

the risk of fetal infection from Rubella vaccination during pregnancy is quite low (Plotkin, 1981).

Fetal research thus played a role in better understanding the congenital Rubella syndrome, in development of vaccines, and in establishing safe practices for human vaccination. An analogous role in establishing scientific background and testing safety and efficacy of gene therapy might also require fetal research for some future applications.

There is no reason to test human gene therapy protocols in human fetuses now because neither fetuses nor pregnant women are contemplated for treatment. Should this change, then tests involving fetuses would be desirable. If a need for application to fetuses or pregnant female patients emerges, then it may depend on study abroad (where fetal research is practiced), relaxation of fetal research guidelines in the United States, or repeal of statutes in those States that prohibit such research (if the research is to be conducted in such States). This issue will be especially difficult to resolve if gene therapy is shown useful for severe diseases of early childhood. This is because gene therapy that is useful in infants is likely, in some cases, to be potentially even more beneficial during fetal development—before the metabolic abnormalities caused by the genetic disease have caused any deformities or irreversible effects on the nervous system.

#### WHAT MIGHT BE THE EFFECTS ON SOCIAL INSTITUTIONS?

Several religious leaders have noted that gene therapy may be one more factor tending to reduce perceptions of humanity to mechanistic interpretations (Zaner, 1982; Siegel, 1982, 1983; World Council of Churches, 1982; National Council of Churches, 1984). Focus on mechanism may lead to diminished attention to social and moral values, and may threaten attitudes about the sanc-

tity of human life. The effects of the new technology on attitudes are not certain, however, and the same commentators note that appreciation of the complexity of life may increase our regard for life more than it attenuates it. The attempt to save lives by gene therapy is itself an attempt to preserve or improve particular lives. The specific effect of gene therapy in changing perceptions is, in any case, likely to be one small part in the general growth of science, complementing other fields that also alter our self-perceptions such as neuroscience, computer science, psychology, evolutionary biology, ecology, and other parts of biology and medicine. If gene therapy is found medically useful, it may prove difficult to deny benefits to needy patients on the basis of long-term shifts of human self-perceptions.

Gene therapy may play a larger role in indirectly altering parental expectations. If genetic therapy is successful for extremely serious diseases, then it might be applied over time to progressively milder medical problems. This prospect raises the possibility that parents may more and more expect “perfect” children. So long as gene therapy is confined to disorders that are recognized as significant burdens, then it will merely be an addition to the medical armamentarium. If it becomes possible to treat more and more disorders, especially if attempts are made to affect intelligence or physical traits, then gene therapy might indeed raise concern about parental expectations of their children. Again, however, the definition of appropriate application is one that must be widely discussed because it is more a social than a medical issue (although medical factors are highly relevant). Discussion of such potential dangers is, given present technology, mere speculation for now; as the technology develops, public discussion may need to be encouraged if it appears that gene therapy is becoming widely applicable.

## The Federal role in gene therapy

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The Federal Government performs several functions that may affect the development and application of human gene therapy. Most biomed-

ical research is supported by the Federal Government through the National Institutes of Health (NIH) and other Executive agencies. Regulation of

pharmaceutical products is the responsibility of the Food and Drug Administration (FDA). Genetic services including manpower training, basic and applied research, genetic screening, and counseling, are partially supported through block grants given to individual states under authority of the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs and Genetic Diseases Act (Reilly, 1977), and administered under the Omnibus Budget and Reconciliation Act. Finally, the Federal Government, through its legislative, judicial, and Executive branches, is often an effective instrument for public discussion and education, through the Department of Health and Human Services, congressional hearings and activities, and such agencies as the President's Commission.

### ***International interests in human gene therapy***

Human gene therapy is widely regarded to be closer to clinical testing in the United States than any other country. Other developed nations will soon follow, however, and international interest in its development has been noted, primarily in Canada and Europe. Canadian research groups have been involved in the design of viruses that might be used in gene transfer (Merz, 1984), and several European government groups have made statements related to gene therapy. The Parliamentary Assembly of the Council of Europe, for example, made a recommendation that '(the rights to life and human dignity . . . imply the right to inherit a genetic pattern which has not been artificially changed,' although this right was explicitly qualified so as to "not impede development of the therapeutic applications of genetic engineering (gene therapy), which holds great promise . . ." (Parliamentary Assembly, 1983). The Parliamentary Assembly also called for the development of a list of diseases that could be treated using gene therapy, based on several criteria:

- seriousness of the disease,
- simplicity of the technique and applicability to only single gene disorders,
- application to a well characterized disease,
- supervision by scientific and ethical review committees,

restriction to centers of demonstrated expertise, and, interestingly, exclusion of genes that are "the object of commerce."

A recent report on reproductive technologies was submitted to the Parliament of the United Kingdom by a committee headed by Dame Mary Warnock. The report recommended that a new governmental licensing agency be created to oversee embryonic and fetal research and its applications. The committee also briefly commented on potential germ line gene therapy, and recommended that the licensing authority give "guidance on what types of research, apart from those precluded by law, would be unlikely to be considered ethically acceptable in any circumstances" (Committee of Inquiry, 1984). The licensing authority would thus monitor gene therapy research and consider whether germ line therapy should be permitted.

