LIFE'S EDGE

The Search for What It Means to Be Alive

CARL ZIMMER

PICADOR

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INTRODUCTION

THE BORDERLAND

In the fall of 1904, the Cavendish Laboratory was full of curious experiments. Clouds of mercury shuddered with flashes of blue light. Lead cylinders pirouetted on copper disks. The ivy-covered building on Free School Lane, nestled in the heart of Cambridge, was the most exciting place for physicists to be, not just in England but in the entire world, a place where they could toy with the fundamental pieces of the universe. Amidst this forest of magnets and vacuums and batteries, it would have been easy to overlook one small experiment sitting forlornly by itself. It consisted of little more than a glass tube capped with cotton, half-filled with a few spoonfuls of brown broth.

But something was coming into being in that tube. In a few months the world would collectively gasp at it. Newspapers would celebrate the experiment as one of the most remarkable achievements in the history of science. One reporter would describe what lurked in the tube as "the most primitive form of life—the 'missing link' between the inorganic and organic worlds."

This most primitive life was the creation of a thirty-one-year-old physicist named John Butler Burke. In photographs from around the time of the experiment, Burke's boyish face has a melancholy cast. He was born in Manila to a Filipino mother and an Irish father. As a boy he traveled to Dublin for schooling and ended up at Trinity College, where he studied X-rays, dynamos, and the mysterious sparks released by sugar. Trinity awarded Burke a gold medal in physics and chemistry. One professor described him as “a man who is gifted with the power of exciting in others the enthusiasm which he brings to bear upon his own lines of investigation.” After finishing his studies, Burke moved from Dublin to England to teach at a series of universities. His father soon died and his mother—“an old lady of very large means,” as Burke later called her—supported him with a generous allowance. In 1898, Burke joined the Cavendish.

Nowhere on Earth had physicists learned so much in so little time about matter and energy. Their most recent triumph, courtesy of the lab’s director, Joseph John Thomson, was the discovery of the electron. In his first few years at the Cavendish, Burke followed up on Thomson’s work by running experiments of his own on the mysterious charged particles, investigating how electrons could light up clouds of gas. But then a new mystery lured him away. Like many other young physicists at the Cavendish, Burke started experimenting with a glowing new element called radium.

A few years beforehand, in 1896, a French physicist named Henri Becquerel had discovered the first evidence that ordinary matter could cast off a strange form of energy. When he wrapped uranium salts in a black cloth, they created a ghostly image on a photographic plate nearby. It soon became clear that the uranium was steadily releasing some kind of potent particle. To follow up on Becquerel’s work, Marie and Pierre Curie extracted uranium from an ore called pitchblende. In the process, they discovered that some of the energy was coming from a second element. They named it radium and christened its new form of energy “radioactivity.”

Radium unleashed so much energy that it could keep itself warm. If scientists set a piece atop a block of ice, it could melt its own weight in water. When the Curies mixed radium with phosphorus, the particles unleashed by the radium made the phosphorus glow in the dark. As news of this rare, exotic substance spread, it became a sensation. In New York, dancers put on radium-coated outfits to perform in darkened casinos. People wondered if radium would become a mainstay of civilization. "Are we about to realize the chimerical dream of the alchemists—lamps giving light perpetually without the consumption of oil?" one chemist mused. Radium also seemed to have a vitalizing power. Gardeners sprinkled it on their flowers, convinced it could make them grow bigger. Some people drank "liquid sunshine" to cure all manner of ills, including even cancer.

It was cancer that would eventually claim Marie Curie's life in 1934, probably because of the radium and other radioactive elements she worked with on a daily basis. Now that we understand the deadly risk posed by radioactivity, it's hard to imagine how anyone could think that radium could have vitalizing powers. But in the early 1900s scientists knew surprisingly little about the nature of life. The best they could say was that its essence lurked in the jellylike substance in cells, a material they called protoplasm. It somehow organized cells into living things and was passed down from one generation to the next. Beyond that, little was certain and all manner of ideas were viable.

