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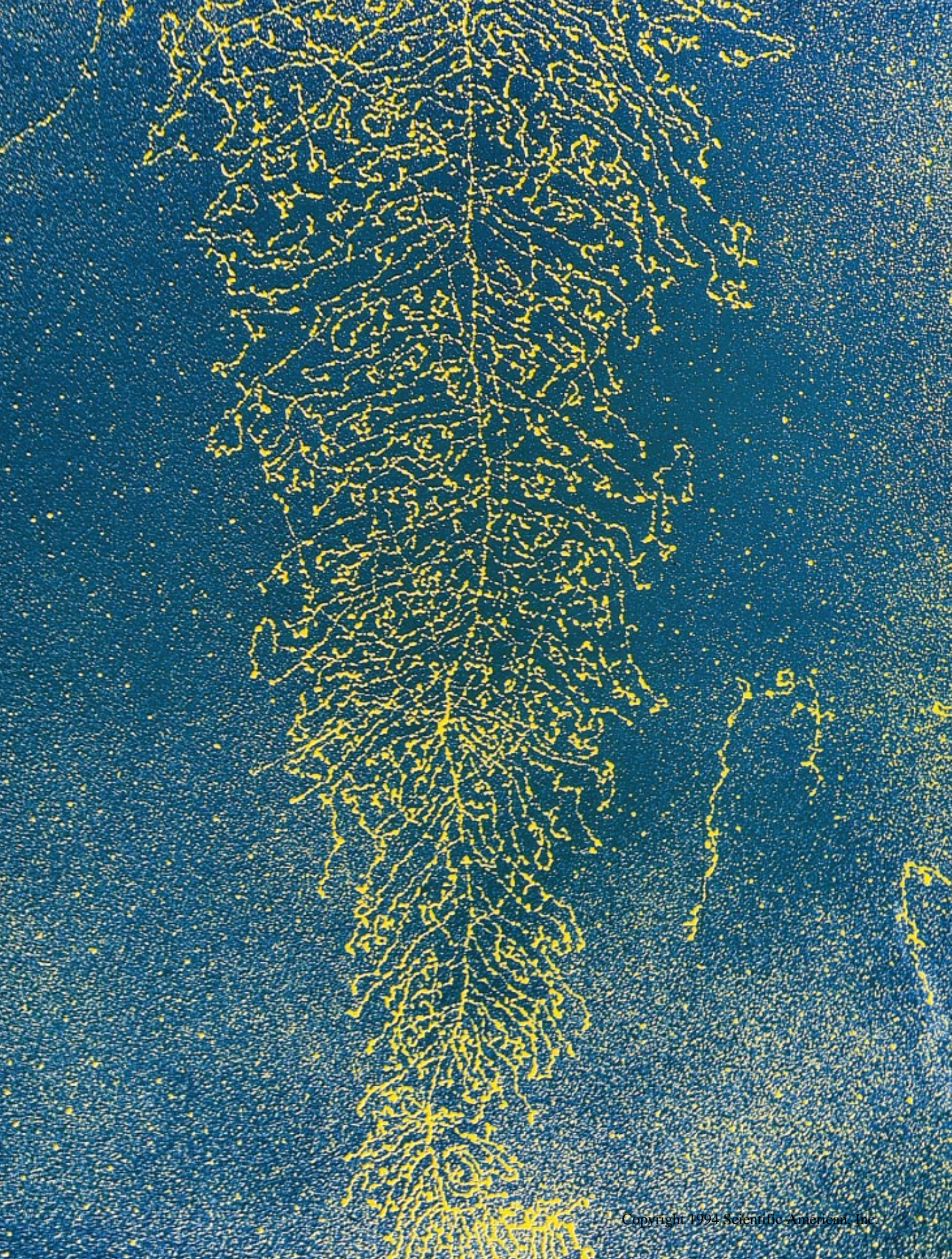
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The Origin of Life on the Earth

*Growing evidence supports the idea that the emergence of catalytic RNA was a crucial early step.
How that RNA came into being remains unknown*

by Leslie E. Orgel

When the earth formed some 4.6 billion years ago, it was a lifeless, inhospitable place. A billion years later it was teeming with organisms resembling blue-green algae. How did they get there? How, in short, did life begin? This long-standing question continues to generate fascinating conjectures and ingenious experiments, many of which center on the possibility that the advent of self-replicating RNA was a critical milestone on the road to life.

Before the mid-17th century, most people believed that God had created humankind and other higher organisms and that insects, frogs and other small creatures could arise spontaneously in mud or decaying matter. For the next two centuries, those ideas were subjected to increasingly severe criticism, and in the mid-19th century two important scientific advances set the stage for modern discussions of the origin of life.

In one advance Louis Pasteur discredited the concept of spontaneous generation. He offered proof that even bacteria and other microorganisms arise from parents resembling themselves. He thereby highlighted an intriguing question: How did the first generation of each species come into existence?

The second advance, the theory of natural selection, suggested an answer. According to this proposal, set forth by Charles Darwin and Alfred Russel Wallace, some of the differences between

individuals in a population are heritable. When the environment changes, individuals bearing traits that provide the best adaptation to the new environment meet with the greatest reproductive success. Consequently, the next generation contains an increased percentage of well-adapted individuals displaying the helpful characteristics. In other words, environmental pressures select adaptive traits for perpetuation.