European political history in dealing with genetic technologies differs from that in the United States. The United Kingdom, for example, has approached the regulation of novel biological technologies from a different perspective (Wolstenholme, 1984). Fetal research is now performed in the United Kingdom and Australia, and so questions regarding its regulation are more prominent there than specific applications to gene therapy. In the United States, fetal and embryonic research has not been federally funded for almost a decade (see below), and the scientific and medical focus of gene therapy has been on *somatic* cell therapies whose development does not entail the use of fetuses or embryos.

### ***Federal agencies potentially involved in gene therapy***

Several Federal agencies potentially have purview over some aspect of human gene therapy. The National Institutes of Health, as the primary sponsor of relevant research and the location of the Recombinant DNA Advisory Commission, is involved in approving both research grants to do gene therapy research and in overseeing compliance with Federal research guidelines.

The National Institutes of Health (NIH), through its Recombinant DNA Advisory Committee (RAC), is currently the most active Federal body involved in monitoring human gene therapy. It was established in 1974 and is charged with recommending guidelines for safe conduct of research involving recombinant DNA (or, by extension, RNA) (Milewski, 1984). The RAC has established a Working Group on Human Gene Therapy, whose members are listed in appendix C, to develop guidelines for research on human applications of gene therapy. The Working Group plans to have guidelines published in 1985, in anticipation of proposals for human gene therapy. The Working Group shall evaluate research proposals received by NIH, and shall report to RAC. RAC shall, in turn, report to the Director of the NIH, who will then approve the proposal or suggest needed alterations. Another function of the Working Group will be to educate the public and to review some broader social implications of human gene therapy that are not included in review by local Institutional Review Boards (Working Group on Human Gene Therapy, 1984).

The Food and Drug Administration (FDA) will also play a role in regulating some aspects of human gene therapy. The FDA has the authority to regulate drugs, including biological products intended for use in the diagnosis, treatment, or prevention of diseases or injuries in humans. The FDA will become involved in human gene therapy if it involves products such as nucleic acids or genetically modified viruses that are subject to agency regulations (under authority of the Food Drug and Cosmetic Act and the Public Health Service Act) (Miller, 1983a). The role of the FDA generally includes review of applications submitted for products used in investigational studies and encompasses the manufacture and quality control procedures applied to such products. The FDA review includes evaluation of the design of clinical and preclinical studies, adequacy of procedures for assessing safety and efficacy, and methods for obtaining informed consent from patient participants (Miller, 1983b).

The FDA authorizes (by approval of a New Drug Application or granting of a license) the marketing of products when a review process has concluded that the data obtained during investiga-

tional trials support the safety and efficacy of the product for its intended labeled claims (Miller, 1983b).

In addition to the NIH and FDA, which are already monitoring human gene therapy, there are several other Federal agencies or bodies that might become involved in the future.

An Ethics Advisory Board (EAB) is an entity composed of non-government experts in ethics, law, medicine, and others with expertise related to a particular topic under consideration. One such board was formed in 1979 to advise the Secretary of Health and Human Services on several topics, most notably fetal research. Federal regulations state that "One or more Ethical Advisory Boards shall be established by the Secretary" (Code of Federal Regulations, 1983) yet no such board exists at present. An EAB was intended to "render advice consistent with the policies and requirements . . . as to ethical issues" (Code of Federal Regulations, 1983). Such a board, if it were now reconstituted, might play a role in coordinating and overseeing the Federal Government's activities regarding human gene therapy, including public education, supervision of NIH, FDA, and other agencies in the Department, and advising the Secretary on other actions. Consideration of the broader questions related to progress in human gene therapy would fall within the mandate established for EABs.

The Federal Interagency Advisory Committee on Recombinant DNA Research, established in 1976, is another group that has not played a direct role in human gene therapy, but could theoretically do so. The Committee is composed of members from several Federal agencies involved in activities related to recombinant DNA research. Members of the Committee agreed to comply with the NIH Guidelines in 1976, thus in effect transferring authority to NIH for biomedical research and clinical investigations. Recently, other agencies, including the Department of Agriculture and the Environmental Protection Agency (both of which have members on the Interagency Committee), have become involved in regulating agricultural and environmental applications of recombinant DNA research. The Committee may thus play a more active role in agricultural, environ-

mental, and other new areas of research, but it is likely that most authority to monitor and regulate human gene therapy will remain at NIH and FDA because these agencies have the most extensive experience with biomedical and clinical applications.

The Office of Science and Technology Policy (OSTP) is an Executive agency, headed by the President Science Advisor, that reports directly to the President. The OSTP has taken a lead in Federal oversight of some areas of science and technology, and has recently coordinated a group of government officials in dealing with the questions surrounding deliberate release of genetically altered organisms into the environment, and other novel applications of biotechnology. The OSTP could conceivably also serve a similar function for gene therapy, although the extensive experience of FDA and NIH in questions relating to health and medical technologies makes OSTP less likely to be involved in human gene therapy than in more general questions such as environmental release or new agricultural applications.

