Viewpoint

Gene therapy for enhancement

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> "Our Western culture is very pluralistic and permissive. We, ourselves, might not want to smoke, use krebiozen to treat our cancer, or ride a rocket over the Snake River Canyon, but we allow others to do what they wish with their own lives and bodies, within broad limits, short of suicide or hurting others. Thus, our society may want to allow someday somatic cell genetic engineering by a competent adult for him/herself. But until we have acquired considerable experience with regard to the safety of somatic cell gene therapy for severe disease, and society has resolved at least some of the ethical dilemmas that this procedure would produce, non-therapeutic use of genetic engineering should not occur."[1]

The increase in fundamental knowledge about human health and the mechanisms of disease during the second half of the 20th century has been extraordinary. A major contributor has been synergism among microbiology, genetics, and biochemistry making it possible to move genes between organisms, yielding both inert and living products of unprecedented usefulness.

Some of the forthcoming major advances in the new biology applied to medicine will be in the area of somatic-cell human gene therapy (SHGT), the insertion of normal or modified genes into somatic (non-germ line) cells of human subjects, in order to correct genetic or acquired disorders via the in-vivo synthesis of missing, defective, or insufficient gene products; or, in the absence of disease, to enhance desirable characteristics, via expression of inserted genes (enhancement engineering). SHGT applied to genetic defects, cancer, and cardiovascular disease may approximate in the first half of the next century what antibiotics have been to the second half of this century.

These rapid advances in biomedical research have stimulated the development of numerous medical technologies and individual products, and their translation into clinical use has raised complex—but not necessarily unique—medical, economic, ethical, and social issues. A recent issue of a UK magazine, *Scrip*,[2] contained this item:

> "The US biopharmaceutical company, AntiCancer Inc, has developed a DNA delivery system that specifically targets hair follicles. Using an in-vitro skin culture system, company researchers said it was possible to determine directly the effects of genes and drugs on hair growth and colour. Gene therapy for all types of hair loss, including baldness and chemotherapy-induced alopecia, may be possible, AntiCancer said."

While an initial response might be, "Gene therapy for baldness? How preposterous!" such an application of SHGT, on reflection, might not appear so extreme, and it can be argued two ways.

Some commentators have suggested that a line can and should be drawn between SHGT for therapeutic or research (eg, cell-marking) purposes on one hand and enhancement engineering on the other.[3,4] Anderson[1] has argued that although SHGT for the treatment of severe disease is consistent with the moral principle of beneficence—having the potential to alleviate human suffering—the same is not true of enhancement. He cites two other reasons that enhancement engineering "would threaten important human values":

> "First, it could be medically hazardous, ie, the risk could exceed the potential benefits and could therefore cause harm, and second, it would be morally precarious, ie, it would require moral decisions that our society is not now prepared to make and which could lead to an increase in inequality and an increase in discriminatory practices."

The nature of the objections on medical grounds is fairly self-evident. Introducing a foreign substance via SHGT is fraught with the same kinds of uncertainty as for a new drug. There are some new wrinkles, to be sure; eg, SHGT might inactivate a cancer suppressor gene or activate an oncogene, but this is similar to concern about carcinogenic or teratogenic potential with more usual therapies. With SHGT, however, the effect of an unexpected adverse reaction could be compounded by the relative irreversibility of the process.

Anderson's second point, concerning the morality of enhancement, is intellectually intriguing. One can certainly describe some scenarios that may verge on "moral precariousness": the introduction into a patient of a gene for an appetite-suppressant hormone, a gene coding for a brain chemical that enhances memory, a growth hormone for a hormonally normal but shorter-than-average adolescent who has short parents, a growth hormone gene for an adolescent of normal height who wishes to play professional basketball, a gene conferring resistance to industrial toxins for someone who works with hazardous chemicals. These scenarios raise issues that are pertinent, but by no means unique to, SHGT for enhancement:

- *The difficulty of defining whether a patient's disease is serious (or, in fact, whether there is a disease at all).* One might consider obesity a serious disease at triple the ideal weight, whereas a person thirty percent above ideal weight might be considered to have a minor disease, and someone near ideal weight but wishing to be thinner for a trip to the Caribbean could be said to suffer only from cultural discomfort.

- *Equality of access to SHGT.* Which societal models will be invoked to determine who gets the therapy? Those with the greatest or most acute need? Those best able to benefit society? First come/first served? Ability to pay?

- *The possibility of coercion.* Would pressure be exerted on workers to have SHGT to make them less susceptible to workplace toxins?

- *SHGT as a therapy for discrimination.* Would coloured people seek genetic "improvement" of skin colour or other traits, in order to improve economic

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and social opportunities for themselves or their progeny?