Repeated generation after generation, natural selection could thus lead to the evolution of complex organisms from simple ones. The theory therefore implied that all current life-forms could have evolved from a single, simple progenitor—an organism now referred to as life's last common ancestor. (This life-form is said to be "last" not "first" because it is the nearest shared ancestor of all contemporary organisms; more distant ancestors must have appeared earlier.)

Darwin, bending somewhat to the religious biases of his time, posited in the final paragraph of *The Origin of Species* that "the Creator" originally breathed life "into a few forms or into one." Then evolution took over: "From so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved." In private correspondence, however, he suggested life could have arisen through chemistry, "in some warm little pond, with all sorts of ammonia and phosphoric salts, light, heat, electricity, etc. present." For much of the 20th century, origin-of-life research has aimed to flesh out Darwin's private hypothesis—to elucidate how, without supernatural intervention, spontaneous interaction of the relatively simple molecules dissolved in the lakes or oceans of the prebiotic world could have yielded life's last common ancestor.

Finding a solution to this problem requires knowing something about that

ancestor's characteristics. Obviously, it had to possess genetic information—that is, heritable instructions for functioning and reproducing—and the means to replicate and carry out those instructions. Otherwise it would have left no descendants. Also, its system for replicating its genetic material had to allow for some random variation in the heritable characteristics of the offspring so that new traits could be selected and lead to the creation of diverse species.

Scientists have attained more insight into the character of the last common ancestor by identifying commonalities in contemporary organisms. One can safely infer that intricate features present in all modern varieties of life also appeared in that common ancestor. After all, it is next to impossible for such universal traits to have evolved separately. The rationale is the same as would apply to discovery of two virtually identical screenplays, differing only in a few words. It would be unreasonable to think that the scripts were created independently by two separate authors. By the same token, it would be safe to assume that one script was an imperfect replica of the other

STRANDS OF RNA (branchlike lines) are being synthesized on DNA (vertical line). Today genetic information usually flows from DNA to RNA, but many investigators think some form of RNA evolved before DNA. This idea is central to the RNA-world theory of how life began, which holds that RNA made possible the evolution of DNA and life itself.

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or that both versions were slightly altered copies of a third.

One readily apparent commonality is that all living things consist of similar organic (carbon-rich) compounds. Another shared property is that the proteins found in present-day organisms are fashioned from one set of 20 standard amino acids. These proteins include enzymes (biological catalysts) that are essential to development, survival and reproduction.

Further, contemporary organisms carry their genetic information in nucleic acids—RNA and DNA—and use essentially the same genetic code. This code specifies the amino acid sequences of all the proteins each organism needs. More precisely, the instructions take the form of specific sequences of nucleotides, the building blocks of nucleic acids. These nucleotides consist of a sugar (deoxyribose in DNA, and ribose in RNA), a phosphate group and one of four different nitrogen-containing bases. In DNA, the bases are adenine (A), guanine (G), cytosine (C) and thymine (T). In RNA, uracil (U) substitutes for thymine. The bases constitute the alphabet, and triplets of bases form the words. As an example, the triplet *CUU* in RNA instructs a cell to add the amino acid leucine to a growing strand of protein.

From such findings we can infer that our last common ancestor stored genetic information in nucleic acids that specified the composition of all needed proteins. It also relied on proteins to direct many of the reactions required for self-perpetuation. Hence, the central prob-

lem of origin-of-life research can be refined to ask, By what series of chemical reactions did this interdependent system of nucleic acids and proteins come into being?

Anyone trying to solve this puzzle immediately encounters a paradox. Nowadays nucleic acids are synthesized only with the help of proteins, and proteins are synthesized only if their corresponding nucleotide sequence is present. It is extremely improbable that proteins and nucleic acids, both of which are structurally complex, arose spontaneously in the same place at the same time. Yet it also seems impossible to have one without the other. And so, at first glance, one might have to conclude that life could never, in fact, have originated by chemical means.

In the late 1960s Carl R. Woese of the University of Illinois, Francis Crick, then at the Medical Research Council in England, and I (working at the Salk Institute for Biological Studies in San Diego) independently suggested a way out of this difficulty. We proposed that RNA might well have come first and established what is now called the RNA world—a world in which RNA catalyzed all the reactions necessary for a precursor of life's last common ancestor to survive and replicate. We also posited that RNA could subsequently have developed the ability to link amino acids together into proteins. This scenario could have occurred, we noted, if prebiotic RNA had two properties not evident today: a capacity to replicate without the help of proteins and an ability to catalyze every step of protein synthesis.

There were a few reasons why we favored RNA over DNA as the originator of the genetic system, even though DNA is now the main repository of hereditary information. One consideration was that the ribonucleotides in RNA are more readily synthesized than are the deoxyribonucleotides in DNA. Moreover, it was easy to envision ways that DNA could evolve from RNA and then, being more stable, take over RNA's role as the guardian of heredity. We suspected that RNA came before proteins in part because we had difficulty composing any scenario in which proteins could replicate in the absence of nucleic acids.

During the past 10 years, a fair amount of evidence has lent credence to the idea that the hypothetical RNA world did exist and lead to the advent of life based on DNA, RNA and protein. Notably, in 1983 Thomas R. Cech of the University of Colorado at Boulder and, independently, Sidney Altman of Yale University discovered the first known ribozymes, enzymes made of RNA. Until then, proteins were thought to carry out all catalytic reactions in contemporary organisms. Indeed, the term "enzyme" is usually reserved for proteins. The first ribozymes identified could do little more than cut and join preexisting RNA. Nevertheless, the fact that they behaved like enzymes added weight to the notion that ancient RNA might also have been catalytic.

