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Gene "Therapy": A Test Case for Research with Children

M. Therese Lysaught, Ph.D.

THE CULTURAL FACE of gene therapy is that of a child. The image of a child has served as the secular icon of the mystery and promises of human gene transfer since its inception in 1990.[1] The particular face of the child changes, determined by the message to be communicated. It is the face of Ashanti De Silva, her identity long obscured behind the veil of confidentiality, who at four years old was the first subject enrolled in a human gene transfer protocol with therapeutic intent. Her identity revealed after years in the protocol, she stands as a symbol of hope and promise. It is a countenance like that of Jacob Sontag, his worried face gracing the cover of the *New York Times Magazine*, drawing observers attention to the desperation of parents and faith in the salvific powers of human gene transfer.[2] It is the image of an Amish child, floating surreally in a vivid sea of ultraviolet light, pointing to the numinous power of human gene transfer and its ability to transcend the most intransigent of social boundaries.[3]

Those familiar with the history of human subjects research and the controversies surrounding recombinant DNA in the late 1970s and 1980s ought to find this iconography of particular interest. For it is a striking phenomenon: the emergence of an entirely new modality of clinical intervention, methods untested, risks unknown yet publicly feared, whose earliest human subjects were children.[4] Moreover, as iconic, these images often function to forestall critique, to displace argument, to garner public support—and public monies—for human gene transfer research.

Despite the high visibility of children in the development and justification of the field of human gene transfer, the topic remains an "orphan issue."[5] A full examination of the use of child subjects in human gene transfer research remains beyond the scope of this essay.[6] Such an account would attend to questions such as: How did this come to pass? What social, political, and/or rhetorical factors account for the fact that children were enrolled in human gene transfer so early in the development of such a controversial field, in fact in only the second clinical trial? How many children have been enrolled in clinical trials of human gene transfer? What have these trials entailed? How have these protocols fitted with the federal regulations and federal and professional policies governing the use of child subjects in research?

Two recent events suggest the timeliness of the investigation. First, there is increasing public pressure to enroll children as subjects in clinical trials. In November 1998, the Food and Drug Administration (FDA) announced a major change in the rules governing the process by which pharmaceutical companies will receive approval for new medications. As will be discussed below, this change requiring companies to submit data on the safety and effectiveness of new drugs and vaccines in children occurred largely as an effect of public, political, and professional pressure for a more aggressive and, some argued, a more just approach to developing therapies for fatal childhood diseases.[7] At the same time, however, questions are being raised about compliance with established guidelines and the effectiveness of public oversight of human gene transfer research. Following in the wake of the tragic and troubling death of Jesse Gelsinger at the University of Pennsylvania in September 1999, emerging findings suggest lack of compliance with enrollment criteria, failure to report of adverse events, and a deeply problematic informed-consent process.[8]

As a first step toward a broader examination of the role of child subjects in human gene transfer research, this essay will examine the tensive interface between federal and professional guidelines governing research with child subjects and research practice. Guidelines and oversight mechanisms exist; how are they interpreted, operationalized, and implemented? These questions will be examined by displaying one particular human gene transfer protocol—one that proposed to enroll HIV-positive children as subjects—as it negotiated the process of oversight and approval. Focusing on a particular protocol provides an opportunity for concrete display of the scientific, clinical, and political dimensions of human gene transfer research involving children. At the same time, it highlights both ambiguities in the guidelines

themselves as well as the tendency of research practice to challenge straightforward criteria. In order to provide a framework with which to examine the protocol, I begin with a brief history and overview of current regulations and policies governing research with children as human subjects.

Children as Research Subjects: Federal Regulations and Policy

Two competing and legitimate tensions govern the question of whether and how to conduct research with children. On the one hand, the historical witness of the abuse of vulnerable human subjects within the U.S. medical system, especially in conjunction with government involvement, has justifiably led to a protectionist stance toward research involving children.[9] Conservative, cautious safeguards are necessary to protect children, who cannot consent and who may experience the burdens of medical intervention as more frightening and excruciating than adults, from being unduly exploited by the interests of researchers, the desperation of their parents, and the relentless momentum of the research imperative. As the recent FDA ruling suggests, however, the legitimate need to safeguard particular children must be balanced with the interests of justice, particularly the need to advance the medical care of children. These tensions inform current federal and professional regulations and policy concerning research involving children.[10]

The history of the federal regulations governing research on children reflects the concern to protect child subjects. Public concern over the cases mentioned above led in part to the congressional institution, in 1974, of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In the same year, the Department of Health, Education and Welfare (DHEW; now known as the Department of Health and Human Services, DHHS) issued its first regulations for the protection of human subjects in research.[11] The first DHEW/DHHS regulations covering research involving children appeared in 1978.[12] Following the counsel of the 1977 report *Research Involving Children* published by the National Commission for the Protection of Human Subjects in

Biomedical and Behavioral Research,[13] the DHHS published its final regulations, providing "additional protections for children involved as subjects in research" on March 8, 1983. These regulations became effective on June 5, 1983, codified as 45 CFR 46, Subpart D.[14]

The precepts of Subpart D have guided research on children for the past sixteen years. These precepts distinguish five categories of research to clarify when children may be enrolled as research subjects. These categories are:[15]

§46.401 [Exempt research].

§46.404 Research not involving greater than minimal risk.

§46.405 Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

§46.407 Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

As is evident from even a brief scan of these categories, the anchoring concept of the regulations is the concept of risk, articulated operationally as "minimal risk." Only once the level of risk is established may deliberations regarding the acceptability of enrolling children move to assessing the prospect of benefit; correlatively, should risk be minimal or less, the notion of benefit to individual child subjects becomes irrelevant. As Janofsky and Starfield note: "only if the IRB determines that a proposed project will in fact entail greater than minimal risk must its members additionally address other issues, such as whether there is prospect of direct benefit to individual subjects. . . . Thus, decisions about risk must be made separately from and before any consideration of possible benefit is judged."[16]

"Minimal risk" is defined earlier in the federal regulations as follows: "'Minimal risk' means that the risks anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (§46.102G)"[17]

The definition for "greater than minimal risk" emerges from §46.406. Research that entails "greater than minimal risk" may be permitted in certain situations, but limits are still set: "The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations."

As will be argued below, human gene transfer protocols proposed to date fall clearly entail "greater than minimal risk" and so must be considered under §§46.405, 46.406, or 46.407.

But as anyone who has sat on an institutional review board (IRB) knows well, determining how to categorize a specific protocol is more an art than a science. For it is in the concrete negotiations of IRB approval that the concern for protectionism competes with the legitimate need to conduct research on children. Even before Subpart D was issued, pediatricians argued that restricting research with children would compromise pediatric medical care. As early as 1968, H. C. Shirkey coined the term "therapeutic orphan," arguing that a reluctance to test the safety and efficacy of drugs on children could dangerously inhibit the development of needed pharmaceutical interventions for children, handicapping pediatric medicine.[18]

Shirkey's concerns were not unfounded. As the Committee on Drugs of the American Academy of Pediatrics (AAP) recently reported:

> A survey of the 1973 *Physician's Desk Reference* revealed that prescribing information for 78% of medications included a disclaimer or lack of dose information for use by children. A subsequent survey of the 1991 *Physician's Desk Reference* showed that 81% of listed drugs contained language disclaiming use in children or restricting use to certain age groups. A survey of new molecular entities approved by the Food and Drug Administration (FDA) from 1984 through 1989 revealed that 80% were approved without labeling for children. In 1992, 19 new molecular entities with potential use in children were approved by the FDA; 79% of these drugs were not labeled for use in children. In most instances drugs are not labeled for use in children because sufficient studies have not been conducted in children.[19]

Adult studies, however, are not sufficient. As Grodin and Alpert note: "children are not little adults."[20] The AAP concurs:

> Growth, differentiation, and maturation can alter the kinetics, end organ responses, and toxicities of drugs in the newborn, infant, child, or adolescent compared to the adult. Drug studies in adult humans may not adequately predict the pharmacokinetic, pharmacodynamic, or toxic properties of drugs in children. When drugs have been administered to children without sufficient pharmacology studies to identify the optimal therapeutic approach, children have occasionally suffered severe toxic effects, including death. These toxic effects could have been avoided with some of the drugs if appropriate drug studies had been undertaken before their widespread use in children.[21]

Given these significant physiological issues, coupled with the crisis in the pharmacological armamentarium, the AAP calls for children to be included "in clinical studies of a drug when the drug offers potential benefits to them."[22]

The recommendation of the AAP recently became public policy. Public pressure, channeled through the lobbying power of Congress and the Clinton White House, led to the recent issue of the National Institutes of Health (NIH) Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. Effective October 1, 1998, the purpose of the policy is explicit: "to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children."[23] The policy holds as follows:

> It is the policy of the NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted by the NIH, unless there are scientific and ethical reasons not to include them . . . proposals for research involving human subjects must include a description of plans for including children. If children will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion. . . . The inclusion of children as subjects in research must be in compliance with all applicable subparts of 45 CFR 46 as well as with other pertinent federal laws and regulations.

