Controversy erupted when influenza researchers announced that they had created an H5N1 influenza virus that was transmissible between ferrets. The controversy escalated when the National Science Advisory Board for Biosecurity (NSABB) recommended that the work be published but recommended significant voluntary redactions. The responses to the NSABB action and to the research itself have been polarized. A readily transmitted H5N1 virus could be extraordinarily lethal; therefore, the risk for accidental release is significant, and deliberate misuse of the data to create a biological weapon is possible. However, the knowledge gained by these and future experiments under appropriate safeguards is likely to allow critical understanding of influenza transmission and virulence. It would be irresponsible to adopt either extreme solution: to prevent and censor the research or to allow unlimited distribution without careful review by an independent group, such as the NSABB.

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There is always a well-known solution to every human problem—neat, plausible, and wrong.
—H.L. Mencken, Prejudices: Second Series, 1920

Controversy erupted when influenza researchers announced at a September 2011 conference in Malta that they had created an H5N1 influenza virus that was transmissible between ferrets (1). They had used a combination of directed mutations and natural selection, suggesting that this H5N1 variant could be efficiently transmitted between humans. Highly pathogenic H5N1 influenza virus first emerged as a cause of human infection in an outbreak in Hong Kong in 1997 and, since 2003, has been causing major epizootics among birds but only sporadic human infections. In humans, it has proved to be highly lethal but poorly transmitted (2). As of January 2012, only 577 people in 15 countries have had documented infection; however, 340 of them (59%) have died (3, 4). The vast majority of infections has resulted from direct avian-to-human transmission, although limited human-to-human transmission has occurred (3). The controversy recently escalated when the National Science Advisory Board for Biosecurity (NSABB) announced its recommendation that the work of the 2 research groups, by then submitted and under review at Nature and Science, be permitted to be published but recommended significant voluntary redactions (5). The NSABB is an external advisory board to the National Institutes of Health; its charge includes providing “advice, guidance, and leadership regarding biosecurity oversight” of research with scientific value but the potential for malicious use (so-called “dual-use research”). The NSABB recommended that the manuscripts, submitted by Drs. Ron Fouchier of Erasmus University in the Netherlands and Yoshiro Kawaoka at the University of Wisconsin, be revised to remove details of their methods and the specific mutations that were identified. However, they recommended that these details be provided to scientists who have a “legitimate need for them in order to achieve public health goals.” This was the first time that the Board recommended a restriction on the contents of a scientific publication. The recommendations are not binding.

Not surprisingly, the responses to the NSABB action and to the research itself have been swift and polarized. Some maintain that the research should not be published in any form because of the risk that terrorists could recreate the experiments to create a catastrophic bioweapon. Some have raised the specter of accidental release and suggested that the experiments should never have been done in the first place (6, 7). In contrast, others strongly objected to any censorship of this scientific work, arguing that the data are critical to our understanding of influenza, science is self-regulating, and an unfettered exchange of data is critical for scientific progress (8). Some argue that the risks of an altered virus have been overstated and that any restrictions begin a slippery slope toward widespread governmental censorship of science. These arguments have merit, but their proponents have called for polarized solutions, either marked restrictions on the research and its dissemination or an unchecked, self-policing system. I believe that, to paraphrase H.L. Mencken, these “neat and plausible solutions” are both wrong. To balance complex risks and benefits, we need a more nuanced solution that permits the development of critical understanding of influenza while ensuring biosecurity.

It is important to begin by considering risk. The mutant H5N1 virus is potentially lethal and may have pandemic potential—readily transmissible H5N1 is therefore a legitimately frightening virus. To cause a pandemic, an influenza virus must meet 3 conditions: little or no preexisting population immunity, able to cause illness in humans, and efficient transmissibility between humans. The

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H5N1 virus currently meets the first and second conditions, and indeed excels at the second one. Although the case-fatality estimate of almost 60% may be artificially high because milder disease may not receive medical attention, serologic studies to date suggest that mild, undiagnosed H5N1 infection is very uncommon among contacts or neighbors (9). Animal experiments also confirm the unusual virulence of H5N1 (10). In contrast, the 1918 Spanish influenza virus had a case-fatality rate of only around 2% but killed 50 to 80 million people in a worldwide pandemic. That H5N1 has not demonstrated effective human-to-human transmission to date despite extensive viral evolution has provided some reassurance that it might be unlikely to cause a pandemic.