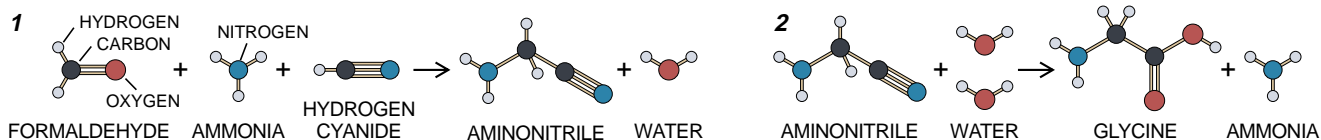
So far no RNA molecules that direct the replication of other RNA molecules have been identified in nature. But ingenious techniques devised by Cech and

The Original Origin-of-Life Experiment

In the early 1950s Stanley L. Miller, working in the laboratory of Harold C. Urey at the University of Chicago, did the first experiment designed to clarify the chemical reactions that occurred on the primitive earth (*right*). In the flask at the bottom, he created an "ocean" of water, which he heated, forcing water vapor to circulate (*arrows*) through the apparatus. The flask at the top contained an "atmosphere" consisting of methane (CH_4), ammonia (NH_3), hydrogen (H_2) and the circulating water vapor. Next he exposed the gases to a continuous electrical discharge ("lightning"), causing the gases to interact. Water-soluble products of those reactions then passed through a condenser and dissolved in the mock ocean. The experiment

yielded many amino acids and enabled Miller to explain how they had formed. For instance, glycine appeared after reactions in the atmosphere produced simple compounds—formaldehyde and hydrogen cyanide—that participated in the set of reactions shown below. Years after this experiment, a meteorite that struck near Murchison, Australia, was shown to contain a number of the same amino acids that Miller identified (*table*) and in roughly the same relative amounts (*dots*); those found in proteins are highlighted in blue. Such coincidences lent credence to the idea that Miller's protocol approximated the chemistry of the prebiotic earth. More recent findings have cast some doubt on that conclusion.

HOW GLYCINE FORMED



Jack W. Szostak of the Massachusetts General Hospital have modified naturally occurring ribozymes so that they can carry out some of the most important subreactions of RNA replication, such as stringing together nucleotides or oligonucleotides (short sequences of nucleotides).

Quite recently Szostak found even stronger evidence that an RNA molecule produced by prebiotic chemistry could have carried out RNA replication on the early earth. He started by creating a pool of random oligonucleotides, to approximate the random production presumed to have occurred some four billion years ago. From that pool he was able to isolate a catalyst that could join together oligonucleotides. Equally important, the catalyst could draw energy for the reaction from a triphosphate group (three joined phosphates), the very same group that now fuels most biochemical reactions in living systems, including nucleic acid replication. Such a resemblance supports the idea that an RNA molecule could have behaved like, and preceded, the protein catalysts that today carry out the replication of genetic material in living organisms. Much remains to be done, but it now seems likely that some kind of RNA-catalyzed reproduction of RNA will be demonstrated in the not too distant future.

Studies of ribosomes, often called the protein factories of cells, have provided support for another important part of the RNA-world hypothesis: the proposition that RNA could have created protein synthesis. Ribosomes, which consist of ribosomal RNA and protein,

travel along strands of messenger RNA (single-strand transcripts of protein-coding genes carried by DNA). As the ribosomes move, they link one specified amino acid to the next by forming peptide bonds between them. Harry F. Noller, Jr., of the University of California at Santa Cruz has found that it is probably the RNA in ribosomes, not the protein, that catalyzes formation of the peptide bonds.

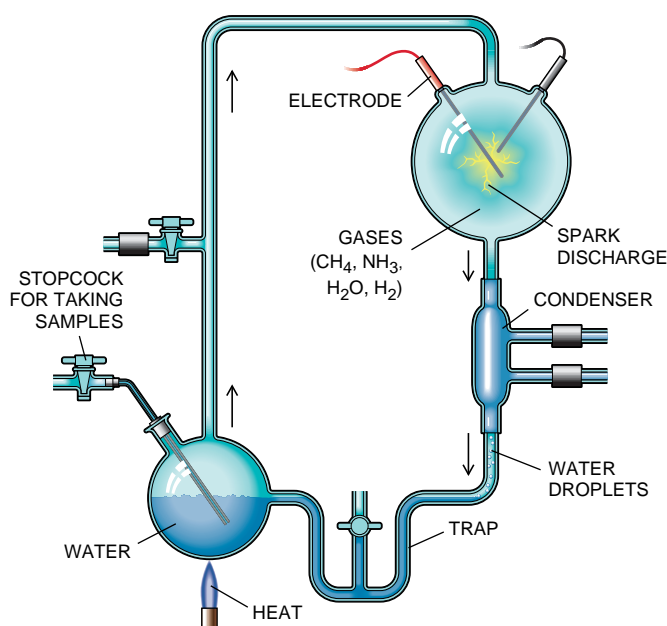
Other work indicates that primitive RNA would have been able to evolve, as would be required of any material that gave rise to the genes in life's last common ancestor. Sol Spiegelman, when at the University of Illinois, and researchers inspired by his ideas have demonstrated that RNA molecules can be induced to take on new traits. For instance, when RNA was allowed to replicate repeatedly in the presence of a ribonuclease (an enzyme that normally breaks down RNA), the RNA eventually became resistant to the degradative enzyme. Similarly, Gerald F. Joyce of the Scripps Research Institute and others have recently applied more sophisticated procedures to derive ribozymes that cleave a variety of chemical bonds, including peptide bonds.