Following the lead of the NIH, on November 27, 1998, the FDA issued new rules (effective April 1, 1999) requiring pharmaceutical companies seeking FDA approval for new drugs and vaccines to submit data on the safety and effectiveness of these modalities in children "if the product is likely to be used in a substantial number of pediatric patients" or if it provides a "meaningful therapeutic benefit" over existing treatments for children of similar ages.[24] The FDA guidelines, as

might be expected, met with strenuous objections from drug companies, who deemed them "impractical and burdensome," costly, and, surprisingly, "unethical, because they might put children at risk."

In the near term, then, it seems that the balance between protectionism and expansionism is shifting toward those who advocate increased involvement of children in biomedical research. Yet even those who recognize the need for research with children recognize that requirements for the inclusion of children might place children at an unacceptable risk. In light of this, a consensus has emerged among federal, professional, and academic commentators alike confirming a long-standing precept in research with child subjects: the necessary priority of research on adults. A survey of statements reveals this consensus.

The 1998 NIH policy outlines a series of seven "justifications for exclusions" by which researchers might legitimately avoid the requirement to conduct studies on children. Of these, the fifth is most pertinent to our discussion.

> 5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.

This caveat first appears in the National Commission's report, where Recommendation 2B states:

> Where appropriate, studies have been conducted first on animals and adult humans, then on older children, prior to involving infants. . . . Whenever possible, research involving risk should be conducted first on animals and adult humans in order to ascertain the degree of risk and the likelihood of generating useful knowledge. Sometimes this is not relevant or possible, as when the research is designed to study disorders or functions that have no parallel in animals or adults. In such cases, studies involving risk should be initiated on older children to the extent feasible prior to including infants, because older children are less vulnerable and they are better able to understand and to assent to participation. In addition, they are more able to communicate about any physical or psychological effects of such participation.[25]

As Robert Levine notes in his commentary on the report, "Investigators who proposed to do research on children without having first done such research on animals and/or adults will be obligated to persuade the IRB that this is necessary. Suitable justification might be that the disorder or function to be studied has no parallel in animals or adults."[26]

Although this recommendation was not included specifically as a regulation in Subpart D, the DHHS states in the Preamble to the 1983 regulations that it expects this recommendation to be followed.[27] In their 1994 work *Children as Research Subjects*, Michael A. Grodin and Leonard H. Glantz propose a set of "Points to Consider in Proposing or Reviewing Research Involving Children." The first of these points asks the following questions:

> 1. Is the use of children as research subjects justified in this instance?
>
> (b) if the research question can be addressed first in adults, has research with adults been conducted?
>
> (c) has the adult research produced results that would indicate that the proposed research would benefit, or not be harmful to, the children?[28]

Finally, the AAP concurs: "In most cases, studies in children should be preceded by initial clinical trials in adults to provide preliminary pharmacokinetic, safety, and efficacy data. In some instances, drugs intended to treat specific diseases that primarily or exclusively occur in children may be studied initially in children."[29]

This prioritization is reflected in the commentary on the regulations found in the *IRB Guidebook* published by the NIH's Office for Protection from Research Risks (OPRR):

> Phase 1 Trials. The issue of Phase 1 drug studies deserves special consideration. The usual approach to designing drug studies involving children as subjects is for appropriate studies to be conducted first in animals, adults, and older children before young children are involved as research subjects. There are some studies, however, in which data may not be entirely generalizable from older populations, and in which the existence of life-threatening conditions for children are important considerations in the IRB's risk/benefit analysis. The requirement for previous testing in adults or older children may thus not be appropriate. Furthermore, some diseases specific to children

> may require that children be involved without data from older groups (e.g., there is no adult model that mimics the state of HIV-infected newborns; Wilms' tumor and various cancers such as neuroblastoma affect infants who do not survive into older childhood). In some cases "tandem" studies in older populations and children may be justifiable. For example, some Phase 1 studies in children might be based on only pharmacologic safety and toxicity data (completed Phase 1 and ongoing Phase 2) but without complete effectiveness data from trials in adults and older children. If the IRB approves a Phase 1 drug trial, the consent document must specify what is known about the probability that, and the degree to which, an intervention will be of possible benefit based on all of these data.[30]

Note here the meaning of "tandem studies" as used by the OPRR: researchers are to initiate Phase I trials in children when Phase I trials have been concluded in adults and adult research has moved to Phase II trials. As we will see, this is an important caveat vis-à-vis human gene transfer research, given that almost all human gene transfer clinical trials to date have been Phase I trials.

Children and Human Gene Transfer Research: The HIV Protocol

While these guidelines may seem relatively straightforward and seem to provide a well-crafted, prudent, and thoughtful balance between protectionism and the legitimate need to enroll children in clinical trials, in practice their application is much more contested. Key terms and criteria of the guidelines are ambiguous to the point of admitting what seems like almost any interpretation. What counts as "minimal risk" or, if that can be established, a "minor increment" over minimal risk? What constitutes a "prospect" of benefit? Is this different from a "possibility," a "hope," an "intention"? How important must knowledge be to be "vital"? While common sense might provide relatively straightforward answers to these questions in the context of a particular protocol, clinical experience may often lead investigators to assess notions such as "risk," "prospect," and urgency differently. In cases where the guidelines are so clear as to raise questions about a particular research endeavor on ethical grounds, reviewers and committees often find themselves assailed with charges of

ignorance or obstructionism, or worse, the ultimate argument stopper, with imperiling the lives of dying children.

Clearly, these issues are not unique to human gene transfer research. The concrete display of the applicability of these guidelines in the context of a human gene transfer protocol, however, simultaneously illumines issues surrounding the guidelines and issues surrounding the conduct of human gene transfer research. For the purposes of this essay, I will focus on a protocol for a Phase I trial entitled: "Transduction of CD34(+) Cells from the Bone Marrow of HIV-1 Infected Children: Comparative Marking by an RRE Decoy Gene and a Neutral Gene."[31] An analysis of the protocol in light of the guidelines as well as a partial narrative of its progress through the review process will highlights the issues identified above.

I was first asked to review this protocol as part of the consolidated review process by the Recombinant DNA Advisory Committee of the National Institutes of Health (RAC) in November 1995.[32] My charge was to determine whether or not the protocol could be approved through consolidated review or whether it warranted review by the entire committee at one of its quarterly meetings.[33]

In this protocol, the investigator proposed to enroll five HIV-1-positive children between the ages of three and eighteen.[34] Through the protocol, the researchers sought to "determine whether the transduced CD34+ cells engrafted and produced peripheral blood leukocytes [T cells and their progenitors] that would have a selective survival advantage." The researchers hypothesized that the transduced gene would make the T cells resistant to HIV infection; they would then produce offspring T cells that would be likewise resistant to infection. Such resistance might, in theory, slow progression of the disease course.

The protocol proposed to subject the child subjects to the following clinical procedures:

- inclusion assessments, including phlebotomy, electroencephalogram, electrocardiogram, and chest X ray;
- bone marrow aspirate to obtain cells for stromal growth;
- preoperative screening assay;
- bone marrow harvest under general anesthesia (10–15 cc/kg);

- cell transduction: CD34+ T lymphocytes were to be isolated and transduced with two different retroviral vectors, one an anti-HIV-1 gene (L-RRE-neo) and the other a neutral marking gene (LN);
- infusion of transduced cells;
- overnight hospitalization;
- post-"treatment" assays, including phlebotomy (approximately ten over a two-year period); and
- a possible additional one or two bone marrow aspirates.

In my (albeit brief) history with the RAC at this point, it seemed clear that this protocol raised certain flags that might ordinarily have triggered the full review process:

It was the first anti-HIV protocol presented to the RAC that proposed to use children as research subjects. Generally, new diseases or new study populations would automatically trigger full RAC review. Four protocols following a similar strategy of intracellular replication inhibition for CD4+ or CD34+ cells had been approved for Phase I clinical trials in adults (9309–057, 9503–103, 9508–117, and 9511–134); three had just been approved in 1995 (March, August, and November respectively). None had yet issued data. None was referenced in the protocol. Hence, while the RAC had reviewed HIV protocols, it had not reviewed an HIV protocol involving children.

