Reconstruing Genetic Research as Research

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Persons even remotely familiar with the field of gene therapy cannot have missed the recent near-death experience of the National Institutes of Health's (NIH) Recombinant DNA Advisory Committee (RAC): its virtual disbanding in May 1996, its year-long hiatus, followed by its reprieve and reconfiguration with significantly diminished oversight, and as yet unclear mandate regarding human gene transfer research. Larry Churchill et al.'s article "Genetic Research as Therapy" provides a helpful window through which to view not only this debacle but also the tensions that have colored the past work of RAC, tensions which must be addressed as RAC works to redefine its role in gene transfer research over the next year. A closer look at RAC's experience provides evidence to support the authors' claims. At the same time, however, this same evidence demonstrates the difficulties encountered by those who want to reconstrue genetic research as research.

In "Genetic Research as Therapy," Churchill et al. identify two important problems that increasingly plague the world of clinical and scientific research. The first of these is the growing tendency mistakenly to construe "research" endeavors as therapeutic, a conflation that is facilitated by a rhetoric of compassion. They correctly suggest that this tension has been present in the work of RAC since the beginning of human gene transfer research. One only needs to look to the minutes of the March 1998 RAC meeting, where RAC discussed the use of children in gene transfer research, for evidence of this. If the authors are correct in their analysis, this tension points to a broader, more disturbing problem, namely, a peculiar anti-rationalism (ironic given that the subject at hand is science). When the determinative justification for pursuing interventions with human subjects becomes a feeling or desire (the investigators' intent to benefit the patient, the investigators' feeling of compassion for the patient, the patient's last hope for a miracle) without, at times, adequate research design or compelling evidence for any likelihood of benefit, rational discourse is thwarted (as the therapeutic dogma goes, "You can't argue with someone's feelings"). Especially insofar as this issue impinges on the valid practice of informed consent, the importance of this issue cannot be overemphasized and deserves further study.

Second, Churchill et al. suggest that the above trend is especially exacerbated when research is conducted in clinical contexts. The problem here is not so much a confusion of roles between patient and subject, but a reduction of these dual roles to one: both the investigator and the volunteer understand the participant as a patient and not as a subject. The authors suggest that this factor has contributed to the erosion of the practice of informed consent, and, insofar as this dynamic has played itself out specifically in the context of gene transfer research, they invite RAC, as well as others involved in the responsible conduct of gene transfer research, to take specific steps to counter these trends and to mitigate their effects.

In the following, I want to contextualize further Churchill et al.'s arguments in the experience of RAC and the history of gene transfer research. Although this contextualization lends further support to the authors' claims, it also complicates matters. For example, as I will argue first, although RAC has clearly succumbed to the above-mentioned problems, it has, at the same time, also strenuously resisted the conflation of research and therapy. Indeed, RAC's counter-cultural attempts to understand research and therapy as separate endeavors was one contributing factor to the proposal to dissolve RAC. Second, even though the authors correctly link this conflation to the prob-
plematic overselling of gene therapy and a truncation of The Belmont Report, a third historical factor must be incorporated into this narrative, namely, the context surrounding the emergence of human gene transfer research in the early 1980s. If the genesis of a problem must be accounted for in order to solve the problem, then this piece of the story cannot be overlooked. Third, this historical context sheds light on the issue of the language used by RAC in its discussions and official documents—that is, the language of patient and therapy and treatment. Although Churchill et al. are correct that the vestiges of this language need to be expunged, it is important to recognize how RAC members have worked to foster a more robust practice of informed consent; these efforts, however, have often met with resistance as well. Finally, I believe the authors’ useful recommendations point to deeper conceptual issues that require further consideration.

Resistance vs. conflation: Research or therapy?
In the proposal to dissolve RAC in 1996, one justification seemed to be central, namely, that RAC oversight of gene transfer research introduced a cumbersome and unnecessary level of regulation that was duplicative of the proper statutory authority of the Food and Drug Administration (FDA). This reason, however, masked an equally operative claim—that even though, as the report of Stuart Orkin and Arno Motulsky notes, "clinical efficacy ha[d] not been definitely demonstrated at this time in any gene therapy protocol," RAC oversight was delaying the progress of gene transfer research and therefore the development of new therapies. Space limits an exhaustive discussion here, but three instances in the experience of RAC illuminate how its understanding of gene transfer protocols as research precipitated conflict with those whose primary interpretive framework was therapy.