Thus, there is good reason to think the RNA world did exist and that RNA invented protein synthesis. If this conclusion is correct, the main task of origin-of-life research then becomes explaining how the RNA world came into being. The answer to this question requires knowing something about the chemistry of the prebiotic soup: the aqueous solution of organic molecules

in which life originated. Fortunately, even before the RNA-world hypothesis was proposed, investigators had gained useful insights into that chemistry.

By the 1930s Alexander I. Oparin in Russia and J.B.S. Haldane in England had pointed out that the organic compounds needed for life could not have formed on the earth if the atmosphere was as rich in oxygen (oxidizing) as it is today. Oxygen, which takes hydrogen atoms from other compounds, interferes with the reactions that transform simple organic molecules into complex ones. Oparin and Haldane proposed, therefore, that the atmosphere of the young earth, like that of the outer planets, was reducing: it contained very little oxygen and was rich in hydrogen (H_2) and compounds that can donate hydrogen atoms to other substances. Such gases were presumed to include methane (CH_4) and ammonia (NH_3).

Oparin's and Haldane's ideas inspired the famous Miller-Urey experiment, which in 1953 began the era of experimental prebiotic chemistry. Harold C. Urey of the University of Chicago and Stanley L. Miller, a graduate student in Urey's laboratory, wondered about the kinds of reactions that occurred when the earth was still enveloped in a reducing atmosphere. In a self-contained apparatus, Miller created such an "atmosphere." It consisted of methane, ammonia, water and hydrogen above an "ocean" of water. Then he subjected the gases to "lightning" in the form of a continuous electrical discharge. After a



AMINO ACID	MURCHISON METEORITE	DISCHARGE EXPERIMENT
GLYCINE	• • • •	• • • •
ALANINE	• • • •	• • • •
α -AMINO-N-BUTYRIC ACID	• • •	• • • •
α -AMINOISOBUTYRIC ACID	• • • •	• •
VALINE	• • •	• •
NORVALINE	• • •	• • •
ISOVALINE	• •	• •
PROLINE	• • •	•
PIPECOLIC ACID	•	•
ASPARTIC ACID	• • •	• • •
GLUTAMIC ACID	• • •	• •
β -ALANINE	• •	• •
β -AMINO-N-BUTYRIC ACID	•	•
β -AMINOISOBUTYRIC ACID	•	•
γ -AMINOBUTYRIC ACID	•	• •
SARCOSINE	• •	• • •
N-ETHYLGLYCINE	• •	• • •
N-METHYLALANINE	• •	• •

few days, he analyzed the contents of the mock ocean.

Miller found that as much as 10 percent of the carbon in the system was converted to a relatively small number of identifiable organic compounds, and up to 2 percent of the carbon went to making amino acids of the kinds that serve as constituents of proteins. This last discovery was particularly exciting because it suggested that the amino acids needed for the construction of proteins—and for life itself—would have been abundant on the primitive planet. At the time, investigators were not yet paying much attention to the origin of nucleic acids; they were most interested in explaining how proteins appeared on the earth.

Careful analyses elucidated many of the chemical reactions that occurred in the experiment and thus might have occurred on the prebiotic planet. First, the gases in the “atmosphere” reacted to form a suite of simple organic compounds, including hydrogen cyanide (HCN) and aldehydes (compounds containing the group CHO). The aldehydes then combined with ammonia and hydrogen cyanide to generate intermediary products called aminonitriles, which interacted with water in the “ocean” to

produce amino acids and ammonia. Glycine was the most abundant amino acid, resulting from the combination of formaldehyde (CH₂O), ammonia and hydrogen cyanide. A surprising number of the standard 20 amino acids were also made in lesser amounts.

Since then, workers have subjected many different mixtures of simple gases to various energy sources. The results of these experiments can be summarized neatly. Under sufficiently reducing conditions, amino acids form easily. Conversely, under oxidizing conditions, they do not arise at all or do so only in small amounts.

Similar studies provided some of the first evidence that the components of nucleic acids could have formed in the prebiotic soup as well. In 1961 Juan Oró, then at the University of Houston, tried to determine whether amino acids could be obtained by even simpler chemistry than had operated in the Miller-Urey experiment. He mixed hydrogen cyanide and ammonia in an aqueous solution, without introducing an aldehyde. He found that amino acids could indeed be produced from these chemicals. In addition, he made an unexpected discovery: the most

