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A ripe time for gaining ground

After three years of heated debate, the advocates and critics of gain-of-function research must work to agree on how best to regulate the work.

Late last week, the White House Office of Science and Technology Policy and the US Department of Health and Human Services announced an immediate pause in all new government funding for gain-of-function (GOF) research — experiments to boost the transmissibility, virulence or host range of pathogens — on influenzas, Middle East respiratory syndrome and severe acute respiratory syndrome.

The pause is to allow time to develop a new policy on how such work should be conducted and regulated. The policy will be informed by a full assessment of the risks and benefits of the work, and by how these compare with those for safer alternatives. In charge of that assessment is the National Science Advisory Board for Biosecurity (NSABB), which is meeting this week for the first time in two years (see page 411). The board will also advise on the policy's content. In parallel, the National Research Council (NRC) of the National Academies will convene a scientific conference on the issues surrounding GOF research, including its risks and benefits. It will also review the NSABB's draft recommendations for the new policy.

Controversy over GOF research was first sparked in late 2011 when the NSABB attempted to stop the publication of the full results of two studies in which the H5N1 avian flu virus had been engineered to become transmissible in mammals. The board and others were worried that information in the papers could help terrorists or other malevolent individuals to develop a bioweapon. Those concerns were finally overruled, and on 24 September, the United States adopted new rules on what is known as dual-use research — work that could be misapplied to do harm — on 15 pathogens or toxins.

A wider concern raised at the time — which has since shifted to front and centre — was the risk of a pathogen that had been engineered to become more dangerous escaping from the lab. In February 2012, the US Department of Health and Human Services added another layer of review for grant proposals involving GOF research, but only for H5N1; this was extended to H7N9 in August 2013. The research community became deeply polarized over the issues surrounding GOF work. Some vaunted the benefits of such research for pandemic preparedness and down-played biosafety and biosecurity risks, whereas others argued that the experiments should not be done because the risks far outweighed the benefits. To allow time for debate, GOF researchers agreed to put their research on hold, resuming work a year later after deciding that enough time had passed.

The decision to implement another moratorium — and to broaden it to pathogens other than the H5N1 and H7N9 flu viruses — is a belated acknowledgement that the issue of how to handle GOF research is far from resolved. And the revelations over the past few months of serious violations and accidents at some of the leading biosafety containment labs in the United States has burst the hubris that some scientists, and their institutions, have in their perceived ability to work safely with dangerous pathogens. The US administration cited these revelations as one reason for the latest review; behind-the-scenes lobbying by critics of GOF research also played a part.

The climate for constructive discussion is now perhaps better than it was: although opinions remain sharply divided, each side now seems to be listening more to the other. In July, almost 300 scientists and policy experts signed up to the 'Cambridge Consensus', which criticized the lack of a proper risk–benefit assessment of the research, and called for exactly what the US government has now agreed to do. More than 200 scientists responded with 'Scientists for Science', which defended GOF research and the ability to carry it out safely, but acquiesced on the possibility of further discussion, as long as it was done "under the auspices of a neutral party", such as the US National Academy of Sciences.

"The climate for constructive discussion is now perhaps better than it was."

In a sign of the potential for common ground, Ian Lipkin, a renowned virus hunter at Columbia University in New York, saw fit to sign both calls. Both arguments have merit, he says, but both are also incomplete. Last week, a group of scientists including both opponents and supporters of GOF flu research, published a sober assessment of the potential and limitations of current approaches to assess the potential pandemic risk of various flu viruses (C. A. Russell *et al. eLife* **3,** 03883; 2014). It paints a much more nuanced picture than some of the bold claims made earlier for GOF research. We need more such balanced analyses, and fewer dogmatic opinions, on both sides. ■

The ice bucket

Social-media fun for medical research bypasses animal sensitivities.

Film-maker Steven Spielberg did it. Nobel laureates Thomas Südhof and Shinya Yamanaka did it. The fashion world's Naomi Campbell and Victoria Beckham did it. Physicist Stephen Hawking — who has the disease amyotrophic lateral sclerosis (ALS) — watched as his children did it on his behalf. They, perhaps you, and millions of others all took the 'ice-bucket challenge'.

Even if the name is unfamiliar, the images are unlikely to be. The challenge involved being filmed as you had a bucket of iced water thrown on you. For the privilege, most people pledged money for research into ALS, also known as motor-neuron disease, and then nominated others to take the challenge. The resulting little movies were posted on the Internet. It was a lot of fun.

As many of the people who took the challenge understand, ALS is a dreadful illness. Motor neurons in the brain and spinal cord degenerate

and lead to paralysis. It is relatively rare, affecting 4–7 in 100,000 people. But there is no cure, and no good understanding of its cause.

The ice-bucket challenge emerged in the United States in July and went viral around the globe, peaking in August. During that month, the ALS Association in Washington DC received more than US$100 million in donations, compared with $2.8 million collected during August 2013. Already, the association has distributed some $20 million of that for research. ALS societies in Germany and the Netherlands hauled in more than $1 million each. Australia managed more than $2 million and Japan more than a quarter of a million. The UK Motor Neuron Disease (MND) Association in Northampton attracted 910,000 donations in just three August weeks, compared with its average monthly score of 13,000. Research has never benefited from a social-media phenomenon to this extent before.