It is noteworthy how early this conflation emerged in the development of gene transfer research; in fact, it arose in discussions surrounding the first protocol. The first gene transfer protocol, approved in May 1989, was a gene-marking protocol proposed as an addition to an ongoing National Cancer Institute protocol, which was testing the efficacy of tumor-infiltrating lymphocytes against advanced cancer. In many ways, this was an ideal protocol: as a marking protocol, it could not fall prey to the research/therapy conflation insofar as, in theory, it was not designed to offer therapeutic benefit to the participant. In granting approval, RAC attached a number of stipulations, among which were that the study would be limited to ten subjects, that the investigators provide additional data before recruiting additional patients or inserting a gene for therapeutic purposes, and that the Human Gene Therapy Subcommittee (HGTS) review any changes or additions prior to review by RAC.

Consequently, the conversation recorded in the minutes of the February 5, 1990 meeting of RAC is striking. One of the principal investigators, Dr. Steven Rosenberg, presented an interim report on data from five of the first participants enrolled, and he expressed an interest in enlarging the study beyond the approved ten. He observed, however, that:

A problem exists with the need for Federal Register notice and the timing of approvals from the RAC, which he felt was going to delay efforts to develop this cancer treatment. Dr. Rosenberg illustrated this by noting 150,000 patients will die in the 4 months between each RAC meeting. He said the current 45-day prior notice and then discussion by subcommittees and RAC approval results in a 6- to 12-month lag time between the first observation of a clinical clue and the time it could be put into operation. Dr. Rosenberg said that since this was a clinical study that needed to be enlarged, there should be a way to accelerate the approval process, thus allowing additional patients to be treated, utilizing the same protocol. Without such approval, the protocol would have to wait for rereview in June by the RAC, and this would mean that the clinical studies would have to stop in another month.

Thus, even at this early juncture—in the first gene transfer protocol, from which a complete set of data had not yet been collected, the objective of which was solely marking—"research" had been cast as "therapy." The stipulations proposed by HGTS/RAC, which are cautiously responsible and clearly reasonable for a research context on a novel initiative, are already being assailed as an obstruction of progress and a delay in therapy, subtly couched in the rhetoric of costing hundreds of thousands of lives.

That this sort of conflation could so easily occur with a gene-marking protocol foreshadowed difficulties to come, as was dramatically demonstrated in two further cases. Churchill et al. note that, following a broader trend, gene transfer research has developed its own "desperate" or "emergency" use guidelines. But in the events that precipitated the development of these guidelines, it seems that it may not have been compassion as much as the condescending pressure brought to bear on RAC and the NIH director which was operative. In October 1992, Senator Tom Harkin (D. Iowa) requested, on behalf of one of his constituents, that then NIH Director Bernadine Healy make an exception to RAC's established processes to allow an unreviewed single-patient protocol to proceed on a compassionate use basis. As the minutes of the December 1992 RAC meeting note, the patient in question (the wife of the chairman of the board of the San Diego Regional Cancer Center), suffering from stage IV glioblastoma, asked the
investigator, Dr. Ivor Royston, if "gene therapy could provide any therapeutic benefit," and proceeded to present "her case strongly to numerous doctors throughout the country and to Federal government officials."²⁸

The record shows that RAC strenuously resisted the notion of "compassionate use" in relation to gene transfer given the infancy of the field (only twenty-four subjects had been entered into human gene transfer protocols at this time), and, although sympathetic, resisted the reduction of criteria to "intent to benefit" or compassion absent reasonable evidence. In light of the events surrounding the Royston protocol, RAC formed a subcommittee to recommend policy regarding requests for compassionate use and submitted a report to the NIH director. The report was discussed at a special meeting of RAC on January 14, 1993. The subcommittee found no basis on which to justify a compassionate plea given that "the field of human gene therapy is still in its infancy," noting that "major deviations from the research review process that has worked well to date are premature."³⁹ Although it outlined alternative review mechanisms, it recommended none of them.

RAC's refusal to reason from compassion and its insistence on maintaining its position on gene transfer as research met with dissent from the NIH director:

Based on this patient's grave condition—the utter failure of other therapies, and an estimated survival time of less than two months—a decision had to be made, and made immediately.... Today I stand by that decision. First and foremost, the decision was a compassionate response to the request of a dying patient.... Your central concerns (in your compassionate-use subcommittee memo of January 11 [sic] were public and patient safety and the need for a reliable knowledge base. However, the memo does not take into account the urgent nature of nonresearch compassionate-plea requests and the fact that they are not meant to expand the knowledge base. The memo implies that compassionate-plea requests that go before the RAC will involve only research. This is not the case.¹⁰

In the end, RAC drafted an alternative-mechanism policy but closed with the recommendation that: "In the development of any documents that are a part of this policy statement, the terms, compassionate use and compassionate treatment, will be deliberately avoided."¹¹