None had used this particular retroviral vector construct. Generally, new vectors would trigger full RAC review. A similar RRE decoy vector had been proposed in the adult protocol approved in November (9511–134). Other protocols had used a similar strategy of intracellular replication inhibition of CD34+ or CD4+ lymphocytes of HIV-positive patients. But the vector proposed here was a new construct.

No animal studies were referenced. This would not have been an unusual situation in and of itself. Many human gene transfer protocols at this point cited the lack of availability of good animal models. Human HIV is notorious for lack of a good animal model. However, this issue was not addressed in the protocol.

The first of these two flags would have served as a sufficient trigger for many protocols reviewed by the full committee. However, reading the protocol against the background of the federal guidelines for research on children raised a host of other issues that seemed worthy

of fuller discussion. While a complete review of the protocol is beyond the constraints of this essay, three areas are worthy of highlight: the degree of risk presented to child subjects by the protocol; the "prospect" of benefit to the child subjects; and the lack of adult data.

As discussed above, the key concept anchoring the federal guidelines is the nature and degree of risk presented to the child subjects by the protocol. Risk assessment for child subjects must take into account not only risks of physical harm but nonphysical "burdens" the subjects will bear as well. In the case of children, these "burdens" take on greater weight, as children cannot truly consent to bear them. Hence, the determination of risks and burdens for this particular protocol would be required to address at least the following:

- the spectrum of preinclusion, preoperative, and follow-up screening procedures;
- the risks associated with sedation and general anesthesia in children and specifically in HIV-positive children;
- the risks associated with the bone marrow harvest procedure—risks of hemorrhage or infection during or after the procedure; risks of osteomyelitis; the possibility that small children might require postharvest blood transfusions to replace blood and marrow lost during the harvest;
- the burden of additional hospitalization and additional medicalization of the lives of these children, including at least two overnight hospitalizations and at least ten follow-up visits;
- the risks and burdens of one bone marrow aspiration with the possibility of one to two additional aspirations;
- the risks associated with the reinfusion of the genetically modified cells, including (as stated in the consent form, Protocol p. 55) "fever, chills, difficult breathing, and rarely, a severe allergic reaction that can lead to death";
- the standard risks associated with human gene transfer, including unpredicted vector integration leading to cancer and germ-line issues.

Given this list, one begins with the question: Does this protocol entail "greater than minimal risk"? For the risks to be categorized as "minimal," as noted above, "the risks anticipated in the proposed

research [must not be] not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Would the above present experiences that these particular children would likely encounter in daily life or in the course of routine examinations? Clearly not. Hence a relatively easy assessment is made that this protocol presents "greater than minimal risk." If so, it must be considered under §§45 CFR 405, 406, or 407.

§45 CFR 405, as noted above, raises the question of "prospect" of benefit. If the risks presented by the protocol are deemed "greater than minimal," research is approvable if it can be demonstrated that there is a "prospect of direct benefit to the individual subjects." As the guidelines note: "The risk is justified by the *anticipated* benefit to the subjects; and the relation of the *anticipated* benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches."

Therefore, to justify the more than minimal risk and burden, the investigators in this case must be able to demonstrate that there is a reasonable "prospect of direct benefit" to the child subjects to be enrolled, that benefits are *anticipated.*

What sort of case did the investigators present? When turning to the text of the protocol itself, one finds some rather clear clues:

> Although *we do not think that this initial study is likely to have a significant medical benefit for the patient,* we believe that it is safe and may provide useful information for progressing to potential beneficial treatments for AIDS. (Emphasis mine; Protocol, nontechnical abstract; similar statement included in the scientific abstract.)

> While this relatively low-risk protocol is *not likely to have significant clinical benefit,* it may provide useful information on the feasibility and potential efficacy of this approach. Positive results in this study may allow consideration of future studies entailing higher risks but higher potential benefits. (Emphasis mine; Protocol, p. 30.)

> Although patients will have routine monitoring of the disease status performed as part of their standard clinical care, it is not a primary endpoint of the study. (Protocol, p. 25.)

The protocol is relatively clear that *no benefit* is anticipated to accrue to the child subjects. Moreover, the protocol was submitted as a Phase I clinical trial, which by definition is not designed to offer benefit.

The audience, however, makes a difference in how the case is presented. When the investigators turn to address the RAC directly, the above disavowals of anticipation and prospect of clinical benefit are offset with a disclaimer about theoretical possibilities:

> While the *possibility* of benefit from the protocol is *unknown,* the *potential* benefits *could be significant.* Slowing or preventing immunologic deterioration could be life-extending or even *life-saving.* (Emphasis mine; Response to NIH "Points to Consider," M-II-A-1, p. 23.)

> In this Phase I study, *it is not known* whether the subjects will receive any benefits. The major goal of the study is to determine if this gene therapy approach is safe and feasible in patients with HIV infection. It is possible that the presence of the RRE decoy gene in some blood cells will allow them to avoid active infection by HIV. This could help maintain immune function and lessen the risk of infection. . . . While we have attempted to not overstate this possibility, it certainly is *hoped* by the investigators that this would be the result. (Emphasis mine; Response to NIH "Points to Consider," M-II-3, p. 26.)

Here, theory takes the place of evidence; hope has replaced warranted anticipation.

A similar shift in rhetoric appears in the Informed Consent form. Here the emphasis on the positive possibilities becomes even more pronounced. The first sentences of the consent form state:

> You/your child [are]/is infected with human immunodeficiency virus (HIV) and are/is eligible to participate in a medical study of gene therapy as a possible *treatment.* A possible form of *treatment* for HIV is gene therapy, where a new gene is put into a patient's cells. . . . If the RRE decoy can bind the HIV protein, *it might prevent the virus from growing in the body.* (Emphasis mine; Protocol, Informed Consent Form, p. 49.)

> It is *not known* whether gene therapy for HIV will be effective. It may be difficult to get the gene into patient's bone marrow stem cells, the gene may not be turned-on in the cells in the body, or the gene may not actually protect the cells. The purpose of this study is to test whether gene therapy with the RRE decoy gene can be performed safely, whether it can get the RRE decoy gene into the cells and whether the RRE decoy gene will inhibit HIV infection of cells. (Emphasis mine; Protocol, Informed Consent Form, p. 50.)

The "Potential Benefits" section of the consent form includes this less optimistic assessment, but alters it significantly with the closing qualification:

> We *do not know* if there will be any direct benefits to you/your child from participating in the study. The major goal of the study is to determine if this gene therapy approach is safe and feasible in patients with HIV infection. . . . If the RRE decoy gene were present in sufficient numbers of cells, *this could help maintain immune function and lessen the risk of infection.* (Emphasis mine; Protocol, Informed Consent Form, p. 51.)

The therapeutic possibilities dangle before the eyes of parents with HIV-stricken children. What parent would not provide their child with this chance?

The institutional IRB noted the ambiguity in this language and that the data did not support the claim to *prospect, probability,* or *likelihood* of benefit. For this reason, upon its initial review, the IRB provided a lengthy critique of the protocol and deferred it.[35]

The investigators made two responses to this critique. First, they pointed to the more positive statements above and argued that "there is *possibility* of direct benefit to the subjects, *if* the hypotheses being tested are found to be correct" (emphasis mine; Protocol, Investigator's Response to IRB, p. 15). The members of the IRB noted that there were a number of "ifs" that would have to occur for possibility to accrue. The investigator notes that he and his colleagues "certainly hope" that this would be the result. However, as Kathryn Whartenby of the FDA noted in her recommendation that this protocol receive full RAC review, there is little proof to substantiate this statement or this hope.[36] In fact, some of the data presented in the protocol seems to argue against clinical benefit.[37]

Secondly, the investigator argued that in the nontechnical abstract, he "thought it best to be pessimistic to not recruit patients with false claims" (Response from Investigator, p. 6).[38] This statement seems difficult to reconcile with the qualified-but-optimistic rhetoric in the informed consent form. In other words, when addressing the scientific community, the investigator seems to be more pessimistic and realistic, acknowledging that the potential benefits of this research will accrue not to the child subjects themselves but to progress in the battle against AIDS. When addressing reviewers and prospective parents, however, realism gives way to hope.

