Did Life Really Start Out in an RNA World?

Conventional wisdom says that it did—but then, conventional wisdom has been wrong before; where did the RNA come from?

IN THE BEGINNING, long before the earth's primordial organisms had evolved proteins or the genetic code, the fundamental chemistry of life was carried out by that complex and versatile molecule known as RNA: ribonucleic acid. Every bit of genetic information on the planet was encoded in RNA. Every chemical reaction in every cell's metabolism was catalyzed by RNA. The infant Earth of some 4 billion years ago was an "RNA World."

Or that, at least, is the conventional wisdom. This idea that life began with RNA gained widespread acceptance in the early 1980s, when Thomas Cech of the University of Colorado and Sidney Altman of Yale University demonstrated that RNA does indeed have the wherewithal to do everything needed for life. Not only is it a key part of the cell's genetic machinery, they found, but it can play a functional role, catalyzing reactions in much the same way as the protein enzymes can—a discovery that earned them the 1989 Nobel Prize in chemistry. By now, the RNA-World scenario has acquired so much cachet that popular discussions, and even some molecular biology textbooks, present it as virtually an established fact.

And yet, within the small community of origin-of-life researchers, one can sense a certain unease with that conventional wisdom. The fact is that the RNA-World scenario fails a crucial plausibility test: No one has yet figured out where the RNA itself came from. RNA is a very complicated molecule, one that's hard enough to synthesize in a test tube. So how could it have formed spontaneously some 4 billion years ago, when there was nothing on Earth but a kind of random, prebiotic chemical soup? The conundrum is so puzzling, in fact, that most origin-of-life researchers are now convinced that some crucial concept is still missing—and a few are convinced that the RNA-World idea is dead wrong.

"You do have your moments when you wonder if this is a solvable problem," admits one RNA loyalist, Alan W. Schwartz of the University of Nijmegen in the Netherlands. "We used to *think* that the RNA World stood at the boundary of life," agrees another, Gerald F. Joyce of the Research Institute of the Scripps Clinic in La Jolla. "But now we realize that it's many millions of years into evolution"—with no hard evidence as to what came before.

What makes this impasse especially frustrating, says Joyce, is that the RNA-World scenario explains so many things so well. Without it, for example, one would be left with an utterly baffling chicken-and-egg paradox: Which came first, proteins or DNA? On the one hand, it's clear that proteins could not exist in the modern cell without DNA, because the genetic information encoded in DNA is what tells the cell how to make the proteins. But on the other hand, DNA could not do its job without protein, because protein enzymes help the DNA in replication, self-repair, and a host of other functions.

Hence the paradox. And hence the appeal of the RNA World, which says that neither came first—because both DNA and proteins are descendants of RNA.

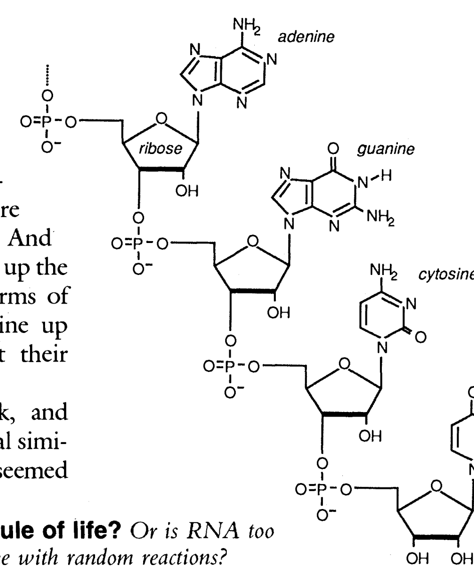
This idea actually dates back to the late 1960s, when it was extensively discussed by Leslie Orgel and Francis Crick of the Salk Institute for Biological Studies in San Diego, and by Carl Woese of the University of Illinois. If you look in detail at how protein synthesis is carried out in the cell, they said, RNA is ubiquitous. The genetic information contained in a given stretch of DNA is first copied onto a molecule of "messenger" RNA, which will serve as a kind of data tape for protein assembly. The messenger RNA then migrates to an RNA-containing structure known as a ribosome, which is the factory site where the assembly will actually take place. And finally, the amino acids that will make up the final protein are brought in by swarms of "transfer" RNA molecules, which line up along the messenger RNA so that their amino acids can be linked in order.