To Burke, life and radioactivity displayed a profound similarity. Like a caterpillar becoming a moth, a radium atom could undergo a transformation that seemed to come from within. "It changes its substance—in a limited sense it lives—and yet it is ever the same," Burke declared in a 1903 magazine article. "The distinction, apparently insuperable, that the biologist holds to exist between living and so-called dead matter, should thus pass away as a false distinction . . . All matter is alive—that is my thesis."

Burke said all this as a scientist, not a mystic. "We must be careful lest our imagination should carry us away, and lead us into regions of pure fancy, to a height beyond the support of experimental facts," he warned. To prove his thesis, Burke designed an experiment: he would use radium to create life from lifeless matter.

To carry out this act of creation, Burke prepared some bouillon, cooking chunks of beef in water and sprinkling in salt and gelatine. Once the ingredients had turned to a broth, he poured some into a test tube and put it over a flame. The heat destroyed any cow cells or microbes that might be lurking in the liquid. All that was left was a sterile bouillon made up of loose, lifeless molecules.

Burke put a pinch of radium salt in a tiny sealed vial, which was suspended over the broth. A platinum wire wrapped around the vial and snaked out a side port. To launch the experiment, Burke pulled the free end of the wire until the vial cracked. The radium tumbled into the broth below.

After he let the radioactive broth stew overnight, Burke saw that it had changed: a cloudy layer had formed on its surface. Burke drew off a little to see if it was made of contaminating bacteria. He spread it over a petri dish loaded with food for microbes. If the cloudy layer had any bacteria in it, they would feast until they grew into visible colonies.

But no colonies formed. Burke concluded the layer must have been formed by something else. Taking another sample of the cloudy layer, he spread it on a glass slide and put it under a microscope. Now he could see that it contained a scattering of specks far smaller than bacteria. A few hours later, when he checked again, the specks had vanished. But the next day they returned, and Burke began drawing them, documenting how they grew in size and changed in shape. Over the course of the next few days they turned into spheres, with inner cores and outer rinds. They stretched into dumbbells. They bulged and pinched into miniature flowers. They divided. And then, after two weeks, they fell apart. Some might say they died.

As Burke sketched these changing shapes, he could tell they

theory of how life evolved. Now, almost a half century later, Burke was wrestling with an even greater mystery: life itself. Chapman and Hall, one of London's leading publishers, gave Burke a contract to write a book about his theory. *The Origin of Life: Its Physical Basis and Definition* came out in 1906.

Whatever caution Burke originally had was now gone. In his book, he held forth on the properties of living matter, on the "borderland between mineral and vegetable kingdoms," on enzymes and nuclei, on his own electric theory of matter, and on something he called "mind-stuff." Burke unhelpfully described mind-stuff as "perception in the universal mind which constitutes the 'great ocean of thought' in which we live and move and have our being."

And with those words Burke reached his Icarus peak. Soon a wave of brutal reviews of *The Origin of Life* came out, scoffing at Burke's hubris. Here was a physicist holding forth on the nature of life when he didn't even know the difference between chlorophyll and chromatin. "Biology is decidedly not his forte," one reviewer sniffed.

An even more devastating verdict soon came from a fellow scientist. W. A. Douglas Rudge, who had also worked at the Cavendish for a few years, decided to run Burke's radiobe experiments for himself. He recognized ways to make them more rigorous—running separate trials with tap water and distilled water, for example. Instead of Burke's "mere drawing," as Rudge called it, he documented his results with photographs. When Rudge cooked his broth with distilled water, he discovered, the radium produced nothing. In tap water, Rudge found some odd shapes, but no sign of the lifelike radiobes Burke had drawn.

Burke tried to smear Rudge as an amateur, but other scientists saw his report to the Royal Society as the final word on radiobes. "Mr. Rudge has carried out the experiments that Mr. Burke should have made long ago," declared Norman Robert Campbell, a physicist at the Cavendish. “Mr. Rudge has produced convincing evidence that the ‘cells,’ or radiobes, are nothing but little bubbles of water produced in the gelatin by the action of the salts upon it.”

