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The Meaning of Life

LAST WEEK, BIOLOGIST J. CRAIG VENTER CROSSED A MOMENTOUS THRESHOLD—CREATING A LIVING ORGANISM WITH NO ANCESTOR. IN 2007, CARL ZIMMER GAVE SEED THIS PROVOCATIVE LOOK AT THE DIFFICULTIES INHERENT IN DEFINING "LIFE."

It's hard to think of a word more charged with meaning—or meanings—than "life." Some of the most passionate debates of our day, over stem cells or the right to die, genetically modified food, or wartime conduct, revolve around it. Whether we're talking about when life begins or when it ends, the sanctity of life, or the danger of playing God, we all have an idea of what we mean when we talk about life. Yet, it often turns out, we actually mean different things. Scientists, despite their intimacy with the subject, aren't exempt from this confusion.

"There is no one definition that we agree upon," says Radu Popa, geobiologist and the author of *Between Probability and Necessity: Searching for the Definition and Origin of Life*. In the course of researching his book, Popa started collecting definitions that have appeared in the scientific literature. He eventually lost count. "I've found at least three hundred, maybe four hundred definitions," he says.

It's a peculiar state of affairs—biologists have learned more in the past decade about how living things work than we've learned collectively over the past several centuries—and an intense debate has arisen over what to do about it. Some are skeptical of science's ability to come up with a definition of life that's accurate enough to be meaningful, while others believe a definition is not just possible but essential for the future of biology.

"A science in which the most important object has no definition—that's absolutely unacceptable," says Popa. "How are we going to discuss it if you believe the definition of life has something to do with DNA and I think it has something to do with dynamic systems? We cannot have a conversation on any level. We cannot make artificial life because we cannot agree on what life is. We cannot find life on Mars because we cannot agree on what life represents."

Recently, a new voice has entered the debate. Carol Cleland, who teaches philosophy at the University of Colorado and works with the NASA Astrobiology Institute—essentially as their philosopher-in-residence—is making a more radical argument: Scientists should simply give up looking for a definition of life. They can't even begin to understand what life really is, she claims, until they find forms of life profoundly different from those we know here on Earth. Only when we can compare alien life with life on our planet will we understand the true nature of this ubiquitous, ephemeral thing.

Cleland believes biologists need to build a *theory* of life, just as chemists built a theory of the elements and physicists built a theory of electromagnetism. Definitions, she argues, are concerned only with language and concepts, not true understanding. By taking the semantics seriously, Cleland is calling for nothing less than a scientific revolution. Only when we change the way we think about life, she argues, will the true study of it begin.

The modern search for a definition of life was framed by a slender book published in 1943, called simply *What Is Life?* Its author was not a biologist, but a physicist. Erwin Schrödinger, who won the Nobel Prize for his work on quantum physics in 1933, was fascinated by how life seemed to defy the laws of physics. While the universe veered toward entropy, living things somehow created order on a molecular scale. And, somehow, living things could pass on that order from one generation to the next for millions of years.

Schrödinger didn't have much of an answer to offer, but his question inspired James Watson, Francis Crick, and many other pioneers of molecular biology. They discovered that DNA carries genetic information and also discovered the genetic code by which cells turn that information into proteins. They mapped the maze of metabolism that turns lifeless matter into biomass. Molecular biologists began their work on the mysteries of life by studying the microbe *Escherichia coli* and a few other model organisms. Over time they discovered that what was true for *E. coli* was for the most part true for all living things, no matter how different they might look on the outside.

Scientists began to define life in molecular terms, by its ability to convert molecules into complex organic compounds, and its ability to store genetic information in those molecules that it could pass down from generation to generation. When NASA began designing probes to search for life on other planets, it relied on these sorts of definitions. In 1976, NASA's Viking probe arrived on Mars equipped with life-detecting devices. It searched for signs of metabolism, observing whether anything in Martian soil could transform carbon dioxide. It also looked for biochemical signs of life, in the form of organic molecules.