Anderson concluded that stepping over the line that separates therapy from enhancement would be opening Pandora's box, and that on both medical and ethical grounds, any form of enhancement engineering should be excluded.

The questions that have been raised by Anderson, Fletcher, and others are important ones and their approach to them has been scholarly. However, their arguments largely ignore the indications for which the testing of medical therapies already occurs. They do not give adequate weight to the latitude that our society affords to citizens who wish to enhance their physical appearance or their health. More prosaic therapies, commonly rubbed on or swallowed, are often merely intended only to grow hair, decrease appetite, or lighten age spots. On what scientific, legal, or ethical basis should SHGT be subjected to a higher standard than liposuction, radial keratotomy, or the application of permanent makeup by tattooing?

SHGT is part of a therapeutic continuum that includes allogeneic organ transplantation, injection of live viruses for vaccination, and the administration of drugs to activate dormant genes.[5] Medical and ethical issues raised by SHGT, however difficult to resolve they may be, are hardly unique. There is no obvious basis for invoking a discriminatory, more restrictive paradigm for SHGT than for analogous experimental therapies. Arguments for prescribing SHGT for enhancement should be considered in the light of society's permissiveness toward experimental medical interventions generally, and those intended for enhancement in particular.

First, there is the argument that SHGT may be medically hazardous and irreversible. This objection can be addressed by regulators requiring that experiments be carried out in a way that is not irreversible: inserting the introduced gene that is to be expressed in a way that it is inducible and under positive control; transducing only cells, such as lymphocytes, that have a finite lifespan; or making the transduced cells surgically accessible (for example, in a skin graft), for ease of removal. These techniques have already been accomplished or are technically feasible.

Second, and philosophically more important, is an argument by analogy. For better or worse, drugs are not infrequently tested for relatively trivial indications, such as modest obesity, stuffy nose, and baldness. There have been numerous clinical trials of appetite suppressants, memory-enhancing or mentation-improving drugs, and human growth hormone for hormonally normal but shorter-than-average children. The number of entities, both local and federal, that regulate SHGT, for whatever purpose—Institutional Review Boards, Institutional Biosafety Committees, the National Institutes of Health's Recombinant DNA Advisory Committee, and the Food and Drug Administration—contrasts sharply with the degree of oversight of, say, a new surgical procedure, which might be completely unregulated or subject only to approval of an Institutional Review Board; or tattooing, which is often overseen only by a municipal authority.

One could add that enhancement is not invariably regarded as trivial—certainly not by the adolescent boy who is six inches shorter than anyone else in his class, or to many people of either sex who suffer hair loss. One need look no farther than the huge societal demand for cosmetics, cosmetic surgery, and health clubs, to be reminded how important people consider it is to look and feel good. The issues surrounding whether a patient suffers from a serious disease (or any disease), equal access to therapy, the possibility of coercion, and the relationship between medical intervention and discrimination, are fundamentally no different for SHGT than for other medical interventions. Therefore, innovations such as SHGT, even when used for enhancement, should arguably be treated similarly to other analogous medical interventions, except as scientific considerations may dictate. Such innovations should not be rejected out of hand, particularly when existing societal oversight mechanisms subject them to a high level of case-by-case review.

Support for a rationalist approach to SHGT for enhancement has come from disparate sources. LeRoy Walters has argued that we should consider the momentous positive impacts on both individuals and society that somatic cell enhancement engineering could have (presentation at Genetics, Religion, and Ethics Conference, Houston, Texas, USA, March 14, 1992). With libertarian zeal, *The Economist* has editorialised,

> "what of genes that might make a good body better, rather than make a bad one good? Should people be able to retrofit themselves with extra neurotransmitters to enhance various mental powers? Or to change the colour of their skin? Or to help them run faster, or lift heavier weights? Yes, they should. Within some limits, people have a right to make what they want of their lives . . ."[6]

Some have asserted that any form of enhancement engineering should be proscribed. However, several arguments may be marshalled against that view: medical risks of SHGT may not be materially different from those of other kinds of medical interventions and are likely to be controllable, or at least evaluable; medical interventions for enhancement are often regarded by patients as not at all trivial; close analogies exist in other tightly-regulated as well as loosely-regulated medical interventions; and existing societal oversight mechanisms are more than adequate to balance the risks and benefits of proposed clinical protocols.

If society is to realise the full spectrum of benefits from human gene therapy, it cannot be considered in a philosophical vacuum from which relevant precedents and experience are excluded; rather it must be judged in the broader context of what people want and what society permits.

References

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6 Anon. Changing Your Genes. *The Economist* 1992; April 25, pp 11–12.