In September 1906, Campbell published a vicious attack on Burke. It was ostensibly a review of *The Origin of Life*, but it read more like a character assassination. “Mr. Burke was not educated at Cambridge; he had been at two universities before he came thither as an advanced student,” Campbell scoffed. “It is misleading to say, in connection with his recent publications, that Mr. Burke is ‘of the Cavendish Laboratory.’ He did some physical research there a few years ago: during his investigations of the biological properties of his radiobes he merely stored in the room in which he had done his former work some of the test-tubes in which those bodies were ‘incubating.’ ”

It was around this time that Burke stopped working at the Cavendish. Whether he quit or was barred, no one can say. In December 1906 the lab gathered again for another end-of-the-year dinner. They had cause to celebrate: Thomson had just won the Nobel Prize. But the song for 1906 was not an ode to the electron. Instead, the mathematician Alfred Arthur Robb wrote a song set to the tune of “The Amorous Goldfish” from the 1896 musical *The Geisha.*

It was entitled “The Radiobe.”

A radiobe swam in a bowl of soup
As dear little radiobes do,
And Butler Burke gave a wild war whoop
As he over his microscope did stoop,
And it came in the field of view.
He said: “This radiobe clearly shows
How all the forms of life arose;
And further plainly shows,” said he,
“What a very great man is J.B.B.!”

In the years that followed, Burke took a long fall—one that only ended with his death forty years later in 1946. After he left the Cavendish, no one offered him a plum professorship. Magazines lost interest in his ideas. He wrote two sprawling manuscripts but struggled for years to find a publisher. His income from lectures and writing dried up at the same time that his mother slashed his allowance. During World War I, Burke managed to support himself with a job inspecting airplanes, but after a few months poor health forced him to quit. In 1916 he begged the Royal Literary Fund for a loan to save him from "the dreaded event of bankruptcy." They turned him down.

As a young man, Burke had seemed on the verge of defining life, of charting its borders. But life got the better of him. In 1931, a quarter century after his brief fame, he published a dubious magnum opus, *The Emergence of Life*. It was a rambling mess. "Burke had gone right off the deep end," the historian Luis Campos later wrote. In the book, Burke flirted with levitation and other psychic phenomena. He remained fiercely loyal to his radiobes, which the world had long forgotten. He argued that life emerged from what he called "time-waves" that flowed between units of mind that make up the universe.

The more Burke thought about life, the less he understood it. At one point in *The Emergence of Life*, he offered a definition of life, but it sounded more like a cry for help: "Life is what IS."

I never learned about Burke when I was growing up. I was taught the standard pantheon of biologists, which is mostly made up of scientists with ideas that turned out to be right: Darwin and his tree of life, Mendel and his genetic peas, Louis Pasteur and his disease-causing germs. It's easier that way: to leapfrog from one designated hero to the next—to ignore the mirages along the way, the failures, the fame that curdled.

When I started writing about biology, I still didn't learn about Burke. I have had the good fortune to get to know many forms of life and many of the scientists who study them. I've hauled hagfish out of the North Atlantic, hiked into North Carolina longleaf pine forests to find Venus flytraps in the wild, and spotted orangutans lounging high in the canopies of Sumatran jungles. Scientists have shared with me what they've learned about the marvelous slime that hagfish make, the insect-destroying enzymes in carnivorous plants, the tools orangutans fashion out of sticks.

The beams of their scientific flashlights are bright, but only because they are narrow. Someone who spends her life tracking orangutans doesn't have enough time to become an expert on Venus flytraps. Venus flytraps and orangutans have something profoundly important in common—they are alive—and yet asking biologists about what it means for something to be alive makes for an awkward conversation. They'll demur, stammer, or offer a flimsy notion that crumbles under even a little scrutiny. It's just not something that most biologists give much thought to in their day-to-day work.

