REPRODUCIBILITY

One paper, two discussions

Anaesthesia journal asks independent experts to draw their own conclusions on studies.

BY DAVID ADAM

How deeply an anaesthetist should sedate an elderly person before surgery is a controversial issue — some studies link stronger doses of anaesthetic with earlier deaths. So it should reassure clinicians to see a study[1] in the *British Journal of Anaesthesia* that investigates and rules out such a link — the paper's discussion section says so explicitly.

But another paper[2] in the journal that discusses the clinical trial analyses the same results and reaches a different conclusion about death rates. It says that the trial didn't include enough patients to reach such a conclusion.

The opposing takes on the mortality link — a secondary finding of the original study — are the result of an unusual peer-review experiment at the journal to tackle reproducibility of results in the field. In the past few years, a reproducibility crisis has plagued anaesthetics research, fuelled by high-profile cases of fraud. That's a problem, because such studies influence clinical practice and can have serious implications for patients.

So, for some papers, the journal now asks independent specialists to write their own discussion. Unlike conventional peer reviewers, they look only at the methods and results sections and are blinded to the paper's conclusions[3]. The two discussions are published together, with similarities and differences highlighted.

Some reproducibility researchers welcome the approach and say that other fields should do the same. Efforts to improve reproducibility have so far focused on methods and results, and need to extend to inferences and conclusions, says John Ioannidis at Stanford University, California, who is one of the authors of the independent discussion and an advocate for better reproducibility in science. From similar results, people can make inferences, create narratives or tell different stories, he says. Authors of the independent discussions are free of "any allegiance bias, conflicts or any reason to favour one result or one interpretation".

"We're all biased and this gives a second pair of eyes."

The move is intended to address the "over-interpretation, spin and subjective bias" that often plague papers' discussion sections, says Hugh Hemmings, editor of the *British Journal of Anaesthesia* and a neuropharmacologist at Weill Cornell Medical College in New York City. The approach is reserved for studies in contentious or high-profile and policy-relevant areas, he says, because those studies are influential and can see their conclusions repeated and quoted.

At present, critiques of papers in the journal can appear weeks or months after publication of the original paper, as guest editorials for example. By publishing the independent discussion at the same time as the peer-reviewed original, the journal hopes to accelerate the self-correcting nature of the literature. "If independent discussion authors find a fatal flaw, then we'll have a bit of a problem. But it won't be the first time," says Hemmings.

The original paper's lead author praises the approach. "We're all biased and this gives a second pair of eyes," says Frederick Sieber, a researcher in anaesthesiology and critical-care medicine at Johns Hopkins Bayview Medical Center in Baltimore, Maryland. Having seen the independent discussion, Sieber agrees that the study was not big enough to robustly measure the link to mortality. "Everything they said is valid." The original paper's main conclusions still stand, he says, because its primary goal was to report the impact of the depth of sedation on delirium, not death — which the independent discussion agrees with.

Not everyone sees value in the extra step. In an accompanying editorial[4], Robert Sneyd, dean of the University of Plymouth Peninsula Schools of Medicine and Dentistry, UK, warns that independent discussions will inevitably draw on the same people who are already asked to review papers. ■

1. Sieber, F. *et al. Br. J. Anaesth.* **122**, 480–489 (2019).
2. Vlisides, P. E., Ioannidis, J. P. A. & Avidan, M. S. *Br. J. Anaesth.* **122**, 421–427 (2019).
3. Avidan, M. S., Ioannidis, J. P. A. & Mashour, G. A. *Br. J. Anaesth.* **122**, 413–420 (2019).
4. Sneyd, J. R. *Br. J. Anaesth.* **122**, 407–408 (2019).

GENE EDITING

CRISPR twins might have shortened lives

Anti-HIV mutation raises odds of dying before 76.

BY SARA REARDON

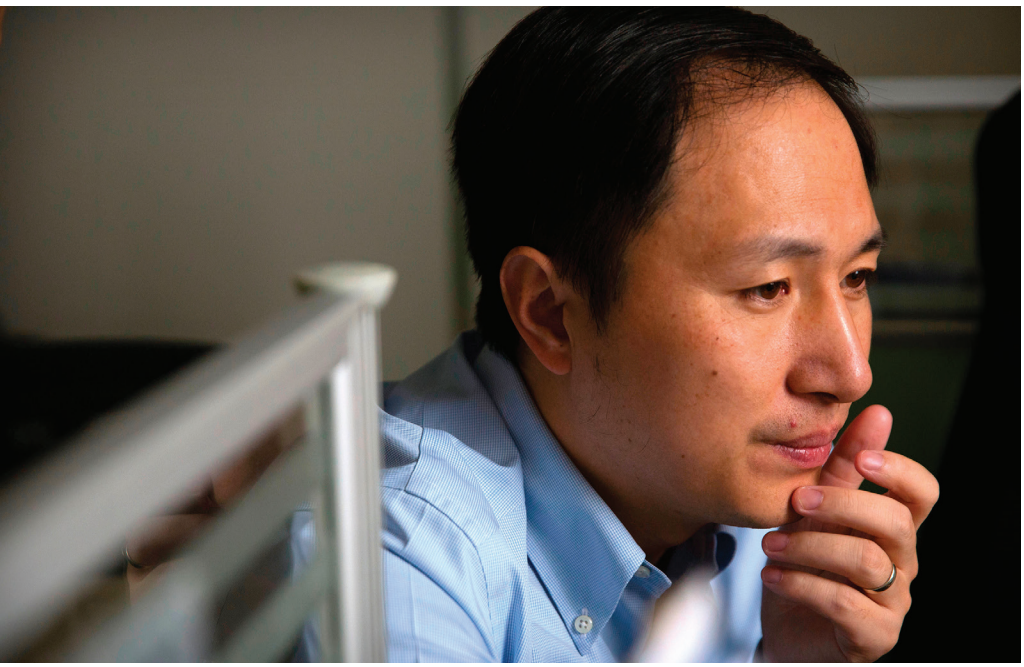
The scientist who edited the genomes of twin girls in an attempt to make them resistant to HIV might have inadvertently shortened their life expectancy. People with two disabled copies of the *CCR5* gene — the version that protects against HIV infection — are 21% more likely to die before the age of 76 than are people with at least one working copy of the gene, according to a study published on 3 June in *Nature Medicine* (X. Wei *et al. Nature Med.* http://doi.org/c6pj; 2019). The reason for the discrepancy is unknown.