Determination of the Federal role in monitoring and public debate about questions relating to bioethics, including human uses of recombinant DNA technology, was a focus of considerable legislative activity in the 98th Congress. Bills to reauthorize the lapsed President's Commission were introduced in both houses, but no further action on those bills was taken. Representative Gore proposed a new President's Commission on Human Applications of Genetic Engineering that eventually became part of the House version of the NIH authorization bill. Senators Hatch and Kennedy proposed creation of a bioethics commission at OTA as part of legislation creating a new National Institute of Arthritis and Musculoskeletal and Skin Diseases at NIH. The Senate and House bills were referred to conference. The conference report authorized a new Biomedical Ethics Board, composed of 6 Senators and 6 Representatives, and a Biomedical Ethics Advisory Committee, composed of 14 appointed individuals and experts in relevant disciplines. The Committee would have performed studies related to bioethics, including two mandated studies: one on fetal research and another on human applications of genetic engineering (including human

gene therapy) (Conference Report, 1984). The legislation reported from conference was passed by both houses, but vetoed by president Reagan on October 30, 1984. The future of a Federal body for investigation of bioethical questions is thus uncertain.

## ***Functions of the Federal Government***

### **SUPPORT OF RESEARCH**

The Federal Government, through the National Institutes of Health (NIH), is the primary sponsor of biomedical research in the United States. The NIH budget for 1983 was \$3.8 billion, accounting for 36 percent of all funds spent in the United States on health-related research (NIH, 1984). In those areas of biological science related to human gene therapy, the NIH funds the bulk of research, although a few companies with expertise in biotechnology are known to be sponsoring some research relevant to gene therapy.

The relative rarity, scientific difficulty, and long term investment necessary to develop gene therapy for any one genetic disease suggest that research may not occur unless there is public funding. Individual genetic diseases are thus "orphan" disorders when taken singly, yet relatively common as a group. The technology to identify or treat one genetic disease often suggests means for approaching biochemically similar disorders, and many aspects of research on one disorder may be directly applied to others. A recent example of this phenomenon is the discovery that the gene for Huntington disease is located on human chromosome 4. This discovery was made by applying a technique developed for general mapping of the human chromosomes to large families in the United States and Venezuela<sup>15</sup> (Gusella, 1983; Wexler, 1984; Rosenfeld, 1984; Kolata, 1984a). The same technique, which may permit earlier diagnosis and eventual identification of the specific gene responsible for the disease, promises to apply to many other genetic diseases. The financial and scientific investments in discovering

<sup>15</sup>The technique, called restriction fragment length polymorphism linkage analysis, was developed to locate genes even when the gene had not been cloned or even identified (Botstein, 1980, 1984). This method for identifying the chromosomal location of genes is described in app. A.

and developing a technique used in locating the Huntington disease gene may thus also pay off for other disorders.

Research on genetic diseases is likely to continue to depend heavily on Federal funding, and so long as gene therapy remains experimental, Federal research policy will be influential in its development. Seminal discoveries related to human gene therapy will likely derive from both clinical research and basic research on molecular genetics and biochemistry. The technologies of recombinant DNA and gene transfer now contemplated for use in human gene therapy are themselves results of basic genetic inquiry, and further practical applications of basic research are likely to emerge. This has been the pattern of development of molecular biology and other biomedical sciences—research in one area leading to breakthroughs in an unexpected and seemingly unrelated discipline. The discovery of DNA's relationship to inheritance was itself such a serendipitous discovery, resulting from Avery's work attempting to identify why certain bacteria caused pneumonia (Thomas, 1984; Judson, 1980).

Research on developing animal models of human genetic diseases may be important in facilitating human gene therapy applications. Such models provide methods for testing the efficacy and safety of treatment methods.

In addition to basic research, some early experimental trials in humans will likely be supported by Federal funds. Decisions about how Federal research funds are expended for research on basic molecular genetics, animal models of genetic diseases, and preliminary human applications will thus directly affect how rapidly gene therapy develops and which diseases will be addressed.

#### REGULATION OF MEDICAL APPLICATIONS

A research proposal involving recombinant DNA is generally originated by a scientist working at a university, industrial laboratory, or other research center. A research proposal includes general background, goals of the experiment, methods to be used, evidence for efficacy, provisions for assuring safety and informed consent of patient participants (and may also include in-

formation on compliance with standards for animal care). The proposal is sent to local review committees that assess its compliance with safety and human subjects protection guidelines. Certain classes of experiments are automatically referred to NIH for approval, and cases that cannot be decided locally are also referred to NIH.

These procedures are the ones followed by scientists and clinicians using Federal funds who act in good faith. Human investigations supported by private firms must also meet human subjects protections guidelines, usually to avoid problems of liability and insurability. Clinical investigations of pharmaceutical products, including genes or modified viruses used in treatment, must also be submitted for FDA review.

**Ensuring Compliance with Human Subjects Protections.**—A process for protecting human subjects in research already exists. In the context of experiments involving human gene therapy, a proposal for an experiment involving human subjects should be sent to an institutional review board (IRB), a local committee that would then review the proposal for compliance with human subjects protection standards, according to the following criteria:

- minimization of risk to the subjects,
- reasonable risks in relation to anticipated benefits,
- equitable selection of subjects,
- assurance of informed consent,
- adequate provisions for monitoring data,
- provisions for protecting patient privacy, and
- assurance that decisions to participate in research will not be coerced (Code of Federal Regulations, 1983).

Approval by a local IRB will be required before proposals are forwarded to NIH for approval. IRB approval may be contingent on approval by the NIH. When received at NIH, the proposal will be published in the Federal Register for public comment and will also be referred to the Working Group on Human Gene Therapy, which will then report to the RAC for review. If the proposed experiments meet the standards of the RAC, then they are referred to the NIH director for approval (Working Group on Human Gene Therapy, 1984).