At first the Viking scientists were intrigued. Something in the Martian soil did indeed seem to consume carbon dioxide. But then Viking failed to find any sign of organic molecules. NASA scientists decided they had not found life, but others think they gave up too quickly. It's possible that something was wrong with Viking's definition of life. In January 2007, Dirk Schulze-Makuch and Joop M. Houtkooper pointed out one potential flaw: While most life forms on Earth have cells filled with water, a few are filled with a mix of water and hydrogen peroxide. If Martian life also contained hydrogen peroxide, the chemical could have destroyed organic molecules in the soil. And when Viking heated up samples of soil during its measurements, it would have caused the Martian microbes to destroy themselves. It would have killed the very life it was looking for.

Despite such questions, NASA scaled back its search for extraterrestrial life after Viking. It channeled more of its resources into basic questions about life itself, and how life originated on Earth from prebiological chemistry. In the 1980s, for example, NASA-funded scientists began marshaling evidence that life on Earth did not begin with DNA as its genetic molecule. RNA, a single-stranded version of DNA, plays many roles in the cell, such as acting as a messenger of genetic information. But they found that RNA can also act like an enzyme, cutting other molecules apart or joining them together. Maybe, some scientists argued, a simple form of life that used only RNA was the ancestor of more complex life that used DNA, proteins, and RNA. Scientists began exploring the possibility that life as we know it evolved from an "RNA world."

Out of this effort came one of the most popular working definitions of life. In 1992, a group of scientists met to advise NASA on the most promising areas of research to understand extraterrestrial life. "We're talking about the search for life and the origin of life, and someone said, 'Do you think we should actually define what it is we're talking about?'" recalls Gerald Joyce of the Scripps Research Institute in La Jolla, California. It didn't take long for the scientists to start drowning in possibilities. By the early 1990s, many definitions were already circulating, each focusing on a different set of features found in all living things.

Over time, the NASA scientists came to agree that what sets life apart is its ability to evolve according to the basic rules Darwin proposed 150 years ago. Life, they decided, was a self-sustaining chemical system capable of Darwinian evolution. It was the origin of this evolving system that marked the origin of life. Now chemicals were organized into cells, into species, into lineages that survived and changed over millions of years in a process that Earth had never seen before. “History starts to be written in molecules,” says Joyce. “That’s why biology is different than chemistry.”

Joyce is quick to point out that no one at the meeting claimed to have found the ultimate definition of life. But they had found a working definition, one that could be a useful tool for applying what’s known about life on Earth to life elsewhere. As science’s 21st-century capabilities yield an increasing abundance of information, biologists are able to develop more sophisticated working definitions. With each refinement, they aim to further their chances of recognizing new life—whether on other worlds or in their own laboratories.

Carol Cleland first began to mull the definition of life in the late 1990s. She had spent much of her career as a philosopher pondering fundamental, metaphysical matters such as cause and effect. But in 1996, when NASA scientists found what looked like microbe fossils inside a meteorite from Mars, Cleland was invited to speak on a panel about the mystery.

Looking into the matter, Cleland concluded that a lot of the controversy came out of confusion. Critics were treating the NASA report as if it were experimental science, with a hypothesis that could be tested with experiments. But it’s impossible to do experimental science on a single 4-billion-year-old rock. Instead, the NASA scientists were doing historical science, which Cleland argued was as legitimate a science as experimental science.

Cleland’s talk resulted in an invitation to join the NASA Astrobiology Institute. There, as she learned how scientists at the Institute thought about the search for extraterrestrial life, something set off Cleland’s philosophical radar. “Everybody was working with a definition of life,” she says. Cleland began to feel that the concept of attempting to define life was deeply flawed, and she made her concerns public at a meeting called “The Nature of Life” hosted by the American Association for the Advancement of Science in 2001. Speaking to an audience of scientists, she said the search for a definition of life was beyond problematic, and they should simply stop looking for one. The quest could either be impossible or scientifically trivial. End of story.

“There was an explosion,” says Cleland. “Everyone was yelling at me. It was really amazing. Everyone had their pet definitions and wanted to air them. And here I told them the whole definition project was worthless.”

Not everyone in the audience was yelling, though. “What she said made a lot of sense to me,” says Christopher Chyba, a professor of astronomy at Princeton University. A student of Carl Sagan’s, Chyba made some of the first estimates of how much organic material might have been delivered to the early Earth by comets and meteorites—material that could comprise some of the raw ingredients of life. Having earned a degree in the philosophy of science at the University of Cambridge while studying to becoming a scientist, Chyba felt a natural affinity for Cleland's perspective. "Carol's a philosopher and I'm not," he says. "But these are issues that have interested me for a long time."