However, even though the "prospect" and "possibility" of direct benefit to enrolled child subjects may have been remote in this case, the research might still have been approvable under §46.406, which allows for "research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition." Again, a number of conditions obtain:

> The risk represents a *minor* increase over minimal risk;
>
> The intervention or procedure presents experiences to subjects that are *reasonably commensurate* with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; *and*
>
> The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition, which is of *vital importance* for the understanding or amelioration of the subjects' disorder or condition. (Emphasis mine; §46.406.)

Here again, the open-ended nature of the terms used in the guidelines leaves room for debate and disagreement. The easiest of these criteria would be the second. It seems relatively clear that the procedures proposed in the protocol, namely, bone marrow aspirates and bone marrow harvest under general anesthesia, would not normally be encountered by HIV-positive children in the course of treatment for their disease. Thus the procedures would not be "reasonably commensurate."

Would the protocol, however, present only a "minor" increase over minimal risk? Here the guidelines become the most ambiguous and have generated the most debate. The investigators argued, for example, that the procedures did indeed represent only "a minor increase over minimal risk" (Response of Investigators to RAC Review, p. 3) and that "the risks and discomforts are relatively minor" (Response of Investigators, p. 12). In response to critiques, the investigator stated that since the bone marrow aspirations are performed under conscious sedation, they are "not significantly more painful than having a phlebotomy," and that children undergoing bone marrow harvests under general anesthesia "have minimal pain post-operatively" (Response of Investigators, p. 3).

As Janofsky and Starfield have noted, clinical experience certainly shapes one's assessment of the magnitude and possibility of clinical risk.[39] These investigators had performed many bone marrow procedures

on children and experienced no adverse events; hence their assessment of the procedures would differ radically from, say, a layperson like myself reading about the procedures.[40]

The third and final criterion of §46.406 is that research entailing greater-than-minimal risk without prospect of benefit to the child subject should provide generalizable knowledge of *vital* importance for the understanding or amelioration of the subject's condition or disorder. But given the improbability of benefit, it was not clear to me how the scientific and molecular findings from this trial would be of "vital" importance to the amelioration of pediatric HIV. How ought this be assessed? According to what criteria? Or is it the case that any findings relative to a terrible disease with certain mortality in children count as "vital," that is, that it is the nature of the disease rather than the nature of the scientific findings that characterizes knowledge as vital?

Clearly, the nature and seriousness of pediatric HIV requires that research be conducted, research that will at some point require enrollment of child subjects, perhaps earlier in the research process than might be otherwise encouraged. However, as the NIH documents on inclusion of children note, "their participation earlier [must be] based on careful risk and benefit analysis."

While physiological differences between children and adults reduce the usefulness of adult models for understanding pediatric HIV, it was not clear that there were no points of contact. Would none of the data from the Phase I adult HIV human gene transfer trials be generalizable to pediatric populations? Or might some of the findings provide at least a modicum of insight? In other words, it seemed that certain research questions might be addressable in adults or other populations.[41] The trials approved by the RAC, however, had not yet had time to be initiated nor had they produced any published findings. This situation seemed to meet well the recent NIH exclusion criterion: "Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment)."

These seemed to be the key questions, and questions on which I wished to have more counsel. However, since the conjunction joining the three criteria given for §46.406 is an "and," it seemed questionable to me that this protocol could be justified under this category.[42]

If §46.406 remained an open question, §46.407 remained an option. Here the guidelines provide a mechanism for "Research not

otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children." Such research might be approved by "the Secretary [for Health and Human Services], after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law), and following opportunity for public review and comment." RAC review would be the ideal vehicle for such consultation.

This, then, was the modest conclusion that I reached in my review: since the arguments for justification under §46.405 and §46.406 remained debatable, the protocol seemed a good candidate for the standard process of full RAC review. Extended consideration by a panel of persons with diverse expertise would help to settle the scientific and ethical questions. I consequently recommended, on December 4, that the protocol ought not be exempted from full RAC review. As the RAC was meeting on December 4 and 5, 1995, the protocol would be considered at the RAC's next meeting, in March 1996.

This recommendation, however, was declined, an artifact equally of challenge to the guidelines and of political circumstances.[43] The March 1996 meeting of the RAC was canceled ostensibly because of "lack of protocols to review"; clearly, by early February, the decision had been made to approve the protocol. In early spring, the then-director of the Office of Recombinant DNA Activity (ORDA) announced that he was retiring from the NIH to accept a position with the Institute for Human Gene Therapy at the University of Pennsylvania. The June meeting of the RAC was likewise canceled. In May, Harold Varmus, then-director of the NIH itself, unilaterally disbanded the RAC, an action that met with controversy—approbation from some and outrage from others. In light of public response, the RAC was later reconstituted, but in a significantly reconfigured form. When it met again in December 1996, its authority to recommend approval or disapproval of protocols had been stripped.

Human Gene Transfer Research and Child Subjects: A Critical Juncture

The preceding analysis and narrative is not presented to suggest that the circumstances surrounding this particular protocol have been typical of

RAC approval of human gene transfer trials involving children. Nonetheless, the history of this protocol, when read in light of the guidelines governing human subjects research with children, raises a number of questions for both research with children in general and the field of human gene transfer research specifically.

With regard to the federal guidelines and professional policies, this particular protocol provides additional evidence for the increasingly perceived disjunction between well-crafted research guidelines and their actual implementation in the clinical research setting. Part of this disjunction stems, no doubt, from the fluidity of terms and criteria contained in the guidelines. Certainly, given the open-ended and creative nature of clinical research, guidelines governing research with human subjects ought to admit of some openness to interpretation. But the regression of interpretability ought not be infinite.

As the U.S. research industry moves toward increased enrollment of children in clinical trials, we must seriously consider how useful the federal guidelines will prove in ensuring that the interests of individual subjects are not sacrificed for the good of future children. This is especially urgent for children enrolled in Phase I protocols or children enrolled as controls, where only risks await them. It clearly falls within the purview of the oversight and ethics community to create clarity and consensus as far as possible. The National Bioethics Advisory Commission (NBAC) or OPRR need to provide guidance to IRBs—which are sometimes plagued with inexperience and at other times faced with institutional pressure—with regard to the interpretation and implementation of key terms and criteria. Research ought to be conducted in the near term to elaborate acceptable boundaries for interpreting phrases such as "greater than minimal risk," "minor increment," "prospect of benefit," and "vital knowledge." These agencies ought to provide criteria for distinguishing between a benefit that is "anticipated" or "likely" and one that is simply "possible," "hoped for," or "intended."

Such clarification would also serve to address a problem endemic to the practice of clinical research in general, but especially troubling with regard to research with children—the deeply problematic conflation of "research" and "treatment."[44] Phase I trials, contrary to the language used in the informed consent document of the HIV protocol above, ought not be classified as "treatment." These endeavors are strictly scientific experiments, designed to test scientific end points

and to assess the toxicity of the compounds being administered. The situation is clearly different with Phase II and Phase III clinical trials, the kind specifically called for by the recent NIH and FDA rulings. Here, the regulatory agencies require pharmaceutical companies to provide dosing and safety information for moieties already proven efficacious in adults. In these instances, the word "treatment" might more reasonably be used in conjunction with the word "experiment." In both cases, however, the OPRR ought to provide guidance to investigators and IRBs on the appropriate language to use in the informed consent process (both the written and the face-to-face components) as well as how to warrant "prospect" of benefit in the case of radically new interventions. The new push to increase child enrollment in clinical trials, the political pressure exerted by parents on regulatory bodies to allow dying children the "right" to be enrolled, and the increased financial power of the biotechnology industry converge to make these issues urgent; unless they are addressed in the near terms, current guidelines may prove to be little more than formalities sacrificed to expediency or desperation.

These issues remain especially urgent for the field of human gene transfer research. The review of the HIV protocol, however, points to an additional set of questions specific to the field. The HIV protocol and the events surrounding the existence and purview of the RAC from 1996 forward provided preludes to the sobering findings that emerged from the Gelsinger case:

- a cavalier and obstructionist attitude on the part of industry and many researchers toward ethical guidelines and broader oversight of research practice;[45]
- the fact that human gene transfer remains a fledgling field in which much basic research remains to be done;[46]
- the fact that the risks of known methods of human gene transfer have perhaps been underreported or downplayed;[47]
- the fact that risks of effective methods of human gene transfer remain largely unknown;
- the fact that human gene transfer's therapeutic promise remains sadly unfulfilled ten years after initiation of the first protocol.

