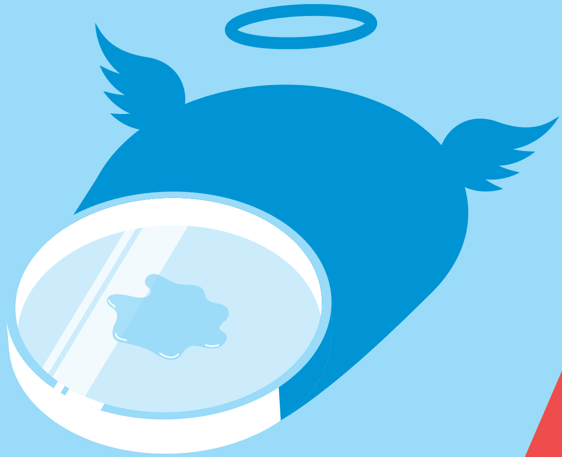
GOOD SCIENCE



WORK ON MUTANT FLU CAUSED A FURORE, BUT IS FAR FROM THE ONLY SUBJECT IN WHICH RISKS MIGHT OUTWEIGH BENEFITS.

BY GEOFF BRUMFIEL

It sounds like a great idea: experimentally mutate a rare but deadly virus so that scientists can do a better job of recognizing dangerous emerging strains. But it also sounds like a terrible idea — the studies could create a virus that is easier to transmit and produce findings that are useful to bioterrorists.

Last year's news that two research teams had done exactly that with the H5N1 bird flu virus was enough to spread fear around the globe and prompt a temporary moratorium on the work. A US biosecurity panel has since lifted its restrictions on publication of the teams' findings in *Nature* and *Science*, arguing that the work has clear potential benefits, that the modified virus seems to be less lethal than the original and that the data are already circulating in the community. But the episode has highlighted how thin the line can be between research that's a blessing and research that's a threat.

Such fraught lines of enquiry exist in many scientific fields. Some could undermine global security, whereas others could create painful ethical dilemmas for families. The four examples *Nature* profiles here are hardly a definitive list, but they do give a sense of how frequently such conundrums arise — and show that scientists must constantly ask themselves whether the benefits outweigh the risks.

NUCLEAR FUEL OR NUCLEAR WEAPONS?

A technology that could quickly and efficiently separate radioisotopes for nuclear power plants and nuclear medicine is one that many physicists might find irresistible. But isotope separation is also key to making nuclear weapons, so such a technology could make it easier both to perform and to conceal illicit work on such weapons.

Naturally occurring uranium ore is mostly uranium-238, which cannot sustain the kind of runaway chain reaction required to produce an explosion. Just 0.7% is fissile uranium-235. Enriching that quantity to 3–5% makes fuel for reactors. To make a bomb, it must be enriched to more than 90%. Because the chemistry of the various isotopes is almost identical, sorting one from another has always been one of the major barriers to the proliferation of nuclear weapons. Today's state-of-the-art technology involves cascades of thousands of centrifuges, and so requires space, a massive amount of electricity, precision-machined parts and time.

Lasers can be more efficient. Tiny differences in the mass of uranium nuclei alter the energy levels of their electron shells. Finely tuned lasers can excite just the levels associated with the desired isotope and, together with other technology, can sort the uranium-235 from the rest. The work can be done quickly and secretly. In 2004, it emerged that scientists in South Korea had used lasers to enrich small quantities of uranium-235 to near weapons purity in a matter of weeks. The work went undetected for years before it was eventually disclosed to international inspectors.

Now, with the advent of cheap and tuneable lasers, laser separation is within relatively easy reach of physicists the world over. A good example is Mark Raizen at the University of Texas at Austin, who is developing lasers to separate medically important isotopes such as calcium-48, used in the diagnosis of bone disorders; and nickel-64, a promising agent for cancer therapy. The world is facing a shortage of medical isotopes[1], Raizen says. "People's lives will depend on finding new sources."

Raizen's technique is straightforward[2]: finely tuned lasers push electrons in the desired isotope into higher energy states, temporarily changing the atoms' magnetic moment. From that point, all that is needed to sort the isotopes is a large, static magnet.

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For more on the mutant flu controversy, see: go.nature.com/mhmibi

J. KRZYSZTOFIAK

BAD SCIENCE

Raizen says he is aware that working with lasers and isotopes poses a proliferation risk. But he argues that it is unlikely that his technique will work well for heavy elements such as uranium.

Others stress that laser-enrichment technology should be undertaken with caution. "I think the risks are high," says Francis Slakey, co-director of the programme on science in the public interest at Georgetown University in Washington DC. Slakey, who has openly opposed the commercialization of laser isotope separation for creating nuclear fuel[3], would like to see a more open debate in the community — especially given that many physicists in the field of atomic and molecular optics could follow lines of enquiry similar to Raizen's. "I think there's value in taking a pause and reflecting," Slakey says.