Chyba and Cleland joined forces. They combined Chyba's expertise on astrobiology with Cleland's philosophical insights, producing a full-out assault on the definition of life. They began to catalogue all the shortcomings of the many proposed definitions of life—how they excluded things we know are alive and included things that aren't. Cleland, for example, doubts that Darwinian evolution, the core of the NASA definition of life, is essential. "I think those arguments are weak," she says. She envisions alien microbes filled with enzymes but lacking genes. The enzymes build more enzymes and the microbes split in two. They couldn't evolve through Darwinian evolution, because they wouldn't have genes. But they might still change, as their environment changed. Cleland doesn't claim any evidence that such things exist, but she argues that scientists can't rule them out.

Cleland and Chyba also determined that there was an even bigger problem with the pursuit of a definition of life—one that lies in the nature of definitions themselves. "If you really understand what a definition is," says Chyba, "it's not up to handling the problem."

In some cases, definitions are simple. The definition of a bachelor, for example, is an unmarried man. In other words, if you're a man, if you're unmarried, you are—by definition—a bachelor. Being a man is not enough to make you a bachelor, nor is being unmarried. This sort of definition does not require a deep understanding of the nature of things. It is simply a way of arranging ideas. "Philosophers have known for a long time that if you want to make a definition, you're just organizing the concepts in your head," says Cleland. "That's what definitions do."

Life is different. Defining it is not just a matter of tying together a collection of concepts. When people try to define life, they choose a few of the features of living things and make them the very essence of life. And that, Cleland and Chyba argue, is a mistake. "We don't want to know what the word life *means to us*. We want to know what life *is*," says Cleland.

In this sense, scientists who try to define life today make the same mistake that alchemists did in the Middle Ages. Alchemists tried to define substances by their properties, without any understanding of the underlying chemistry. Water, for example, was defined according to its ability to dissolve different solids. This definition led alchemists into confusion. Since ice couldn't dissolve anything, it couldn't be water. Alchemists gave the name "water" to things that we know now are nothing of the sort. They called nitric acid *aqua fortis*, or strong water, because it could dissolve most metals. *Aqua regia*, or noble water, was actually a mixture of hydrochloric acid and nitric acid that was powerful enough to dissolve even gold and platinum, the so-called noble metals.

Searching for a better definition of water would have not gotten alchemists out of this mire. A solution only came in the 18th century, as scientists formulated a theory of chemistry. The behavior of water and other substances suddenly makes a lot of sense when you realize that they are all composed of atoms, which are in turn composed of smaller particles. Chemists can now say water is H_2O. However, "'Water is H_2O' isn't a definition," says Cleland. "It's a discovery."

Instead of trying to formulate a definition of life, Cleland and Chyba argue, we need to develop a *theory* of life—an overarching explanation of nature that joins together a myriad of seemingly random phenomena. Biologists have discovered a number of theories—the germ theory of disease and Darwin's theory of evolution by natural selection, for example—yet they have no full-fledged theory of life itself. The underlying uniformity of life is one of the great discoveries of modern biology, but it's also an obstacle. It represents only a single data point, and blinds us to the possibilities of "weird life." We have no idea exactly which features of life *as we know it* are essential to life as we *don't* know it.

A theory of life would allow us to understand what matters to life, what possible forms it can take, and why. It would let us see connections that we might otherwise miss, just as chemists can see the hidden unity between a cloud in the sky and a block of ice. Scientists are already trying to build a theory of life. A number of researchers have been developing a theory in which life is a self-organized system that can be described using the same principles physicists use to describe hurricanes or galaxies. As biologists learn more and more about how the millions of molecules in a cell work together, these theorists can put their ideas to more precise tests.

For Cleland, the most promising way to build a theory of life is to look for alien life. In 2013, the European Space Agency plans to put a rover back on Mars. Called Exomars, it will drill into the Martian crust to seek out signs of life. NASA has plans of its own on the drawing board, including one possible mission that would bring Martian soil back to Earth for intense study. Meanwhile, other promising habitats for life, such as some of the moons of Jupiter and Saturn, beckon. Cleland argues that finding alien life would allow us to start figuring out what is truly universal about life, rather than just generalizing from life as we know it. Only when we have more data, she reasons, will we have a basis for comparison. As it stands now, says Cleland, "we have no grist for the theoretical mill."

