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EDITORIAL

Virus Research: Fuelling New Fears

Oswald Avery's identification of DNA, in the 1940s, as the 'pneumococcal transforming principle' may be justly regarded as the first step in establishing the chemical nature of genes. Genetics, midwifed into existence by Mendel in the 19th century, suddenly seemed connected to chemistry. Almost exactly half a century has passed since the Nobel prize recognized the unprecedented insights into the chemistry of heredity, provided by the Watson–Crick double helical structure of DNA. DNA's monotonous chemistry revealed a robust and efficient mechanism for storage and transmission of information over generations. Molecular biology's advance, in the years that followed the postulation of the DNA structure, has been blinding, at times. Even twenty five years ago few would have imagined that the entire sequence of the human genome would be available by the turn of the century. The methodologies of sequencing and synthesising DNA have reached a level of sophistication and automation that these operations are best done by companies for a price. Cloning is a term that is now commonly used. A new discipline of 'synthetic biology' is rearing its head. Techniques imported from physics and chemistry, available on superbly engineered instrumental platforms, have provided a near atomic level view of molecules and their interactions, which define cellular chemistry. The cell, with its thousands of chemical constituents, is now the unit of discussion in biology. Chemicals and chemistry allow cells, and indeed organisms, to communicate and interact. Biology's explosive growth has held out great promise for revolutions in areas central to the human condition – health and agriculture. Biology's transformation over the last half a century has propelled the discipline to the forefront in public perception of science; rivalled only by the attention bestowed on information and communication technologies, which have also exploded over the past few decades. It is fashionable today to envision a brave new world developing at the confluence of biotechnology, information technology and the emerging field of nanotechnology.

The 'gene revolution' in biology quickly brought to the fore the possibility of 'genetic engineering'. Many questions, once the domain of imaginative authors of science fiction, could be legitimately asked. Can new organisms, with new characteristics, be created? Can long extinct organisms be resurrected? Michael Crichton's *Jurassic Park* captured the imagination of dinosaur fans (and there are undoubtedly many). Purists were quick to pounce on the scientific inaccuracies that render Crichton's scenario implausible. In the early days of recombinant DNA technology and genetic engineering, fears about the new advances in biology were widespread, even amongst molecular biologists. The 1975 Asilomar meeting, initiated and organized by leading researchers in the emerging field of recombinant DNA technology, was critical in setting standards and allaying fears, 'allowing geneticists to push research to its limits without endangering public health'. Paul Berg, the 1980 Nobel laureate in chemistry, describes the background to the 1975 meeting in California and its outcome which opened up the new field of genetic engineering (*Nature*, 2008, **455**, 290). Berg notes that 'the conference marked the beginning of an exceptional era for science and the public discussion of science policy'.

The experiences of the Asilomar conference will undoubtedly be recalled repeatedly in the aftermath of a recent move to remove key experimental details from two papers on the H5N1 avian influenza virus, which are currently being considered for publication in *Science* and *Nature*. The papers establish that viruses that possess a specific protein, a hemagglutinin, from the H5N1 influenza virus can become transmissible in an animal model. These studies conducted using ferrets may help further understanding of how viruses found in nature become capable of transmission amongst humans. The authors based in The Netherlands and the United States have taken the unprecedented step of 'a voluntary pause of 60 days on any research involving highly pathogenic avian influenza H5N1 viruses, leading to the generation of new viruses that are more transmissible in mammals'. The self-imposed moratorium has been advanced to provide time for discussions on the issue as 'organizations and governments around the world need time to find the best solution for opportunities and challenges that stem from the work' (Fouchier, R. A. M., García-Sastre, A. and Kawaoka, Y., *Nature*, 2012, **481**, 443).

The move to review and possibly 'censor' scientific papers as a result of biosecurity concerns is unprecedented. The National Science Advisory Board for Biosecurity (NSABB), apparently a body with no regulatory authority, suggested to *Science* that key details necessary for reproducing the results be omitted. The journals are apparently agreeable 'if the government delivered a "transparent plan" for sharing the details' (Enserink, M. and Malakoff, D., *Science*, 2012, **335**, 22). Thus far, all discussions have involved the US government and its