Given all that, said Orgel, Crick, and Woese, and given the strong structural similarities between RNA and DNA, it seemed plausible that the RNA system could have evolved first, and that DNA could have arisen later as a variant molecule specialized for preserving genetic information. At the same time, one could imagine RNA catalysts—if they existed—gradually taking on bits of protein to improve their function, until the protein took over completely.

Orgel and Crick's idea was undeniably appealing. Without that evidence for RNA catalysis, however, it lay dormant until the early 1980s—when it was revived in spectacular fashion by the findings of Cech and Altman. The result has been the current wave of enthusiasm for the RNA-World hypothesis, accompanied by a rush to the lab bench by chemists and molecular biologists trying to find out just how much RNA can do.

A lot, as it turns out. Catalytic RNA segments—"ribozymes"—have proved to be quite adroit at cutting, joining, and moving around pieces of other RNA molecules. And there are even some intriguing hints that ribozymes can recognize and manipulate amino acids directly—which makes it conceivable that they might be able to make proteins directly. If so, says Cech, "that would be spectacular, the last remaining frontier" in demonstrating that RNA could really do everything needed for life.

And yet, as Joyce points out, the weakest link in the whole RNA-World hypothesis is still this question of origin. If life began with RNA, then the RNA itself must have formed by spontaneous chemical reactions among simpler molecules. On the face of it, this is not such a problem, he says: Precursor molecules such as hydrogen cyanide (HCN) and formaldehyde (H_2CO) were probably abundant on the primitive Earth. A variety of experiments have shown that they are formed quite naturally when common gases such as water vapor, carbon



The first molecule of life? *Or is RNA too complicated to make with random reactions?*

dioxide, and nitrogen are hit with energy from sources such as lightning discharges or solar ultraviolet radiation.

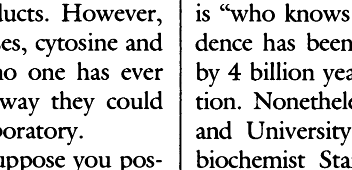
However, says Joyce, RNA formation does become a problem when you ask why, out of all the things that these precursor molecules could have generated, they came up with *that*. Consider ribose, he says, the five-sided sugar molecule that helps form the backbone of RNA. Experiments show that it could have been produced easily enough under prebiotic conditions by a cascade of formaldehyde reactions. But then, that same cascade also produces sugars such as glucose and fructose, not to mention a menagerie of less familiar compounds with names like arabinose, psicose, and lyxose. What is so special about ribose that evolution should have singled it out? Nothing compelling, says Joyce.

And then there are the bases: the adenine, guanine, cytosine, and uracil molecules that encode genetic information by the order in which they line up along the RNA backbone. Experiments show that the first two, adenine and guanine, can be formed easily enough by a cascade of hydrogen cyanide reactions triggered by ultraviolet light—although again, there is no obvious reason for evolution to have selected these molecules over a host of similar products. However, says Joyce, the final two bases, cytosine and uracil, remain a mystery: no one has ever come up with a plausible way they could have formed outside the laboratory.

And finally, says Joyce, suppose you postulate that nature does find a way to single out ribose. Suppose that all four of the bases are somehow formed and then attached to ribose sugars—no mean trick—and suppose that the sugar-base units somehow start to link up into a full RNA chain—another impressive feat, since the linkage involves a tricky reaction with intervening phosphate groups. Then you can still run into trouble.

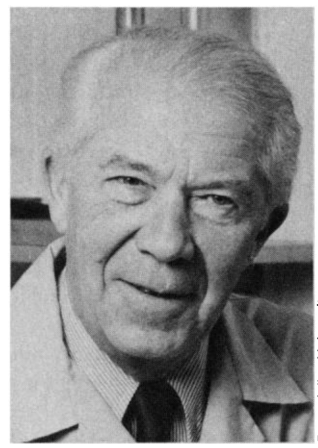
Imagine, Joyce says, that you could take the chemical bond between a ribose molecule and its base and twist it halfway around. As it happens, the bond can exist just as easily in this twisted configuration as in the "correct" configuration. The upshot is that any primordial reaction would almost certainly have given rise to a mixture of ribose "isomers": closely related, but chemically inequivalent versions of the same compound.

