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Biosecurity with 'bio-sense'

In the chill of early January 2003, the US National Academy of Sciences (NAS) organized a Washington, DC, meeting of international journal editors and security experts to explore how best to deal with manuscripts containing data that could be put nefarious ends, or 'dual-use' biology. The editors issued a statement acknowledging their key role in upholding the integrity of the scientific literature and in ensuring that data are published with sufficient detail for verification and reproducibility. Simultaneously, they voluntarily agreed to evaluate manuscripts perceived to contain dual-use information with the help of expert advice on biosafety risks, along with the usual peer review. Almost two years have elapsed since that meeting. Is a consensus building on where to draw some lines concerning benefit to the public versus the risk of misuse?

The anthrax attacks in 2001 created an atmosphere of anxiety. Into this milieu were dropped a few publications that probably would have slipped below the public's radar pre-9/11, but were instead held up to close scrutiny. These papers caught the eye of the press, and the public questioned whether they were too risky for the public literature. In early 2002, Jackson *et al.* reported in the *Journal of Virology* the construction of an interleukin-4-containing mousepox strain to be used as a vehicle for a contraceptive vaccine. Aiming only to skew the immune response toward antibody production, the altered virus could kill genetically resistant mice that had been vaccinated to mousepox. The public feared that the same technique might be used by bioterrorists to engineer a more virulent strain of smallpox. Often lost in the discussion were why the experiments were performed and the fact that cytokine genes were already known to increase virus fitness. Of course, placing the data in the open literature allowed the scientific community to better understand the potential danger of such approaches and generated interest in the pursuit of countermeasures.

Another paper engendered even more controversy. In the summer of 2002, Wimmer and colleagues reported in *Science* the synthesis of infectious poliovirus *in vitro* from oligonucleotides. This proof-of-principle was criticized for providing a virtual cookbook for bioterrorists and yet little new biological insight. Although the former could preclude publication in any journal, it pays to remember that the latter only affects the decision of where, not if, to publish the work. Publication proceeded because the journal decided the paper did not present a biosecurity risk; polio is not a terrific choice for a terrorist attack, and most viruses are easier to grow from viral templates than to synthesize from scratch.

After the 2003 NAS meeting, editorial decisions about biosafety did not become easier to make. In October of that year, however, an NAS report helped in the identification of those papers that would benefit from expert security advice. The committee, chaired by Gerald Fink, Massachusetts Institute of Technology, generated some commonsense and useful guidelines to seven classes of experiments that should give cause for concern. These are experiments that render a vaccine ineffective, confer resistance to useful antibiotics or antivirals, enhance virulence of pathogens or nonpathogens, increase the transmissibility of a pathogen, alter the host range of a pathogen, render the pathogen harder to detect, or 'weaponize' biological agents or toxins.

Since the NAS meeting, more dual-use papers have been published. Among the findings that attracted public scrutiny were the sequencing of the anthrax genome (*Nature*, May 2003), the solving of the crystal structure of a receptor-binding conformation of the hemagglutinin from the pandemic 1918 strain of influenza (*Science,* March 2004) and, in *Nature* this past October, Kawaoka's construction of a virulent hybrid flu strain containing pieces of influenza 1918 virus, a study that provided insight into the molecular mechanism behind its lethal intensity. Also during this time, the SARS virus was identified and many variants were sequenced and published, to accolades from the public.

The attention and discussion in the community of most of these papers had a different tone than before the 2003 NAS meeting. Perhaps this was due to more effective efforts by the journals in not only explaining to the public the usefulness of these data but also clearly emphasizing the safety precautions under which they were obtained. Perhaps some credit can also be given to journals for quietly implementing NAS meeting–inspired procedures to obtain advice from biosecurity experts, enabling more informed decisions and giving editors the confidence to publish what should be published.

Ultimately, the benefits of publication largely outweigh the risks of restricting biological information. Knowing the mechanisms by which microbes outwit our immune systems or increase their virulence is essential for dealing with the very real public health problems of existing and emerging infectious disease, as well as for enabling an effective reaction to any bioterrorist actions. Open publication of pathogenic genomes, such as that of SARS, has proven to be instrumental in the identification, detection and surveillance of such menaces. Carefully conducted investigations that use hybrid pathogens, such as Kawaoka's October *Nature* paper, are accepted as critical in our battle against scourges like the flu, which annually kills almost half a million people worldwide. Thus, a faint line guiding what should be published is, indeed, beginning to emerge in the sand.

Given the energy and activity of the legitimate bioscience enterprise, governments are duty-bound to harness, rather than hinder, this international resource. And given the international nature of biomedical research, any local concerted effort to curtail experimentation or publication will only hasten its appearance elsewhere. We should instead continue to use informed editorial vigilance, with its accumulating credible record, as the 'bio-sensible' avenue to tread.