This reluctance has long mystified me, because the question of what it means to be alive has flowed through four centuries of scientific history like an underground river. When natural philosophers began contemplating a world made of matter in motion, they asked what set life apart from the rest of the universe. The question led scientists to many discoveries but also many blunders. Burke was hardly alone. For a brief time in the 1870s, for example, many scientists came to believe that the entire ocean floor was carpeted with a layer of throbbing protoplasm. More than 150 years later, despite all that biologists have learned about living things, they still cannot agree on the definition of life.

Puzzled, I set out on a trip. I started out in the heart of life's territory: in the confidence that each of us has that we are alive, that we have a life that is bounded by birth on one side and by death on the other. Yet we feel our own life more strongly than we understand it. We know that other things are alive, too, like snakes and trees, even if we can't ask them. Instead, we rely on the hallmarks that all living things seem to have. I took a tour of these hallmarks, getting to know creatures that display them in their most impressive, most extreme forms. Eventually my travels took me out to life's edge, to the foggy borderland between the living and the nonliving, where I encountered peculiar things with some of life's hallmarks but not others. It was here, at last, that I first encountered John Butler Burke and came to appreciate that he deserves a place in our memory. It was here that I met his scientific descendants who still grope their way around life's edge, trying to figure out how life began or how weird it might get on other worlds.

Someday humanity may draw a map that will make this journey easier. In a few centuries, people may look back at our understanding of life and wonder how we could have been so blinkered. Life today is like the night sky four centuries ago. People gazed up at mysterious lights that wandered, streaked, and flared across the dark. Some astronomers at the time were getting the first inklings of why the lights traced their particular paths, but many of the explanations of the day would turn out to be wrong. Later generations would look up and instead see planets, comets, and red giant stars, all governed by the same laws of physics, all manifestations of the same underlying theory. We don't know when a theory of life might arrive, but we can hope, at least, that our own lives last long enough to let us see it.

skin. There, they created electric charges in twisted tubes that wrung water out of the surrounding cells. Sweat ran down my back.

My conscious self was annoyed with the brain that generated it. One of the few shirts I had brought with me was now drenched in salt water. I could not actually sense the trill of voltage spikes that shuttled information from skin to brain. I didn't feel a surge of blood in the center of my head as the heat-regulating part of my brain swung into action. In the moment, by the sea, I simply felt myself sweating. I felt annoyed. I felt alive.

As I felt aware of my own life, I also recognized other lives on the beach. A man walked lazily south, carrying a white-and-blue surfboard. Far to the north, a paraglider launched off from the top of the cliffs. The corkscrewing of the yellow paraglider wing spoke of intentions that arose in some human's brain and produced signals to hands gripping brake handles.

Along with human life, I could see feathered life as well. Sandpipers skittered along the surf. Their seed-sized brains sensed the flash of incoming waves and the cold foam around their legs, contracting muscles to keep their bodies upright, to scuttle to higher ground, to poke the sand for buried snails. The snails didn't quite have brains but rather fretworks of nerves that produced signals of their own for slowly, relentlessly burying their bodies into the earth. I contemplated the thousands of other subterranean nervous systems inside the mud dragons and the Pismo clams and other creatures buried below my feet. Out in the ocean, down the underwater canyon, other brains were swimming, carried along inside the buoyant bodies of leopard sharks and stingrays while the nerve nets of jellyfish drifted by.

After a few minutes of walking along the water, I stopped and looked down. A gigantic neuron, six feet long, lay on the sand. Most of it was made up of a glistening, caramel-colored axon. It curved gently like a heavily insulated electric cable. At one end it swelled into a bulb-shaped soma, which was crowned in turn by branches of dendrites. It could have been all that survived from a kraken that died in a battle with a pod of killer whales somewhere between here and Hawaii.

This fantastical neuron was, in fact, a stalk of elk kelp. It had washed up from an underwater forest a mile out to sea. What I had imagined to be an axon was the kelp's stipe, a trunk that not long ago anchored the organism to the ocean floor. What looked like a neuron's soma was in reality a gas-bloated bladder that kept the kelp upright in the ocean currents. The branching dendrites were the elk kelp's antlers, on which long blades had once grown. And the blades acted like the leaves of plants, catching what little sunlight filtered down through the seawater and fueling the growth of the elk kelp to heights that rivaled the palm trees that crowned the cliffs behind me.

