



The Hazards of Human Developmental Gene Modification

BY STUART A. NEWMAN

The completion of one of the stated benchmarks of the Human Genome Initiative (HGI)—the attainment of a nearly full set of raw human DNA sequences—is certain to give new impetus to proposals to utilize genetics to refashion human biology. The development during the past quarter century of sophisticated *in vitro* fertilization methods, pre-implantation DNA analysis, improved techniques for gene transfer, insertion, or conversion, and embryo implantation procedures, have placed such interventions on the agenda of biotechnologically-oriented medicine. Currently, the fevered commercial expectations surrounding the HGI over the past decade, along with hyperbole from portions of the scientific community, have lent new urgency to calls for genetic engineering.

Genetic modification of human embryos or fetuses, referred to here as *developmental* modification, has been

proposed for purposes of both prevention of disease and enhancement of capacity. The hazards of genetic modifications to humans have usually been discussed in terms of *somatic* (body cell) modification, in which only nonreproductive tissues are affected, and *germline* (egg or sperm cell) modification, in which changes to an individual's DNA can be passed down to future generations. (See the Council for Responsible Genetics' 1992 Position Paper on Human Germline Manipulation: http://www.gene-watch.org/programs/Position_Germline.html). Indeed, this division has led to the general belief that the only, or main, hazard of developmental modification is the potential of transmission of undesired alterations in the germline. But it is clear that the hazards to both mothers and infants of developmental gene modification are much more extensive.

The hazards of germline transmis-

sion of DNA modification are no longer speculative; the literature on transgenic animals contains numerous examples. For example, germline introduction of an improperly regulated normal gene into mice resulted in progeny with no obvious effects on development, but enhanced tumor incidence during adult life. Such effects may not be recognized for a generation or more.

It is important to recognize that many of these hazards are not eliminated if there is no germline transmission. The biology of the developing individual will still be profoundly altered by the manipulation on his/her genes at an early stage. Laboratory experience shows that miscalculations in where genes are incorporated into the chromosomes can lead to extensive perturbation of development. The disruption of a normal gene by insertion of foreign DNA in a mouse caused lack of eye development, lack of development of the semicircular canals of the inner ear, and anomalies of the olfactory epithelium, the tissue that mediates the sense of smell.

Attempts at developmental gene modification will certainly be subject to experimental error, but this is not the only source of potentially unfavorable consequences. Certain genes undergo a process of "imprinting" during development, in which the version of the gene inherited from the father or the mother is blocked from contributing to the individual's biological constitution. This phenomenon is part of a wider group of processes known as "allelic interaction" or "paramuta-

CRG CENTRAL PRINCIPLES

Too often, the debates about the social and ethical implications of biotechnology have been left to the scientific "experts." As a link between scientists and lay people, the CRG is working to encourage public understanding and involvement in these debates.

The central principles that guide the vision of the CRG are:

- The public must have access to clear and understandable information on technological innovations.
- The public must be able to participate in public and private decision-making concerning technological developments and their implementation.
- New technologies must meet social needs.
- Problems rooted in poverty, racism and other forms of inequality cannot be remedied by technology alone.

tion," in which the expression of one version, or "allele," of a gene is influenced by another allele. These phenomena are poorly understood, but it is clear that they are essential to healthy development. Failure of a certain gene to be correctly imprinted, for example, leads to Beckwith-Wiedemann syndrome, which is characterized by organ overgrowth and several different childhood cancers. Simply inserting a desired gene into the embryo in place of an undesired one does not ensure that allelic interaction will proceed appropriately, and experience with farm animal embryo manipulation suggests that it is readily disrupted and results in malformations.

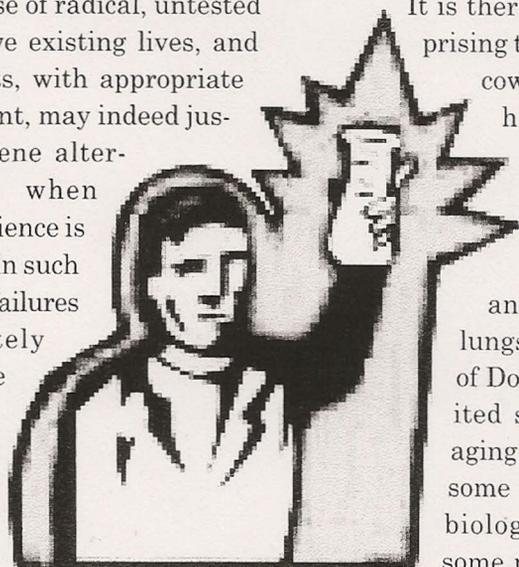
The developmental process is inherently complex, and there is no coherent, scientifically accepted understanding of its overall coordination. And even if this understanding were available, it is clear that the ramifications of developmental manipulation would be inherently unpredictable. For these reasons attempts to genetically alter developed tissues (somatic modification) and attempts to genetically alter embryos (developmental modification) have profoundly different scientific and ethical implications. The tissues of a developed organism are in some sense modular—if blood, or skin, or a heart, or a liver is diseased or damaged it can be replaced by a substitute without changing the "nature" of the individual. Similarly with gene alteration in a developed individual: in reasonable candidate cases the gene is playing a defined and well-understood role in a particular tissue or organ, and the goal of the modification is to replace or correct the poorly functioning gene in one or a very limited set of tissues. Any protocol that sought, in contrast, to introduce into a patient a gene known to have "pleiotropic" (i.e., affecting several systems) physiological effects

(a neurotransmitter molecule that mediates communication between nerve cells, for example) would have a difficult time getting approved. It would be like introducing a drug with drastic side effects, but which could not be withdrawn if the patient reacts badly.

