Politics and genes

Human germline therapy is in our future. Other once unimaginable forms of therapy have entered mainstream medicine. Just as surely the day will come when gene therapy, now confined to somatic cells, will extend to egg and sperm. The diseases of the parents will no longer be passed on to their children, or their children's children.

Since the advent of recombinant DNA techniques a generation ago, any medical intervention involving the human genome has caused anxiety among scientists, ethicists, and laymen alike. After all, the majority of people instinctively think of genes not as unromantic pieces of deoxyribonucleic acid, but as the biological seat of our humanity. The essence of humanness, which resided in the heart until transplant surgeons came along, now resides on the X and Y chromosomes. But it will not remain so. When germline therapy becomes safe and effective, it will become a part of medicine, like any other. The challenge then is to use it wisely. Perhaps we should stop looking for human nature in our anatomy.

During the 1980s, when debate about the ethics of somatic cell gene therapy was at its height in the United States, discussion of germline therapy was left to future ethical combatants on grounds that manipulation of the germ line was technically infeasible and likely to remain so for decades to come. Meanwhile, the governments of France and Germany banned germline therapy outright.

Now, as a news story in this issue of *Nature Medicine* (pages 186–187) reports, advances in the nascent field of *in utero* therapy for the developing embryo bring germline engineering closer to reality. Thus, it is time to consider issues that were supposed to wait until the next century.

Already, the Institute of Medicine of the National Academy of Sciences is preparing to study the ethical issues unique to germline therapy and a subcommittee of the US Food and Drug Administration will look at the question in the broader context of treatment of the fetus. The real challenge will be to separate emotion from medicine while remembering that no amount of abstract, ethical reasoning will alter the fact that, when it comes to public opinion, germline therapy is feared emotionally, not intellectually.

A brief review of the gene therapy debate in the 1980s holds some lessons. The discussion began with arguments for and against the notion that using genes to cure genetic diseases amounted to "playing God." But the emotionally laden attitude that certain life-saving procedures are out of human bounds oversimplifies the case. Transplant surgeons are no longer accused of usurping God's ultimate power over life and death; cancer specialists never were. The hubris does not lie in trying to save lives but only in believing that medicine will win over death in the end.

Many participants in the debate, including physicians in North America and Europe, along with groups representing patients with lethal genetic diseases, began to replace romanticism with chemistry. A therapeutic gene, in this context, became an unromantic bit of DNA, a drug like any other. A missing gene is added and does its curative work by expressing itself as normal protein. This is what happened in the first gene therapy trial at the NIH in 1990 when the gene for adenosine deaminase (ADA) was transfused into a child with ADA deficiency and consequent immune dysfunction. The ethics of the experiment were debated for nearly three years before it ever took place. Eventually, the issues boiled down to those that apply to any human experimentation: safety, efficacy, and informed consent.

When in 1993 gene therapy was tried with partial success on a woman with inherited hypercholesterolemia (modified genes were transfused into her resected liver) no one blinked. With gratifying regularity, gene therapy is moving out of the laboratory and into clinical medicine for the potential treatment of diseases ranging from cystic fibrosis to cancer (including brain tumours), AIDS, and rheumatoid arthritis, among others.

Safety is an important issue in human gene therapy of either somatic or germ cells. A great and justifiable worry is that the insertion of a gene in the wrong place along a strand of DNA could cause an undesirable mutation or even cause cancer. Again, this concern is real but not unique. It is well known, though not often pointed out, that radiation and chemotherapy can damage the DNA of healthy cells, sometimes causing a second cancer in patients who have been successfully treated for the first. That this could happen with gene therapy is, indeed, a risk — one to be avoided if at all possible by the careful design of the vectors that carry therapeutic genes into cells.

Does a different risk/benefit equation apply to germline therapy? Perhaps so. Certainly an obligation to succeeding generations must be considered. And yet, the seeds of cancer are already being passed from generation to generation by natural means. Breast cancer is a cruel example. The only ethical answer to this dilemma, once germline therapy is possible, may be to let each person (or parent) decide for himself what degree of risk is acceptable.

Then, of course, one must confront the fear of eugenics. Many people consider it acceptable for a couple to decide not to have children who would suffer from Tay-Sachs disease or some other early killer. It is quite another matter to contemplate, as Hitler did, the genetic manipulation of an entire community of people. Every sane man and woman ought to abhor such viciousness, but it does not follow that the application of germline therapy to alleviate serious human disease is therefore immoral — or even undesirable. When the time is right (when the techniques are well developed and safety standards are met), genetic therapy of diseases transmitted through the germline should be approved.

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