The success of the activity is an endorsement of medical research by the general public. The associations that benefited have been careful to explain that the money will be distributed through expert review. This means that only the best research will be funded. Yet during all the excitement, what mention was made of the fact that research leading to effective treatments will eventually, one way or another, require the use of animals?

The research collaborations chosen on 2 October in the ALS Association's first round of funding are mostly based on human genomic and stem-cell approaches, which tactfully avoids the animal issue. By contrast, beneficiaries of the MND Association's windfall include both clinical research and research that uses animal models. ALS is a disease that can be caused by different factors in different people. Because its aetiology is so poorly understood, the animal models generated so far — in, for example, flies, mice and monkeys — are not totally reliable. Much will be gained from the human-genetic approaches now under way. They could help to develop better animal models.

Would members of the public have participated so joyously in the activity if they had known that research on animals might benefit from their donations? Had that sensitive question been raised, the mood might have been different and its consequences for medical research damaged. But glossing over the reality of such research is not a good strategy for avoiding crises; instead, life scientists and their organizations should take every opportunity to say when animals have been used in research, and to explain why. Societal discussions about responsible animal research need to take place outside periods of crisis.

It is encouraging to see the tide slowly turning towards such openness — witness the MND Association's upfront funding of the full spectrum of necessary research. And outside the ice-bucket excitement, last week saw another major advance. On 13 October, the US Society for Neuroscience and the Federation of European Neuroscience Societies combined their might to publish, for the first time, a public statement in support of a neuroscientist under attack: Nikos Logothetis, a director at the Max Planck Institute for Biological Cybernetics in Tübingen, Germany, who works with monkeys. His lab had been infiltrated by an animal activist who filmed the primates there, and the videos were used as propaganda by organizations opposed to any research on animals. (An independent investigation at the institute declared that there were no systematic problems with animal care there.)

"There are many ways to support medical research."

This sort of vocal support for research is important. Logothetis's work on the brain is fundamental, but applied research on degenerative diseases, including ALS, will be aided by a better understanding of the complex organ in which the diseases originate.

There are many ways to support medical research. Engaging people's enthusiasm with actions such as the ice-bucket challenge is an important one. Public support by scientific organizations for the responsible actions of their members is another. The challenge is great, the need even greater. ■

Toxic influence

Europe must act to stop livestock drugs from wiping out its vulture populations.

A dead vulture in Spain could herald a crisis for raptor populations, because a drug that has killed hundreds of thousands of birds and driven some species to the brink of extinction in Asia now threatens to do the same in Europe. The European Medicines Agency (EMA) must clamp down on the drug.

The Spanish bird died two years ago. Now, the probable cause has been identified as a drug given to livestock (I. Zorrilla *et al. Conserv. Biol.* http://doi.org/wf5; 2014). Events in Asia show how serious the consequences could be. In the 1990s, vultures on the Indian subcontinent started dying in huge numbers. Some populations lost more than 95% of their animals. The consequences were catastrophic. As the skies cleared, dead livestock were left to rot in fields.

Research finally pinned the blame on the anti-inflammatory drug diclofenac, which had become widely used in cattle for problems ranging from pneumonia to mastitis. Although harmless to bovines, it is highly toxic to vultures that feed on the carcasses (J. L. Oaks *et al. Nature* **427,** 630–633; 2004).

As a result, India, Pakistan and Nepal placed heavy restrictions on the use of the drug in livestock. And although campaigners say that large vials officially designated for human use are often repurposed by veterinarians, the threat to the vultures of Asia has decreased. Numbers have not yet recovered, and in some cases are still declining, but the birds at least now stand a chance.

Europe is heading in the opposite direction. Despite warnings from scientists, Spain — home to the vast majority of Europe's vultures — last year licensed diclofenac for livestock use. The EMA is considering the risks posed by the drug, and is scheduled to reach a decision by the end of November.

The discovery that the 2012 vulture was probably felled by a related drug, called flunixin (see *Nature* http://doi.org/wfx; 2014), is worrying for two reasons. First, it shows that diclofenac is not the only product in the class known as non-steroidal anti-inflammatory drugs (NSAIDs) that has the potential to kill vultures and other birds of prey. Second, it shows that carcasses containing significant quantities of these drugs are reaching the wild-animal food chain in Europe — in this case, probably through the Spanish tradition of wild-animal feeding stations known as *muladares*.

Two things should now happen. The EMA must move to heavily restrict — if not ban — the use of diclofenac in livestock. An alternative drug that does not harm vultures — meloxicam — is already available, and vets should use this in preference. And, as urged by the researchers who reported the flunixin-killed vulture, regulators should look at the effects of all NSAIDs used in livestock on vultures. Although diclofenac could well be the most deadly, we must know what other drugs also pose a threat to birds that feast on carrion, and how they might be managed.

In the longer term, regulators in Spain and the rest of the European Union need to ask how a drug with such evidence of environmental damage was allowed to come onto the market.

Spain is an important stronghold for vultures, and this alone would be reason enough to look seriously at restricting the use of diclofenac. But the European Union needs to set an example for the rest of the world. If it allows diclofenac use to continue, countries such as India could well decide to ease their restrictions, and African nations may rethink their plans to ban it. ■

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