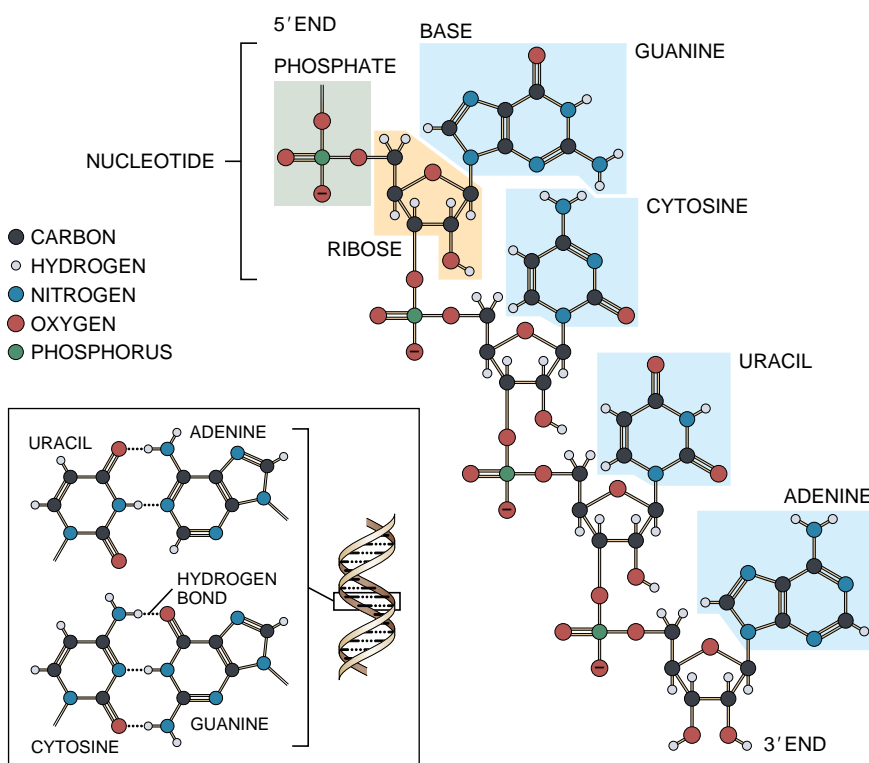
abundant complex molecule identified was adenine.

Adenine, it will be recalled, is one of the four nitrogen-containing bases present in RNA and DNA. It is also a component of adenosine triphosphate (ATP), now the major energy-providing molecule of biochemistry. Oró's work implied that if the atmosphere was indeed reducing, adenine—arguably one of the most essential biochemicals—would have been available to help get life started. Later studies established that the remaining nucleic acid bases could be obtained from reactions among hydrogen cyanide and two other compounds that would have formed in a reducing prebiotic atmosphere: cyanogen (C₂N₂) and cyanoacetylene (HC₃N). Hence, early experiments seemed to indicate that under plausible prebiotic conditions, important constituents of proteins and nucleic acids could have been present on the early earth.

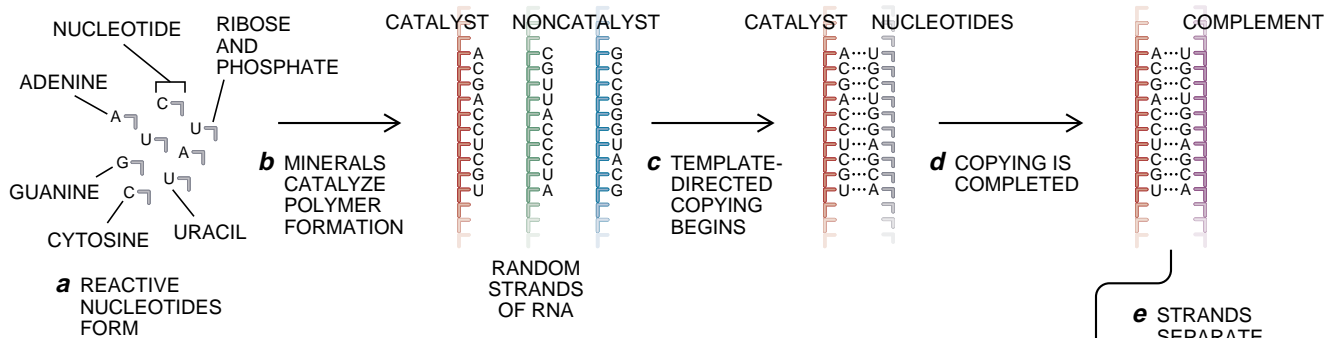
Strikingly, many of the same compounds generated in these various experiments have also been shown to exist in outer space. A family of amino acids that overlaps strongly with those formed in the Miller-Urey experiment has been identified in carbonaceous meteorites, along with the purine bases (adenine and guanine). Furthermore, the family of small molecules that laboratory experiments have implicated as participating in prebiotic syntheses—water, ammonia, formaldehyde, hydrogen cyanide and cyanoacetylene—is abundant in interstellar dust clouds, where new stars are born.

The coincidence between the molecules present in outer space and those produced in laboratory simulations of prebiotic chemistry has generally been interpreted to mean that the simulations have painted a reasonable picture of the chemistry that occurred on the young earth. I should note, however, that this conclusion is now shakier than it once seemed. Doubt has arisen because recent investigations indicate the earth's atmosphere was never as reducing as Urey and Miller presumed. I suspect that many organic compounds generated in past studies would have been produced even in an atmosphere containing less hydrogen, methane and ammonia. Still, it seems prudent to consider other mechanisms for the accumulation of the constituents of proteins and nucleic acids in the prebiotic soup.