Ensuring Safety and Efficacy.—Mechanisms for reviewing research proposals to ensure safety potentially fall under the authority of several groups. Assurance of safety is analogous to human subjects protection, including review by NIH and FDA after approval by local safety and human subject committees. Each investigator must submit his research proposal to his or her local Institutional Biosafety Committee (IBC), which assesses compliance of the proposed experiments with NIH safety guidelines for recombinant DNA research. In the case of human gene therapy, the risks and benefits of proposed experiments will also be reviewed, followed by approval by the NIH and FDA before commencement (Krause, 1984, p. 17847).

There are several weaknesses in this regulatory schema. Only research conducted at institutions accepting federal funds for recombinant DNA experiments are obligated to conform to the NIH Guidelines by law, although to date private research groups have voluntarily submitted to RAC Guidelines. (Private corporations have complied at least in part because of the risk of public censure, potential loss of insurance coverage, and possible added legal liability in civil suits if they do not.) The formal penalty for not conforming to NIH guidelines is denial of Federal research funds to the institution submitting the proposal. This is quite powerful for universities and most research centers, but is not a direct economic incentive for compliance in some privately sponsored research.

Another feature of the current review process is the lack of evaluation of research goals. IRBs are specifically precluded from assessing the ‘long-range effects of applying knowledge gained in the research’ (Code of Federal Regulations, 1983). This is quite appropriate in the context of a particular experiment involving patients with specific defects, and IRBs cannot be expected to do more than investigate specific protocols. The lack of purview over goals, however, leaves a vacuum for determining which experiments are contrary to public policy. The NIH has formed the Human Gene Therapy Working Group in part to fill this vacuum, but there are potential questions of conflict of interest because NIH is also the primary sponsor of biomedical research. Assessment of public policy on goals for research, including

human gene therapy, could be performed by an EAB, congressional commission or other Federal body.

In addition to review of research proposals on human gene therapy by the NIH, the Food and Drug Administration (FDA) also has authority over human experiments involving therapeutic products. Genes introduced for gene therapy could constitute such a biological product under FDA jurisdiction and would thus involve FDA approval before commencing (Miller, 1983b). FDA oversight would follow regulator procedures used for other products: submission of evidence for safety and a rational basis for introduction of the product into humans (stemming from animal experiments, *in vitro* studies, and relevant previous clinical trials). Investigator submissions must include data showing that the product is adequately pure and sufficiently potent to justify clinical trials (Office of Biologics Research and Review, 1983). The FDA then evaluates the evidence and determines whether risk and benefit considerations support clinical trials.

FDA authority may, in some circumstances, overlap that of the NIH, whose Guidelines explicitly provide for oversight of human gene therapy and experiments that involve recombinant DNA (or molecules derived from rDNA).

Whatever the mechanism or agency involved, protocols and products will be evaluated case by case. This will certainly involve local IRBs, NIH, and FDA, and may eventually include other Federal agencies as well. If individual applications of human gene therapy becomes standard medical practice, or even widely available, they will then be governed primarily by professional standards, civil suits, or local authorities, like other medical technologies.

For early experiments on human somatic cell gene therapy, present oversight methods that involve local IRBs, RAC, NIH, and FDA appear adequate. For more controversial applications of gene therapy involving germ line alterations, wider public discussion, open goal setting, and greater government oversight may prove necessary to avoid undue controversy and assure prudent public policy.

### PAYMENT

If gene therapy were to become incorporated into routine medical practice, the Federal government might become involved in paying for its use. As long as gene therapy is experimental, most costs will be borne by research funds. Typically, as a therapy is used more widely, funding becomes much more complex. Many regulatory decisions are made about reimbursement at the Federal and State levels, and individual insurers make reimbursement decisions that are subject to State and Federal regulations.

Medicare reimbursement of gene therapy might apply, for example, to those instances (probably quite rare) involving people over age 65 or who suffer from chronic kidney disease that could be treated by gene therapy (polycystic kidney disease is a dominant trait that leads to kidney failure, but is not now a candidate for somatic cell gene therapy because the gene has not been identified and its mechanism of causing disease is not understood).

Medicaid is joint State and Federal health program that pays for medical services provided to indigent individuals. Medicaid reimbursement would involve both State and Federal policy, and might be used to pay for gene therapy of pediatric patients in indigent families.

Little has been written about how to pay for gene therapy. If other medical technologies are taken as examples, early costs are likely to be relatively high, and drop as clinical experience and technical innovations accumulate. Decisions will be made about applications to specific disease entities rather than for gene therapy in general, and there will likely be regional and institutional variation among payers as to which applications are reimbursable. Mechanisms of payment could range from complete public subsidy to total payment from personal income at each stage of development. If gene therapy proves successful in its early applications, more attention will need to be devoted to sources of payment.

### PUBLIC EDUCATION AND DISCUSSION

The high level of interest in topics relating to genetics suggests that mechanisms need to be developed that permit discussion at all levels of

society. Several issues relating to genetics, such as practices in a particular laboratory or individual patient-physician decisions, must be made locally. Other issues of national importance, such as research policy, health policy, and civil rights, may require attention by the Government and international agencies.

