The Lessons of Asilomar and the H5N1 "Affair"

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ABSTRACT In mid-1974, soon after the first recombinant DNA molecules were replicated in *Escherichia coli*, scientists called for, and observed, a voluntary moratorium on certain experiments. One goal of the moratorium was to hold a conference (Asilomar) to evaluate the risks, if any, of this new technology. The Asilomar conference concluded that recombinant DNA research should proceed but under strict guidelines. The furor surrounding the recent genetic manipulation of the transmissibility of avian influenza virus H5N1 led to a short-term moratorium that has been extended indefinitely. The question is how long should the moratorium remain in place, or should it be permanent? Voltaire observed, "History never repeats itself; man always does." I believe the parallels of Asilomar can be applied to the problem facing biomedical science today. We should move forward to establish standardized guidelines, using common sense and scientific creativity. The onus of responsibility falls on the individual scientist and involves the education of a new generation of scientists into the social and ethical implications of genetic engineering in a new age of genomics and synthetic biology. In addition, scientists who work with infectious agents must deal not only with biosafety but also, alas, with bioterrorism. The H5N1 "affair" is not a question of freedom of inquiry or the dissemination of scientific research; it is a question of the social responsibility of science and scientists to ensure that the public understands why this work is beneficial and worthwhile.

Prepublication concerns, rumors, and the subsequent publication of two studies that reported the generation of mammalian-transmissible H5N1 virus in the laboratory have launched a passionate dialog among biomedical scientists about biosafety, biosecurity, and bioterrorism, not to mention the social responsibility of scientists. Because of the language and intensity of the discussion, the influenza virology community agreed to a voluntary 60-day pause of any research that involved highly pathogenic avian influenza H5N1 viruses and led to the generation of viruses that are more transmissible in mammals. Although originally planned for 60 days, this self-imposed moratorium remains in place, and there is a great deal of pressure to continue the moratorium until the multiple issues that have been raised about this research and its implications are dispassionately discussed at the worldwide level. The issues are not trivial. Some argue that research of this kind pushes the limits of legitimate scientific inquiry. Others argue that the research is essential for world health, epidemic surveillance, and vaccine development. The research is viewed in the broader context of genetic engineering and so-called dual-use research of concern (DURC). At a more fundamental level, there is a need to explain both the benefits and the hazards of such research to the public.

I have been asked to take a historical perspective of these questions based on my active participation in the Asilomar meeting of 1975 and my role as one of the original members of the recombinant DNA committee charged with drafting the first recombinant DNA research guidelines.

I think research on virus transmissibility is an essential focus of contemporary research not just for H5N1 but for all infectious agents. It is a foundation for effective vaccines and other preventive measures. How such experiments are performed needs to be discussed openly, with more attention paid to the science rather than to the rhetoric. The University of Wisconsin and Erasmus University groups had their H5N1 mammalian transfer experiment work approved by their local Institutional Biosafety Committee (IBC) and peer reviewed by NIH. The work was clearly identified at the outset as being DURC. It was unknown at the time how their research would progress or if they would be successful.

However, based on what we learned at the time of the recombinant DNA debate, I would argue that "once the first ferret sneezed," it would have been prudent for the investigators to have initiated a self-imposed moratorium and, once again, address the consequences of their research with the IBC and the NIH and plan a way forward. And perhaps they did. But the full implications of the work with regard to DURC were not realized, and the world was treated to an unexpected announcement at an International Virology meeting that H5N1 recombinants infectious to mammals had been created in the laboratory. Thus, I believe the moratorium should have been established sooner than it was and the work should have been subjected to a wider discussion of the broad issues facing science precipitated by the discovery of these recombinant viruses. It is akin to the discomfort and self-imposed moratorium put in place when it was realized in 1974 that a recombinant DNA molecule made in the laboratory with genes from the tumor virus SV40, *Escherichia coli*, and a bacterial virus was happily replicating in a strain of the human commensal bacterium, *E. coli*.

At the time of the recombinant DNA controversy, there was a moratorium on the cloning of toxins and certain genes from pathogens. This was immediately obvious. What is not as well remembered is that there was also a broad moratorium on cloning certain eukaryotic genes, for example, insulin into *E. coli*, until such time that the experiments could be done in an approved "safe" vector and "safe" host. It took several years before these

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prerequisites were available, and the moratorium remained in place until that time. Even when these experiments could be safely performed, the first experiments were done under biosafety level 3 (BSL3) conditions rather than at the more secure BSL4. The adoption of safe laboratory practices and the training necessary to conduct these experiments safely were implemented worldwide. The inclusion of nonscientists in forming these policy decisions strengthened and legitimized the efforts and led to an increased public awareness of this research and a more general willingness to accept biological research using DNA technologies. The entire process was open to reporters and journalists to keep the public updated with the decisions that would potentially guide the creation of new organisms and protect the environment.

I think that one answer to the dual-use problem and the dark specter painted by the critics of genetic engineering, including the H5N1 experiments, is the immediate implementation of training for investigators in the principles and practices of research that may have public health or social consequences. This approach is one reason the recombinant DNA research guidelines worked so well.

It will also be necessary to discuss and understand the risks posed by the information generated by the work rather than the risks posed by the physical agent or material (i.e., biosecurity rather than biosafety), a concept new to many of us. What about experiments that generate information with serious possibilities of misuse?

Critics have asked, "Why did no one in authority at the NIH or at the institutions where the research was conducted think through the consequences of this research before it was given the go-ahead?" I think when these matters arise, the responsibility must be placed on the individual investigator. The IBC, the study sections, and grant program oversight are only as effective as the information provided by the investigator. Once we train a generation of young scientists in what constitutes responsible research that may have unintended social consequences, it will become part of the research culture, as did the recombinant DNA guidelines. Mind you, this is not something that needs to await an international meeting. Every concerned biomedical scientist can begin to educate themselves and, more importantly, their students, staff, and colleagues now. The training materials already exist and can be employed to educate the lay public and the future members of an IBC and study section. In my view, this should not be a government-initiated or -driven program but rather a standardized program devised by working scientists and the professional organizations to which they belong.

The success of scientific leadership during the recombinant DNA debate of the mid-1970s was the result of a progression of experience, new technology, and education. This can be accomplished again even as more complex technology is available and the ability to alter the gene pool of the planet becomes experimental reality. The study of genomes of all living (even once living) things and their manipulation dominates much of contemporary research and thought in biology. It has altered both the way scientific questions are formulated and the way experiments are designed and carried out. It must be approached thoughtfully using, one hopes, common sense as well as scientific creativity.

In spite of widespread consternation among many scientists about the validity of the concerns, the H5N1 moratorium has been observed and ought to be continued. Recall that one goal of the self-imposed recombinant DNA moratorium was to provide time for an international conference(s) to be organized that would evaluate the state of the new technology and the risks associated with it. The Asilomar conference had a lasting impact on science and society. This is a new time, and an analogous event that calls for similar action. It makes sense to draw up guidelines and progress slowly. It is also a good time for scientists to learn how to talk effectively to the public and, in an age of instant reporting, to the press and media.

Finally, I should note that, in my mind, this current debate is not so much an issue about the freedom of scientific inquiry and the dissemination of scientific research as it is about the social responsibility of science and scientists. The (very privileged) social contract by which science is sustained depends on the public continuing to understand why this work is beneficial and worthwhile.

The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.