agencies. A feature in *Nature* (January 19, 2012) provides views of ten experts, not all of whom agree on the issue. One of the authors of the controversial papers, Ron Fouchier, asks 'whether it is appropriate to have one country dominate a discussion that has an impact on scientists and public health officials worldwide'. He notes that 'there is no global equivalent of NSABB' and concludes that 'an issue this big should not be decided by one country, but by all of us' (Fouchier, R. and Osterhaus, A., *Nature*, 2012, **481**, 257). The major fear about the H5N1 papers appears to be that publication of detailed protocols for engineering a more transmissible influenza virus would provide a new avenue for bioterrorists. While procedures for producing incendiaries, explosives and even nuclear devices are accessible, the prospect of biological weapons in the wrong hands appears to engender greater fear. This is undoubtedly due to the transmissibility of pathogens in human populations, a process that occurs silently and insidiously. Are there other concerns? It would appear that an even more immediate worry is the danger of laboratory infections. A brief and sharply worded point of view suggests the probabilities of infections accidentally acquired in the laboratory are significant and that the probabilities of chance escape will increase as the number of investigating labs increases. Indeed, 'regulators should not be sitting idly by, while the threat of a man-made pandemic looms' (Klotz, L. and Sylvester, E., *Nature*, 2012, **481**, 258). The importance of the new papers on H5N1 for understanding how viruses move from one host to another is evident to most commentators in the field.

For specialists in the area of influenza virus research, the H5N1 episode must evoke memories of an earlier discussion when the virus that caused the 1918 Spanish influenza pandemic was resurrected (Tumpey, T. M. *et al.*, *Science*, 2005, **310**, 77; Kaiser, J., *ibid*, 2005, **310**, 28). The viral genome was reconstructed based on complete coding sequences of viral RNA determined from genomic RNA 'recovered from frozen, unfixed lung tissues from an Alaskan influenza victim who was buried in permafrost in November 1918'. The 1918 virus was extraordinarily virulent and has been held responsible for 'up to 50 million deaths worldwide, including an estimated 675,000 deaths in the United States'. By contrast, contemporary H1N1 viruses are relatively benign. Resurrecting the 1918 virus allowed Tumpey *et al.* to identify the mechanisms underlying the high virulence. Most importantly, the resurrected virus strains could be killed by currently available antiviral drugs, oseltamivir (*Tamiflu*) and amantadine (*Symmetrel*) and were sensitive to the seasonal flu vaccine. One of the authors of the 1918 Spanish Flu virus paper in a strongly worded comment on the H5N1 controversy argues that 'life-saving science' should not be censored. In recounting the story of the resurrection of the 1918 virus he notes: 'Had we not reconstructed the virus and shared our results with the community, we would still be in fear that a nefarious scientist would recreate the Spanish flu and release it on an unprotected world. We now know such a worst-case scenario is no longer possible'. Curiously, the 2005 paper on the Spanish flu virus was also considered by NSABB and eventually published in full. In considering what is euphemistically called 'dual use research', the perspectives of researchers immersed in biology can differ sharply from those interested solely in biosecurity. Critics of the H5N1 research have raised grim possibilities: 'It is a virus that is capable of killing half its victims, a proportion greater than that for any endemic disease. Were that coupled with the transmissibility of a pandemic flu virus, it would have characteristics of an ultimate biological weapon unknown even in science fiction. We should not publish a blueprint for constructing such an organism' (Henderson, D. A., *Nature*, 2012, **481**, 258).

In many ways, the discussion that has begun is reminiscent of the mood that preceded the Asilomar conference in 1975. Writing over three decades later, Paul Berg asks: 'Apart from laying the foundations for an effective safety regime, what else did Asilomar achieve?' His answer: 'I feel that scientists were able to gain the public's trust – something that is now much more difficult for researchers working in biotechnology'. He concludes: '…there is a lesson in Asilomar for all of science: the best way to respond to concerns created by emerging knowledge or early stage technologies is for scientists from publicly funded institutions to find common cause with the wider public about the best way to regulate – as early as possible. Once scientists from corporations begin to dominate the research enterprise, it will simply be too late' (*Nature*, 2008, **455**, 290).

In the mid-1970s terrorism was not yet the major concern that it is today. However, under the impregnable cover of 'national security' a great deal of research that would have raised public alarm was indeed carried out. Berg noted the difficulties of regulation once corporate interests begun to dominate. This is also true of research that has for decades been protected by the security umbrella of advanced countries. Although biology's advances sometimes raise concerns, most often the new technologies provide fascinating insights into our past, DNA extracts from bones and teeth recovered from cemeteries near London where victims of the 'Black Death' of 1347–51 were interred, have yielded information to reconstruct the genome of the bacterium *Yersinia pestis* responsible for the medieval plague (Schuenemann, V. J. *et al.*, *Proc. Natl. Acad. Sci. USA*, 2011, **108**, E746). Characterising ancient pathogens will undoubtedly provide insights into the evolution and epidemiology of human infectious disease. Will the bacterium itself be resurrected? Time alone will tell. But a commentary in *Nature* (October 27, 2011, p. 444) notes that while 'this may sound alarming … such a strain could be easily treated with modern antibiotics'. There is a great deal of history embedded in DNA waiting to be read. Avery, one of modern science's unsung heroes, would be surprised at the turn of events.

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