During development the situation is even more complicated. During this period, tissues and organs are taking form and the activity of genes is anything but modular. In the course of development almost any gene can have pleiotropic effects, and not just on physiology, but on the architecture of organs, and the wiring of the nervous system, including the brain. One can argue for the use of radical, untested methods to save existing lives, and such arguments, with appropriate informed consent, may indeed justify somatic gene alteration even when scientific experience is still primitive. In such cases, even the failures can legitimately add to the store of useful knowledge. In contrast, there are no good rationales for using untested "heroic" procedures to alter the course of embryonic development except among those who consider that the risks of producing individuals with experimentally produced morphological or neurological aberrations, or increased risks of cancer, are preferable to the options of abortion, or of bearing the unmodified child.

Cloning is another example of developmental modification, with hazards that extend beyond any potential effect on the germline. Intact eggs and sperm are the components that evolution has yielded to produce a new individual. The fact that an enucleated egg and the nucleus of a somatic cell can cooperate to give rise to something

that looks and acts like the animal they were derived from is almost fortuitous. DNA is chemically modified during the normal developmental process. Hence, the genes that the somatic cell nucleus is providing to the novel assemblage are aberrant starting materials for initiating the development of a new embryo. The only reason anyone would think that a somatic nucleus is equivalent to a zygotic nucleus is a simplistic genetic reductionism that imagines that the nucleus equals its DNA, and the only function of DNA is exerted via its sequence of bases. Both these propositions are incorrect.



It is therefore not at all surprising that cloned mice and cows have exhibited a high rate of unexplained postnatal deaths, as well as anomalies such as enlarged hearts and grossly abnormal lungs, and that the cells of Dolly the sheep exhibited signs of premature aging. Recent reports that some cloned animals are biologically younger by some measurements than their chronological ages only highlight the uncertainty in outcomes of these manipulations.

In protocols that attempt somatic "gene therapy" for life-threatening illnesses, saving the life of the individual patient is a value that must be balanced against developmental risks, including those to the germline of that individual, and indeed, such considerations also pertain to chemotherapy in cancer patients, by which mutations may be introduced into the germline. With respect to deliberate developmental modifications, the story is quite different. Not only is the "patient" (embryo or fetus) and its prog-

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news media even if it was scientifically misleading. As one of the participants summarized the challenge before them: “[The problem of convincing the public that the hazards are exaggerated] is what you have to deal with. It may not mean a thing, but that is very easy to do. It’s molecular politics not molecular biology, and I think we have to consider both, because a lot of science is at stake.”

“Molecular politics” won the day: the worst-case experiment was never performed. The experiment with the weakened bacteria—acknowledged to be primarily a public relations exercise—was performed, published, and duly claimed (at a press conference held on March 1, 1979) to demonstrate that “this form of research is perfectly safe.” As the scientists at the NIH meeting had anticipated, the results were beamed across America as evi-

dence that the investigators found there was little or no risk. The *New York Times* duly reported that “the risks are considerably less than had been feared.”

But even in this case, the conclusion that the experiments demonstrated “no significant hazard” was questioned by well-qualified scientists. The test animals did indeed develop tumors in a variety of circumstances. One result, showing that cutting the tumor virus DNA enhanced tumor induction, had the NIH campus buzzing at the time. These results now appear significant in the light of recent scientific work on the fluidity and adaptability of the DNA molecule. But in the late 1970s, all concerns about the hazards of genetic engineering were dismissed by promoters of the “benefits” of the field.

A few further risk assessment experiments were carried out, virtually all with weakened strains of bacteria. None were conclusive since they did not use organisms able to survive effectively in the environment. None were published in leading scientific journals. None underwent broad scientific review outside the National Institutes of Health. Nevertheless, the results were used to claim that the entire field had been cleared: there was no significant hazard. As a reporter for the British journal *Nature* observed in 1978: “One must now accentuate the positive. The new evidence, however, does not seem substantial.”

Substantial or not, these arguments were used repeatedly in the 1980s and 1990s to defend the safety not only of organisms intended to be contained in experiments or industry, but also—by a further grand leap of logic—of plants and microbial pesticides to be released into the environment.

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eny at risk from the procedure, but so is the pregnant woman. If the genes are introduced *in utero*, such genes can also infect the woman’s tissues, including her own germline, and entail other risks to herself, such as cancer. Clearly she is not in a position to give informed consent on behalf of herself or the developing embryo for a procedure that has not yet been tested in humans. In addition, the procedure promises no direct benefits to her health (the usual justification for experimentation on humans). However, she will inevitably be under pressure to assume such risks for the sake of her baby.

Even if the procedure is to be done *in vitro* rather than *in utero*, the basis for informed consent remains problematic. There is no existing person whose life is in jeopardy, but rather an embryo in a petri dish that the egg or sperm donor (or whoever else may gain the right to its disposition) would like to modify genetically. No truly informed consent on the part of the potential parents is possible, because no reliable information about the consequences would be available.

Furthermore, no amount of data from laboratory animals will make the first human trials anything but experimental. Under such circumstances, where the life of an existing person is not at issue, and the procedure is inherently experimental—threatening to profoundly alter the biology of the developing individual—contraindication on the basis of safety or unpredictability of outcome (which may be counterbalanced when a life is at stake) becomes an ethical contraindication as well. ♦

Stuart Newman, PhD is professor of Cell Biology and Anatomy at New York Medical College, where he directs a research program in vertebrate developmental biology. Dr. Newman is also a member of CRG’s Board of Directors, and he chairs the CRG’s Human Genetics Committee. Please contact the CRG office if you are interested in the references for this article.