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A BULLETIN OF THE COUNCIL FOR RESPONSIBLE GENETICS

Australian Mouse Study Confirms CRG Warning

BY STUART A. NEWMAN

A recent news item ("Australians Create a Deadly Mouse Virus," *New York Times*, January 23, 2001) provides an apt occasion to reflect on the origin of the Council for Responsible Genetics (CRG) and to note the lag that may occur between judicious warnings about adverse consequences of biotechnology and their eventual realization.

During the late 1970s the specter of novel pathogens arising by accident or on purpose through use of the recently developed gene splicing technologies led to what has been termed the "recombinant DNA debate." Robert Pollack, a virologist at the Cold Spring Harbor Laboratory, was the first to bring these concerns to his colleagues, and this led to a letter of warning in *Science* magazine from a group of scientists central to the field in 1974. This group included the Nobel laureate James Watson, the future Nobelists Paul Berg, David Baltimore and Daniel Nathans, and the bacterial geneticist Stanley N. Cohen. This letter was followed by a conference in Asilomar, California, in 1975, where a set of guidelines for the conduct of recombinant DNA research was promulgated under a precautionary framework. Robert Sinsheimer, a microbial geneticist at Caltech, characterized the precautionary principle in a 1977 forum at the National Academy of Sciences, "In the broadest sense we are here, through the creation of wholly new gene combinations, intervening profoundly in the evolutionary process...we should take every possible precaution to keep these creations out of our biosphere."

CRG has been issuing warnings on all troublesome aspects of biotechnology during the more than two decades of its existence.

Although a version of the Asilomar guidelines was adopted in 1976 by the National Institutes of Health (NIH), the major U.S. public funder of biomedical research, by 1978 a new view had taken hold in the scientific establishment under the leadership of several of the signers of the 1974 *Science* letter and their allies. This view entirely abandoned the precautionary approach. In a 1977 *New Republic* article, for example, James Watson asserted that the Asilomar conference was "an exercise in the theater of the absurd" and that the effort to assess and control genetic engineering was "a massive miscalculation in which we cried wolf without having seen or even heard one." This shift led to the weakening of the NIH Guidelines and to attempts to dismantle them entirely. A detailed history of this policy rever-

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sal, which occurred under the impetus of increased federal funding and avid commercial interest, but in the absence of any new scientific findings that might have dispelled the original concerns, can be found in *Molecular Politics* (Univ. Chicago Press, 1994) by Susan Wright of the University of Michigan, a founding member of CRG.

The 1976-78 period was also when CRG began to take form (originally as the Coalition for Responsible Genetic Research), through the organizational efforts of Francine Simring of Friends of the Earth. The founding members of the Coalition were natural and social scientists who saw no basis for abandoning the original concerns about the biological novelties certain to arise from gene splicing methodologies, and who therefore helped organize a widening public discourse on this issue. For example, Liebe Cavalieri of the Sloan-Kettering Institute, in a 1976 article in the *New York Times Magazine*, was the first scientist to raise concerns about the production of novel pathogens by gene splicing technology before a national audience. Sheldon Krimsky of Tufts University, Jonathan King of MIT, Ruth Hubbard of Harvard University, and Nobel laureate George Wald, also of Harvard, participated in various hearings and public forums in Cambridge, Massachusetts in 1976 as advocates of the public's right to control the implementation of a new and uncertain technology (discussed in S. Krimsky, "Genetic Alchemy" MIT Press, 1982). Krimsky was also a member of the NIH Recombinant DNA Advisory Committee, where he was among the few voices in opposition to weakening the Guidelines and to the fortunately unsuccessful move to make them completely voluntary.

Whereas the failure of an unforeseen pathogen to emerge from recombinant DNA research during the following two decades provided ammunition for the Watson anti-regulatory position, the Australian study shows this confidence was premature. In the new article (R. J. Jackson et al., (2001). "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cyto-lytic Lymphocyte Responses and Over-comes Genetic Resistance to Mousepox." *J. Virol.* 2001, 75, 1205-1210) the investigators report transforming a smallpox-like virus, to which the strain of mice they were working with was resistant, into a virus that is fatal for that strain. They did this by arming the mousepox virus with a gene for a protein (interleukin-4), normally made by the mouse itself, but in different tissues and different amounts. Even mice that had been vaccinated against mousepox died after being infected with the genetically-engineered virus.

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The scientists told *Times* reporter William J. Broad that their goal had been to render the mice infertile and that the lethality of the new virus took them by surprise. Broad quotes Ronald M. Atlas, a microbiologist at the University of Louisville and president elect of the American Society for Microbiology, as saying "If there's a lesson in this, it's that you can create a more virulent pathogen," he said. "In 99 percent of the cases you would not, but in the others you can, and here's an example." Another scientist working for the U.S. Defense Department on germ defenses said, "It demonstrates a frightening message. Maybe it's easier to do these things than we think."

The accidental creation of a novel pathogen occurred as the result of altered biological properties that emerged with new combinations of genes, as anticipated by those who raised concerns in the 1970s. This unpredictability is a hazard that also exists with newer applications of these technologies such as genetically engineered crops (see M. Teitel and K. A. Wilson, *Genetically Engineered Food: Changing the Nature of Nature,* Park Street Press) and prospective genetically engineered humans (see S. A. Newman, "The Hazards of Human Developmental Gene Modification," *GeneWatch* vol. 13, No. 3). But it is clear that this research also enables the intentional production of new germ warfare agents (see S. Wright, *Preventing a Biological Arms Race*, MIT Press, 1990). According to Bob Seamark, director of the Cooperative Research Center for Pest Animal Control, a governmental group in Australia that coordinated the mouse virus research, "The best protection against any misuse of this technique was to issue a worldwide warning." CRG has been issuing such warnings on the various problematic aspects of biotechnology during the more than two decades of its existence. ◆

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