For instance, the amino acids and nitrogen-containing bases needed for life on the earth might have been delivered by interstellar dust, meteorites and comets. During the first half a billion years of the earth's history, bombardment by meteorites and comets must



RNA IS COMPOSED OF NUCLEOTIDES, each of which consists of a phosphate group (green box) and the sugar ribose (yellow box) linked to a nitrogen-containing base (blue boxes): guanine (G), cytosine (C), uracil (U) or adenine (A). Uracil on one strand of RNA can pair with adenine on another strand, and cytosine can pair with guanine, producing a double helix (inset). Such complementary base pairing is thought to have contributed to the ability of early RNA to reproduce itself.



RNA REPLICATION FIRST BEGAN, according to one scenario, after reactive nucleotides (a) on the primitive earth came together into random polymers (b), one of which was a catalyst (red). Free nucleotides then lined up on the catalyst (c)—as well as on other polymers (not shown)—and joined (d) to form a complementary strand (purple). After the catalyst and its complement separated (e), the catalyst set about “copying” (making a complement of) the complement (at left in f). It thereby produced a replica of itself (red strand at right in f). Catalytic copying of the catalyst (at left in g) and of its complement (at right in g) then ensured repeated replication (h) of both strands. Consistent with this idea, workers have achieved template-directed synthesis of strands complementary to short polymers (c and d). But no one has reproduced an original polymer without help from proteins.

have been intense, although the extent to which organic material could have survived such impacts is debatable. It is also possible, though less likely, that some of the organic materials required for life did not originate at the earth’s surface at all. They may have arisen in deep-sea vents, the submarine fissures in the earth’s crust through which intensely hot gases are cycled.

Even if we assume that one process or another allowed the constituents of nucleic acids to appear on the prebiotic planet, those of us who favor the RNA-world hypothesis still have to explain how self-replicating RNA was created from these constituents. The simplest hypothesis presumes that the nucleotides in RNA formed when direct chemical reactions led to joining of the sugar ribose with nucleic acid bases and phosphate (which would have been available in inorganic material). Next, these ribonucleotides spontaneously joined to form polymers, at least one of which happened to be capable of engineering its own reproduction.

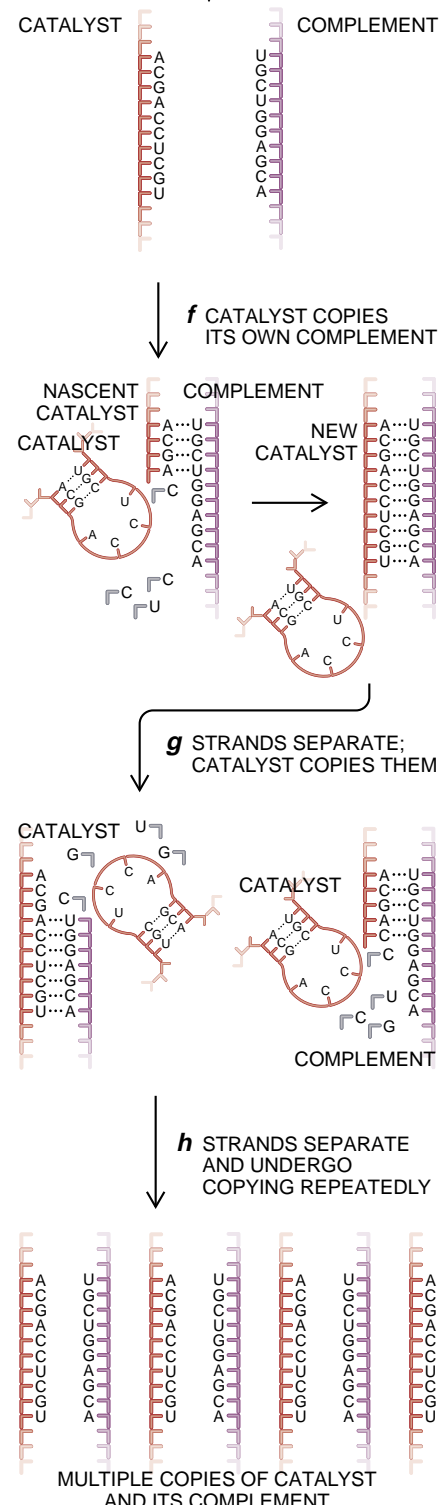
This scenario is attractive but, as will be seen, has proved hard to confirm. First of all, in the absence of enzymes, workers have had trouble synthesizing ribose in adequate quantity and purity. It has long been known that ribose can be produced easily through a series of reactions between molecules of formaldehyde. Yet when such reactions occur, they yield a mixture of sugars in which ribose is always a minor product. The relative paucity of ribose would militate against development of an RNA world, because the other sugars would combine with nucleic acid bases to form

products that inhibit RNA synthesis and replication. No one has yet discovered a simple, complete chain of reactions that ends with ribose as the main product.

What is more, attempts to synthesize nucleotides directly from their components under prebiotic conditions have met with only modest success. One encouraging series of experiments has yielded purine nucleosides—that is, units consisting of ribose and a purine base but not including the phosphate group that would be present in a finished nucleotide. Unfortunately, investigators have been unable to produce pyrimidine nucleosides (combinations of ribose with cytosine or uracil) efficiently without the aid of enzymes.

