HUMAN GENE THERAPY

Advances in molecular biology have triggered an unprecedented expansion of knowledge about human genetics. The rise of new genetic technologies, and their implied power, has engendered concerns among religious, scientific, and civic leaders that these new technologies may be growing more rapidly than our ability to prudently control and productively use them. The ability to insert human genes into human patients to treat specific genetic diseases–human gene therapy–has been one of the concerns noted by those observing the evolution of genetic technologies.[1]

Human gene therapy will first be considered in a clinical situation where it might be possible to treat with a human gene an individual patient suffering from a genetic disease. Gene therapy would be attempted only when there is no other therapeutic alternative, or when the alternatives are judged to be of greater risk or less potential benefit. Application of gene therapy for a human genetic disease should require evidence that it is safe, might prove beneficial, is technically possible, and is ethically acceptable. Judgments should be made in a procedurally sound and objective regulatory framework.

Some of the concern about the potential abuse of gene therapy may be allayed by considering the following points:

- The most promising prospects for human gene therapy involve treatment of specific genetic diseases by methods that are not designed to cause inherited changes, and the ethical concerns may thus be similar to those associated with other medical technologies, such as vaccination or drug administration, currently in use (President's Commission, 1983; Shinn, 1982; Fletcher, 1982, 1983; Siegel, 1982, 1983).
- The capability for human gene therapy will almost certainly develop in small increments, like other medical technologies. This likelihood, combined with the lack of inheritance of anticipated genetic alterations, suggests that decisions to proceed will not lead to irreversible population effects.
- Inherited alterations, the most controversial potential applications of gene therapy, are unlikely to be undertaken in humans in the near future because they are technically too difficult, are perceived as ethically problematic, and may not prove superior to existing technologies.
- There is a regulatory framework already in place for considering the first applications of human gene therapy. The existence of established procedures cannot guarantee that they will be followed, because some scientists or physicians may choose to deviate from them, but there are laws in place that can be enforced. The existence of such a regulatory framework distinguishes gene therapy from many other novel biological technologies.

The primary justification for attempting human gene therapy is the number and severity of genetic diseases. There are 2,000 to 3,000 known genetic diseases—i.e., diseases whose roots can be traced to specific genes or known inheritance patterns (McKusick, 1983), As many as 2 percent of newborn infants suffer from a genetic disease (Lubs, 1977). For most such diseases, the defective genes have not been identified or located. For several, including some of the most severe childhood diseases, the gene that causes the disease ***has*** been found, and for a few such diseases, copies of the normal gene are available through use of recombinant DNA technology. Human gene therapy will be feasible only for those diseases in which the defect has been identified and the normal gene has been isolated and cloned. All of the diseases presently under consideration for gene therapy are rare.

Gene transfer experiments in animals have produced some inherited changes, but the ethical questions and relative inefficiency of ***current*** techniques preclude application to humans. Because most of the serious concerns that human gene therapy might cause long-term changes in human populations presume ***inheritance*** of characteris-

[1]The development of recombinant DNA and other advanced techniques of molecular biology have permitted novel applications of biological methods in industry and health care through the new biotechnology. This background paper is not about industrial or medical applications of biotechnology, but rather about deliberately changing genetic information in humans.

tics, the present state of the technology does not pose fundamentally new ethical problems. Human gene therapy that does lead to inherited changes, however, would likely incite deep-seated apprehensions about premature application. There should be ample opportunity for public discussion before germ line gene therapy is tested in humans. The body of this background paper will explicate these statements by surveying the technical prospects for human gene therapy and discussing the public policy considerations.

Direct genetic alterations have been successfully practiced in bacteria, yeasts, fruit flies, and some mammals. To date, scientists have not succeeded in applying these same techniques to correct the action of defective genes or directly to change the genome of a human being. The barriers to correcting the genetic defects that cause a few human diseases, however, are now primarily technical, and these barriers may be overcome within the next few years. There are already grant applications to the National Institutes of Health that could lead to clinical testing of human gene therapy. Requests for permission to begin the actual clinical research that would involve humans have not, however, been received to date.

"Human gene therapy," for the purposes of this report, refers to the deliberate administration of genetic material into a human patient with the intent of correcting a specific genetic defect. This would include, for example, replacement of the defective gene in bone marrow cells of a child affected by genetic immune deficiency. Most discussion in this background paper centers on noninherited gene therapy because it is the type expected to be considered soon.