Careful public policy decisions about novel technologies require an educated public. Federal agencies have been directly involved in educating the public about gene therapy, through congressional hearings such as Human Genetic *Engineering* held by the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology in November 1982, symposia such as the Public Forum on Gene Therapy sponsored by NIH in October 1983, and publications such as *Splicing Life* issued by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

Several scientists have expressed concern that the nuances of genetic technologies, such as the distinctions between somatic and germ cell manipulations, may not be completely understood by the public (Baltimore, D., in Friedmann, 1983, p. 59). One basis for such concern is the experience with the early debates about the safety of recombinant DNA, when laboratory research involved precautions and preservation of detailed records on laboratory safety of recombinant DNA work that were considered onerous by some scientists (Weissmann, 1981). Rancorous public debates occurred before the City Council of Cambridge, Massachusetts, and other places about whether certain recombinant DNA research should be permitted (Wade, 1984). While recognizing the need for caution in research on recombinant DNA, some believe that public concern led to overly stringent regulation triggered by baseless fears. One scientist noted, "It seemed that we had lost track of the serious scientific and health considerations and were operating in a climate of hysteria—some of which passed for responsibility" (Leder, 1984).

Public education is, many believe, the best solution to misapprehensions about genetic technologies (Beckwith, 1984; Capron, 1984a, b). Increased public education was designated a high priority by President's Commission, and was in-

eluded as the first of the major functions of any Federal agency overseeing the development of genetic technologies (President's Commission, 1982, pp. 82-84). The consensus on a need for public education does not, however, necessarily imply agreement that public education is primarily a function of a Federal oversight body (H. I. Miller, 1984).

Equitable social policy is another reason to foster public discussion. The governmental role in developing, regulating, and applying gene therapy is crucial, as noted in other sections of this Background Paper. Informed public decisions presuppose not only adequate knowledge, but also a process for ensuring that all views are fairly represented.

The need for wide public discussion of human uses of gene therapy and other genetic technologies has been noted by religious groups (World Council of Churches, 1982; National Council of Churches, 1984), by the President's Commission (President's Commission, 1982), by ethicists and scientists (Grobstein, 1984), and in congressional hearings (Gore, 1982). Opinion on this issue appears to have converged from many quarters, involving scientists, ethicists, politicians, and religious leaders, and resulting in what one observer has called an "amazing consensus" about the need for continued oversight and discussion at the Federal level (Nightingale, 1984). The functions of such discussion include definition of goals, identification of public policy issues, inclusion of conflicting views held by different constituencies, and consideration of short- and long-term consequences of genetic interventions of concern to various scientific, medical, religious, and consumer groups.

There are some potential problems that even an effective Federal forum for discussion may not accomplish, however. It is doubtful that any commission can resolve the differences that emerge from moral and social plurality in the United States. For example, what conditions should be treated by gene therapy? Disorders such as baldness or short stature that are considered minor annoyances by one person might merit somatic gene therapy as judged by another.<sup>16</sup> No regula-

<sup>16</sup>Neither of these conditions is sufficiently understood to be a candidate for somatic cell gene therapy. They are mentioned only to illustrate a point, not to indicate technical feasibility.

tory apparatus is suited to resolving such dilemmas. Public debate can air differences, but should not be expected to eliminate them.

In addition, there is a danger of gratuitous additional regulation that would impede the development of legitimate human applications of genetics if new agencies are created, or overly stringent regulations imposed (H. I. Miller, 1984).

Finally, public debate cannot and should not intervene in the decisions best made by individual patients and the health professionals who provide care. Personal choice is a value that should be constrained as little as possible in establishing public policy.

#### FAIR DISTRIBUTION OF BENEFITS AND COSTS

The costs and benefits of gene therapy are uncertain because the technology is in its infancy. If gene therapy becomes a part of routine medical practice, however, then many issues relating to distribution of costs and benefits may arise. In general, these would be similar to those raised by other medical technologies: payment, informed consent, and fair access. Fair distribution of costs and benefits would be one of the considerations in reimbursement decisions mentioned above. It may fall to government to rectify reimbursement decisions that do not provide equal access to all social sectors and ethnic groups. Access to gene therapy by the indigent or by minorities especially prone to certain genetic diseases, for example, might prove of special concern.

Decisions made now about research funding will also influence the future distribution of benefits from gene therapy. Because different genetic diseases are more common in some racial groups, decisions about which diseases to investigate can be expected to influence the later availability of gene therapy or other treatments among such groups. Neglect of hemoglobin disorders, for example, would be of more concern to Blacks and those of Southern Mediterranean extraction than to other Caucasians. Federal decisions about which diseases are addressed in genetic research thus have potential distributional consequences, and the large share of genetic research supported by the Federal Government makes such decisions important in determining which populations may eventually benefit from available technologies.



### PROTECTION OF INDIVIDUAL RIGHTS

Some individual rights protected by the Federal Government may be influenced by gene therapy, as by any new medical technology. Any threat to such rights is, however, more likely to derive from new diagnostic techniques of genetic testing than from gene therapy. Maintaining the privacy of genetic diagnostic information about disease risks is likely to be a much larger problem for individuals' rights than performing gene therapy because: 1) more people will be affected, 2) more information will be generated by diagnostic techniques than therapeutic interventions, 3) the diseases for which genetic risk factors might be assessed are common and have large economic consequences for employers and insurers, and 4) problems in protecting individual rights for gene therapy are quite similar to the problems arising from other therapies, while genetic diagnostic technologies may make much more information available of a new type. These issues are briefly addressed in appendix B.

