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Historical Perspectives Pertaining to the NIH Recombinant DNA Advisory Committee

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Abstract

Science is host to a constantly emerging series of new paradigms, and it is this characteristic that makes science both interesting and dynamic. As a part of this continuum, it became possible to create recombinant DNA molecules. Immediately it was recognized that there was a potential for serious adverse events associated with this new technology. Following two scientific conferences at Asilomar, California, the National Institutes of Health moved quickly to create the Recombinant DNA Advisory Committee (RAC). For approximately 38 years the RAC has served as an open forum for review of various recombinant DNA experiments, and for the last 23 years it has played a pivotal role in the oversight of human gene therapy. The RAC's existence obviated the need for more restrictive governmental legislation and has supported the development of genetic interventions that are leading to actual human therapies.

Introduction

As a result of the continuing and successful developments in the area of recombinant DNA technology, concerns arose about the safety of these experiments. In 1971, Paul Berg was able to construct the first recombinant viral vector system by splicing genes into the simian virus, SV40. Members of the scientific community began a peer exchange of views that resulted in the first Asilomar conference, held in January 1973. This meeting produced the first detailed discussion about potential hazards that could be inherent in recombinant DNA research. Following the conclusion of the conference, a letter was published in *Science* that confirmed the paucity of knowledge about the consequence of this type of experimentation (Berg *et al.,* 1974). Shortly thereafter, the National Academy of Sciences established a committee to study recombinant DNA technology; this move brought the matter to the attention of both the press and the public. The second Asilomar conference was convened in February 1975, and this resulted in an extensive debate about the putative dangers of recombinant DNA experimentation. Inevitably, there were definitive differences of opinion, but the participating scientists agreed to a voluntary moratorium on certain kinds of experiments. On the first day following the conference, Dr. Donald Fredrickson, then director of the National Institutes of Health (NIH), set in motion the machinery that resulted in the formation of the NIH Recombinant DNA Advisory Committee (RAC). Members of the RAC began the formidable task of creating the *NIH Guidelines for Research Involving Recombinant DNA Molecules.* On June 23, 1976, the *NIH Guidelines* were first published in the *Federal Register.*

A comment about the *NIH Guidelines* is merited at this point. It must be noted that the NIH is not a regulatory agency, and as such, this agency has no statutory authority to promulgate regulations. This state of affairs proved to be a very tactical advantage in that the *NIH Guidelines* could be amended much more easily than regulations. As history has shown, many, many amendments have been required over the last 37 years.

A Chronology of Events Leading to Human Gene Therapy Oversight

The original membership of the RAC was dominated by scientists who were bacterial geneticists. This was occasioned by the fact that much of the pertinent research was being done in prokaryotic systems. At this time, there were no nonscientific or ''public'' members on the committee.

As the field forged ahead, the public became more aware of scientific developments. On June 20, 1980, a letter signed by the general secretary of the National Council of Churches (Protestant), the general secretary of the Synagogue of America, and the general secretary of the United States Catholic Conference was sent to President Jimmy Carter. They expressed reservations about the changes inherent in

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genetic engineering in the context of religious, moral, and ethical considerations. There was a noted concern about the necessity of maintaining the fundamental nature of human life along with the dignity and worth of the individual human being.

Within a few months, Dr. Martin Cline of the University of California at Los Angeles (UCLA) School of Medicine attempted to perform gene therapy by using the calcium phosphate method to transfect the beta-globin gene into autologous bone marrow cells into two patients with thalassemia (one in Israel and one in Italy). This particular protocol had been disapproved by the Institutional Review Board at UCLA. When knowledge of these experiments became public, there began a series of proceedings that led to censure by the NIH and withdrawal of research funding. There is a specific provision in the *NIH Guidelines* that allows for withdrawal of research grants if a violation occurs. (Note: Some legal scholars have advanced the contention that the penalty clause in the *NIH Guidelines* makes them *de facto* regulations. However, this contention has never been challenged through legal proceedings.)

