international attention. A starting point could be the guiding principles issued last December by the Neuroethics Working Group of the NIH BRAIN Initiative, which held a 2018 workshop on research with human neural tissue[15].

Citizens must be part of the process. Engaging non-scientists in delineating the ethical boundaries of this research doesn't guarantee its public acceptance in the future; and nor should it, necessarily. But not engaging other stakeholders could help to precipitate its rejection.

In our view, discussion about the appropriate path for this research should not wait for follow-up studies. The Yale group was conscientious and consulted the local institutional IACUC, Yale bioethicists, NIH programme officers and even the NIH Neuroethics Working Group. The researchers did what they could, and probably more than many would have done, to ensure that they were acting appropriately in a void of ethical analysis on the issue.

Now is the time to fill that void. ■

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Pig brain study could fuel debates around death

The restoration of some functions in pig brains after death raises tensions over when to take human organs for transplant, warn **Stuart Youngner** and **Insoo Hyun**.

In this week's *Nature*, researchers describe restoring certain structural and functional properties to pigs' brains, even four hours after the animals had been killed[1]. They used an artificial perfusion system called Brain*Ex*.

Electrophysiological monitoring did not detect any kind of neural activity thought to signal consciousness, such as any evidence of signalling between brain regions (see 'Between life and death'). Nonetheless, the study challenges the long-held assumption that large mammalian brains are irreversibly damaged a few minutes after blood stops circulating. It also raises the possibility that researchers could get better at salvaging a person's brain even after the heart and lungs have stopped working.

Advances following on from the Brain*Ex* study could exacerbate tensions between efforts to save the lives of individuals and attempts to obtain organs to donate to others. (Such advances could also affect the use of human brains and brain tissue in research; see page 299.)

In our view, as the science of brain resuscitation progresses, some efforts to save or restore people's brains might seem increasingly reasonable — and some decisions to forego such attempts in favour of procuring organs for transplantation might seem less so.

The transplant community, neuroscientists, emergency medical personnel and other stakeholders must debate the issues[2]. Eventually, it might be useful for groups such as the US National Academy of Medicine to offer guidelines for physicians and hospitals. These would help to protect the interests of individuals for whom sufficient recovery is a possibility, as well as the interests of potential organ recipients.

DETERMINATION OF DEATH

For decades, bioethicists and transplantation-policy researchers have had to wrestle with the question of when to switch from trying to save someone's life to trying to save their organs for the benefit of another person.

Invariably, this comes down to a moral decision — namely about futility, which is a contentious and value-laden concept[3]. There are few data to support decisions. And clinicians disagree about when there is a chance of recovery. There is also little consensus on what level of recovery is 'good enough' from the perspective of patients and their families, as well as when these factors are weighed against limited medical resources.

In most countries, a person can be legally declared dead if they show irreversible loss of all brain function (brain death) or irreversible loss of all circulatory function (circulatory death).

In recent decades, most organs for transplant have been taken from those who have been declared brain dead, often after a catastrophic brain injury resulting from a stroke, trauma or prolonged lack of oxygen to the brain, caused for instance by drowning. (In these cases, the person's heart and lung functions are maintained in the intensive care unit.)

Increasingly, however, those who are declared dead after their hearts and lungs have stopped working are being deemed eligible for organ donation. This shift has largely been driven by an increased need for organs as transplantation surgeries have become more successful. According to the US non-profit organization the United Network for Organ Sharing, someone is added to the US transplant waiting list every ten minutes. In 2017, around 18 people in the United States died every day while waiting for a transplant.

"Someone is added to the US transplant waiting list every ten minutes."

If technologies similar to Brain*Ex* are improved and developed for use in humans, people who are declared brain dead (especially those with brain injuries resulting from a lack of oxygen) could become candidates for brain resuscitation rather than

Surgeons in Berlin operate on a woman who has been declared brain dead to remove her liver and kidneys for transplantation.

FABRIZIO BENSCH/REUTERS

organ donation. Certainly, it could become harder for physicians or family members to be convinced that further medical intervention is futile.

For people who have been declared dead on the basis of circulatory criteria, matters could become even more complex.

Today, there are two main protocols for obtaining organs in these cases. One occurs in individuals who have severe brain injuries but are not brain dead. It is called controlled donation after circulatory determination of death (controlled DCDD)[4].

Here, after carers obtain consent, they switch off the person's mechanical ventilator and any other life support that might be in use in the operating room. The patient is then declared dead 2–5 minutes after their heart stops beating. Because adequate testing for brain death is impossible in the race to obtain healthy organs, it is assumed that the individual has had an irreversible loss of brain function.

The second protocol (uncontrolled DCDD) is practised mainly in Europe[5]. It generally occurs after a person has had a heart attack in a non-medical setting[4]. In these cases, after paramedics have declared resuscitative efforts futile, nothing is done for around 5–20 minutes[5]. Next, steps are taken to try to preserve the organs. These might include resuming cardiopulmonary resuscitation to restore circulation; introducing cooling fluids through an artery in the groin; or even a technique that oxygenates the blood and pumps it throughout the body (known as extra corporeal membrane oxygenation, or ECMO).

