On the Origin of Life on Earth

AN AMAZON OF WORDS FLOWED FROM Charles Darwin's pen. His books covered the gamut from barnacles to orchids, from geology to domestication. At the same time, he filled notebooks with his ruminations and scribbled thousands of letters packed with observations and speculations on nature. Yet Darwin dedicated only a few words of his great verbal flood to one of the biggest questions in all of biology: how life began.

The only words he published in a book appeared near the end of *On the Origin of Species*: "Probably all the organic beings which have ever lived on this earth have descended from some one primordial form, into which life was first breathed," Darwin wrote.

Darwin believed that life likely emerged spontaneously from the chemicals it is made of today, such as carbon, nitrogen, and phosphorus. But he did not publish these musings. The English naturalist had built his argument for evolution, in large part, on the processes he could observe around him. He did not think it would be possible to see life originating now because the life that's already here would prevent it from emerging.

In 1871, he outlined the problem in a letter to his friend, botanist Joseph Hooker: "But if (and Oh! what a big if!) we could conceive in some warm little pond, with all sorts of ammonia and phosphoric salts, light, heat, electricity, etc., present, that a protein compound was chemically formed ready to undergo still more complex changes, at the present day such matter would be instantly devoured or absorbed, which would not have been the case before living creatures were formed."

Scientists today who study the origin of life do not share Darwin's pessimism about our ability to reconstruct those early moments. "Now is a good time to be doing this research, because the prospects for success are greater than they have ever been," says John Sutherland, a chemist at the University of Manchester in the United Kingdom. He and others are addressing each of the steps involved in the transition to life: where the raw materials came from, how complex organic molecules such as RNA formed, and how the first cells arose. In doing so, they are inching their way toward making life from scratch. "When I was in graduate school, people thought investigating the origin of life was something old scientists did at the end of their career, when they could sit in an armchair and speculate," says Henderson James Cleaves of the Carnegie Institution for Science in Washington, D.C. "Now making an artificial cell doesn't sound like science fiction any more. It's a reasonable pursuit."

Raw ingredients

Life—or at least life as we know it—appears to have emerged on Earth only once. Just about all organisms use double-stranded DNA to encode genetic information, for example. They copy their genes into RNA and then translate RNA into proteins. The genetic code they use to translate DNA into proteins is identical, whether they are emus or bread mold. The simplest explanation for this shared biology is that all living things inherited it from a common ancestor—namely, DNA-based microbes that lived more than 3.5 billion years ago. That common ancestor was already fairly complex, and many scientists have wondered how it might have evolved from a simpler predecessor. Some now argue that membrane-bound cells with only RNA inside predated both DNA and proteins. Later, RNA-based life may have evolved the ability to assemble amino acids into proteins. It's a small step, biochemically, for DNA to evolve from RNA.

THE YEAR OF
DARWIN

This essay is the first in a monthly series, with more on evolutionary roots online at **blogs.sciencemag.org/origins**

In modern cells, RNA is remarkably versatile. It can sense the levels of various compounds inside a cell and switch genes on and off to adjust these concentrations, for example. It can also join together amino acids, the building blocks of proteins. Thus, the first cells might have tapped RNA for all the tasks on which life depends.

For 60 years, researchers have been honing theories about the sources of the amino acids and RNA's building blocks. Over time, they have had to refine their ideas to take into account an ever-clearer understanding of what early Earth was like.

In an iconic experiment in 1953, Stanley Miller, then at the University of Chicago, ignited a spark that zapped through a chamber filled with ammonia, methane, and other gases. The spark created a goo rich in amino acids, and, based on his results, Miller suggested that lightning on the early Earth could have created many compounds that would later be assembled into living things.

By the 1990s, however, the accumulated evidence indicated that the early Earth was dominated by carbon dioxide, with a pinch of nitrogen—two gases not found in Miller's flask. When scientists tried to replicate Miller's experiments with carbon dioxide in the mix, their sparks seemed to make almost no amino acids. The raw materials for life would have had to come from elsewhere, they concluded.

In 2008, however, lightning began to look promising once again. Cleaves and his colleagues suspected that the failed experiments were flawed because the sparks might have produced nitrogen compounds that destroyed any newly formed amino acids. When they added buffering chemicals that could take up these nitrogen compounds, the experiments generated hundreds of times more amino acids than scientists had previously found.

Cleaves suspects that lightning was only one of several ways in which organic compounds built up on Earth. Meteorites that fall to Earth contain amino acids and organic carbon molecules such as formaldehyde. Hydrothermal vents spew out other compounds that could have been incorporated into the first life forms. Raw materials were not an issue, he says: "The real hurdle is how you put together organic compounds into a living system."

Step 1: Make RNA

An RNA molecule is a chain of linked nucleotides. Each nucleotide in turn consists of three parts: a base (which functions as a

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"letter" in a gene's recipe), a sugar molecule, and a cluster of phosphorus and oxygen atoms, which link one sugar to the next. For years, researchers have tried in vain to synthesize RNA by producing sugars and bases, joining them together, and then adding phosphates. "It just doesn't work," says Sutherland.

This failure has led scientists to consider two other hypotheses about how RNA came to be. Cleaves and others think RNA-based life may have evolved from organisms that used a different genetic material—one no longer found in nature. Chemists have been able to use other compounds to build backbones for nucleotides (*Science*, 17 November 2000, p. 1306). They're now investigating whether these humanmade genetic molecules, called PNA and TNA, could have emerged on their own on the early Earth more easily than RNA. According to this hypothesis, RNA evolved later and replaced the earlier molecule.