Because of the letter from religious officials and the Martin Cline affair, a presidential commission was formed to carry out a detailed examination of the ethical issues attendant to molecular genetics and the capacity for intervention into the human genome. In 1982, this commission published a document, *Splicing Life*, that summarized its findings. Its most important conclusion was that there were no fundamentally new ethical issues inherent in implementing recombinant DNA technology for human use (President's Commission, 1982). Most importantly, it was strongly emphasized that there needed to be a well-organized matrix of public scrutiny for any human gene therapy protocols that might be proposed. Since the NIH RAC had been in existence since 1975 and functioning as a review body since 1976, it was correctly noted that it had the most expertise and real-time experience in analyzing many types of recombinant DNA experiments. As noted previously, the original RAC membership was restricted to scientists, but in 1978, the secretary of health education and welfare, Joseph Califano, required that nonscientific or ''public'' members be added to the committee. With the advent of this change in membership (25 members; two-thirds scientists and one-third nonscientists), the newly reconstituted committee was referred to as the ''second generation'' RAC. Later on, there were further committee changes that came to pass when the RAC was preparing for the actual review of human gene therapy protocols. This entailed the formation of a Human Gene Therapy Subcommittee (HGTS), and with this change, a ''third generation'' RAC was created.

During this period the U.S. Congress maintained a continuing interest in human genetic engineering, and at one time, there were 16 pieces of proposed legislation that could have developed into regulation of recombinant DNA research. Fortunately, the existence of the RAC and its proven track record served to allay many of the political fears and no formal statutes were passed. Subsequent to the report of the Presidential Commission, the House Committee on Science and Technology convened its Subcommittee on Investigations and Oversight to review major issues relevant to human genetic engineering. It is interesting to note that this subcommittee was chaired by Albert H. Gore, Jr., then a young congressman from Tennessee.

On April 11, 1983, the chair of the RAC asked his committee if it would study and respond to the report of the Presidential Commission. There was an affirmative response, and two goals were established. First, a mechanism would be created for review of human gene therapy protocols, and second, there would be a responsibility for review of these protocols at such time when they would be presented. The HGTS was then formed for the express purpose of creating a document that would serve as a guideline for the review of human gene therapy protocols. By early 1985 the HGTS had completed the initial draft of a document entitled ''Points to Consider in the Design and Submission of Somatic Cell Human Gene Therapy Protocols'' (Wivel and Anderson, 1998).

This ''Points to Consider'' document was published in the *Federal Register* with the request for public comment, and the document was refined in response to these comments. A revised version was published in the *Federal Register* for a second time and additional modifications were made. On September 23, 1985, the ''Points to Consider'' document was presented to the full membership of the RAC and approved.

By February 1986, the executive secretary of the RAC sent a letter to all interested parties, calling for the submission of preclinical data that might pertain to human gene therapy research proposals. There were multiple seminal discussions at the meetings of the HGTS during 1986 and 1987. Topics that were discussed included retroviral vectors, transgenic animals, and the Food and Drug Administration (FDA) process for the regulation of investigational new drugs. By 1987, French Anderson and his collaborators had developed and presented for review a sizeable tome entitled ''Preclinical Data Document'' (Wivel and Anderson, 1998). Because of the vast amount of data that was included and the sheer size of the document, it was humorously designated as the ''telephone book.'' It created considerable work for the subcommittee, and its detractors used less complementary terms when describing it.

On July 29, 1988, the initial request for a clinical trial was formally presented to the HGTS by French Anderson, Steven Rosenberg, and their colleagues. This was not a true gene therapy proposal, but instead it was a ''gene-marking'' experiment that was designed to demonstrate that a retroviral vector containing the transgene encoding for neomycin resistance could be given to research subjects without inducing serious side effects. At this point, the HGTS formally decided to extend the range of its oversight to both gene transfer and gene therapy protocols. Following the initial review, approval was deferred pending the receipt of additional data. A second deferral was issued in September 1988 with the request for more data. On October 3, 1988, the RAC approved this protocol by a majority vote but the director of NIH, Dr. James Wyngaarden, did not give his approval, and on October 18, 1988, he requested that the protocol be resubmitted to the RAC with additional qualifying information. On December 9, 1988, the RAC approved the protocol, and subsequently, the NIH director gave his approval.

On January 30, 1989, the NIH director publicly announced approval of the gene-marking protocol, and immediately the Foundation for Economic Trends (FET) filed

a lawsuit to prevent research subjects from enrolling. Jeremy Rifkin of the FET, a long-time opponent of all developments related to biotechnology, successfully made his case in federal district court. He indicated that a telephone conference call during which the RAC approved the protocol was not a public meeting and therefore violated the *NIH Guidelines*. It took approximately 6 months for this matter to be resolved.