Even now, clinicians and bioethicists disagree over how long is long enough for paramedics to keep trying to resuscitate. Practitioners use various rules of thumb, such as 'declare death after 30 minutes of unsuccessful resuscitative efforts', and can refer to published guidelines[6]. But as the US neurologist James Bernat has pointed out, such rules "are difficult to apply in practice because each CPR is a unique event with different variables"[7]. Data are scant, but one study of people who died of heart attacks in hospitals in the United States found that patients were declared dead with more certainty after longer resuscitative efforts[8].

Questions about the term 'irreversible' haunt both protocols. Does this mean that the care team is unable to reverse a situation, or that they have reasonably decided not to attempt to? Unsurprisingly, most advocates for transplantation favour the latter view. Some have even argued that further efforts to restore people's brains at the expense of organ procurement would divert much-needed medical resources and potentially increase the number of people with severe disabilities[9].

Heightening the tension are concerns among bioethicists and medical practitioners that brain function could be recovered in some bodies that have been put on ECMO. Some organ-recovery teams in the United States[10] and Taiwan[11] have tried to prevent this by inserting a thoracic aortic occlusion balloon to stop the pumped blood from reaching the brain. This intervention was deemed a "serious problem" by a US Department of Health and Human Services panel because it raises "causation questions about physicians' active complicity in the patient's death"[4].

Lastly, there is considerable variation between countries about what is morally and legally acceptable. In France and Spain, ECMO equipment can be transported in a

BRAIN REBOOT?

Between life and death

How were some cellular functions and structures restored to pig brains hours after the animals had been killed?

The researchers (largely at the Yale School of Medicine in New Haven, Connecticut) used around 300 pig heads from a US Department of Agriculture abattoir[1]. After optimizing the technology, the team connected 32 pig brains to the Brain*Ex* system (4 hours after the pigs had been killed, and after removing the brains from the skulls). This computerized network of pumps, heaters and filters controlled the flow, temperature and constituents of a proprietary perfusate solution for six hours.

There was no evidence of the kind of neural activity that is thought to signal consciousness, or the ability to perceive the environment and experience sensations such as pain or distress. But, incredibly, Brain*Ex* did restore and sustain circulation to major arteries, small blood vessels and capillaries, cellular responsiveness to drugs and cerebral metabolism. A drug that increases blood flow in people's brains, for instance, dilated pig blood vessels and increased the rate of flow of the perfusate.

Some large-scale anatomical and small-scale morphological features were restored and preserved, thanks to a reduction in swelling and other changes that would otherwise have led to cell damage and cell death. Electrodes inserted into slices of brain tissue (cultured in standard medium) detected electrical activity in individual neurons; neurons fired action potentials in response to an electrical stimulus and even displayed spontaneous synaptic activity. All of this was detected at normal body temperature.

It is not known how long uninterrupted perfusion could have sustained these functions. The team stopped the experiment after six hours, mainly because of the limited availability of fresh perfusate and the difficulties of having someone continually monitor and adjust the Brain*Ex* system.

The study was designed to investigate whether any physiological and cellular functions can be restored in a large, intact mammalian brain several hours after death. Such work could, in principle, help investigators to develop therapies for brain injuries resulting from a lack of oxygen, and even enable the study of intact human brains (see page 299). **S.Y. & I.H.**

LEON NEAL/GETTY

In some countries, ambulances carry special equipment to restore circulation to the organs of people who have been declared dead after a heart attack.

special ambulance to wherever the patient is. In the United States, the technique is controversial and rarely used.

These debates and decisions could become much more fraught if advances in research challenge assumptions about the brain's inability to recover from an absence of oxygen, or even just hint at the possibility that consciousness can be restored after a person's heart has stopped beating. Ultimately, more people could become candidates for brain resuscitation rather than for organ donation.

HEALTHY DEBATE

Balancing the competing interests of developments in resuscitation and transplantation comes down to values, as well as science. Different people have different ideas about how to best save and improve lives.

In our view, the Brain*Ex* study, and the follow-up work it will surely inspire, flag the need for more open discussion. Debate involving everyone — from neuroscientists and policymakers to patients and medical personnel — could help to clarify which criteria make someone eligible for organ donation versus resuscitation. Such discussions can also explore how to ensure that organ donation can be integrated into end-of-life care with minimal controversy.

Two institutions are well placed to take the lead and bring the relevant stakeholders together: the US National Academy of Sciences (NAS) and the UK Nuffield Council on Bioethics. Both have held public meetings and produced multidisciplinary reports on controversial areas of science, medicine and ethics for decades. In 2006, for example, workshops held over a year involving researchers, health-care professionals and comments from the public led to an NAS report evaluating various proposals to increase organ donations, and their potential impact on people from minority ethnic groups and those who are socio-economically disadvantaged[12].

Researchers are a long way from being able to restore structures and functions in the brains of people who would today be declared dead. But, in our view, it is not too early to consider how this type of research could affect the growing population of critically ill patients who are waiting for kidneys, livers, lungs or hearts. ■

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