Raizen is pushing ahead, driven by the excitement of using physics for the good of society. As for the risks, "you can't stop scientific ideas", he says. If he didn't do it, somebody else would. He expects his first results, on light atoms such as lithium, in a matter of months.

BRAIN SCANNING ◀ OR ▶ BIG BROTHER?

A machine able to accurately read a person's thoughts could be an extraordinary boon — allowing security officials to catch terrorists before they act, for example, or providing a new voice to some brain-damaged patients who cannot move or communicate. But such a device could also be the stuff of science-fiction nightmares, raising the spectre of Big Brother and ever-vigilant thought police.

That may be why the scientists doing such 'mind-reading' research prefer to call it 'brain scanning' or 'brain decoding'. "The whole concept of 'mind' comes with a lot of baggage," says Adrian Owen, a neuroscientist at the University of Western Ontario in London, Canada.

Nevertheless, these researchers have made extraordinary progress in understanding the human mind. The key has been functional magnetic resonance imaging (fMRI), which allows researchers to monitor blood flow throughout the brain. Blood flow is believed to be a reasonable proxy for neural activity, so fMRI gives a picture of the brain in action.

Owen, for example, has worked with patients who have been left in an apparently vegetative state by traumatic injuries. By asking specific questions to stimulate activity in different parts of their brains, he has been able to establish that around 16% of such patients can respond[4], suggesting that they have at least some level of awareness.

Jack Gallant, a neuroscientist at the University of California, Berkeley, has developed algorithms that track patterns of activation in the visual cortex as people watch videos. Reversing those computer codes can create shadowy movies of whatever people are looking at. Gallant thinks that this work could lead to even more advanced methods of communication with locked-in patients, who are paralysed but aware, or brain–machine interfaces that allow people to operate devices with their thoughts.

Going further still, John-Dylan Haynes, a neuroscientist at the Charité Medical University of Berlin, is looking for intent. Haynes scans the brain to see whether he can pick out patterns of activity that correspond to a person's decision to act. It works in simple cases[5]: he can see whether an individual decides to press a button up to seconds before the button is pressed, for example.

Whether this work could be extended to real-world applications such as lie detection or counter-terrorism is another matter. For one thing, says Gallant, each person's brain is different; it's far from clear that scientists will ever come up with a general-purpose 'mind-reading' algorithm applicable to everyone. For another, says Haynes, fMRI machines could not easily be deployed in airports. Even if they were, a simple shake of the head would throw them off. "You can't build a detector that says 'this person is going to blow up a plane now'," Haynes says.

Nevertheless, even the prospect of such a device raises hackles. "The thought that someone could use a machine to gain access to your most secret inner thoughts is not pleasant," says Gallant.

Yet entrepreneurs are already dabbling in this arena. Two US companies have fielded fMRI lie-detection services, and the world of advertising has embraced the concept of 'neuromarketing' — the use of fMRI and other techniques to measure people's subconscious emotional responses to stimuli. So far, concerns raised by such efforts seem hyped. Most courts have listened to scientists' doubts about fMRI lie-detection, and are not admitting them as evidence, says Steven Laken, chief executive of Cephos, an fMRI lie-detection firm in Tyngsboro, Massachusetts. Neuromarketing "is even more dubious", says Haynes. But Gallant thinks that the applications of the technology will come. "It'll go way further than you think," he says.

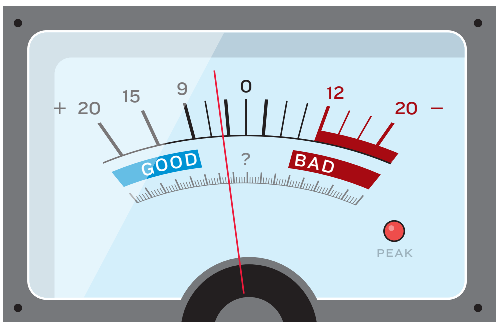
CLIMATE SAVIOUR OR CLIMATE DISASTER?

To hear proponents talk, humanity's best hope to escape the ravages of global warming may be geoengineering: manipulating Earth's environment on a planetary scale. This might involve solar-radiation management — spraying tiny particles high into the stratosphere, for example, where they could cool things down by reflecting some of the incoming sunlight. Or it might involve the removal of carbon dioxide, perhaps by seeding the ocean with iron to create algal blooms that would take up carbon dioxide from the air and then carry it to the ocean floor when they die.

To critics, geoengineering would be reckless in the extreme — and might further inflame the volatile politics of climate change.

