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BIOTECHNOLOGY AND HEALTH

The Biggest Questions: What is death?

New neuroscience is challenging our understanding of the dying process—bringing opportunities for the living.

by **Rachel Nuwer**

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The Biggest Questions is a mini-series that explores how technology is helping probe some of the deepest, most mind-bending questions of our existence.

Just as birth certificates note the time we enter the world, death certificates mark the moment we exit it. This practice reflects traditional notions about life and death as binaries. We are here until, suddenly, like a light switched off, we are gone.

But while this idea of death is pervasive, evidence is building that it is an outdated social construct, not really grounded in biology. Dying is in fact a process—one with no clear point demarcating the threshold across which someone cannot come back.

Scientists and many doctors have already embraced this more nuanced understanding of death. As society catches up, the implications for the living could be profound. "There is potential for many people to be revived again," says Sam Parnia, director of critical care and resuscitation research at NYU Langone Health.

Neuroscientists, for example, are learning that the brain can survive surprising levels of oxygen deprivation. This means the window of time that doctors have to reverse the death process could someday be extended. Other organs likewise seem to be recoverable for much longer than is reflected in current medical practice, opening up possibilities for expanding the availability of organ donations.

To do so, though, we need to reconsider how we conceive of and approach life and death. Rather than thinking of death as an event from which one cannot recover, Parnia says,we should instead view it as a transient process of oxygen deprivation that has the potential to become irreversible if enough time passes or medical interventions fail. If we adopt this mindset about death, Parnia says, "then suddenly, everyone will say, 'Let's treat it.'"

Moving goalposts

Legal and biological definitions of death typically refer to the "irreversible cessation" of life-sustaining processes supported by the heart, lungs, and brain.

The heart is the most common point of failure, and for the vast majority of human history, when it stopped there was generally no coming back.

That changed around 1960, with the invention of CPR. Until then, resuming a stalled heartbeat had largely been considered the stuff of miracles; now, it was within the grasp of modern medicine. CPR forced the first major rethink of death as a concept. "Cardiac arrest" entered the lexicon, creating a clear semantic separation between the temporary loss of heart function and the permanent cessation of life.

Around the same time, the advent of positive-pressure mechanical ventilators, which work by delivering breaths of air to the lungs, began allowing people who incurred catastrophic brain injury—for example, from a shot to the head, a massive stroke, or a car accident—to continue breathing. In autopsies after these patients died, however, researchers discovered that in some cases their brains had been so severely damaged that the tissue had begun to liquefy. In such cases, ventilators had essentially created "a beating-heart cadaver," says Christof Koch, a neuroscientist at the Allen Institute in Seattle.

These observations led to the concept of brain death and ushered in medical, ethical, and legal debate about the ability to declare such patients dead before their heart stops beating. Many countries did eventually adopt some form of this new definition. Whether we talk about brain death or biological death, though, the scientific intricacies behind these processes are far from established. "The more we characterize the dying brain, the more we have questions," says Charlotte Martial, a neuroscientist at the University of Liège in Belgium. "It's a very, very complex phenomenon."

Brains on the brink

Traditionally, doctors have thought that the brain begins incurring damage minutes after it's deprived of oxygen. While that's the conventional wisdom, says Jimo Borjigin, a neuroscientist at the University of Michigan, "you have to wonder, why would our brain be built in such a fragile manner?"

Recent research suggests that perhaps it actually isn't. In 2019, scientists reported in Nature that they were able to restore a suite of functions in the brains of 32 pigs that had been decapitated in a slaughterhouse four hours earlier. The researchers restarted circulation and cellular activity in the brains using an oxygen-rich artifi cial blood infused with a cocktail of protective pharmaceuticals. They also included drugs that stopped neurons from firing, preventing any chance that the pig brains would regain consciousness. They kept the brains alive for up to 36 hours before ending the experiment."Our work shows there' s probably a lot more damage from lack of oxygen that's reversible than people thought before," says coauthor Stephen Latham, a bioethicist at Yale University.

In 2022, Latham and colleagues published a second paper in Nature announcing that they'd been able to recover many functions in multiple organs, including the brain and heart, in whole-body pigs that had been killed an hour earlier. They continued the experiment for six hours and confirmed that the anesthetized, previously dead animals had regained circulation and that numerous key cellular functions were active.

"What these studies have shown is that the line between life and death isn't as clear as we once thought," says Nenad Sestan, a neuroscientist at the Yale School of Medicine and senior author of both pig studies. Death "takes longer than we thought, and at least some of the processes can be stopped and reversed."

A handful of studies in humans have also suggested that the brain is better than we thought at handling a lack of oxygen after the heart stops beating. "When the brain is deprived of life-sustaining oxygen, in some cases there seems to be this paradoxical electrical surge," Koch says. "For reasons we don't understand, it's hyperactive for at least a few minutes."

In a study published in September in Resuscitation, Parnia and his colleagues collected brain oxygen and electrical activity data from 85 patients who experienced cardiac arrest while they were in the hospital. Most of the patients' brain activity initially flatlined on EEG monitors, but for around 40% of them, near-normal electrical activity intermittently reemerged in their brains up to 60 minutes into CPR.

Similarly, in a study published in Proceedings of the National Academy of Sciences in May, Borjigin and her colleagues reported surges of activity in the brains of two comatose patients after their ventilators had been removed. The EEG signatures occurred just before the patients died and had all the hallmarks of consciousness, Bojigin says. While many questions remain, such findings raise tantalizing questions about the death process and the mechanisms of consciousness.

Life after death

The more scientists can learn about the mechanisms behind the dying process, the greater the chances of developing "more systematic rescue efforts," Borjigin says. In best-case scenarios, she adds, this line of study could have "the potential to rewrite medical practices and save a lot of people."

Everyone, of course, does eventually have to die and will someday be beyond saving. But a more exact understanding of the dying process could enable doctors to save some previously healthy people who meet an unexpected early end and whose bodies are still relatively intact. Examples could include people who suffer heart attacks, succumb to a deadly loss of blood, or choke or drown. The fact that many of these people die and stay dead simply reflects "a lack of proper resource allocation, medical knowledge, or sufficient advancement to bring them back," Parnia says.

Borjigin's hope is to eventually understand the dying process "second by second." Such discoveries could not only contribute to medical advancements, she says, but also "revise and revolutionize our understanding of brain function."

Sestan says he and his colleagues are likewise working on follow-up studies that seek to "perfect the technology" they have used to restore metabolic function in pig brains and other organs. This line of research could eventually lead to technologies that are able to reverse damage—up to a point, of course—from oxygen deprivation in the brain and other organs in people whose hearts have stopped. If successful, the method could also expand the pool of available organ donors, Sestan adds, by lengthening the window of time doctors have to recover organs from the permanently deceased.

If these breakthroughs do come, Sestan emphasizes, they will take years of research. “It’s important that we not overexaggerate and promise too much,” he says, “although that doesn’t mean we don’t have a vision.”

In the meantime, ongoing investigations into the dying process will no doubt continue to challenge our notions of death, leading to sea changes within science and other realms of society, from the theological to the legal. As Parnia says: “Neuroscience doesn’t own death. We all have a stake in it.”

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