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Commentaries

Off the RAC

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Should the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) continue in its advisory role regarding gene therapy? The workshop held August 6, 2013, in Washington, D.C., by the National Academies to assess the value of the RAC elicited a fascinating set of testimonies and comments on the contributions of the RAC since its inception and the potential contributions as gene therapy moves forward. The Institute of Medicine (IOM) Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee, based in part on the aforementioned testimonies, found sufficient reason for the RAC to continue, albeit in a restricted role (Rebecca N. Koehler, Bruce M. Altevogt, and Lawrence O. Gostin, eds.; Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee; 2013, in press). Furthermore, they suggested a standing RAC-type entity be empowered to monitor all novel, high-impact, life-sciences technologies.

Personally, I remain uncertain about the need for, practicality of, and utility of such an NIH-sponsored general review committee. But that argument is for another day. Let us focus on the RAC and whether or not it should continue. My own view, contrary to the majority of those who testified as well as the committee recommendation, is that while gene therapy still requires careful and informed oversight, I do not think the RAC is the appropriate vehicle to fulfill our needs. I do not believe it can credibly protect subjects in novel genetic research or keep the public well informed about the ethical considerations regarding new forms of gene therapy or gene transfer.

The contributions of the RAC in regards to providing oversight for gene therapy is decidedly mixed. It has created useful reports, helped provide scientific input in the assessment of clinical trials that might not otherwise have been available, and, in its earliest days, provided necessary assessments on investigators inclined to move forward with too much speed relative to maintaining the safety and utility of gene therapy (Wivel, current issue, 2014). Yet, despite the RAC spending a good deal of time fine-tuning informed consent documents for human gene therapy trials (Greely, current issue, 2014), the RAC's presence and input did very little to anticipate or avert problems in the gene therapy experiment at the University of Pennsylvania, during which a young subject, 18-year-old Jesse Gelsinger, died. There was a good deal of recrimination about the adequacy of consent used in recruiting Gelsinger, the failure to adequately highlight and clarify conflicts of interest associated with the trial, and the failure of the NIH to adequately monitor subjects in all early gene therapy trials (Stolberg, 2000).

The death of Gelsinger, arguably one of the most important instances of the failure of research oversight in the history of human experimentation since the 1970s, contains many lessons for gene therapy researchers (Wenner, 2009). But few have pointed to an enhanced role for the RAC as a key step to ensuring a subject's safety or understanding.

The RAC has always been a very unusual regulatory body. It is charged with offering advice to the NIH director, and interested third parties may attend to its insights through public hearings and written reports, but it has never had any formal authority from Congress, the Food and Drug Administration (FDA), or any other federal entity to set limits on research, mandate researcher conduct, or modify institutional behavior. Moreover, its review mandate has been confined to NIH-sponsored research. Neither of these limits permits the RAC to be useful at this point in the evolution of the genetic engineering of human beings for diagnostic and therapeutic purposes.

There are major ethical challenges facing the field of gene therapy. Increasingly, research is being sponsored by industry and not the NIH. The presence of powerful industry support, often in partnership with academic institutions, requires the elucidation of management strategies for dealing with conflicts of interest that are outside the ambit and expertise of the RAC. Patients are beginning to show interest in gaining access to gene therapy trials at earlier stages in the research process (Daniak, current issue, 2013; Farmer, current issue, 2013). This requires attention to be paid to the ethics of compassionate use regarding gene therapy. But again, the RAC is not the body to undertake either the assessment of the adequacy of existing rules and policies nor the entity to consider and respond to requests for early access.

Issues continue to arise about the permissibility of using gene therapy and transfer that might involve heritable forms

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of DNA being permanently altered. Again, the RAC is not the right entity to undertake an assessment of therapeutic interventions with momentous significance to society and future generations. And while there is keen interest in future efforts to utilize genetically engineered microbes to treat human disease, again, the RAC is not constituted with the expertise, either scientific or ethical, to provide the best advice on the future of applying synthetic biology or its products to human use.

The RAC played a very useful role in its earliest days. By creating the RAC, the NIH staved off Congressional and regulatory activity that, in retrospect, would have stifled important inquiry and set back efforts to advance the health of the public. That said, the RAC has outlived its usefulness. Gene therapy, gene transfer, tweaking genes to silence or activate them, and the genetic engineering of microbes for use in humans has evolved to the point that more regulatory guidance from Congressionally accountable federal agencies such as the FDA; more attention from the Office of Science and Technology Policy (OSTP); more international agreement on how to manage a rapidly growing area of clinical research (Tremblay *et al.*, 2013); and tighter local control by institutional review boards (IRBs), conflict of interest committees, and institutional biosafety committees is essential.

The RAC was best suited as a nimble source of quasi-independent advice publicly whispering in the ear of the NIH director. The rapidly maturing and increasingly promising field of human genetic engineering needs more input from wider perspectives and greater independence from the NIH. The rapidly evolving world of privately sponsored research; multisite and multinational clinical trials; and private, independent IRBs and data safety and monitoring boards needs to be brought into line with human genetic engineering and other cutting-edge fields of clinical research. Neither the RAC nor something closely resembling it that is housed inside the NIH and dominated by scientific perspectives identified by the NIH is the place to achieve this important ethical and policy work.

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