In his presentation before RAC on December 4, 1992, Dr. Royston made an interesting claim. He noted that "the constitutional rights of this patient to receive the therapy that she wants is the real issue."¹² This theme was echoed again in early 1997, shortly after the reinstitution of RAC. On March 4, 1997, Dr. Kim Lyerly of Duke University submitted a letter to the NIH Office of Recombinant DNA Activities (ORDA) to notify NIH of his intent to initiate the first human clinical trial involving transfer of a "naked" RNA vector. For a variety of reasons, confusion arose as to whether this protocol fell under RAC jurisdiction. After clarification, RAC recommended full review of the protocol and informed Dr. Lyerly that the protocol would be reviewed at its upcoming meeting in June.¹³

Shortly thereafter, on April 18, a congressional inquiry was submitted to the NIH Office of Legislative Policy and Analysis. This was precipitated by letters to President Clinton (copied to CNN, ABC, CBS, and NBC, among others) and to Senators Arlen Spector (R. Penn.) and Charles Robb (D. Va.) from the wives, friends, and individuals who had, unbeknown to ORDA and RAC, already been enrolled in the protocol and with whom preliminary procedures had been initiated.¹⁴ What is significant for our purposes is the language employed in this correspondence. The letters refer to the intervention as "a new treatment program"; "every test has indicated that this treatment will be effective to eradicate any remaining disease"; that the "program may mean, literally, the difference between life and death" but that the "treatment is now being held up by a committee." The writer of one of the letters had clearly been well informed of RAC's recent struggles and issues over its role in protocol approval. "How many lives," one writer asks, "is this committee affecting?" Although fault for these misunderstandings was laid squarely at the feet of cultural hype about the promises of gene therapy and the patients' own desperate, wishful thinking, troubling questions remained unanswered regarding the dynamic of the informed consent process.¹⁵

These three accounts demonstrate how Churchill et al.'s claims regarding the conflation of the notions of research and therapy in the wider cultural climate, with the reduction of reasoning to compassion, have played themselves out in the field of gene transfer research in specific instances. RAC's processes—which reflect an understanding of gene transfer protocols as primarily research endeavors—have been assailed as unnecessarily duplicative, obstructionist, and delaying or depriving patients of life-saving therapies. That patients are willing to marshal congressional pressure and invoke putative rights to a phantom therapy shows how desperate the situation has become.

The genesis of gene therapy

Churchill et al. suggest that two sources have contributed to the misconstrual of genetic research as therapy—a historical erosion in the practice of informed consent based on a truncated use of The Belmont Report and the widely recognized problem of the overselling of gene therapy. If, however, we are to remedy this confusion effectively, a third factor must be recognized, namely, the context in which gene transfer research arose.
Those familiar with genetics will recall the climate surrounding genetic engineering in the 1970s and early 1980s, a climate fraught with diabolical specters of eugenics and transgenic freaks, threats to human freedom and integrity, and fears of environmental release and uncontrollable plagues. It was in response to these fears that RAC was initially created, as a forum through which research in genetic engineering could be held to public accountability. In addition, it was in part the scandal surrounding two unauthorized and scientifically ill-founded human gene transfer experiments (the 1970 case of Dr. Stanfield Rogers and the 1980 case of Dr. Martin Cline) as well as the controversial decision in *Diamond v. Chakrabarty* that catalyzed public discussion regarding the application of recombinant DNA to humans. One of the most important outcomes of this discussion was the 1982 publication of *Splicing Life*, the report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research regarding gene transfer into humans. In considering the various forms that human gene transfer could assume, *Splicing Life* offered a framework of argument justifying only one: somatic cell gene therapy. Somatic cell human gene therapy would be acceptable, the report argued, because it aimed at correcting a disease in an individual patient and, given that it resembled or differed little from other forms of medical treatment, it raised no new ethical issues.

Thus, gene transfer for the treatment of serious and disabling diseases—and only this—was deemed ethical and permissible. In addition, *Splicing Life* was written in the context of the recently published *The Belmont Report* and subsequent federal regulations concerning human subjects research, and thus drew on the new consensus regarding the rubrics of beneficence, justice, and respect for persons. This framework of *Splicing Life*, then, provided the basic premises and assumptions for RAC's Working Group on Human Gene Therapy (later HGTS) as it developed the "Points to Consider." Thus, these premises and assumptions were dictated in large part by the social context in which human gene transfer emerged, as policy-makers sought to render a practice of human gene transfer that would be accepted by an anxious, wary public.