The kelp had the kind of complexity that marks living things. But as I looked down at it, I could not say whether this particular kelp was still alive. I couldn't ask it how its day was going. It had no heartbeat I could check, no lungs to lift and lower a chest. But the kelp still glistened, its surfaces intact. Even if it could no longer capture sunlight, its cells might still be carrying on, using up its remaining fuel to repair its genes and membranes. At some point, maybe today or next week, its death would become certain.

But along the way, it would also become a part of life on land. Microbes would feast on its tough cuticles. Beach hoppers and kelp flies would follow, nibbling on its tender tissues. These wrack-feasting creatures would themselves become food for the sandpipers and terns. Plants would be fertilized by the kelp's nitrogen soaking into the ground. And a sweaty human being, his brain packed with thoughts of brains on this beach, would carry away in his neurons a memory of the kelp's neuron-like body.

The next morning I walked along the tops of the cliffs. North Torrey Pines Road cut north through La Jolla, California, alongside groves of looming tower cranes. With a stream of rush-hour traffic flowing by me, it was hard to remember the ribbon of wild coast tucked away close by. I crossed a eucalyptus-lined parking lot to get to the Sanford Consortium for Regenerative Medicine, a complex of glassed-in labs and offices. Once inside, I found my way to a third-floor laboratory, and there I met a scientist named Cleber Trujillo—Brazilian-born, with a close-cropped beard. Together we suited up in blue gloves and smocks.

Trujillo led me to a windowless room banked with refrigerators, incubators, and microscopes. He extended his blue hands to either side and nearly touched the walls. “This is where we spend half our day,” he said.

In that room Trujillo and a team of graduate students raised a special kind of life. He opened an incubator and picked out a clear plastic box. Raising it above his head, he had me look up at it through its base. Inside the box were six circular wells, each the width of a cookie and filled with what looked like watered-down grape juice. In each well a hundred pale globes floated, each the size of a housefly head.

Every globe was made up of hundreds of thousands of human neurons. Each had developed from a single progenitor cell. Now these globes did many of the things that our own brains do. They took up nutrients in the grape-juice-colored medium to generate fuel. They kept their molecules in good repair. They fired electrical signals in wavelike unison, keeping in sync by exchanging neurotransmitters. Each of the globes—which scientists call organoids—was a distinct living thing, its cells woven together into a collective.

“They like to stay close to each other,” Trujillo said as he looked at the undersides of the wells. He sounded fond of his creations.

The lab where Trujillo worked was led by another scientist from

Brazil named Alysson Muotri. After Muotri immigrated to the United States and became a professor at the University of California at San Diego, he learned how to grow neurons. He took bits of skin from people and gave them chemicals that transformed them into embryo-like cells. Dousing them with another set of chemicals, he steered them to develop into full-blown neurons. They could form flat sheets covering the bottom of petri dishes, where they could crackle with voltage spikes and trade neurotransmitters.

Muotri realized that he could use these neurons to study brain disorders that arose from mutations. Instead of carving out a piece of gray matter from people's heads, he could take skin samples and reprogram them into neurons. For his first study, he grew neurons from people with a hereditary form of autism called Rett syndrome. Its symptoms include intellectual disability and the loss of motor control. Muotri's neurons spread their kelp-like branches across petri dishes and made contact with each other. He compared them to the neurons he grew from skin samples taken from people without Rett syndrome. Some differences leaped out. Most noticeably, the Rett neurons grew fewer connections. It's possible that the key to Rett syndrome is a sparse neural network, which changes the way signals travel around the brain.

But Muotri knew very well that a flat sheet of neurons is a far cry from a brain. The three pounds of thinking matter in our heads are a kind of living cathedral, if a cathedral were built by its own stones. Brains arise from a few progenitor cells that crawl into what will become an embryo's head. They gather together to form a pocket-shaped mass and then multiply. As the mass grows, it extends long, cable-like growths out in all directions, toward the forming walls of the skull. Other cells emerge from the progenitor mass and climb up these cables. Different cells stop at different points along the way and begin growing outward. They become organized into a stack of layers, known as the cerebral cortex.