The far reaches of the cosmos are not the only place where scientists may need to know how to recognize a new kind of life. Indeed, some argue that the first place we encounter unique forms of life may not be on another planet, but in a laboratory where scientists are currently trying to make life from scratch. "It's going to happen in our lifetime," promises Mark Bedau, cofounder of the European Center for Living Technology.

Genome-sequencing pioneer Craig Venter and his colleagues are trying to come up with a minimal catalog of genes essential to keep an organism alive. They plan to synthesize this bare-bones genome and inject it into a hollow cell. If the cell boots up, it will begin to make proteins from its artificial genome, it will grow, and it will reproduce.

Other teams are moving from the ground up. Jack Szostak of Harvard Medical School is leading an effort to build RNA-based life. He and his colleagues have found that RNA molecules can spontaneously slip inside microscopic vesicles, and the vesicles can grow and divide. Szostak, for one, doesn't think that a definition of life is important to his work. "I've never been particularly interested in defining life, or in the debates and philosophical speculations that this topic engenders," says Szostak. "I'm happy to just get on with the work, which I hope will continue to shed light on possible pathways for the origin of life."

Other researchers disagree. Knowing how to recognize life is important not just scientifically, they argue, but ethically as well. Scientists need to know when their tinkering with chemistry has crossed over into a tinkering with life itself, says Bedau. But Bedau—who is also a philosopher at Reed College—doesn't think conventional definitions of life will do the trick. "It's maybe not so useful to focus on a definition of life as to focus on milestones," he says. "Whether something is alive or not is more a matter of degree."

Bedau has been pondering just what those milestones might be. To qualify as fully alive, he argues, a system needs three basic features. Life needs a container; it needs a way to encode and replicate information; and it needs a way to capture and use energy.

What makes this triad special in living things is that each feature depends on the other two. Our DNA can only survive inside a cell membrane, and it depends on our metabolism to power its replication. But membranes depend on our DNA in turn to encode the proteins that can build them. To make metabolism possible, the cell stores its energy and the genes to encode the necessary enzymes. Genes and membranes depend on metabolism to provide their raw ingredients.

In the past, scientists have joined together two parts of the triad at a time. And only now are they starting to join all three. For Bedau, to witness this last milestone will offer the opportunity for a close inspection of life's process—one that may reveal more than we expect.

Does it benefit science to abandon these working definitions, these milestones of life? Is it even possible? Can scientists make any progress without them? Will their search toward a theory of life advance more quickly without them?

Cleland, for one, thinks so. By arguing that scientists abandon definitions of life, she doesn't mean that they should throw their hands in the air. "Some scientists view my arguments as leaving them with nothing to constrain their search, but I don't think that's true," says Cleland.

As we explore the universe, Cleland thinks we should leave all of our preconceptions about what life has to be at home. "When you go into outer space, you're going to find weird physical systems," she says. "Some of them are going to be living, but a lot of them are going to be non-living. There are lots and lots of phenomena discovered on Mars and Titan that nobody has been able to figure out. So we're going to be running into weird stuff period when we go to other worlds. The most important thing is to search for anomalies."

It's anomalies, Cleland points out, that have always pushed science forward, as scientists have recognized inconsistencies in their old ideas. They expose the flaws in old ways of thinking. They both force and allow scientists to expand the scope of their vision. If Cleland is right, scientific anomalies have the potential to truly broaden our understanding of life. In some cases, they may turn out to be little more than peculiar chemistry that has nothing to do with life. But in other cases, they may actually be "life" that defies all our expectations of what the term may comprise.

If the work of Cleland, Chyba, and others is any guide, biology may be looping back to its ancient roots. The first biologist was Aristotle, who, 2,400 years ago, offered the earliest recorded accounts of life. Of course, Aristotle was also a great philosopher, and his biology and philosophy were intimately connected. Science and philosophy parted ways in the Enlightenment, but today, as biologists push deeper and deeper into the fundamental workings of life, philosophers are turning out to have important things to say about what's found there. Now, as biology enters a new era, and increasingly incorporates the principles of physics and philosophy, we may be on the cusp of a consilience that will allow us to finally make sense of the whole picture, and not just its parts.