On March 30, 1990, French Anderson and Michael Blaese formally submitted a gene therapy protocol for the study of the form of severe combined immune deficiency (SCID) caused by adenosine deaminase deficiency (ADA). By June 1, the HGTS gave provisional approval for the trial, pending receipt of additional data. On July 30 and 31, 1990, a number of seminal events occurred. On July 30, the HGTS approved two protocols, the ADA protocol and a protocol for cancer using tumor-infiltrating lymphocytes (TILs) to deliver the tumor necrosis factor (TNF) to melanoma cells. At the RAC meeting on July 31 both protocols were approved. (NIH, 1990a, b, and c).

On September 14, 1990, Ashanti DiSilva was admitted to the Clinical Center at the NIH, where she was given approximately 10^9 autologous peripheral blood T lymphocytes containing the normal ADA gene. With this event, human gene therapy clinical research commenced. For an excellent account of this chronology, see Walters (1991) and the published minutes of the RAC meetings (NIH, 1989a and b).

Up to this point, the discussion of human gene therapy oversight has focused on protocol review at the national level (HGTS and RAC). In effect, there is another important component of the NIH-directed oversight and that occurs at the local level of review at individual institutions, usually academic medical centers. At the local level, two separate committees are involved, the Institutional Review Board (IRB) and the Institutional Biosafety Committee (IBC). The former is an ethics and scientific panel charged with protecting research subjects from unnecessary research risks, while the IBC origins are embedded in the requirements of the *NIH Guidelines.* Although generalizations can be tied to inaccuracies, the early phases of gene therapy review revealed that the IBCs tended to focus on the scientific aspects of the protocols while the IRBs gave a particular emphasis to the informed consent. However, both of these boards faced the challenges that occur with the advent of any new departure in the field of clinical research. Often there is a relative lack of expertise in confronting new paradigms.

As is often the case, the most knowledgeable people in the field in a given institution are the investigators who sponsor protocols, and such individuals confront the problem of a direct conflict of interest when defending the merits of a particular proposal. Such a problem is not unique to gene therapy. In the early days of local gene therapy oversight, the IBCs and IRBs gave protocols a provisional approval and then deferred to the HGTS and RAC before issuing a final approval. Such developments could aptly be described as the ''growing pains'' associated with the development of a new technology such as gene therapy.

For guidance, both local and national review bodies had to adhere to a compendium of specific requirements that evolved from the original ''Points to Consider.'' Such requirements became Appendix M of the *NIH Guidelines*. A more complete discussion of Appendix M is presented elsewhere (Wivel and Anderson, 1998). There have been continuing modifications of Appendix M since its origins in 1985, and many of these changes reflect an accrual of experience and the addition of new virus vector systems. The fundamental questions concerning a given trial are little changed from the first formulations.

The Evolution of RAC Oversight of Human Gene Therapy

Change is inevitable when a new technology is in its developmental stages. However, there was one feature of RAC deliberations that remained fairly constant over time. Because of the ''hybrid'' membership of the RAC (scientists and nonscientists), there evolved a partition of duties. The nonscientists were at a definite disadvantage when it came to the scientific aspects of the protocols. As a result, the ''public'' members devoted essentially all of their efforts to a review of the informed consent documents. Throughout its history of protocol review, the RAC debates over the form and substance of informed consent documents were marked by considerable entropy. Despite the frustrations of some of the ''public'' members, there was the underlying reality that the RAC's role with regard to informed consent was strictly advisory. The federal government had already established the Office of Protection from Research Risks, and its mandate was derived from a code of federal regulations (Protection of Human Subjects, 1983). Thus, the administrative responsibility for informed consent procedures was not even assigned to NIH, but was rather the province of a discrete entity within the Department of Health and Human Services. Through 45CFR46, the final control over the content of informed consent documents was delegated to the individual institutions sponsoring the research and administered through their IRBs. Although the RAC could make suggestions concerning the informed consent, there were instances where the IRBs chose not to accept those suggestions. Although the RAC was limited to a consultative capacity, there is little doubt that it had a measurable role in shaping the text of informed consent documents.

In the formative stages of human gene therapy research in the United States, there were two complete and independent systems for the review and approval of protocols. NIH controlled an oversight process while the FDA conducted a regulatory process mandated by a federal statute, the Food, Drug and Cosmetics Act. The NIH almost always conducted its reviews in a completely open forum while the FDA reviews were closed because of legal requirements pertaining to the protection of proprietary information. There is no question that the public review process did much to allay public fears concerning this new type of genetic intervention. Even prior to the approval of the first gene therapy protocol, a Lou Harris poll revealed that 52% of the participants believed gene therapy was not morally wrong, although 63% admitted to a serious paucity of knowledge about genetic engineering (Office of Technology Assessment, 1987).