These nonbiological isomers never crop up in modern RNA, says Joyce, because the cell's mechanisms for making RNA simply never let them form. But in primordial RNA, they would have been ubiquitous—which means that you would never have gotten a chain at all, but a series of abortive, incompatible fragments. Moreover, even if you imagine that a few hundred million years of trial and error would have allowed a long sequence of the correct isomers to line up by chance, there's still a quandary. To inherit the earth, says Joyce, that serendipitous RNA molecule would have had to reproduce itself—presumably by using its own sequence of bases as a template to build a complementary sequence in a new stretch of RNA. But as soon as it tried to do so, it would find the complementary sequence contaminated with the same mix of isomers as before. The result: no new chain.



A simpler alternative. *A primitive, RNA-like glycerol unit (left) could evolve into a ribose unit (right) by adding just one carbon.*

So in the end, says Joyce, the most reasonable assumption is that life did *not* start with RNA. It must have started with something simpler, something that could have worked out all these problems in advance. The question is, what?



Rockefeller University

RNA skeptic: *"Quite incredible," says Christian de Duve.*

The only correct answer is "who knows?": The evidence has been obliterated by 4 billion years of evolution. Nonetheless, Orgel, Joyce, Schwartz, and University of California, San Diego, biochemist Stanley Miller have spent the past few years exploring some plausible candidates. One of their favorites is the molecule glycerol, a flexible, three-carbon chain that is more stable than ring-shaped ribose and that could have accumulated on the primordial Earth in relatively large amounts. Glycerol also could have combined with adenine and the other bases without producing the "nonbiological" isomers that plague ribose. And finally, the resulting glycerol-base unit would have been equivalent to a ribose-base unit with one carbon atom snipped out of the ribose ring—which means that evolution could have slowly converted a chain of these glycerol units into modern RNA simply by inserting that carbon, presumably to make the chain stiffer and more durable.

However, there is only one problem with this scenario: It doesn't work very well. So far, anyone who has taken glycerol to the laboratory and tried to make it perform the tricks that look so good on paper has gotten mediocre results at best. "If this goes on for several more years," says Schwartz, who is perhaps the most active researcher in this effort, "we'll be truly discouraged."

Others are less patient. A vocal minority of origin-of-life researchers has rejected the RNA World entirely, with perhaps the most notable among them being Nobel laurate cellular biologist Christian de Duve. "I think [the RNA World] is quite incredible," says de Duve, who divides his time between Rockefeller University and the International Institute for Cellular and Molecular Pathology in Brussels. "It's far too complicated."

His theory, which he sets out in his forthcoming book *Blueprint for a Cell*, hearkens back to an older idea: namely, that life originated with a kind of primitive metabolism. In particular, de Duve argues that random chemical reactions on the early Earth would have produced a variety of polypeptides—short amino acid chains—along with a multitude of other organic fragments. He then points out that many such compounds are known to have crude catalytic properties, which means that once they are formed, they can begin to guide those original chemical reactions in nonrandom directions. Thus, the concentration of certain compounds would be preferentially enhanced. And these, in turn, would start to catalyze still more reactions.

Eventually, says de Duve, a network of interrelated catalysts and reaction products would begin to rise above the chemical "noise," thus providing a form of natural selection without genetics. Among these selected catalysts, moreover, would be the primitive ancestors of today's enzymes.

Joyce, for one, finds a lot to admire in de Duve's theory, which also includes scenarios for how these catalytic networks could give rise to energy metabolism and—eventually—the genetic code. "[*Blueprint for a Cell*] is a very literate book, by a man who knows cell biology like few others," he says. True, he personally doesn't find this metabolism-first hypothesis as convincing as de Duve obviously does. And indeed, de Duve himself admits that none of the key steps have yet been demonstrated in the laboratory.

Yet Joyce is the first to point out that no one has a monopoly on truth in this game. "There is *no* theory of the origin," he says, "that is without problems."

■ M. MITCHELL WALDROP