Much more basic research needs to be done in order to understand the diverse molecular mechanisms governing the array of disorders potentially amenable to gene transfer technologies. Ironically, it was just at the juncture when this conclusion was first publicly stated that the power of public oversight of human gene transfer research was disabled.[48] One of the main reasons given for disbanding the RAC in 1996 was that it attended too much to issues of ethics; as Harold Varmus stated: "the RAC had begun to exhibit a taste for *trivia:* it often got bogged down in debates over the wording of patient consent forms."[49] Perhaps it is the case, however, that issues of patient well-being and the protection of human subjects are not quite so trivial after all.

Moreover, the HIV protocol points to a global question with regard to the field of human gene transfer as a whole. It was a Phase I protocol. Almost all of the human gene transfer protocols initiated to date, whether with adult subjects or child subjects, have likewise been Phase I studies. The first human gene transfer protocol began May 22, 1989. It was a "marking" protocol that accompanied an immunotherapy study in adult patients with metastatic melanoma with a life expectancy estimated at up to 90 days. By definition, long-term risks would be impossible to assess in this population. On February 5, 1990, the investigators presented preliminary data from five of the first six patients treated to that point. The second protocol, the famous SCID-ADA protocol, was approved by the RAC on July 31, 1990, and enrolled its first patient on September 14, 1990.

This situation and the significant participation of children in the early days of human gene transfer return us to one of the few points of agreement noted earlier between those who hold a protectionist stance on the issue of research on children and those who advocate a more expansionist approach: Phase I trials in children ought to be initiated only after Phase I trials in adults have provided important indications on both safety and efficacy. Had sufficient research been conducted by 1990 or 1993 to assess the risks that might be presented to child subjects? Was there sufficient evidence in this phase to substantiate "prospect" of benefit from adult studies?

These are larger questions than can be entertained here. Clearly severe combined immunodeficiency (SCID), neuroblastoma, some of the leukemias studied, as well as the single-gene disorders, are serious childhood illnesses. They have no parallel in adults. But this alone does

not warrant their further subjection to experimentation.[50] Human gene transfer as a proposed therapeutic modality is, as the bulk of the protocols and the general rhetoric surrounding genetic intervention witnesses, an intervention with potential application to a broad range of diseases that afflict adults as well as children. A number of the research questions faced by early researchers in human gene transfer could have been answered by adult studies. Hence human gene transfer seems a logical candidate for OPRR's proposal for "tandem" research:

> In some cases "tandem" studies in older populations and children may be justifiable. For example, some Phase 1 studies in children might be based on only pharmacologic safety and toxicity data (completed Phase 1 and ongoing Phase 2) but without complete effectiveness data from trials in adults and older children. If the IRB approves a Phase 1 drug trial, the consent document must specify what is known about the probability that, and the degree to which, an intervention will be of possible benefit based on all of these data.[51]

This, however, was not the route chosen by the field of human gene transfer. Hence we remain faced with an important question: How was it that this new, untried, and controversial research endeavor moved so quickly to the use of children as subjects?

The preliminary answer, I will hazard at this point, is as much a matter of the sociopolitical context of NIH-funded research as it is a matter of clinical science. Is it a coincidence that the Human Genome Project and the field of human gene transfer research, whose icon was a vulnerable child suffering from an incurable disease, were launched almost simultaneously? The elaboration of that answer must await another day.

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NOTES

1. As Larry Churchill, et al., argue in "Genetic Research as Therapy: Implications of 'Gene Therapy' for Informed Consent," *Journal of Law, Medicine, & Ethics* 26:1 (1998):38–47, the phrase gene "therapy" often serves rhetorically to mask the fact that human gene transfer interventions ought properly to be classified as research. See also my response, "Commentary: Reconstruing Genetic Research as Research," *Journal of Law, Medicine, & Ethics* 26:1 (1998):48–54.

2. Michael Winerip, "Fighting for Jacob," *New York Times Magazine* (December 6, 1998), recounts the story of Richard and Jordana Sontag, who fought an emotionally excruciating political and PR battle to enroll Jacob, afflicted with Canavan disease, in a disputed clinical trial of human gene transfer.

3. Denise Grady, "At Gene Therapy's Frontier, the Amish Build a Clinic," *New York Times* (June 29, 1999). Grady reports here on a planned clinical trial that would enroll three Amish children in a human gene transfer protocol designed to address Crigler-Najjar syndrome, a deadly autosomal recessive disorder caused by the lack of a liver enzyme required for removing bilirubin from the blood. Affected children, of whom there is a disproportionately high population within Pennsylvania Amish communities due to their habits of intermarriage, currently combat the syndrome with high-tech light therapy. The images are most striking.

4. A retrospective study of human gene transfer protocols with child subjects (see note 7) reveals that children were the intended subjects of 50 percent of the protocols in 1990 and of 50 to 63 percent of approved protocols in 1991 (depending on the age limits used to define "child"). This percentage dropped in 1992 as the overall number of protocols approved began to climb, but overall, in 1992, the total percentage of protocols enrolling children remained at 33 percent. This figure eventually leveled off and stabilized at around 20 percent.

5. Only two articles to date come close to this issue. The first, by John C. Fletcher, "Ethical Issues in and beyond Prospective Clinical Trials of Human Gene Therapy," *Journal of Medicine and Philosophy* 10 (1985):293–309, questions the wisdom of enrolling terminally ill children in the first trials because desperation may be used to justify unreasonable risk. This article was written, however, five years before the first trial commenced. The second piece seems that it would come close to this issue, given where it appears. This is Nancy Ondrusek, "Ethical Issues in Gene Therapy," in *Ethics in Pediatric Research*, ed. Gideon Koren (Malabar, Fl.: Krieger Publishing, 1993), 155–70. However, Ondrusek's essay is simply a standard overview of ethical issues in human gene transfer research; she gives little attention to the issue of children as subjects.

6. Such a full examination is under way. Spurred by the events surrounding the RAC in 1996, I embarked on a retrospective study of human gene transfer research involving children. This study is currently ongoing. At this point, we have obtained copies of the approximately thirty protocols involving children approved by the RAC from 1989 to 1996 (the point of its hiatus) and are in the process of conducting a qualitative review of these protocols in light of the federal regulations governing research with children.

7. Robert Pear, "F.D.A. Will Require Companies to Test Drugs on Children," *New York Times* (November 28, 1998). The NIH issued a similar policy, effective October 1998; see *NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects*, available from http://grants.nih.gov/grants/guide/notice-files/not98–024.html.

8. An eighteen-year-old subject in a clinical trial targeting ornithine transcarbamylase deficiency, Jesse Gelsinger, being under twenty-one years of age, would have qualified as a "child subject" according to certain guidelines. For an account of the findings of the initial inquiry at the December 8–9, 1999, meeting of the RAC, see Sheryl Gay Stolberg, "F.D.A. Officials Fault Penn Team in Gene Therapy Death," *New York Times* (December 9, 1999).

9. The current list of classic cases includes the Tuskegee Syphilis Study, the injection of live cancer cells into chronically ill patients, the hepatitis studies on mentally handicapped children at Willowbrook State Hospital in New York, Henry Beecher's exposé of ethically suspect research published in respected, peer-reviewed, scientific journals, controversy around research involving live and aborted fetuses, and the U.S. radiation experiments. For an overview of these cases in the context of Nazi experimentation and the resulting Nuremberg and Helsinki Codes, see Gregory Pence, *Classic Cases in Medical Ethics*, 3rd ed. (San Francisco: Harper, 2000).

10. As historians of human subjects research know well, the basic outlines of this tension were initially mapped in the debates between Paul Ramsey and Richard McCormick in the early 1970s. For more on this see, among others, Richard A. McCormick, "Proxy Consent in the Experimentation Situation," *Perspectives in Biology & Medicine* 18 (1974):2–20; Paul Ramsey, "Proxy Consent for Children," *Hastings Center Report* 7 (1977):4ff; Richard A. McCormick, "Experimentation in Children: Sharing in Sociality," *Hastings Center Report* 6 (1976):41–46; Paul Ramsey, "The Enforcement of Morals: Nontherapeutic Research on Children—A Reply to Richard McCormick," *Hastings Center Report* 6 (1976):21–30.

11. *Federal Register* 43:18 (1974), 914.

12. *Federal Register* 30:31 (1978), 786.

13. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research involving Children.* (Washington, D.C.: DEHW Publication No. (OS) 77–0004, 1977). In 1979, the commission published the landmark Belmont Report, outlining the ethical framework upon which its recommendations regarding human subjects was premised. See National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* DHEW Publication No. (OS) 78–0012, Appendix 1, DEHW Publication No. (OS) 78–0013, Appendix II. (Washington, D.C.: DHEW Publication No. (OS) 78–0014, 1978).

14. 45 CFR 46, Subpart D (1983).

15. For those not familiar with the federal guidelines, a summary of the components relevant to the discussion in this essay is provided here. The complete text of §45 CFR 46 is available from http://www.med.umich.edu/irbmed/FederalDocuments/hhs/HHS45CFR46.html.

§46.401 Exempt research

Certain research is exempt for all human subjects following specifications in §46.101. Exemptions include certain educational tests; the collection of existing data, documents, records, pathological specimens, or diagnostic specimens; certain research and demonstration projects; and tests of taste, food quality, and consumer acceptance.

§46.404 Research not involving greater than minimal risk

HHS will conduct or fund research, in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects

HHS will conduct or fund research, in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

The risk is justified by the anticipated benefit to the subjects;

The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research, in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

The risk represents a minor increase over minimal risk;

The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition, which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406, only if:

The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and

The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law), and following opportunity for public review and comment, has determined either:

That the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or

The following: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

16. Jeffrey Janofsky and Barbara Starfield, "Assessment of Risk in Research on Children," *Journal of Pediatrics* 98 (1981):843.

17. U.S. Department of Health and Human Services, "Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects," *Federal Register* 46 (January 26, 1981): 8387.

18. See H. C. Shirkey, "Therapeutic Orphans," *Journal of Pediatrics* 72 (1968):119–20; and Robert Levine, *Ethics and the Regulation of Clinical Research*, 2nd ed. (Baltimore, Md.: Urban and Schwarzenberg, 1986), 240–41. The term "therapeutic orphan" has shifted from its initial meaning, now referring more general to "orphan diseases," those so rare that therapies, if developed, would not meet a significant enough market to result in profitability. Hence drug companies do not invest their resources in finding the cause or therapies for these diseases; many single-gene disorders qualify as "orphan diseases." See also Levine, *Ethics and the Regulation of Clinical Research:* "the prevailing practice in the United States is to ignore the orphaning clauses on the package labels. Consequently, we have a tendency to distribute unsystematically the unknown risks of drugs in children and pregnant women, thus maximizing the frequency of their occurrence and minimizing the probability of their detection. Parenthetically, it should be noted that most drugs proved safe and effective in adults do not produce unexpected adverse reactions in children; however, when they do, the numbers of harmed children tend to be much higher than they would be if the drugs had been studied systematically before they were introduced into the practice of medicine."

19. Committee on Drugs, American Academy of Pediatrics, "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations," *Pediatrics* 95 (1995):286.

20. Michael A. Grodin and Joel J. Alpert, "Children as Participants in Medical Research," *Pediatric Clinics of North America* 35 (1988):1391.

21. American Academy of Pediatrics, 286.

22. American Academy of Pediatrics, 287.

23. *NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.*

24. Robert Pear, "F.D.A. Requires Companies to Test Drugs on Children," *New York Times*, November 28, 1998. Pear notes, "If, for example, a new drug is urgently needed to treat a life-threatening disease in children and if there is no adequate therapy on the market, the Government may insist that the manufacturer immediately begin tests in children, before full data on adults are available."

25. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research involving Children: Report and Recommendations* (Washington, D.C.: DHEW, 1977), 2–3. In the late 1970s and early 1980s, this position was likewise echoed by the FDA and the American Academy of Pediatrics. See Paolo L. Morselli and Francois Regnier, "Ethics in Pediatric Research for New Antiepileptic Drugs," in *Antiepileptic Drug Therapy in Pediatrics*, ed. P. L. Morselli, C. E. Pippenger, and J. K. Penry (New York: Raven Press, 1983), 310.

26. Robert J. Levine, "Research involving Children: The National Commission's Report," *Clinical Research* 26 (1978):62.

27. Department of Health and Human Services, "Additional Protections for Children Involved as Subjects in Research," *Federal Register* 48 (1983):9814–20; at 9816.

28. Michael A. Grodin and Leonard H. Glantz, eds. *Children as Research Subjects: Science, Ethics, and Law* (New York: Oxford University Press, 1994), 215.

29. American Academy of Pediatrics, 287. This recommendation is also found in the Canadian National Council on Bioethics in Human Research, "Revised Recommendations of *the NCBHR Report on Research Involving Children,*" 4 (1993):11; and the American Medical Association, *Current Opinions of the Council of Ethical and Judicial Affairs on Clinical Investigation* (1992):5. Sujit Choudhry, in his "Review of Legal Instruments and Codes on Medical Experimentation with Children," *Cambridge Quarterly of Healthcare Ethics* 3 (1994), draws as his first conclusion: "(1) There seems to be a general consensus that pediatric research is permissible but should only be conducted when research with adults cannot yield the same information," (570). The AAP also notes: "[The investigator] must strive to obtain as much information as possible about the safety and efficacy of a drug before enrolling children as subjects" (287). "The investigator must be aware of possible conflicts between their own academic, professional, and financial interests; the 'need to know'; and the interests of the child subject" (287).

30. Available from http://ohrp.osophs.dhhs.gov/irb/irb_chapter6.htm (April 18, 2003).

31. Donald B. Kohn, "Transduction of CD34(+) Cells from the Bone Marrow of HIV-1 Infected Children: Comparative Marking by an RRE

Decoy Gene and a Neutral Gene," NIH/RAC Protocol 9602–147. The protocol itself, as well as all relevant documents referred to below, were made available as part of the public record at the December 1996 and March 1997 RAC meetings. Copies can be requested through the Office of Biotechnology Activities (formerly the Office of Recombinant DNA Activities; ORDA) of the National Institutes of Health. The protocol itself, my review, the IRB review, Kathryn Whartenby's letter, the investigator's responses to my review and the IRB review, and the then-director of ORDA's correspondence with the investigators were included in the materials for the December 1996 meeting of the RAC. My response to the director of ORDA's correspondence was included in the meeting materials for the March 1997 meeting of the RAC. Citations to these documents will be included parenthetically in the text.

32. My interest in these questions stems from my work with the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health. From June 1995 to June 1998, I had the considerable privilege of serving as a member of the RAC.

33. A word may be in order here about the responsibilities of the RAC as well as the history and process of consolidated review. At that time, the RAC's charter outlined a broad scope of responsibilities for the committee, all in an advisory capacity to the Director of the NIH and the Secretary of Health and Human Services. As the 1994 charter stated:

> Function: The Recombinant DNA Advisory Committee shall advise the Secretary (Department of Health and Human Services), the Assistant Secretary for Health, and the Director, National Institutes of Health (NIH), concerning the current state of knowledge and technology regarding DNA recombinants, and recommend guidelines to be followed by investigators working with recombinant DNA.
>
> As noted in the *NIH Guidelines for Recombinant DNA Research* (51 FR 16958), the Director, NIH, must seek the advice of the Recombinant DNA Advisory Committee before taking the following actions: changing containment levels for types of experiments that are not explicitly considered in the *NIH Guidelines;* certifying new host-vector systems; promulgating and amending a list of classes of recombinant DNA molecules to be exempt from the *NIH Guidelines;* permitting experiments specified by Section III-A of the *NIH Guidelines;* adopting other changes in the *NIH Guidelines;* interpreting and determining containment levels upon request by the Office of Recombinant DNA Activities; revision of the Classification of Etiologic Agents for the purposes of the *NIH Guidelines.*

In the late 1970s and early 1980s, the RAC reviewed all recombinant DNA research performed in institutions receiving federal funds for such research. Over time, its responsibilities shifted. As data accrued regarding the relative safety of such experiments, the RAC rather quickly transferred the bulk of the responsibility for review to local institutional biosafety committees. With the advent of human gene transfer in 1989, the RAC's attention shifted almost exclusively to this new rDNA application. While continuing to advise the NIH director about changes in the NIH guidelines concerning containment levels, new host-vector systems, and the classification of etiologic agents, the majority of its work in the 1990s focused on advising the director whether or not to "permit experiments specified by Section III-A of the NIH Guidelines."

The RAC provided such advice to the NIH director through protocol review. Each human gene transfer protocol submitted to the NIH for funding was likewise submitted to the RAC. Following the practice established by many IRBs, at this time each protocol was assigned to three primary reviewers, one of whom was to be a "nonscientist"; the reviewers would identify questions and issues and lead the discussion of the protocol at one of the RAC's quarterly meetings.