This outer rind of the human brain is where we carry out much of the thinking that makes us uniquely human—where we make sense of words, read inner lives on people's faces, draw on the past, and plan for the distant future. All the cells that we use for these thoughts arise in a particular three-dimensional space in our heads, awash in a complex sea of signals.

Fortunately for Muotri, scientists came up with new recipes to coax reprogrammed cells to multiply into miniature organs. They made lung organoids, liver organoids, heart organoids, and—in 2013—brain organoids. Researchers coaxed reprogrammed cells to become the progenitor cells for brains. Provided with the right signals, those cells then multiplied into thousands of neurons. Muotri recognized that brain organoids would profoundly change his research. A disease like Rett syndrome starts reworking the cerebral cortex from the earliest stages in the brain's development. For scientists like Muotri, those changes happened inside a black box. Now he could grow brain organoids in plain view.

Together, Muotri and Trujillo followed the recipes that other scientists laid down for making organoids. Then they began creating recipes of their own to make a cerebral cortex. It was a struggle to find the blend of chemicals that could coax the brain cells onto the right developmental path. The cells often died along the way, tearing open and spilling out their molecular guts. Eventually the scientists found the correct balance. They discovered to their surprise that once the cells set off in the right direction, they took over their own development.

No longer did the researchers have to patiently coax the organoids to grow. The clumps of cells spontaneously pulled away from each other to form a hollow tube. They sprouted cables that branched out from the tube, and other cells traveled along the cables to form layers. The organoids even grew folds on their outer surface, an echo of our own wrinkled brains. Muotri and Trujillo

“Yeah, they all look quite good,” he said. “They’re rounded, and they more or less have the same size. You don’t see them fusing or clustering together.” He rolled his chair back from his computer. “So this is all good news. I’m happy. This is fantastic.”

Even in space, Muotri could tell his organoids were alive.

In late 2015, Muotri and Trujillo got their first chance to use their organoids to learn something about brains. In Brazil, doctors were struggling to understand why the brains of thousands of babies were drastically deformed. Their cerebral cortices were practically missing. It turned out that their mothers had been infected by a mosquito-borne virus called Zika, which had never before been found in the Americas. Muotri and Trujillo got a supply of Zika viruses and began infecting brain organoids. They wondered if they’d see a change.

“It was night and day,” Muotri told me.

The Zika viruses immediately destroyed progenitor cells in young organoids. Without those cells, an organoid could not sprout cables to build a cortex. The experiments revealed that Zika viruses do not kill the cerebral cortex, so much as prevent it from growing in the first place. Once the scientists figured out how Zika viruses wreak their havoc, they were able to discover drugs that could block them. Those drugs then went into tests on animals to see if they could help prevent brain damage.

Word spread that Muotri was growing brain mimics by the thousands. Graduate students and postdoctoral researchers wanted in. When they joined his lab, they first had to train with Trujillo for months, learning the fine art of making organoids. I asked a graduate student named Cedric Snethlage to describe his education. Making a brain organoid wasn’t just a matter of reading temperatures and pH levels off a protocol, he explained. Snethlage had to learn how to carry out each step by intuition—how far, for example, to tilt the wells to keep the organoids from sticking to the bottom. I told Snethlage that he sounded like he had just gone through cooking school.

“It’s more like making a soufflé than making chili,” he said.

Snethlage wanted to learn how to grow organoids to study neurological disorders. Other graduate students had come to Muotri’s lab to discover how to make organoids more brain-like. Brain cells need nutrients and lots of oxygen to thrive, and the ones at the center of an organoid can starve. So some of Muotri’s students were adding new cells to organoids that could develop into artery-like tubes. Others were adding immune cells to see if they might sculpt the branches of the neurons into more natural shapes.

Meanwhile, Cleber Trujillo’s wife, Priscilla Negraes, began listening to the chatter going on between the organoid cells.