As the field continued to develop, many of the earliest concerns about the safety of human gene therapy failed to materialize. A conservative approach is entirely appropriate at the outset, but the acquisition of knowledge and experience forces a constant reevaluation of oversight paradigms.

Beginning in 1991, the RAC and its HGTS had to confront the reality that there was an unnecessary redundancy in the dual review process. The dual review process was prolonging review without enhancing the safety or quality of the protocols. At its meeting on October 7–8, 1991, the RAC agreed to disbanding the HGTS and merging its membership with the RAC (NIH, 1991). This decision was made with the recognition that now the principal business of the RAC was the review of human gene therapy protocols. At the RAC meeting of February 10–11, 1992, the HGTS was formally disbanded and all protocol review was ceded to the RAC (NIH, 1992). RAC meetings were increased from three per year to four per year, and a one-year transition period was established to allow for members of the HGTS not already on the RAC to be appointed to the RAC.

A dominant pattern of disease targeting occurred during the period from 1990–1992 in that most of the protocols addressed cancer in its various forms. There was a repetitive strategy expressed in that most protocols utilized retroviral vectors to deliver cytokine genes such as IL-2 and GMCSF to autologous tumor cells with the goal of creating immune recognition and induction of cytotoxic T cells that would be tumor specific. Although the data from these trials showed some evidence of immune response, this did not translate into clinical effects.

All rules are subject to requests for exception, and in December 1992, two investigators (Drs. Ivor Royston and Robert Sobol) asked the director of NIH and the commissioner of the FDA to grant them a compassionate plea exemption so that they could treat a single patient with the brain tumor glioblastoma multiforme. This particular person happened to be a friend of Senator Tom Harkin of Iowa. It should be noted that Senator Harkin had a long record of being very supportive of the NIH.

However, this request represented a significant departure from all the established oversight procedures utilized by the RAC. There was less of an issue for the FDA because this agency had an in-place mechanism for approving compassionate treatment of single patients in lieu of a full-fledged regulatory review.

The RAC convened in December 1992 and expressed grave reservations about this alternative approach to approving protocols. Here was a new field of research in which all the protocols represented Phase 1 trials, and there was no evidence of efficacy in any of the trials that were underway. The investigators in question did not have any preclinical data, and they had no experience with retroviral vectors. They had obtained their vector as a gift from an experienced investigator. After a spirited discussion, members of the RAC agreed that expedited review could be tenable if the protocol in question represented a minor variation of a previously approved protocol. Since this particular protocol did not fit the minor variation category, the RAC did not approve the request. Subsequently the NIH director and the FDA commissioner approved the request on a compassionate plea basis, a completely legal procedure since they were federal government agency heads. Like other committees, the RAC is advisory to the NIH director; committee recommendations can be accepted or rejected. It is noteworthy that there have never been any additional requests of this type.

Subsequently, Dr. Bernadine Healy, who was then director of the NIH, came to the RAC in spring 1993 to defend her decision to grant the compassionate plea request. A tense discussion ensued and, suffice it to say, many acerbic comments were directed her way. Such is the nature of scientific debate!

In 1994, a new challenge to NIH oversight of gene therapy arose. A government advisory committee, the National AIDS Task Force on Drug Development, was created by the Department of Health and Human Services. This committee had a very mixed membership consisting of government officials, physicians, AIDS clinical researchers, pharmacologists, pharmaceutical company executives, and members of several AIDS activist groups. There was a great discontent expressed by the AIDS activists; they contended that the approval procedures for gene therapy protocols were totally redundant in that both NIH and FDA had to consent. It was proposed by the AIDS activists that the RAC be abolished and that sole review and approval be assigned to the FDA. This request was taken under advisement by the NIH director and FDA commissioner since they were both members of the task force. As a result of their deliberations, a compromise counterproposal was submitted to the task force. Under the provisions of this proposal, both the NIH and the FDA would review all new AIDS protocols simultaneously and appropriate staff members of the two agencies would consult. If a given protocol represented a significant departure in design or concept, as compared to previous protocols, it would receive dual agency review. If the protocol was not significantly different from the previous ones, it would receive a single review by the FDA. This proposed scheme for review was accepted by the task force and the RAC voted to approve changes in Appendix M of the *NIH Guidelines* that would accommodate the consolidated review process (NIH, 1994).

