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Reservations Concerning Gene Therapy

The attention recently given the prospects of gene therapy requires a realistic appraisal of the potential as well as a sober consideration of the liabilities of this therapeutic approach.

There is no doubt that the development of techniques for transfer of genes and chromosomes in laboratory studies of mammalian cells will provide a powerful research tool toward comprehension of both normal and abnormal cellular processes and will ultimately provide a rationale for the treatment of many human diseases. Gene therapy, however, involves direct application of this technology to individuals suffering from genetic disease. Possibilities under discussion include: introduction of DNA or of chromosomes either directly or by somatic cell fusion; transfer of genetic material from one host to another by virus-like particles containing DNA of the host cell; infection with active or inactive virus containing genes that can determine some particular biochemical function; or infection with a viral nucleic acid to which some cellular gene has been coupled.

Although the number of newborns suffering from disorders that can be described as genetic is very large, only a small fraction of these disorders would even in principle be amenable to intervention by any of these techniques. Neither genetically dominant disorders, nor multigenic traits, nor disorders resulting from extra chromosomes could be alleviated. The major remaining class is that of the recessive "inborn errors of metabolism." These occur with a collective frequency of about 1 per 1000 individuals and include, conservatively, between 100 and 1000 different disorders. Gene therapy would be likely to involve the isolation of somatic cells from a diseased individual, the alteration of their genetic endowment in vitro, and their replacement in the individual. For example, it seems unlikely that sickle-cell anemia would be relieved if a few percent of the blood-forming cells were replaced by cells capable of producing normal hemoglobin, or that the consequences of phenylketonuria would be relieved by the presence of a few somatic cells capable of converting phenylalanine to tyrosine. On the whole, it does not seem probable that more than a small fraction of the inborn errors could be helped by these techniques, and, with new developments in the understanding of the immune response, these disorders will probably be treated more easily and effectively by tissue transplantation or some sort of enzyme therapy.

Furthermore, there are certainly hazards, both known and unknown, that accompany the presently conceived strategies. Many of the procedures are likely to be mutagenic, and who can guess how many dominant effects, visible only in the whole individual, might appear? Most of the viruses under consideration as vectors are tumor-producing. Even the fractionated virus-like particles containing cell DNA are certain to include some particles containing viral DNA. Damaging alterations of regulatory processes and even uncontrolled tumor-like growth could easily be the consequences of introducing additional chromosomes or a host of viral genes.

The promises offered by the proponents of gene therapy largely ignore its limitations and hazards. To mislead the public in this regard risks another period of disappointment and reaction. We are still primarily in a descriptive phase in our understanding of human genetics, with little, if any, idea of how to intervene safely at any level. Let us not do to ourselves what we have done to our environment. Let us now seek public support for research toward a better understanding of normal and abnormal human biology, rather than promise quick glamorous cures.—MAURICE S. FOX, *Massachusetts Institute of Technology*, and JOHN W. LITTLEFIELD, *Harvard Medical School*