Witness the controversy that has swirled around the UK-government-funded Stratospheric Particle Injection for Climate Engineering (SPICE) project, which involves researchers from the universities of Bristol, Cambridge, Edinburgh and Oxford, as well as the UK Met Office and Marshall Aerospace in Cambridge. SPICE is a proof-of-principle project designed to test solar-radiation management. The idea is to pump water up a 1-kilometre-long hose and spray it into the air. The altitude is too low to alter the climate, and there is plenty of water vapour already up there, says David Keith, a geoengineering specialist at Harvard University in Cambridge, Massachusetts. "It doesn't pose a risk other than the hose falling on someone's head," he says.

Nevertheless, environmentalists sounded the alarm on SPICE as soon as they caught wind of it last year. Quite aside from geoengineering's potential for unintended consequences — such as accidentally shifting rainfall patterns and triggering droughts — there is a moral hazard to such work, argues Pat Mooney, executive director of the ETC Group, an environmental organization based in Ottawa, Canada. With climate negotiations stalled around the world, the very presence of such an experiment may make politicians think that there's a way to wriggle out of emissions caps. "It will be an easy way for governments to sidestep their obligations," Mooney says.



ETC and other groups petitioned the British government to halt SPICE last autumn, saying it would hurt the country's credibility in this year's climate talks in Rio de Janeiro, Brazil. "It did get a little bit bumpy at the time," says Phil Macnaghten, a geographer at Durham University, UK, who is overseeing an ethical and societal assessment of SPICE. In September 2011, Macnaghten and others recommended that the experiment pause while researchers engage with the public and interest groups — at present, it is still on hold.

Mooney wants to see internationally agreed rules that would include prohibitions on geoengineering experiments with transnational consequences until major questions are answered. For example, will geoengineering even work? And what unintended consequences might it have? But as global temperatures continue to rise, Macnaghten believes that, provided researchers answer public concerns, the science should be allowed to continue. "When you don't know what you don't know, then it's very hard to know how to progress," he says.

BABY BLESSING OR BRAVE NEW WORLD?

Within a pregnant mother's blood is her unborn child's full genetic sequence. Soon, say geneticists, the question will no longer be how to get at it, but how to use it to understand the baby's future behaviour and health — and how to cope with the thorny ethical issues that will inevitably ensue.

The key to this new form of prenatal diagnosis lies in the fragments of DNA that float freely through every person's bloodstream. In pregnant women, around 15% of that DNA comes from the fetus, according to Dennis Lo, a pathologist at the Chinese University of Hong Kong, who is working to develop fetal genetic screening with Sequenom, a biotechnology company based in San Diego, California.

The trick is figuring out which DNA belongs to the fetus and which belongs to the mother. Finding the father's genetic contribution is easiest. Researchers extract DNA from the expectant mother's blood and look for variations in common with the father's genetic code to separate his half of the fetal DNA. The mother's half is tougher to identify because it is identical to the rest of the DNA in her blood. To find it, researchers count the number of times particular versions of genes are sequenced. Those held by the child and mother will appear fractionally more frequently than those held by the mother alone.

Screens for specific diseases based on this method are already nearing the market, says Lo. Scientists can check for Down's syndrome, a disorder that arises when an embryo receives three copies of chromosome 21, instead of the usual two. The test is more than 95% sensitive, making it comparable to more invasive tests such as amniocentesis[6]. Because it carries no risk, Lo believes that it will soon become nearly universal.

It may sound positive that many more parents will be forewarned of Down's syndrome and other genetic diseases such as cystic fibrosis, but it raises some thorny societal questions, says Henry Greely, a bioethicist at Stanford University in California. With universal screening, many more pregnancies might be terminated — and women who choose to carry a child with, say, Down's syndrome to term could face social and legal stigmas, he warns. "There are countries that are very concerned about mental retardation and might be willing to enforce genetic selection to avoid it," he says. Private insurers or public-health services might resist paying for the care of disabled children if their birth could have been avoided. These dystopian developments aside, some patient advocates fear that a sudden drop in the number of children with these diseases could mean less social support and fewer research dollars for their conditions.

Going beyond targeted diseases, full sequencing of the fetal genome is technically possible and will soon be affordable, says Stephen Quake, a researcher at Stanford University who works with Verinata Health, a fetal-screening company in Redwood City, California. And that, says Greely, will raise even more contentious issues. "People who come from a family with Alzheimer's might choose to terminate a pregnancy at high risk of Alzheimer's even though that Alzheimer's might occur 65 years into the future," he says — or might never occur at all, given that it is currently impossible to predict whether this condition or the vast majority of other diseases will occur on the basis of genetic information alone.

At present, there are no guidelines on how to counsel prospective parents about the avalanche of genetic information they may be about to receive. Lo says that he would be wary of telling parents before birth about a disease that could be cured within a child's lifetime. "Who knows where medical science will be in 60 years?"

But that is no reason to stop the research, says Quake, who has a cousin with Down's syndrome. He says he has thought long and hard about the issues raised by early testing, but in the end feels that the benefits greatly outweigh the risks. "The earlier parents find out, the better prepared they are," he says. ■ SEE EDITORIAL, P.415

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