In 1995, then NIH director, Dr. Harold Varmus, appointed an *ad hoc* committee, co-chaired by Drs. Stuart Orkin and Arno Motulsky, to assess the review activities of the RAC, provide recommendations about a possible change in its role, define ways to modify its operations, and determine how it should function in its relation to gene therapy research. After multiple meetings, the committee issued an executive summary of its findings on September 8, 1995. A list of major recommendations included the following:

1. The RAC should no longer carry out a case-by-case review of every clinical gene therapy protocol in order to avoid duplication of effort and unnecessary delay.
2. Review of protocols by the RAC in an open public forum should be limited to those situations in which a particular protocol represents a significant departure from familiar practices. Examples would include the use of novel vectors involving human pathogens such as herpes viruses or lentiviruses, gene transfer *in utero*, potential germ-line gene modification, and gene transfer in normal human volunteers.
3. The RAC should continue to provide the NIH director with advice on policy matters relating to gene therapy and other recombinant DNA issues.
4. There should be an established means to systematically collect data needed for monitoring clinical gene transfer protocols even though all the protocols are no longer reviewed (NIH, 1995).

In May 1996, Dr. Varmus announced that he had made a decision concerning the future of the RAC. It was his intent

to abolish the RAC and replace it with a new smaller group of scientists and ethicists who would meet on an *ad hoc* basis to advise the director on relevant public policy issues affecting human gene therapy research. In 1996, a notice of intent was published in the *Federal Register*, with a request for public comment (Notice of Intent, 1996). Approximately 60 comments were received, and the vast majority echoed the notion that the RAC should be retained as the primary advisory body for all recombinant DNA research. In September 1996, Dr. Varmus announced that he would retain the RAC but would institute major changes regarding its make-up and responsibilities. The membership was reduced from 25 to 15, the approval process for human gene therapy protocols was to be abolished, and the RAC would organize regularly scheduled policy conferences concerning such topics as novel vectors, use of gene transfer in enhancement, and germ-line gene modification. To facilitate these changes, the *NIH Guidelines* were amended and the latest version of this document was published in October 1997 (NIH, 1997).

In keeping with its new mandate, the RAC established a streamlined review process that did not require approval of new gene therapy protocols, either from the RAC or the NIH director. All protocols were submitted to the RAC, and upon receipt, three RAC members were assigned to an initial review. Unless the protocol was deemed to represent a significant departure from existing practices or disease targets, it was not sent to the full RAC for public review. For those protocols reviewed in public by the full RAC, a series of suggestions for improvement were given to the principal investigators. These suggestions were not binding, but it should be noted that FDA officials were always in attendance at RAC meetings and could later choose to impose those suggestions as a part of their own review and approval process.

In keeping with its new mandate, the RAC began to organize and conduct a series of gene therapy policy conferences beginning in 1997. Among the topics discussed were: using lentiviruses as gene delivery vehicles; using gene transfer techniques for enhancement; *in utero* gene therapy; and inadvertent germ-line gene modification. Despite the significant operative changes, the ''fourth-generation'' RAC has continued to exert a telling influence on the field of recombinant DNA research.

For the past 13–15 years, the current format for RAC review has been in place. A vast majority of the new gene therapy protocols have not required public review. The only continuing reporting requirements imposed on investigators concern data from the actual clinical trials, and this information is entered into the Genetic Modification Clinical Research Information System (GEMCRIS) database.

It has been approximately 23 years since the first gene therapy trial was initiated, and well over a thousand trials have occurred since. After considerable periods with little success, there have been recent accomplishments that are noteworthy. One of the first achievements involves Leber's Familial Amaurosis, in which adeno-associated virus (AAV) vectors are used to deliver RPE65 to the retinas of affected patients. Given the considerable success of this work, it may well become the first FDA-approved gene therapy in the United States. Although gene therapy originated in the United States, several other countries have already granted regulatory approval to certain protocols. In China, an oncolytic herpes virus is used for the treatment of head and neck cancer, and recently the European Union has approved gene therapy for lipoprotein lipase deficiency.

The question of burdensome oversight has progressively increased over the past several years. Gene therapy has reached a sufficient maturation level so that one can question whether or not it is more problematic than other emerging technologies. Stem cell therapies have just as much potential for adverse events as gene therapy, and there is no national oversight committee for public review of this type of human experimentation.

The American Society for Gene and Cell Therapy (ASGCT) has taken the lead in questioning continued RAC review as it currently exists. Each year the senior officers of the ASGCT meet with the director of NIH and the various institute directors. In 2012, these meetings focused on the need to consider a termination of individual protocol review by the RAC. Dr. Xandra Breakefield, then president of the ASGCT, provided both spoken and written commentary about the need to drop individual protocol review by the RAC.