Knowledge that a person has undergone gene therapy should be accorded the same privacy safeguards applied to other medical information. In addition to ensuring the privacy of genetic information, including medical information about gene therapy, the Federal Government has accepted a role in protecting the interests of research subjects. Such protections include IRB's and, in the case of gene therapy, the RAC at NIH. FDA oversight also includes attention to informed consent of participating patients.

A few weaknesses persist in the present methods of research subject protection. Children and mentally incompetent patients cannot consent to treatment because they cannot understand the consequences of such consent. The process of informed consent requires different standards in different court jurisdictions (see app. B and Andrews, 1984a), but all standards involve a competent patient or surrogate decisionmaker who can rationally balance risks and potential benefits. In cases of disagreement with physicians or other health professionals, families often are involved in making decisions in the best interests of the patient. In some instances, especially when there is disagreement between medical professionals and families, it is not clear who can and who can-

not give consent for treatment or participation in experiments. The problem of surrogate informed consent is especially likely for gene therapy, because many genetic diseases primarily affect children or cause mental incapacity in adults. There are special guidelines for IRB's to consider in approving research protocols that involve children (Code of Federal Regulations, 1983). Uncertainty about informed consent can act as an impediment to research on the one hand, and may leave some patients insufficiently protected on the other. Some states are drafting legislation to deal with the problem (Andrews, 1984a). State and local initiatives may eventually clarify the legal status of surrogate informed consent, but, in the interim, responsibility for monitoring the informed consent process for research participation will fall to IRB's and the courts.

### *Case histories*

#### IN VITRO FERTILIZATION

Some lessons from Federal policy relating to research and clinical applications of in vitro fertilization (IVF) may be applicable to the development of gene therapy technologies. In vitro fertilization is the process of obtaining sperm and eggs from donors, uniting the gametes in the laboratory, and implanting the products of fertilization in a woman's womb. This technology was developed in the 1950s, and first successfully applied to humans in 1969. Improvements in fertilizing eggs in the laboratory led to the first human applications of in vitro fertilization a decade later: Louise Brown, a normal infant conceived using in vitro fertilization, was born on July 25, 1978. She has been followed by more than 700 pregnancies resulting from in vitro fertilization and embryo transfer (Hodgen, 1984).

The primary intent of those using in vitro fertilization in humans is to permit infertile couples to have children (Hodgen, 1984) although other applications are technically possible.

In vitro fertilization is related to gene therapy because, for technical reasons, attempts at germ line genetic alterations are most likely to be attempted on early embryos. Germ line gene therapy would involve either extraction of a fertilized embryo from a woman (before the embryo had

implanted in the uterine wall) or, more likely, in vitro fertilization either immediately preceded or followed by addition of genetic material. Availability of in vitro fertilization is thus a precondition for successful germ line gene therapy (Ryan, 1983) and so policy affecting in vitro fertilization practices will also affect germ line gene therapy.

Even if in vitro fertilization were not directly related to gene therapy, the history of Federal policy on it would still be of interest because it is a controversial biological technology analogous to gene therapy in some respects. A brief review of decisions made about in vitro fertilization may highlight potential pitfalls that could also occur in connection with gene therapy.

There has been a de facto moratorium on Federally sponsored research on human in vitro fertilization in the United States since 1975. There are nonetheless at least 60 centers and 200 programs offering it in the United States (Abramowitz, 1984; Hodgen, 1984). The research leading to these early efforts was performed primarily in the United Kingdom and Australia. American centers have adopted the technology developed in other nations, or have treated patients using private moneys paid by patient fees.

Congress imposed a temporary moratorium on Federally sponsored human in vitro fertilization research in 1973, after NIH received its first request for a grant for fetal research. The 13 month moratorium was technically lifted in 1975, when guidelines proposed by the Ethics Advisory Board (EAB) of the Department of Health and Human Services (then the Department of Health, Education, and Welfare) were published. The guidelines sanctioned carefully constrained research, provided that strict procedures were observed, including:

the intent of the research was to improve understanding of fertilization and assess risks, the information could not be obtained by other means, informed consent, including disclosure of risks, was obtained, and other regulations on human subjects research were observed, embryos beyond the fourteen-day stage of development were excluded if embryos were

not to be implanted back into prospective mothers, measures were taken to ensure that possible risks to the public were disclosed, only gametes from married couples were employed if embryos were implanted in prospective mothers, and, most importantly, approval was obtained from the EAB, in addition to IRB review, before commencing.

The findings of the EAB have never been accepted by a Secretary of HHS (or HEW), the EAB has been disbanded, and no Federal grants have been approved for research on in vitro fertilization. The NIH authorization bill from the 98th Congress, as passed by both houses and vetoed by the President, would have mandated a further 3 year moratorium on human fetal research, and the new congressional bioethics board would have undertaken a study of it (Conference Report, 1984). The moratorium on human fetal research will continue, however, until an EAB that could approve it is reconstituted by the Secretary of Health and Human Services.

The Federal moratorium on research in the United States did not prevent the development of in vitro fertilization technology or its clinical application, although its development has probably been somewhat slowed (Abramowitz, 1983). There is some concern that the technology has developed with less than usual Federal oversight, and that some desirable steps, such as testing in non-human primates, have been skipped in the transition from experiments in lower mammals to human clinical applications (Ryan, 1983). Experiments have not been subject to the NIH peer review process, and may have "circumvented systematic accumulation of knowledge" (Ibid., p. 152). The Federal Government may have lost some ability to monitor and control the technology by failing to sponsor research (Ibid., pp. 151-153) or at least to provide a mechanism for Federal oversight. Furthermore, the technology developed in spite of the lack of a consensus about its moral acceptability (Ibid., p. 153).