Attending to informed consent

This historical context accounts for the fact that, until March 1997, entry into gene transfer protocols was restricted to individuals with significantly disabling or life-threatening diseases or disorders, that is, patients. It likewise accounts for the use of terms such as gene therapy, patients, and treatment in NIH guidelines and "Points to Consider," terms that Churchill et al. suggest should now be deleted from these documents. This is an important suggestion, and RAC has already taken steps to implement it. The "Points to Consider," indeed, the entire NIH Guidelines of which it is a part, is an organically developing document. Having been subjected to a number of revisions to date, the predominant language is now that of "human gene transfer (research, protocol[s] or experiment[s])," "transfer of recombinant DNA," or "recombinant DNA research." In June 1997, RAC again formed a subcommittee to revisit and revise the "Points to Consider," in part to adapt to RAC's changing role and the continuously evolving context of gene transfer research. As the "Points to Consider" is revised, it will be an easy task to remove the last remaining vestiges of the historical language.

At the same time, while working within this conceptual and linguistic framework, the record indicates that RAC, though unable to influence the informed consent process directly, has made a consistent effort to improve the quality of the informed consent documents that accompany human gene transfer research. Indeed, because of the efforts of RAC, informed consent documents for human gene transfer have arguably been more thoroughly examined than for any other area of human subjects research. Protocol reviewers have consistently requested changes in the language of informed consent documents approved by institutional review boards (IRBs)—to diminish the tone of therapeutic intent or probability, to remove terms like therapy, immunotherapy, vaccine, drug, and cure, to include the term experiment, and to insert language advising subjects that they will not benefit from the study, in addition to raising other issues pertinent to informed consent, such as the counsel to use contraception and information about compensation for research-related costs or injuries. In addition, Appendix M-III, the section of the "Points to Consider" that deals with informed consent, was revised during 1993–1994 by a subcommittee under the aegis of then member Doris Zallen. This section is a model for future revisions, using terms such as potential subjects, potential participants, human gene transfer, research, experiment, and eschewing the word treatment.

Ironically, the assiduous attention of these RAC members to issues of informed consent likewise proved problematic for RAC, being cited as one of the reasons why NIH Director Harold Varmus dissolved it. In Eliot Marshall's first report of RAC's demise in *Science*, he notes: "In any case, Varmus said, RAC had begun to exhibit a taste for trivia: It often got bogged down in debates over the wording of patient consent forms." Reviewers' critiques of informed consent documents have generally met with courteous but unenthusiastic responses from investigators, who tend to shift the responsibility for the documents to their institutions and IRBs. Likewise, many RAC members themselves have expressed impatience with these critiques, seeing them as peripheral to the proper focus of RAC and as under the jurisdiction of local IRBs or the Office for Protection from Research Risks (OPRR).
Issues for further consideration

Churchill et al. have offered important recommendations aimed at reconstruing genetic research as research. The experience of RAC, however, indicates that implementing these recommendations will be neither easy nor quickly done. Revision of RAC documents would be a helpful start, but this would only address symptoms of deeper problems to which the authors’ final three recommendations point. Further conceptual work is needed on three issues, with regard to which I make brief remarks.

First, Churchill et al. note that the language of beneficence needs to be reexamined; I would press them further. Problems arise not only from equating beneficence with compassionate intent. Problems also arise from using the term beneficence to refer to two distinctly different moral considerations: individual benefit and benefit to society. These are conceptually different issues, which ought to be described with distinct moral language. Although this equivocal use is omnipresent—from the ethics literature to the federal guidelines—it may be time to reassess our terminology. The goal of benefit to society may more properly be assigned to the sphere of justice. One might also ask how potential research subjects perceive the rhetorical suasion of calls to beneficence versus calls to justice, and how the former might also negatively impact the process of informed consent.

Second, not only does this conceptual confusion surrounding beneficence complicate matters in human subjects research, but the language of the federal guidelines may also inadvertently exacerbate the matter. The regulations stipulate only that the investigator provide “a description of any benefits to the subject or to others which may reasonably be expected from the research.” However, as I suggested to Churchill et al., what ought to be stated is not a description of “Possible Benefits” (the usual heading), but rather a section entitled “Evidence for Benefit” or “Probability of Benefit,” giving participants the kind of information they would need to make an autonomous decision. This would be revolutionary, at least in my experience with gene transfer informed consent forms. Insofar as this is the kind of information that ought to be presented in the conversation/process of informed consent in the clinical or research setting, it ought to be transcribable to the consent form. Can a potential research subject engage in a valid risk-benefit analysis if the bases for the determination of risk or benefit (and, therefore, the relative weights) are not made clear to them? Given the current federal guidelines, an assessment of the likelihood of risk and benefit is not necessarily made by the research participant, but may well be made by the investigator or the IRB with no requirement that their formula or reasoning be disclosed. Research participants often seem to be portrayed as those who are not completely capable of understanding the intricacies of scientific research or whose reasoning processes are impaired by illness, a rendering that may be accurate but may call into question the ethical validity of much human subjects research.