Formation of nucleotides by combining phosphate with nucleosides has been achieved by simple prebiotic reactions. But the kinds of nucleotides that occur in nature arose along with related molecules having incorrect structures. If such mixtures were produced on the young planet, the abnormal nucleotides would have interacted with the normal ones to interfere with catalysis and RNA replication. Hence, although each step of ribonucleotide synthesis can be achieved to some extent, it is not easy to see how prebiotic reactions could have led to the development of the ribonucleotides needed for producing self-replicating RNA.

One way around this problem is to assume that inorganic catalysts were available to ensure that only the correct nucleotides formed. For instance, when the components of nucleotides became adsorbed on the surface of some mineral, that mineral might have caused them to combine only in specific orien-



tations. The possibility that minerals served as useful catalysts remains real, but none of the minerals tested so far has been shown to have the specificity needed to yield only nucleotides having the correct architecture.

It is also possible that nonenzymatic reactions leading to the efficient synthesis of pure ribonucleotides did occur but that scientists have simply failed to identify them. As a case in point, Albert Eschenmoser of the Swiss Federal Institute of Technology recently managed to limit the number of different sugars generated when ribose was made from the polymerization of formaldehyde molecules. In his experiments, he substituted a normal intermediate of the ribose-forming reaction with a closely related, phosphorylated compound and then allowed the later steps to proceed. Under some conditions, the main end product of the process was a phosphorylated derivative of ribose. The phosphate groups on this product would have had to be rearranged in order to produce the phosphorylated ribose found in ribonucleotides. Nevertheless, the results do suggest that undiscovered reactions in the prebiotic soup could have led to the efficient synthesis of ribonucleotides.

Let us assume investigators could prove that ribonucleotides were able to emerge nonenzymatically. Workers who favor the simple scenario described above would still have to demonstrate that the nucleotides could

assemble into polymers and that the polymers could replicate without assistance from proteins. Many researchers are now struggling with these challenges. Once again, minerals could conceivably have catalyzed the joining of reactive nucleotides into polymers. Indeed, James P. Ferris of the Rensselaer Polytechnic Institute finds that a common clay, montmorillonite, catalyzes the synthesis of RNA oligonucleotides.

It is harder to conceive of the steps by which RNA might have begun to replicate in the absence of proteins. Early work in my laboratory initially suggested that such replication was possible. In these experiments, we synthesized oligonucleotides and mixed them with free nucleotides. The nucleotides lined up on the oligonucleotides and combined with one another to form new oligonucleotides.

To be more specific, since 1953, when James D. Watson and Francis Crick solved the three-dimensional structure of DNA, it has been known that adenine in nucleotides pairs with thymine in DNA and with uracil in RNA. Similarly, guanine pairs with cytosine. Such coupled units are now known as Watson-Crick base pairs. The oligonucleotides that emerged in our experiments arose through Watson-Crick base pairing and were thus complementary to the original strands. For example, a template that was made solely of cytosine-bearing ribonucleotides directed construction of a complementary polymer consisting entirely of guanine-bearing ribonucleotides.

Forming such complements from an original template—a process I shall refer to as “copying”—would be the first step in prebiotic replication of a selected strand of RNA. Then the strands would have to separate, and a complement of the complement (a replica of the original strand) would have to be constructed. The experiments described above clearly established that the mutual attraction between adenine and uracil and between guanine and cytosine is sufficient by itself to yield complementary strands of many nucleotide sequences. Enzymes simply make the process more efficient and allow a broader range of RNAs to be copied.

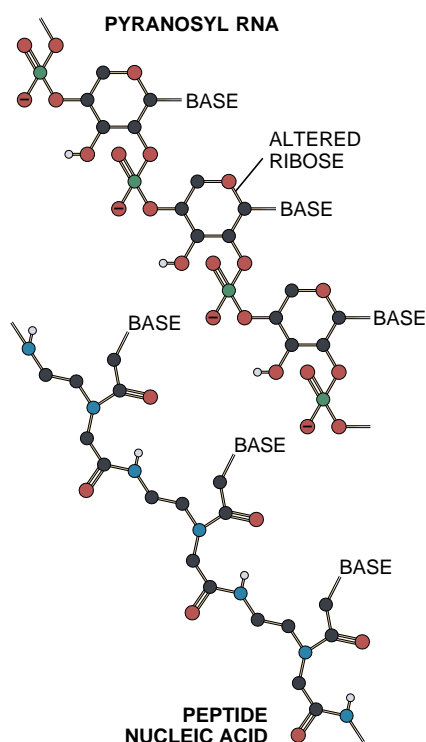
After years of trying, however, we have been unable to achieve the second step of replication—copying of a com-

plementary strand to yield a duplicate of the first template—without help from protein enzymes. Equally disappointing, we can induce copying of the original template only when we run our experiments with nucleotides having a right-handed configuration. All nucleotides synthesized biologically today are right-handed. Yet on the primitive earth, equal numbers of right- and left-handed nucleotides would have been present. When we put equal numbers of both kinds of nucleotides in our reaction mixtures, copying was inhibited.