In 2013, Dr. Francis Collins, the current NIH director, requested that the Institute of Medicine (IOM) of the National Academy of Sciences undertake a study to determine the best future role for the RAC. Central to that study is the question of individual protocol review. Two meetings of the IOM committee have already been held, and a number of expert witnesses have testified. The committee planned to issue its findings by December 2013. Pending the NIH response to those findings, there may be a ''fifth generation'' RAC in place, or it is possible that the RAC could cease to exist. However, the later possibility may be unlikely.

RAC Epilogue

It has been 40 years since the first Asilomar conference convened. Recombinant DNA research has moved from laboratory experiments involving prokaryotes to the development of gene therapy techniques that are on the cusp of FDA approval. Once again, one is forcefully reminded that the development of new scientific technologies is a long, slow, and laborious process. Organ transplantation and monoclonal antibody therapy developed over decades and saw serious adverse events as a part of the price of maturation. Differentially, gene therapy had the advantage of a public forum in the RAC, resulting in the most thoroughly reviewed experiments in the history of biomedical research.

There are a number of unusual aspects of the RAC that merit comment. In terms of its ''genetic'' origins, it was not a product of the usual government bureaucracy but was a quixotic exception. It was not created by Congress, and thus it has no statutory origins. However, its creation persuaded Congress to resist legislation that could have crippled the field. Because the NIH is not a regulatory agency, the guiding document was necessarily the *NIH Guidelines*. Undoubtedly, the most attractive feature of the guidelines is the inherent ability to modify them quickly and easily. The *NIH Guidelines* have been modified scores of times in response to changing scientific needs and thus can be classified as a ''living'' document.

There are those outside the scientific community who are less than enthralled with the *NIH Guidelines*, and it should

not be surprising that the dissenters are in the legal community. It was previously noted that some lawyers view the guidelines as a *de facto* regulation because of the penalty clause. Still other legal scholars have suggested that the guidelines violate the Administrative Procedures Act because of improper lineage in creating the document. Under usual circumstances, the Secretary of Health and Human Services would order the creation of a set of guidelines, but fortunately the NIH director, Dr. Fredrickson, was not inhibited by such bureaucratic encumbrance and moved quickly in response to the deliberations of the second Asilomar conference.

The RAC has created another unusual conundrum concerning conflict of interest (Walters, 1991). As it exists, the RAC is an advisory committee to the NIH and was originally charged with fulfilling its role in a critical and independent manner. Yet the RAC sponsor is the chief funding agency for biomedical research in the United States. This has thrust the agency into the position of funding research on the one hand and simultaneously conducting quasi-regulatory oversight on certain aspects of that research. However, an objective observer would have to say that the two areas of responsibility have been carried out with no evidence of significant compromise.

Another quixotic facet of the RAC's existence concerns the nature of the review process. At the outset, RAC review was essentially concerned with safety, and most of the effort was spent on assuring adequate containment for the proposed experiments. In many cases, the science was assumed to be high quality. With the advent of gene therapy, new dimensions were added to the review process in that human subjects were now directly involved. Quality of science was always a major issue. Although this was a peer review process, there were fundamental differences as compared to the traditional NIH study sections. Although the matter of scientific quality was constantly discussed at the RAC, and investigators were repeatedly asked for additional data, protocols were never assigned priority scores. Since the RAC had no funding authority it could not assign priority scores, and thus gene therapy protocols did not compete against each other. Both RAC members and observers were known to remark that some of the approved gene therapy protocols would have had a modest priority score in a traditional study section. On balance, the RAC did commit to an unvarying concern for safety, and the repeated requests for additional data elevated the quality of the science.

In summary, the RAC has served as an important public forum that has facilitated scientific advancement. It could well serve as a model for other areas of science that would benefit from public oversight. In particular, stem cell research comes to mind. Like gene therapy at the outset, stem cell therapy has been given a lot of endorsement in the absence of supporting data. Unrealistic expectations have a way of creating backlash, and this was a problem that gene therapy had to confront. Many of the potential adverse events that confronted gene therapy also pose problems in the use of stem cells, in particular, the development of cancer as an unwanted complication.

It is well known to the scientific community and to some members of the public that new technologies always require justification for their existence. In a democratic society where public funding provides the bulk of research support, the public needs access to open discussion of the relevant scientific issues, particularly when progress is often muted and confusing. This open access is a most tolerable price to pay for new therapies that can improve the human condition.

Author Disclosure Statement

The author declares no competing financial interests.

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