The unusual development of in vitro fertilization research is exemplified by one technique of in vivo fertilization of an egg in one woman fol-

lowed by transfer of the embryo to another. The technique permits obtaining the fertilized egg without subjecting the donating woman to a major surgical procedure. This technique has been developed with corporate funds in the United States, and those who sponsored the research have applied to patent some of the instruments involved, as well as the process itself (Annas, 1984; Chapman, 1984). A patent for a medical procedure is unusual, although not unprecedented (Brotman, 1983); if granted, it would give the sponsoring corporation the ability to limit the application of surrogate embryo transfer to those who obtained a license. Such limitation might increase costs and diminish access to the technology, but might also permit enhanced quality and controlled diffusion of the procedure. One of the arguments used in favor of patenting the process is that the research was privately sponsored, and so the investors merit a return on their investment (Chapman, 1984; Annas, 1984).

The example of in vitro fertilization technology shows that techniques developed in other countries can be imported, and such applications made available in the United States, even in the absence of Federal research support. Widespread clinical use of in vitro fertilization also shows that technologies whose appropriateness is seriously questioned may nevertheless enter clinical practice without extensive Federal oversight or regulation, and in the absence of pervasive public discussion.

Gene therapy is different from in vitro fertilization because there is no moratorium on gene therapy research, and so the bulk of research is funded, like other biomedical research, through the Federal government. Such research necessarily falls under the oversight purview of NIH, and consequently the RAC and its Human Gene Therapy Working Group. There are many agencies with jurisdiction over gene therapy, including local IRBs, NIH, and the FDA (for specific products). These bodies are now preparing to deal with the incremental medical advance embodied in *somatic* gene therapy. Review by these bodies may not be adequate for extension of gene therapy to reproductive cells. Several authors refer to the need for national public discussion of the greater ethical and social implications raised by *germ line* alterations before commencing such research (although the authors do not uniformly

suggest that such discussion necessarily take place through the Federal Government) (Fletcher, 1983b; Grobstein, 1984; Nightingale, 1984). The lack of a forum for conducting public debate holds also for fetal research and in vitro fertilization.

Human gene therapy may be less attractive to corporate investors than in vitro fertilization research. The investment incentives for gene therapy are diminished by the relatively small number of individuals with any given genetic disease. This restriction does not hold, however, for all diseases and does not necessarily preclude the development of profitable products. Gene therapy applicable to certain diseases such as sickle cell anemia or cystic fibrosis might have a market large enough to justify corporate interest. In addition, a general approach to gene therapy that could apply to many genetic disorders might be patented, analogous to the Cohen-Boyer patent for recombinant DNA, or kept as a trade secret. The incentives for private investment may thus be weaker than for in vitro fertilization, but may nonetheless be sufficient to induce corporate research and development.

There is a prominent regulatory difference between in vitro fertilization and human gene therapy: in vitro fertilization is not clearly under the jurisdiction of FDA or NIH, but human gene therapy is subject to both. Gene therapy is likely to involve new pharmaceutical products, and hence be regulated by FDA, because experiments will involve introduction of new genes or modified viruses into human cells or into patients. In contrast, in vitro fertilization is more a process than a product. Further, in vitro fertilization is applied to correct infertility, a problem that is not necessarily considered a disease or injury, and thus may not fall under FDA purview. In vitro fertilization has passed through the early phases of technological development to clinical application with little regulation or Federal oversight, but human gene therapy is receiving extensive public scrutiny and Federal oversight despite its technological infancy.

#### EARLY ATTEMPTS AT HUMAN GENE THERAPY

The Rogers Cases.—Between 1970 and 1973, Dr. Stanfield Rogers, an American, assisted a German physician in treating three sisters with the

genetic disease arginemia. The sisters were infected with the Shope papilloma virus, which had activities that physicians believed might supplement an enzyme activity missing in the three girls. The treatment was unsuccessful.

The Shope virus experiments were performed before ethics review boards, IRB's, or IBC's existed. The experiments were discussed openly, although much of the debate about their propriety did not take place until after the clinical trial. The debate centered on whether there was sufficient evidence to anticipate patient benefit, and whether the intervention had been undertaken at a time when it could best benefit the sisters (Fletcher, 1983). The ethical debate about the Shope virus experiments is thus unresolved, although it is clear that no institutional or legal precepts were violated.

The Cline Cases.—Martin Cline, an American scientist and physician primarily working at the University of California at Los Angeles (UCLA), became the first investigator to attempt gene therapy using recombinant DNA in 1980, when he attempted to treat two patients who had thalassemia. One patient was treated in Italy, and the other in Israel. Dr. Cline withdrew samples of bone marrow from each of the patients, treated them with DNA containing a normal hemoglobin protein gene, and restored the treated bone marrow cells to the patients. The process for returning the bone marrow involved killing a portion of the native cells by radiation, so that the treated cells would have a location in which to grow. The experiment was the first attempt at somatic gene therapy using recombinant DNA techniques.