As one can imagine, with the first human gene transfer protocols, this process was quite rigorous and careful. Over time, as a base of knowledge and experience had been laid, it was determined that many protocols raised no new issues. Using similar vectors, similar clinical procedures, treating the same or similar diseases, it seemed unnecessary to devote scarce committee time to these protocols. Consequently, in 1995, the RAC instituted a policy of "consolidated review." Each protocol submitted to the NIH would continue to be carefully reviewed by three primary reviewers (one nonscientist), but if the reviewers deemed that the protocol presented no new issues or raised no concerns, their review was sufficient and the protocol was exempted from review by the full committee. If, on the other hand, the reviewers felt the protocol presented a new methodology or raised clinical, scientific, or ethical issues worthy of further discussion, they were to recommend that the protocol be reviewed by the full committee at its next meeting.

34. The institutional IRB approved the protocol only for children aged seven years or older.

35. Upon its initial review, the IRB at the researcher's home institution had refused approval, citing a number of reservations in addition to the above including:

> This procedure has not been previously performed in humans.
>
> There is no animal data because there is no animal model of human HIV infection.

> The principal investigator states that this approach is not likely to have clinical benefit (Protocol, p. 8).

The IRB further states: "Discussion arose about the bone marrow aspirate(s) in children for research purposes only. These children would not receive this procedure if they were not in the research protocol. The risk is mainly pain, however it does appear to be greater than minimal risk as defined in 45 CFR 46.102. . . . The investigator does not believe that this protocol provides significant clinical benefit to the subjects. Thus, one can not justify the risks of the bone marrow aspirate(s) based on potential benefits to the subject" (Protocol, IRB Review, 10).

36. As Whartenby notes: "The major issues associated with this protocol are of an ethical nature: First, the use of this product in children may not be justified, considering the invasiveness of the required procedures and their associated risks. Although the investigators state that some potential for benefit may exist, there is little proof. The investigators also contend that benefit may not be observed in adults, but since the purpose of a phase I trial should be to evaluate toxicity, this point may not be sufficient to justify testing this product in children" (Memorandum, Katherine A. Whartenby, Ph.D. to Philip Noguchi, November 22, 1995).

37. Scientific indications against prospect of benefit are presented by two preclinical/clinical studies the investigators presented in support of the protocol. The first is an *in vitro* study that demonstrates that CD34+ cells can be isolated from cord blood and normal bone marrow, can be transduced with anti-HIV-1 vectors including the vectors proposed for use in this research, that these vectors do not interfere with the normal function of the cell, and that these vectors significantly suppress the replication of HIV-1 *in vitro*. This data appears strong, except for one point: these *in vitro* cultures have been selected by G418 for the transduced cells. The suppression of replication of HIV-1 occurs in cultures where over 70 percent of the cells have been transduced. The investigator himself notes that "challenge of cultures with 30–40 percent of the cells transduced, as achieved directly after gene transfer, fails to show significant inhibition of HIV-1 probably due to the virus production by the non-transduced cells." One might propose that the latter scenario more closely approximates the *in vivo* situation. Elsewhere the authors estimate that the transduced cells will be present *in vivo* at a level of 1 in 10,000 or 1 percent.

The second clinical study cited was the amended SCID-ADA protocol of Dr. Michael Blase, involving the capture of cord blood from newborn prenatally diagnosed infants with SCID. This cord blood was subjected to a similar protocol to that proposed here: the ADA gene was transduced into hematopoetic stem cells, which were reinfused into the patients. This study demonstrated that the transduced cells would engraft and that from a very small (in fact undetectable) number of transduced stem cells, the immune systems of these patients could be reconstituted. It is this study that demonstrated the presence of transduced PBMCs at a level of 1 in 10,000 or CD34(+) cells at a level of 1 percent after one year. Yet the investigators' conclusions regarding the effects of gene expression at these levels were unclear. While this protocol seemed to alleviate concerns surrounding the risks of reinfusion of transduced cells, only three children had been enrolled at that time.

Furthermore, even if this small number of transduced cells in the SCID-ADA protocol was to be demonstrated to have a clinically significant effect, the mechanism of effect for SCID-ADA and HIV-1 inhibition seemed to be markedly different. If the desired outcome was the production of a missing protein, a cell population of 1 percent might be adequate to produce sufficient quantities of the needed enzyme. However, if the desired outcome was to repopulate the immune system through cell replication, a starting point of 1 percent cell population seemed to have a different significance.

The investigators raised further questions regarding the significance of the SCID-ADA study to support the claim to prospect of benefit in their article entitled "Engraftment of Gene-Modified Umbilical Cord Blood Cells in Neonates with Adenosine Deaminase Deficiency," *Nature Medicine* 1:10 (1995), which was included as supporting material for the protocol. Here they stated: "The frequency of vector-containing progenitor cells exceeds by 100-fold the frequency of vector-containing cells in the mature haematopoetic cell compartments. The explanation for this dichotomy is unknown. Potentially, the expression of the ADA gene is beneficial for progenitor cell proliferation and allows expansion of the committed DC34+ progenitor pool in a fashion similar to that expected for T-lymphoid progenitors. However, the relatively high frequency of progenitor cells containing the vector is not reflected in mature leukocytes. . . . This observation suggests that although primitive progenitor cells may engraft without cytoablative therapy, they fail to undergo complete maturation *in vivo*. Alternatively the presence of the vector may interfere with mature haematopoietic cell production. Some reports have suggested that the neomycin phosphotransferase gene (*neo*) may impair hematopoietic cell function" (1021).

Thus information from the SCID-ADA study, coupled with questions from *in vitro* data on the replication of HIV-1 in a culture of 40 percent transduced cells, seems to argue against the anticipation of "prospect" of benefit for the children enrolled.

38. It appears that it was on the basis of these two responses and the claims outlined in note 43 below that the IRB at the investigator's home institution finally approved the protocol.

39. Janofsky and Starfield, "Assessment of Risk in Research on Children." For further description of the wide variability in the assessment of "minimal risk" with regard to protocols involving children, see Benjamin Freedman, Abraham Fuks, and Charles Weijer, "In Loco Parentis: Minimal Risk as an Ethical Threshold for Research upon Children," *Hastings Center Report* 23 (1993):13–19; and Saul Krugman's defense of the Willowbrook Hepatitis Study in Krugman, "The Willowbrook Hepatitis Studies Revisited: Ethical Aspects," *Reviews of Infectious Diseases* 8 (1986):157–62.

40. I was concerned that I was perhaps allowing the names of the procedures to weigh more heavily in my assessment of their risk than they warranted. Therefore, in the process of my initial review, I consulted a handful of individuals and colleagues in the field of pediatrics familiar with the issues of research on children. When asked whether they would consider bone marrow aspirations and harvests in children a procedure entailing only a "minor increase over minimal risk," the almost unanimous opinion was that the bone marrow procedures themselves entailed significantly "greater than minimal risk." This is certainly not a scientific sample, but it did address the concern about clinical versus lay perceptions.

41. In my review, I suggested possible alternatives. The investigators themselves had noted that certain scientific questions might be addressed in SIV or SCID/nu mice (Protocol, p. 88). They did not, however, elaborate or show that these experiments had been conducted. I also proposed that, given the information they provided about the physiology of pediatric HIV, an argument might be made for initially attempting this approach in HIV-positive newborns using retrieved umbilical cord blood and either proceeding within the neonatal period or waiting to see whether or not these infants seroconvert. This approach would test a number of the same concepts and greatly minimize the risk and burden associated with the bone marrow process.

42. If one concludes that these children will most likely not benefit directly from this research, there are still two additional justifications for research on children that must be considered. The first would be that children are the only population in which this particular condition is found. While that is the case for a disease like SCID or PNP-deficiency, it is not the case for HIV.

Alternatively, one could argue that the physiology of children is sufficiently different from that of other human populations that research on, for example, adults will not provide helpful information. This argument is made by the investigator. He states in response to the IRB critique that pediatric HIV infection must be studied in children for four reasons: "(1) Pediatric AIDS has a number of unique clinical aspects and therefore the efficacy of gene therapy for HIV-1 infected children cannot adequately be studied in adults, (2) the procedure may only be effective or be more effective in young children (e.g., <12 years old) because the level of thymic function which would be needed for the transduced CD34+ cells to become functional T lymphocytes is greatest *earliest in life* (emphasis mine); and (3) gene transfer into CD34+ cells is most effective with younger donors. [Therefore], it may be possible that these methods would fail to show efficacy in adults and yet be beneficial if applied to children" (Protocol, Response to IRB, 15).