When a brain organoid reaches a few weeks in age, its neurons become mature enough to generate spikes of voltage. Those spikes can travel down an axon and trigger neighboring neurons to fire as well. Negraes and her colleagues created an eavesdropping device that could pick up the crackle. At the bottom of miniature wells, they placed eight-by-eight grids of electrodes. They filled the wells with broth and rested an organoid atop each array.

On her computer, the readout from the electrodes formed a grid of sixty-four circles. Whenever one of the electrodes detected a firing neuron, its circle swelled, turning from yellow to red. Week after week the circles reddened and swelled more often, but there was no pattern Negraes could see to the bursts. The cells in the organoids spontaneously fired on their own from time to time, creating neurological static.

But as the organoids got more mature, Negraes thought she saw some order emerge. Sometimes a few of the circles would all suddenly swell red together. Eventually all sixty-four electrodes registered signals at once. And then Negraes began to see them turn on and off in what looked like waves.

Was Negraes seeing actual brain waves developing in the organoids? She wished that she could compare the patterns she was seeing in her wells with the developing brains of human fetuses. But scientists had yet to figure out how to detect their electrical activity in the womb. The closest that anyone had managed was to study babies born premature, putting miniature EEG caps on their orange-sized heads.

Negraes and her colleagues enlisted a University of California, San Diego, neuroscientist named Bradley Voytek and his graduate student Richard Gao to compare organoids to premature babies. The earliest-born babies, with the least developed brains, produced sparse bursts of brain waves separated by long spells of disorganized firing. The babies that were born closer to term had shorter lulls, their bursts of brain waves growing longer and more organized. Organoids displayed some of the same trends as they got older. When a young organoid first began making waves, they came in sparse bursts. But as the organoid developed over months, they grew longer and better organized, their lulls growing smaller.

This unsettling discovery did not mean that Negraes and her colleagues had created baby brains. For one thing, a human infant's brain is a hundred thousand times bigger than the biggest organoids. For another, the scientists only mimicked one part of the brain—the cerebral cortex. A working human brain has many other parts: a cerebellum, a thalamus, a substantia nigra, and on and on. Some of its parts take in smells. Others handle sight. Still others make sense of different kinds of input. Some parts of the brain encode memories; some jolt it with fear or joy.

Still, the scientists were unsettled. And they had every reason to suspect that, with more research, brain organoids might become more brain-like. A blood supply might let them grow bigger. Researchers might connect a cerebral cortex organoid to a retinal organoid that could sense light. They might link it to motor neurons that could send signals to muscle cells. Muotri even dabbled with the idea of linking an organoid to a robot.

What might happen then? When Muotri started growing organoids, he assumed they could never become conscious. “Now I’m more unsure,” he confessed.

So were bioethicists and philosophers. They began gathering to talk about brain organoids and how to think about them. I called one—a Harvard researcher named Jeantine Lunshof—to get her opinion.

Lunshof wasn’t too worried about Muotri accidentally creating conscious creatures in a dish. Brain organoids were so small and simple that they still fell far below that threshold. What concerned her was a simple question: What on earth are these things?

“In order to say what you should do with it, you first have to say, ‘What is it?’ ” Lunshof explained to me. “We’re making things that were not known ten years ago. They were not in the catalog of philosophers.”

In La Jolla, Lunshof’s question came to my mind as Trujillo showed me his latest batch of organoids.

“This is just a mass of cells,” he said, pointing to one of his wells. “It does not get close to a human brain. But we have the tools to make a more complex mini-brain.”

“So you feel okay with this,” I said, groping for the right words, “because obviously it’s not a human brain—”

“Human cells!” Trujillo clarified.

“So they’re alive,” I half said, half asked.

“Yes,” Trujillo replied. “And they’re human.”

“But they’re not a human being?”

“Yes,” he said.

“But where would you start to approach that line?” I asked.

Trujillo had me imagine an organoid rigged up to an electrode. “You can do a pattern of electrical shocks,” he said.

Trujillo was sitting in front of a microscope as we talked. He extended two of his fingers and rapped them on the counter, producing galloping beats.

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