At the time the experiments were performed, approval by the local review committees was pending. The gene therapy experiments were attempted on July 10 and July 15, 1980, and Dr. Cline's proposal to the UCLA Human Subject Protection Committee was disapproved on July 16 (Talbot, 1982). Dr. Cline had prior approval for a gene therapy experiment by the local board in Israel, but not for the one, involving recombinant DNA, that he actually performed.<sup>17</sup>

<sup>17</sup>The Israeli board had approved insertion of genetic material that included the normal hemoglobin protein genes. Dr. Cline contends that the use of recombinant form was a technical detail that did

In contrast to the Shope virus experiments, there was a consensus that Dr. Cline's experiments were premature and unethical. Dr. Cline resigned his division chairmanship, and the NIH terminated two grants. To prevent future abuses, NIH also added several requirements, including the need to submit an assurance of compliance with human subjects safeguards, prior review by the local IBC and NIH of all recombinant DNA experiments, and inclusion of the NIH report of the events to the review groups for his subsequent new applications for NIH grants (Talbot, 1982). The special sanctions were in effect until May 1984.

The issues raised by the Cline experiments are likely to recur in any debate about the propriety of human gene therapy, and so a summary of the justifications and objections is instructive, followed by a review of Federal policy in the Cline clinical trials.

There were several justifications for undertaking clinical trials of human gene therapy, as noted in previous sections. Those used to justify the experiments involving the patients with thalassemia included:

- The condition was irreversible.
- Alternative therapies were unpleasant, expensive, led to deleterious side effects, and did not cure the cause of the disease, but merely diminished its effects (Wade, 1980; Cline, 1982).
- The Human Subjects Protection and Institutional Biosafety Committees had been considering the proposals in the period between May 1979 and July 1980 without approving or disapproving them. There was also an apparent logjam, with the Human Subjects Committee requiring that the IBC approve the protocol before it would assess it, and the IBC awaiting the review of the Human Subjects committee. Attempts to refer the matter to the RAC were thwarted because NIH refused to consider the proposals, reasoning that the human subjects aspects were much more im-

not add to the danger of the experiments, because the genes tend to combine in the cell even if they are not in recombinant form when first inserted (Cline, 1982),

portant than the recombinant DNA technology itself (Wade, 1981a).

The Israeli experiments were approved by three committees in Israel, although not for the protocol involving *recombinant* DNA (Wade, 1981b).

Those who criticize the Cline experiments do not disagree with these facts, but interpret them differently, and add the following considerations:

- The patients selected had an irreversible disease, but were not in a terminal state (as called for in the protocol). They were alive more than two years after the experiments were undertaken, despite lack of any benefit deriving from the experiments (Cline, 1982).
- The human experiments were never published and were based on other animal experiments that had not been peer-reviewed at the time (and about which there are disagreements regarding interpretation) (Cline, 1982).
- There were no data on the safety of the procedure, because directly analogous experiments had not been attempted in animals (Williamson, 1982).
- Dr. Cline personally decided to deviate from his protocol, using a recombinant molecule rather than separated genes. While this decision may have been scientifically valid, Dr. Cline failed to notify the Israeli committees, committees in the United States, and even the patients and his collaborators, of his decision to use *recombinant* DNA (Wade, 1981a; Cline, 1982).
- The ambiguities about which committee should first approve the protocol had been resolved by the time the experiments took place. The decision to refrain from using recombinant DNA removed the need for IBC approval, leaving only the local Human Subjects Protection Committees to approve the protocol (Wade, 1980).
- The Human Subjects Protection Committee in the United States was not dallying, but awaiting expert comments from four consultants to assess the scientific basis of the experiments. The process took time, and the comments were passed on to Dr. Cline and

his collaborators as they were received; the investigators knew that there were objections to starting the experiments (Wade, 1980).

The issues raised by the controversial Cline experiments point out the importance of Federal research policy decisions. The research in question was funded, in large part, through NIH, and the review procedures for application to humans were specified by the NIH. The sanctions rendered against Dr. Cline were imposed by the Department of Health and Human Services, based on NIH review; many believe that one reason that the sanctions were relatively stringent was because of congressional concern about previous laxity on the part of NIH in punishing those who violated research guidelines (Sun, 1981; Wade, 1981 b).

Some of the consequences of the Cline experiments are less tangible than receipt or denial of grant applications. Many believe that the Cline experiments are one reason for the current prominence of gene therapy in the debate about recombinant DNA. Critics of the technology may cite Dr. Cline's experiment in arguing for tighter restraint on scientists because they cannot be trusted to behave responsibly (Wade, 1980).

A de facto moratorium on somatic and germ line gene therapy has reigned since 1980. The Cline experiments may have catalyzed formation of a consensus that the time was not ripe for such experiments (Walters, 1982), and the opprobrium directed at Dr. Cline may have made scientists aware of the public sensitivity of the issue. The case, above all, highlighted the changing milieu for making decisions about human subjects in clinical research, and the growth of research oversight by the Federal Government. The results have been summarized by John Fletcher, a specialist in bioethics at NIH:

Dr. Rogers treated the German sisters before prior group review became institutionalized. Dr. Cline, on the other hand, attempted to bypass that safeguard by withholding information from those who passed judgment on the wisdom of the experiment. The censure falling on Dr. Cline because of his deception indicates the strength of prior group review as a structure to guide somatic gene therapy when it becomes feasible (Fletcher, 1983b).