The analysis is based on genetic and health data from nearly 410,000 people enrolled in the UK Biobank research project. The study's authors did not have enough data to estimate survival probabilities beyond the 76-year mark.

He Jiankui, a biophysicist at the Southern University of Science and Technology in Shenzhen, China, faced widespread condemnation after revealing last November that he had used CRISPR technology to make the first babies with edited genomes. Scientists and ethicists are still grappling with the implications of altering a person's genes in ways that can be passed on to future generations.

And many scientists questioned He's choice of gene. *CCR5* encodes a protein that allows HIV to enter immune cells. Deleting part of the gene can disable it — mimicking a naturally occurring mutation, *CCR5-Δ32*, that confers resistance to HIV. Scientists were also concerned about evidence suggesting that the mutation makes people more susceptible to the effects of influenza and West Nile virus.

The latest finding casts further doubt on the wisdom of disabling *CCR5*, says Philip Murphy, a molecular immunologist at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. "If you're unlikely to make it to your third birthday, and could go beyond it if you simply edited a specific gene, that would be a risk worth taking," he says. But current treatments for HIV allow many people with the virus to live into old age.



Biophysicist He Jiankui helped to create the world's first gene-edited babies.

MARK SCHIEFELBEIN/AP/SHUTTERSTOCK

Around the time of He's announcement, evolutionary biologist April Wei of the University of California, Berkeley, was developing a computational tool to link genetic mutations with lifespan, using data from the UK Biobank. She and geneticist Rasmus Nielsen, also at Berkeley, decided to test the tool with *CCR5*. "It's an interesting gene on its own," Wei says.

All mammalian genomes contain a version of *CCR5*, suggesting that it has an important role in these animals' biology. Yet the *CCR5-Δ32* mutation is common in some human populations. About 11% of the UK population carries the mutation in at least one copy of the *CCR5* gene, for instance. The prevalence of *CCR5-Δ32* suggests that, at least in some cases, disabling the *CCR5* gene can confer an evolutionary advantage, Murphy says. But scientists don't know what that might be.

David Melzer, an epidemiologist at the University of Exeter, UK, says that the apparent link between the *CCR5-Δ32* mutation and life expectancy is interesting, but not surprising. One of the genetic markers that Wei and Nielsen used to test for the mutation is associated with autoimmune conditions — such as Crohn's disease and type 1 diabetes — that can shorten a person's life. But Melzer says that the evidence for a link between *CCR5* and lifespan is nowhere near as strong as that for many other genes' influence on longevity.

And Murphy says that the study is limited because its data came from people who were aged 41 or older, which excludes anyone who died earlier.

To Wei, the findings reinforce the idea that disabling *CCR5* in human embryos is a bad idea. "It's really hard to prove that a gene is unconditionally beneficial," she says. "Even if we resolve the technical difficulties and ethical issues, could we really edit a gene if we don't know if it might have a deleterious effect?"

Alcino Silva, a neuroscientist at the University of California, Los Angeles, agrees. "It's just foolhardy at this point to go ahead and start mutating genes in humans," he says. "No matter how well-intentioned we may be when we design these genetic manipulations, we simply don't know enough to be doing this." ■

CELL BIOLOGY

Blood stem cells produced in vast quantities in the lab

A glue ingredient was key to making the mouse cells grow.

BY DAVID CYRANOSKI

Researchers have managed to grow large numbers of blood-forming stem cells in the lab using a surprisingly simple ingredient found in glue. And when injected into mice, the cells started producing key components of blood.

"The finding is very unexpected and exciting," says John Dick, a stem-cell biologist at the Prince Margaret Cancer Centre in Toronto, Canada.

If the technique can be applied to humans, it could be used to grow blood stem cells for use in people with blood cancers such as leukaemia whose immune systems have been damaged by chemotherapy. The approach could also provide a safer way to treat people with blood disorders, such as sickle-cell disease, who currently have to undergo a risky procedure to suppress their immune systems before receiving a bone-marrow transplant.

Researchers have been trying for decades to grow in the lab large numbers of 'haematopoietic' blood stem cells (HSCs), which regenerate themselves and give rise to other blood components. But until now, none had been able to produce the number needed to reliably engraft — or start producing blood cells — when reintroduced into the body.

Stem-cell biologist Hiromitsu Nakauchi, who leads teams at the University of Tokyo and Stanford University in California, reports in *Nature* how his team managed to successfully engraft HSCs in mice (A. C. Wilkinson *et al. Nature* http://doi.org/gf3h99; 2019). The researchers first expanded a cluster of mouse HSCs to almost 900 times its original level in just a month, then transplanted them back into a different set of mice, where they thrived and developed into blood components. "This has been my life goal," Nakauchi says.

Usually, an animal's immune system will try to destroy donor cells that aren't a genetic match. That is why immune systems have to be eliminated or suppressed before most transplants. But when Nakauchi injected the cells into healthy mice with intact immune systems, the cells thrived, possibly, he says, because of the large numbers introduced. Nakauchi is now working on adapting the ▶