Gene therapy, as defined here, would not include genetically enhancing general characteristics such as behavior, intelligence, or physical appearance. These are excluded from the definition, although the prospects for influencing such traits in the population through genetic methods are discussed in some sections because concern about such prospects has been raised in public debate (Subcommittee on Investigations and Oversight, 1982; Siegel, 1983; Rifkin, 1983; Foundation on Economic Trends, 1984; National Council of Churches, 1984; World Council of Churches, 1983). Enhancement of complex human traits may never be practical or socially accepted and it is not "therapy" for a specific disease.

The definition used in this report thus focuses on correction of specific genetic defects in individual patients, except when social concerns about other applications or general issues are explicitly recognized. This background paper summarizes the technical, medical, and social considerations that arise from consideration of genetic manipulation in humans and how they relate to Federal policy.[2]

[2]Genetic technologies that do not involve gene *therapy*, including agricultural, pharmaceutical, and other industrial applications, have been discussed in several earlier reports issued by the Office of Technology Assessment (OTA) of the U.S Congress. ***Impacts of Applied Genetics,*** issued in 1981, dealt with non-human applications of biotechnology *The Role of" Genetic Testing in the Prevention of' Occupational Disease,* issued in 1983, covered the use of genetic screening in the workplace; and ***Commercial Biotechnology: An International analysis,*** issued in January 1984, surveyed and analyzed the commercial development of biotechnology in Japan Western Europe, and the United States. Issues and topics considered in these other OTA publications are not repeated here; rather, this background paper explores new issues relating to gene therapy in humans.

Why is Congress interested in human gene therapy now?

Congressional interest in human gene therapy stems from general awareness of the rapid progress in molecular genetics combined with concern about the potential power and impact of new biological technologies. Some believe that the deliberate "engineering" of humans who are physically or intellectually "superior" is morally repugnant or politically dangerous, and there is fear that the new techniques might be used to attempt such engineering (Rifkin, 1983; Foundation on

Economic Trends, 1984). Human gene therapy that leads to inherited changes, in particular, has been identified as a "fundamental concern for the protection of the integrity, value, and health of human life, both of individuals and of large numbers. The putative possibility of performing germ line therapy, however noble in intention, would incur risks of unknown magnitude to future progeny" (Nelson, 1984b). Several events contributing to the public interest in molecular genetics are of particular interest.

History

In 1972, scientists joined DNA fragments from two species, resulting in the first deliberately created recombinant DNA molecule (rDNA) (see Technical Notes 1 and 2 for further details). In 1973, rDNA molecules were first duplicated and grown in bacteria. Concern about the safety of recombinant DNA laboratory research led scientists to call for a worldwide moratorium on certain types of experiments. Several scientific and political meetings, some of them quite contentious, were held that focused on issues of safety (Wade, 1984). In 1974, the Recombinant DNA Advisory Committee (RAC) was formed to advise the National Institutes of Health in formulating guidelines for research; the first guidelines were issued in 1976 (Milewski, 1984).

Commercial interest in biotechnology became evident in 1976 when the first new firm, Genentech, was established specifically to apply recombinant DNA technology to medicine and other areas. Since that time, more than 200 firms have been founded to exploit the new technologies (Office of Technology Assessment, 1984). Two patent decisions in 1980 highlighted the commercial potential of new biological technologies. In one, a bacterial strain was patented that had been developed using traditional methods of selecting for genetic traits, and without resort to recombinant DNA technology.3 This was the first patent issued for a living organism. The second patent was issued for the technique of making certain types of recombinant DNA molecules.[4]

Wall Street responded to the promise of biotechnology in 1981 by setting a record for the fastest price-per-share increase when Genentech's initial public offering of stock rose from $35 to $89 per share in 20 minutes. Optimism was again noted in 1982 when Cetus made a large and successful initial public offering ($115 million). Early commercial expectations were encouraged when the first commercial product using recombinant DNA technology was introduced to the market in 1982: human insulin, sold as Humulin (Office of Technology Assessment, 1984, ch. 4). Many of the expectations of rapid economic bonanza have been tempered by the length of time and magnitude of effort required to bring products to the market, but long-term prospects for commercial applications of biotechnology remain promising (Office of Technology Assessment, 1984).

Developments in regulation, law, and finance were attended by continued advances in genetic research. The surprising discovery of "split" genes occurred through the use of recombinant DNA technologies in 1977.[5] That same year, two independent techniques were developed for determining the DNA sequences that contain genetic information, permitting direct inspection of the genetic material and analysis of its functions (Watson, 1984).