A number of problems are presented by this claim. First, the investigator makes this claim *solely* in the context of the response to IRB critique; except for the first point above (which is not elaborated upon), the investigator does not raise these issues in the context of the protocol. Moreover, neither in the response nor in the protocol does the investigator provide any citations or data in support of these claims. He states that pediatric HIV infection is unique, but does not say how. He does address the second point in the protocol, but the claim is different; he states that "thymic functions, which may be necessary for stem cells to undergo differentiation to mature T lymphocytes, is likely to be *best early in the disease course*" (emphasis mine, Protocol, 33). This is a different claim. Nor is data included on the relationship between age and CD34+ cell transduction.

Whartenby also raises concerns relevant to these claims. As she notes: "The investigators would like to test this product in children because of their less developed immune system, but the protocol is written for patients aged 3–18. This age span seems to encompass more than one patient population, since the immune system of an 18-year-old should be more similar to that of an adult than that of a 3-year-old. Use of the older group may be more ethical, but may not provide any more information than use in adults. It is not clear how this group should be divided or how the issue of an appropriate age group should be handled" (Whartenby memorandum). This issue becomes more complicated by the IRB amendment that the patient population be restricted to children aged seven or older. Many of these children might well not be "early in the disease course."

Finally, the investigator's third claim above is problematic as well: it certainly may be the case that a given procedure fails to show efficacy in adults but is beneficial in children. But the investigator does not provide data to indicate that this approach has been tried in adults and has failed. It may in fact be the case that this approach could be tried in adults *and might work*. This would provide clinical data which could be useful in informing a pediatric protocol.

43. The end of the narrative of this particular protocol may be of interest to some. As noted above, I had submitted my review on December 4, 1995. On February 1, 1996, I received via fax, the investigator's response to my questions and critiques. Then, on approximately February 5, RAC members

received notice that the March 1996 meeting had been canceled, ostensibly due to "lack of protocols to discuss." It seemed apparent that my recommendation had been overturned and the decision about the protocol had been made. On February 8, however, I received a phone call from Dr. Nelson Wivel, then-director of ORDA. As quickly became clear, Dr. Wivel was calling to urge me to reconsider my recommendation that the protocol go before the entire committee. Playing the card of the urgency of pediatric HIV research, he made it clear to me that he had greater expertise regarding issues related to research involving children and that my concern was, frankly, out of line. I made it clear to Dr. Wivel that I understood the justifications and parameters for nonbeneficial research involving pediatric subjects, especially in the case of lethal diseases, but I also made it quite clear that I was not convinced that the HIV protocol met established guidelines for the ethical conduct of such research. I reiterated that I had reviewed the investigator's materials and responses thoroughly, that I had conducted a significant amount of outside research into this question specifically in light of this protocol, and that because of this research, I remained convinced that the protocol deserved consideration by the full RAC. I also stated that, as I had just been informed that the March meeting had been canceled, it seemed obvious that the decision about this protocol had already been made and that my comments and position were no longer relevant. I told him, nonetheless, that my own opinion remained unchanged. The phone call ended.

Since the RAC did not meet again until December 1996, it was not until this meeting that documents relevant to this protocol were made part of the public record and circulated to members of the RAC. In those materials, appended to the protocol, was a letter from Dr. Wivel to the principal investigator, dated February 8, 1996, the day of our phone conversation. Wivel herein stated:

> I apologize for the somewhat prolonged delay in responding to your letter and the significant amount of information that you presented in response to the comments of Dr. Lysaught. As I think that you are well aware, the two scientific reviewers of your protocol made the judgment that it should be exempt from RAC review. . . . Your materials were forwarded to Dr. Lysaught for her review. Subsequently I had the opportunity to speak to her, and it is my assumption that she has a clearer concept of the necessity for Phase I trials involving pediatric research subjects who have lethal diseases, notwithstanding the fact that there may be no benefit to a particular subject. After careful evaluation of all the available information, it has been determined that the protocol . . . is exempt from RAC review.

I had not been copied on this letter. One of my scientific colleagues on the RAC, who found the tenor of the correspondence rather problematic, brought it to my attention. My written response to this letter was made part of the public record in the materials of the March 1997 RAC meeting.

44. Again, for more on this, see Churchill, et al., "Genetic Research as Therapy"; and Lysaught, "Commentary: Reconstruing Genetic Research as Research."

45. Information emerging from the continued inquiry into the practices surrounding Jesse Gelsinger's death reveal what has been characterized as a "95 percent failure rate" in the reporting of adverse events from investigators conducting clinical trials of human gene transfer involving adenoviral vectors; see Sheryl Gay Stolberg, "Agency Failed to Monitor Patients in Gene Research," *New York Times*, (February 2, 2000). The University of Pennsylvania, in its official response to the RAC/FDA findings released in December 1999, characterized the failures in their program as "little more than 'minor deviations' in bookkeeping"; Sheryl Gay Stolberg, "Scientists Defend Suspended Gene Therapy," *New York Times*, (February 15, 2000).

46. See Stuart H. Orkin and Arno G. Motulsky, National Institutes of Health Ad Hoc Committee Report, *Report and Recommendations of the Panel to Assess the N.I.H. Investment in Research on Gene Therapy* (December 7, 1995), available from http://www.nih.gov/news/panelrep.html.

47. Paul Gelsinger, Jesse's father, reports that "he and his son had no idea there were risks" entailed in the procedure and were not informed of adverse events that had occurred with other subjects. Moreover, he reports that he was told by an investigator involved with the protocol that "the treatment was already working in some patients"; Sheryl Gay Stolberg, "Youth's Death Shaking Up Field of Gene Experiments on Humans," *New York Times*, (January 27, 2000). The FDA/NIH investigation revealed that "the informed consent form that the investigators gave patients deviated from the one the agency [the FDA] had approved, in that it omitted information about the death of monkeys that had received treatment similar to that given Mr. Gelsinger, although much more powerful"; Stolberg, "FDA Officials Fault Penn Team in Gene Therapy Death").

48. The Orkin/Motulsky Report (see note 46 above) was issued in December 1995, at about the time the decision was made to abolish the RAC.

49. Eliot Marshall, "Varmus Proposes to Scrap the RAC," *Science* 272 (1996):94 (emphasis added).

50. This point was also relevant to the HIV protocol. The investigator noted that 80 percent of the pediatric AIDS population is African American or Latino and that 75 percent of the younger patients followed at the investigator's institution were likewise African American or Latino. This raises social

and ethical questions regarding whether children who are possibly already doubly disadvantaged—socioeconomically and by their disease—are being asked to assume an additional undue burden of nonbeneficial research. It is a catch-22 (if research is not conducted, this disadvantaged population is further disadvantaged by this terrible disease) unless clinical trials are designed with a serious prospect of benefit.

51. Available from http://ohrp/osophs.dhhs.gov/irb/irb_chapter6.htm (April 18, 2003).

16

Science, Ethics, and Policy: Relating Human Genomics to Embryonic Stem-Cell Research and Therapeutic Cloning

Gerard Magill, Ph.D.

THIS CHAPTER discusses a value-based connection between the emerging technologies of human genomics, embryonic stem-cell research, and therapeutic cloning. The goal is to provide an ethics analysis that seeks to promote and protect society's interests in the current environment of scientific progress and technological breakthroughs.

To set the scene of the emerging capacity of bioengineering today, I present a case study into the treatment of Molly and Adam Nash, the first documented medical therapy to combine human genomics and embryonic stem-cell research. My argument is that human life constitutes the most basic human value that must permeate an ethical analysis of life sciences research today. The emphasis on the value of human life is evident in both human genomics and embryonic stem-cell research, including therapeutic cloning. The breakthroughs in human genomics raise many ethics concerns. But the first death of a patient in a gene therapy trial in 1999 gave prominence to a profound concern about patient safety in human genomics research. Second, the announcement by President Bush in August 2001 permitting federal funding of research on a limited number of embryonic stem cells generated widespread debate about the meaning of embryonic human life. Moreover, dubious claims about a private cloning company called Clonaid having cloned human babies in late 2002 and early 2003 have heightened the rhetoric of policy discussion about embryonic stem-cell research and human cloning.[1] Despite such claims, science continues to encounter such serious difficulties with cloning