But it could also be that RNA wasn't put together the way scientists have thought. "If you want to get from Boston to New York, there is an obvious way to go. But if you can't get there that way, there are other ways you could go," says Sutherland. He and his colleagues have been trying to build RNA from simple organic compounds, such as formaldehyde, that existed on Earth before life began. They find they make better progress toward producing RNA if they combine the components of sugars and the components of bases together instead of separately making complete sugars and bases first.

Over the past few years, they have documented almost an entire route from prebiotic molecules to RNA and are preparing to publish even more details of their success. Discovering these new reactions makes Sutherland suspect it wouldn't have been that hard for RNA to emerge directly from an organic soup. "We've got the molecules in our sights," he says.

Sutherland can't say for sure where these reactions took place on the early Earth, but he notes that they work well at the temperatures and pH levels found in ponds. If those ponds dried up temporarily, they would concentrate the nucleotides, making conditions for life even more favorable.

Were these Darwin's warm little ponds? "It might just be that he wasn't too far off," says Sutherland.

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> —HENDERSON JAMES CLEAVES, CARNEGIE INSTITUTION FOR SCIENCE

Step 2: The cell

If life did start out with RNA alone, that RNA would need to make copies of itself without help from proteins. Online in *Science* this week (www.sciencemag.org/cgi/content/abstract/1167856), Tracey Lincoln and Gerald Joyce of the Scripps Research Institute in San Diego, California, have shown how that might have been possible. They designed a pair of RNA molecules that join together and assemble loose nucleotides to match their partner. Once the replication is complete, old and new RNA molecules separate and join with new partners to form new RNA. In 30 hours, Lincoln and Joyce found, a population of RNA molecules could grow 100 million times bigger.

Lincoln and Joyce kept their RNA molecules in beakers. On the early Earth, however, replicating RNA might have been packed in the first cells. Jack Szostak and his colleagues at Harvard Medical School in Boston have been investigating how fatty acids and other molecules on the early Earth might have trapped RNA, producing the first protocells. "The goal is to have something that can replicate by itself, using just chemistry," says Szostak.

After 2 decades, he and his colleagues have come up with RNA molecules that can build copies of other short RNA molecules. They have been able to mix RNA and fatty acids together in such a way that the RNA gets trapped in vesicles. The vesicles are able to add fatty acids to their membranes and grow. In July 2008, Szostak reported that he had figured out how protocells could "eat" and bring in nucleotides to build the RNA.

All living cells depend on complicated channels to draw nucleotides across their membranes, raising the question of how a primitive protocell membrane brought in these molecules. By experimenting with different recipes for membranes, Szostak and his colleagues have come up with protocells leaky enough to let nucleic acids slip inside, where they could be assembled into RNA, but not so porous that the large RNA could slip out.

Their experiments also show that these vesicles survive over a 100°C range. At high temperatures, protocells take in nucleotides quickly, and at lower temperatures, Szostak found, they build RNA molecules faster.

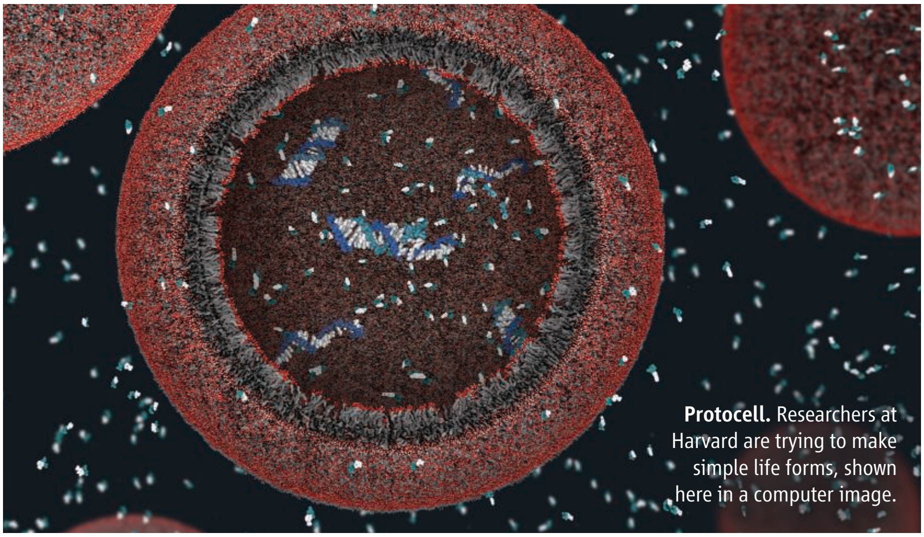
He speculates that regular temperature cycles could have helped simple protocells survive on the early Earth. They could draw in nucleotides when they were warm and then use them to build RNA when the temperature dropped. In Szostak's protocells, nucleotides are arranged along a template of RNA. Strands of RNA tend to stick together at low temperatures. When the protocell warmed up again, the heat might cause the two strands to pull apart, allowing the new RNA molecule to function.

Now Szostak is running experiments to bring his protocells closer to life. He is developing new forms of RNA that may be able to replicate longer molecules faster. For him, the true test of his experiments will be whether his protocells not only grow and reproduce, but evolve.

"To me, the origin of life and the origin of Darwinian evolution are essentially the same thing," says Szostak. And if Darwin was alive today, he might well be willing to write a lot more about how life began.

–CARL ZIMMER

Carl Zimmer is the author of *Microcosm:* E. coli *and the New Science of Life*.



Protocell. Researchers at Harvard are trying to make simple life forms, shown here in a computer image.

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