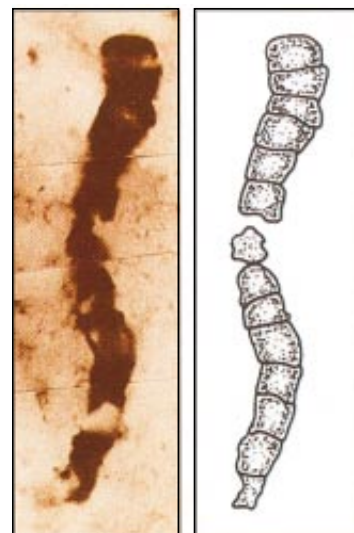
All these problems are worrisome, but they do not completely rule out the possibility that RNA was initially synthesized and replicated by relatively uncomplicated processes. Perhaps minerals did indeed catalyze both the synthesis of properly structured nucleotides and their polymerization to a random family of oligonucleotides. Then copying without replication would have produced a pair of complementary strands. If, as Szostak has posited, one of the strands happened to be a ribozyme that could copy its complement and thus duplicate itself, the conditions needed for exponential replication of the two strands would have been established [see illustration on preceding page]. This scenario is certainly very optimistic, but it could be correct.

Because synthesizing nucleotides and achieving replication of RNA under plausible prebiotic conditions have proved so challenging, chemists are increasingly considering the possibility that RNA was not the first self-replicating molecule on the primitive earth—that a simpler replicating system came first. In this view, RNA would be the Frankenstein that finally displaced its inventor. A. Graham Cairns-Smith of the University of Glasgow was the first to speculate on this kind of genetic takeover. He and others argue that the components of the first genetic system were either very simple or could at least be generated simply. Cairns-Smith has also put forward one of the most radical proposals for the nature of this early genetic system.

Some 30 years ago he proposed that the very first replicating system was inorganic. He envisaged irregularities in the structure of a clay—for example, an irregular distribution of cations (pos-



TWO MOLECULES RELATED TO RNA have been constructed recently (hydrogen atoms on carbon atoms are not shown). Pyranosyl RNA (top) differs from RNA in that its ribose contains a six-member, instead of five-member, ring. Peptide nucleic acid (bottom) has nucleic acid bases but a proteinlike backbone. In prebiotic times polymers with similar features might have formed and replicated more readily than did RNA; RNA might have evolved from one such molecule.



MODERN STROMATOLITES (*left photograph*), structures built by cyanobacteria (blue-green algae), grace Shark Bay, Australia. Elsewhere in Australia, J. William Schopf of the University of California at Los Angeles has found remnants of 3.6-billion-year-old stromatolites lying near fossils of 3.5-billion-year-old

cells that resemble modern cyanobacteria; the fossils (*right photograph*) apparently represent strings of microscopic cells (*diagram*). Schopf's discoveries indicate that, regardless of how life got started, it was well established within just a billion years after the earth first formed.

itively charged ions)—as the repository of genetic information. Replication would be achieved in this example if any given arrangement of the cations in a preformed layer of clay directed the synthesis of a new layer with an almost identical distribution of cations. Selection could be achieved if the distribution of cations in a layer determined how efficiently that layer would be copied. So far no one has tested this daring hypothesis in the laboratory. On theoretical grounds, however, it seems implausible. Structural irregularities in clay that were complicated enough to set the stage for the emergence of RNA probably would not be amenable to accurate self-replication.

Other investigators have also begun to take up the search for alternative genetic materials. In one intriguing example, Eschenmoser has created a molecule called pyranosyl RNA (pRNA) that is closely related to RNA but incorporates a different version of ribose. In natural RNA, ribose contains a five-member ring of four carbon atoms and one oxygen atom; the ribose in Eschenmoser's structure is rearranged to contain an extra carbon atom in the ring.

Eschenmoser finds that complementary strands of pyranosyl RNA can combine by standard Watson-Crick pairing to give double-strand units that permit fewer unwanted variations in structure than are possible with normal RNA. In addition, the strands do not twist around each other, as they do in double-strand RNA. In a world without protein enzymes, twisting could prevent the strands from separating cleanly in prep-

aration for replication. In many ways, then, pyranosyl RNA seems better suited for replication than RNA itself. If simple means for synthesizing ribonucleotides containing a six-member sugar ring were found, a case could be made that this form of RNA may have preceded the more familiar form of the molecule.

In quite a different approach, Peter E. Nielsen of the University of Copenhagen has used computer-assisted model building to design a polymer that combines a proteinlike backbone with nucleic acid bases for side chains. As is true of RNA, one strand of this polymer, or peptide nucleic acid (PNA), can combine stably with a complementary strand; this result implies that, as is true of standard RNA, peptide RNA may be able to serve as a template for the construction of its complement. Many polymers with related backbones may behave in a similar way; perhaps one of them was involved in an early genetic system.

Both pyranosyl RNA and peptide nucleic acids rely on Watson-Crick base pairs as the structural element that makes complementary pairing possible. Investigators interested in discovering simpler genetic systems are also trying to build complementary molecules that do not depend on nucleotide bases for template-directed copying. So far, however, there is no good evidence that polymers constructed from such building blocks can replicate. The search for antecedents of RNA can be expected to become a major focus of experimentation for prebiotic chemists.

Whether RNA arose spontaneously or replaced some earlier genetic system, its development was probably the watershed event in the development of life. It very likely led to the synthesis of proteins, the formation of DNA and the emergence of a cell that became life's last common ancestor. The precise events giving rise to the RNA world remain unclear. As we have seen, investigators have proposed many hypotheses, but evidence in favor of each of them is fragmentary at best. The full details of how the RNA world, and life, emerged may not be revealed in the near future. Nevertheless, as chemists, biochemists and molecular biologists cooperate on ever more ingenious experiments, they are sure to fill in many missing parts of the puzzle.

FURTHER READING

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