe. The risks are so high and the documented efficacy is so low for gene transfer that it could not compare favorably to straightforward prenatal diagnosis even when a compelling need for therapy exists, as in cases of genetic disease. The use of gene transfer for elective purposes such as enhancement would stray far beyond the limits of acceptable medical intervention.

To attempt genetic enhancement with extant methods would clearly be medically unacceptable, but attempts to ban gene transfer legally could be a cumbersome approach to limiting its clinical use. Verification of compliance would be difficult. The diverse resources required for gene transfer necessitate that the procedure be carried out in facilities equipped for in vitro fertilization. Direct inspection would be required to uncover gene transfer procedures in such facilities. This would impose on the privacy of patients undergoing accepted assisted reproduction procedures such as sperm injection. Moreover, gene transfer can be easily concealed; in the case of pronuclear microinjection, only a few seconds are needed to complete the process. Legal restrictions can also be easily avoided by performing the procedure outside the area of jurisdiction.

Finally, and perhaps most important, broad legal restrictions incur the risk of limiting invaluable research. Exemplifying this problem is the current overly broad ban on federal funding for experiments with human embryos. The recent derivation of human embryonic stem cells from preimplantation embryos (*12*) has created important new research opportunities, accompanied by pressure to provide federal funds for the work. This pressure has led to the odd situation in which federal funds will likely be allowed for research with embryonic stem cells but not for manipulating human embryos to produce embryonic stem cell lines. If, as a society, we feel compelled to make a statement against genetic enhancement, we need not enact anticipatory legislation. Instead we can evaluate such manipulations as we would any other invasive clinical procedure. If we require that gene transfer be accompanied by informed consent, that it have a reasonable possibility of succeeding, that its cost not be excessive, that it have acceptable side effects and toxicities, that it not be accompanied by a burdensome requirement for long-term follow-up evaluation, and that it compare favorably with other treatment options, we will currently reject the procedure on all counts as medically unethical. Were entities such as the National Bioethics Advisory Commission or Congress to make such statements formally, no responsible physician would attempt genetic enhancement. Irresponsible use of technology can never be stopped, even by legislation.

Fear of genetic manipulation may encourage proposals to limit basic investigations that might ultimately lead to effective human gene transfer. History has shown that effort is far better spent in preparing society to cope with scientific advances than in attempting to restrict basic research. Gene transfer studies may never lead to successful genetic enhancement, but they are certain to provide new treatment and prevention strategies for a variety of devastating diseases. No less significant is the potential for this research to improve our understanding of the most complex and compelling phenomenon ever observed—the life process. We cannot be expected to deny ourselves this knowledge.

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