Previous attempts to create an H5N1 variant that was transmissible between ferrets were unsuccessful (11–14). However, the work of Fouchier and Kawaoka, if correct, suggest that any biological barrier to the evolution of a transmissible H5N1 virus may not be sufficiently robust. Although we should use caution in drawing conclusions, ferrets are an extremely useful, albeit imperfect, model of influenza transmissibility and pathogenicity. In many ways, the ferret model mimics human disease (15); however, until the papers are published, it is impossible to evaluate the experiments in detail.

In regard to concerns over accidental release, the current experiments were apparently done under enhanced biosafety level–3 precautions in laboratories with extensive experience. However, laboratory requirements for air handling and personal protective equipment alone are not enough to provide true biosecurity. The systems for screening personnel and evaluating ongoing compliance with biosafety and biosecurity requirements can and should be improved.

In addition, we cannot ignore the potential for intentional use of pathogens as weapons. There is substantial evidence that several groups have pursued development of biological weapons (16). Yet, a highly virulent strain of influenza would make a relatively poor choice of biologic weapon for political terror. Compared with other potential agents, such as Bacillus anthracis, H5N1 would require substantial scientific skill to manipulate, even if the handler had knowledge of the precise methods used in these studies. Nonetheless, it would be ill-advised to provide a complete roadmap to the creation of H5N1 with pandemic potential.

There are strong arguments for doing these and future studies under the appropriate safeguards and sharing the information gained. Our understanding of the molecular determinants of virulence, species specificity, and transmissibility of influenza viruses is very incomplete (17). These crucial characteristics are complex and polygenic and have partial overlap. Human-adapted influenza viruses bind to α2-6–linked sialic acid containing glycoconjuncts that are located predominantly on nonciliated cells of the mucosa of the nose and upper airway. The H5N1 virus and other avian strains predominantly bind to α2-6–linked sialic acids that are present in the ciliated cells of the lower respiratory tract in humans (18). In the 1918 virus, alteration of only 2 amino acid residues was enough to abolish transmissibility (19); however, binding to α2-6 sialic acid is necessary but not sufficient for transmission in humans and ferrets. Adaptations in other genes, including the polymerase complex, seem to be necessary. Understanding which genes and which regions must change, and ultimately understanding the structural and phenotypic changes that allowed the creation of a readily transmissible H5N1 virus, can provide critical information. These insights can facilitate screening of H5N1 strains and other novel influenza viruses for pandemic potential and, more important, provide critical insights to develop targets for antiviral or immunologic therapies.

How, then, can society balance the risks and benefits of research on this and other highly virulent pathogens that have the potential for “dual use”? The risks and benefits should be considered well in advance. Plans for appropriate biosafety and biosecurity must be rigorously reviewed. Whether current oversight of training and adherence to biosafety requirements, either in the United States or internationally, is adequate remains unclear. Improved training for investigators in all these areas is needed, as has been emphasized by the NSABB (20, 21). Free and open exchange of data is a cornerstone of modern science. However, there are circumstances in which the information generated creates a significant risk for misuse. Review by an independent, expert, accountable, and transparent group of scientists, such as the NSABB, is an appropriate method and I believe much more acceptable than direct oversight by government authorities. The advantages of NSABB review were already demonstrated after the remarkable creation of replicating an infectious 1918 pandemic influenza virus using sequences generated from molecular fragments recovered from lung tissue of a victim and formalin fixed tissue (22, 23). At the time, some security experts contended that the data were too dangerous to publish. The manuscripts were reviewed by the NSABB, which recommended publication with only minor revisions to describe the biosafety precautions and to emphasize the potential value of the work. Since then, characterization of the 1918 virus has continued to provide critical insights into influenza pathogenesis (24–27). In my opinion, the NSABB has, to date, successfully navigated between the Scylla of zealous censorship by security officials and the Charybdis of facilitating deliberate misuse of the data. However, we still seem to lack a readily transparent and thoughtful mechanism to provide the details to those with a legitimate need for the data and to decide who those individuals should be. We now have an unprecedented ability to learn about pathogenicity and epidemic potential in nature, often by creating potentially more dangerous pathogens in our laboratories. We must have a careful and balanced approach that is neither too timid in per-
mitting the performance and sharing of critical research nor too irresponsible in confronting the biosecurity issues posed by that research.

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