Advances in medical applications also occurred. Recombinant DNA techniques were first used for the prenatal detection of sickle cell disease in 1982 (Chang and Kan, 1982; Orkin, Little and Kazazian, 1982). Use of enzymes that specifically cut DNA, in combination with probes that detect specific

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[3]The first patent for a microorganism was granted to Ananda Chakrabarty of the General Electric Corp. for a strain of Pseudomonas bacterium that digests certain petrochemicals. Dr Chakrabarty developed the strain by growing rare and mutant forms of the bacteria in new artificial environments until a strain with the desired characteristics resulted. The decision to grant the patent was made by the U.S. Supreme Court in a 5 to 4 vote on June 16, 1980

[4]This patent was granted to Stanley Cohen of Stanford University and Herbert Boyer of the [University of California at San Francisco for the basic process of constructing recombinant DNA molecules. The patent is questioned by some, but has not been seriously challenged at the time this is written (Office of Technology Assessment, 1984, ch. 16). The patent has since been complemented by a process patent for the same technology that was granted in August 1984.

[5]Scientists confirmed their expectations that the genes were more complicated in higher animals rompared to bacteria. Genes in higher organisms are often divided into regions: the sequence for a protein, for example, may be separated into several units, and the units must be rearranged and "spliced" together to form the sequence that is eventually used to produce the protein (Leder, 1978).

sequences of DNA, led to development of a method for determining the location of genes, even when their function had not been determined and the genes had not been isolated (Botstein, 1980; Botstein, 1984). The technique, first described in 1980, has great promise for both promoting understanding of human genetics and assisting in the diagnosis of hereditary diseases (see app. A). In 1980, the first inherited alteration of genes in the germ line of mice was achieved (Gordon and Ruddle, 1981) and in 1982, the gene for rat growth hormone was introduced into mice (Palmiter, 1982, 1983). The mice that incorporated the rat growth hormone genes into their cells could be induced, using a special diet containing zinc, to grow to twice normal size. The response to zinc was due to a special DNA sequence that the scientists had included with the growth hormone gene that caused zinc to "turn on" the inserted gene. The progeny of the genetically altered mice also inherited the new foreign gene, making them "mighty mice" as well.

The human experiments of Martin Cline, a physician from the University of California at Los Angeles, contributed to the ethical apprehensions of many observers. Dr. Cline attempted gene therapy using recombinant DNA in two patients suffering from thalassemia, a disease causing severe anemia (see Technical Note 5)—one in Israel and one in Italy. The propriety of the experiments was widely questioned in the scientific literature (Wade, 1980; Wade, 1981). Many scientists and clinicians judged the human experiments premature (Fletcher, 1982a, 1982b; Anderson, 1982) and pointed out that Dr. Cline did not even follow the protocol that had been approved by the foreign human subjects review boards. He also failed to wait for approval by such committees in the United States (Talbot, 1982). Professor Cline was penalized by the National Institutes of Health by termination of two grants, and he resigned chairmanship of his division at the University of California (Sun, 1981, 1982; Talbot, 1982). (Dr. Cline's experiments and the dispute over their propriety are described in greater detail below.) The history of human gene therapy thus did not have an auspicious start, although many scientists and clinicians would not consider Dr. Cline's experiments bona fide attempts at human gene therapy.

Concern among religious leaders

Increasing commercial interest, progressive movement of the technology into the relatively unregulated private sector, possible premature applications to humans, and impressive technical improvements all attracted attention to molecular genetics in the early 1980s. The general secretaries of three large religious bodies—the U.S. Catholic Conference, the Synagogue Council of America, and the National Council of Churches—sent a letter to President Carter in 1980 in which they expressed concern that prowess might surpass prudence in the human application of genetic technologies. They noted that we had entered an "era of fundamental danger triggered by the rapid growth of genetic engineering)" and appealed to the President to look into how molecular genetics might be applied to humans (President's Commission, 1982, pp. 95-96). The letter noted that there was no governmental agency or committee investigating the ethical, social, and religious questions raised by the new technologies. Such questions included concern for fair distribution of risks and benefits, control of genetic experimentation, and long-term consequences of genetic interventions.

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (hereafter called the "President's Commission") responded by investigating some uses of recombinant DNA in humans. The Commission's inquiry resulted in publication of Splicing Life in November of 1982 (President's Commission, 1982). In that same month, the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, U.S. House of Representatives, held hearings for 3 days entitled ***Human Genetic Engineering.***

A resolution signed by 56 religious leaders and 8 scientists and ethicists rekindled interest in human genetics when it was sent to Congress in June of 1983 and introduced by Senator Mark O. Hatfield ***(Congressional Record,*** June 10, 1983, S 8202-8205). The resolution urged that '(efforts to engineer specific genetic traits into the germ line of the human species should not be attempted" (reprinted in: Foundation on Economic Trends, 1984). The signatories of the resolution came from