This leads us to the third issue, namely, the nature of the person enrolled in the protocol. The authors rightly find the referent patient to be problematic, insofar as it changes the dynamic of the research encounter and can rhetorically import unwarranted therapeutic hope. But, as I suggested to the authors, the language of subject is not ideal either. One the one hand, the terminology of patient does highlight the fact that most of the persons enrolled in gene transfer research to date are a special class of research subjects—namely, sick persons who present special vulnerabilities and require special protections not relevant to healthy, “normal” subjects. The federal guidelines clearly recognize this conflicting phenomenology, but the preferred term subject seems to mask it. At the same time, subject carries with it a passive connotation that may no longer fit with the current consensus on research as a shared endeavor and informed consent as a process of collaborative decision making. Here RAC’s language in its revision of section M-III may provide a helpful alternative, where the language of subject alternates with that of participant. Although participant does not capture the vulnerability of patients, it does eliminate one source of the tendency to define those who take part in research in terms of emotion and desperation to whom a sufficient response is compassion. The language of participant may better capture the image of one to whose reason one must appeal, to whom one must provide evidence of benefit so that he/she can truly make a fully informed decision about whether to undergo the burdens and risks of the research as research.

In closing, then, in addition to Churchill et al.’s recommendations, I suggest that further conceptual work is needed on the above issues. To address all these issues will require a systematic and sustained interagency forum, one whose work can inform that of more focused bodies (for example, RAC, FDA, and the NIH intramural ethics program). Given its current focus on human subjects research, the National Bioethics Advisory Committee, in conjunction with OPRR, may be the proper place to begin the work required to reconstrue human subjects research in general as research.

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7. Id. at 366.


12. See Recombinant DNA Advisory Committee, supra note 8.


14. These letters are part of the public record of materials for the June 1997 Recombinant DNA Advisory Committee (RAC) meeting. Copies of these documents should be available on request from the Office of Recombinant DNA, National Institutes of Health.


19. See Friedman, supra note 17, at 177-79; Fletcher, supra note 17, at 66; Murray, supra note 17, at 51; and R. Cooke-Deegan, "Human Gene Therapy and Congress," Human Gene Therapy, 1 (1990): 163-70.


23. Vestiges of the original language remain in the NIH Guidelines, but only in a few short sections, specifically in Appendix M, the "Points to Consider," and Appendix D, "Major Actions Taken Under the NIH Guidelines." In Appendix M, use of the phrase gene therapy is limited to the discussion of the historical background of human gene transfer research (pp. 92-93) and as vestiges of the original guidelines in sections M-II, "Description of the Proposal," and M-IV, "Privacy and Confidentiality" (pp. 93-98). The terms patients and treatment are more problematic, but again are limited to sections M-II and M-IV and should be easy to revise.

24. Appendix D, "Major Actions Taken Under the NIH Guidelines," presents a different and perhaps more intractable set of issues. Appendix D lists the various human gene transfer protocols approved by RAC, in addition to a number of recombinant DNA protocols. This section documents well the conceptual shifts regarding human gene transfer research that have occurred since 1989. For example, the early entries use only the term patient, the later entries use only the term subject, and the middle entries mix the terms. The appendix is consistent in referring to the protocols as experiments, but likewise vacillates between the phrases gene therapy experiment and gene transfer experiment. Early on, these phrases were used to differentiate between potentially therapeutic protocols and gene-marking protocols. Relatively quickly, the use of the phrase gene therapy essentially disappears; this reflects the March 1993 decision of RAC that the phrase gene transfer should be used for all unproven, phase I trials. See Recombinant DNA Advisory Com-
Committee, National Institutes of Health, “Minutes of Meeting, March 1–2, 1993” (visited Apr. 12, 1998) <http://www.nih.gov/od/orda/docs.html>. Thus, Appendix D provides an interesting window into the historical evolution of RAC’s conceptualization of these issues. However, insofar as Appendix D contains the record, it is unclear how amenable it is to revision. The phrase gene therapy will be the most difficult to eliminate insofar as it used in the context of the recently instituted program “Gene Therapy Policy Conferences,” created by Harold Varmus. This comprises the bulk of the uses of this phrase in the Guidelines.
