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BIO/TECHNOLOGY, 65 Bleecker St., New York, NY 10012. Telephone: (212) 477-9600. Telex: 668497UW.
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THE FIRST WORD

AN HONEST BEGINNING

Gene therapy, some argue, is not properly the province of biotechnology at all, as though the techniques of genetic engineering became somehow different in kind when applied to human marrow stem cells rather than *Escherichia coli*. Yet the barest whisper of an ability to genetically engineer humans raises difficult questions—fascinating questions—about man, society, and even the eternal. These most fundamental answers, if they come, will teach us how to think about biotechnology in the context of society.

Thus, one reads the Office of Technology Assessment's *Human Gene Therapy—A Background Paper* with great hopes, bound for disappointment. The report is intended for the lay reader as Congress's report to its constituents. It is also a working document, the beginnings of Congress's effort to get a conceptual handle on research likely to start within the terms of Representatives just elected. As such, it concentrates on somatic cell therapies, generally bone-marrow "replants" engineered to correct inherited enzyme deficiencies.

Despite the report's obvious attempts at reportage rather than advocacy, certain themes emerge: "In the view of many religious and ethical thinkers," says *Human Gene Therapy*, "gene therapy restricted to somatic cell corrections of single gene traits differs little from other medical therapies." At the same time, very few people stand to benefit directly from this first phase of research—perhaps three-score victims of adenosine deaminase deficiency or purine nucleoside phosphorylase deficiency. (Both conditions cripple the immune system and generally kill the carrier by the age of two.) The report's message seems to be that somatic cell therapy is nothing special, and anyway, nobody will be doing much of it.

This picture of somatic cell therapies is comforting—perhaps too comforting. Because it is intended for a general audience, the OTA briefing is necessarily short on the technical details that would allow even the dilettante reader to anticipate some of the difficulties. One finishes the OTA report with the impression that retroviral vectors should be quite reliable and easy to control; a more technical analysis (like W.F. Anderson's in *Science* 226:4673) better points up the problems of regulation, placement, oncogenicity, and alteration.

The report also leaves the reader with the idea that bone-marrow replants will raise the level of deficient enzymes throughout the immune system, curing the disease syndromes. A recent analysis by John A. Barranger (The New England Journal of Medicine, 311:25, 1629) indicates that enzymes produced by the replanted cells tend to remain where they were made. Any system-wide drop in the level of intermediate products (the missing enzymes' substrates) is apparently due solely to a concentration gradient between diseased and repaired cells. Only the transplanted cells are fully functioning. Complete health depends on the altered cells' ability to drive out the diseased cells. In the meantime, even a fraction of a functioning immune system is bound to benefit the patient more than no immune system at all. The refined understanding does not contraindicate replantation, but it does limit one's expectations for improvement.

Human Gene Therapy repeatedly skirts the vexed issue of germline manipulation, arguing that technical and ethical problems make it unlikely that such therapies will be attempted in the near future. Those fascinated by the engineering of races of bacteria, fruit flies, and giant scions of dwarf rodents may see evasion in these dismissals. For these, the "Reasons Germ Line Therapy May Be Unnecessary" may be especially thought-provoking.

Still, we feel we have been cheated of our meat. Perhaps we are too eager for discussion of our pet questions—discussion outside specialized working groups and symposia. While it would be wrong to look to the government for tutelage in ethics, we had hoped for a compelling review of passionate arguments. What we found were a few bland, cautious summaries. Time after time, we have seen writers evade ethical issues with the bland observation that widespread discussion is necessary. Only die-hard opponents seem ready to suffer the discomfort of grappling unfashionably—and in public—with the ideas of right and wrong. It's time for the debate to begin.

—Douglas McCormick