Special Issue—Scripps Centennial

Origins of Life

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"Life is not a miracle. It is a natural phenomenon and can be expected to appear whenever there is a planet whose conditions duplicate those of the earth."

—Harold C. Urey, *Time* magazine,
November 24, 1952

May 15, 2003 marked the fiftieth anniversary of a paper published in the journal *Science* that revolutionized our thinking about one of the fundamental scientific questions that confronts humanity-how did life began on Earth? The paper was authored by Stanley L. Miller (1953), at that time a graduate student of Nobel Laureate Harold Urey's at the University of Chicago. The experiment described in his paper demonstrated how, by using a simple apparatus designed to mimic the ocean-atmosphere system of Earth, could be used to synthesize essential biological compounds such as amino acids. If a similar type of process had taken place on early Earth, this could have produced the raw materials needed for the origin of life

In 1958, five years after the publication of the paper, Urey moved to La Jolla to help set up the new University of California, San Diego (UCSD) campus, whose headquarters were temporarily housed at Scripps. Charged with helping build a first-rate science university, Urey began recruiting top-notch scientists such as Miller, who arrived at UCSD in 1960. Miller's initial office and laboratories were in Sverdrup Hall at Scripps and are in fact the same ones that I occupy today. Scripps and UCSD soon became home to one of the world's foremost centers of research on the question of the origin of life, a tradition that continues to this day. In 1992, Scripps was selected as the host institution for the NASA Center of Research and Training in Exobiology (NSCORT/Exobiology), a center that has received more than 10 years of continuous funding to research how life began on Earth and whether this process may indeed be as universal as Urey suggested in his 1952 Time magazine quote.

This article focuses on both the general question of the origin of life and how researchers based at Scripps and UCSD, as well as San Diego's Salk Institute and Scripps Research Institute, have contributed to helping solve a problem that at one time seemed intractable.

To evaluate how life may have begun on Earth, we must first access what Earth was like during its early history and under what conditions the processes thought to be involved in the origin of life took place. We assume that there are two fundamental requirements for origin of life as we know it: the presence of liquid water and the presence of organic polymers such as nucleic acids and proteins-the molecules that carry out the central biological functions of replication and catalysis. Without these functions, as far as we know, life is impossible.

The Primitive Earth

Soon after the accretion of Earth some 4.56 billion years (Gyr) ago, the decay of radioactive elements heated the interior of the young planet to the melting point of rocks. The melted rocks liberated gases such as hydrogen, ammonia, methane, carbon dioxide, and water vapor. These gases were vented to the surface and provided the raw materials for the formation of the primitive atmosphere and ocean. It is thought that most of the water in the oceans today came from early degassing of the interior (Dauphas et al., 2000). Melting of the interior also resulted in the segregation or differentiation of Earth into regions of differing density; heavy elements such as iron and its cousins sank to the middle of Earth and formed a molten core, while the lighter silicates floated to the surface. This stratification of the planet in turn gave rise to tectonics, the geologic process involved in continental formation and destruction.

In its infant stages, Earth was peppered with comets and asteroids at such a high rate that the impact-generated energy far exceeded the energy coming from the faint young Sun (Figure 1). These impacts also probably blasted away any of the original atmosphere that remained when Earth accreted and at the same time helped to supply it with a new one. In addition, the comets and asteroids colliding with Earth during these hectic early stages may have brought with them some of the water that contributed to the global oceans, as well as organic compounds and their breakdown products. Some of these impacts released enough energy to boil any water present on the surface. It is unlikely that Earth could have had extensive water oceans early in its history because of the high surface

Figure 1. *A depiction of the infant, moonless Earth as seen from space. The impacts of large asteroids and comets (one is shown in the background) frequently traumatized the surface of the young planet (painting by William Hartmann).*

Figure 2. *The young Earth-Moon system soon after colliding. Large impacts on both the Moon and Earth are still common events (painting by William Hartmann).*

temperatures; it was likely covered by an ocean of nearly molten rock.

Earth is the only one of the four inner rocky planets in our solar system that has a moon, although it apparently did not have a moon when first formed. At a symposium sponsored by Scripps to commemorate the centennial anniversary of the University of California in 1968, Urey mentioned that, at the time of the Apollo missions, the Moon was thought to have been captured by Earth early in its history (Urey, 1968). Recent determinations give an age for the Moon of between 4.5 and 4.52 Gyr, some 30 to 50 million years (Myr) younger than the age of Earth (Lee et al., 1997). The slight age difference means that the Moon must have formed after the accretion of Earth, when the rest of the solar system was essentially complete. The most likely scenario is a truly spectacular one (Hartmann and Davis, 1975): A violent collision took place between the infant and still moonless Earth and a Mars-sized object that was one of many other young planets that were zipping around the Sun in the inner solar system. When the smaller planet smashed into the young Earth, it was vaporized along with a good fraction of Earth in a truly spectacular fireball. Some of the debris generated from the collision went into orbit around the traumatized Earth, and soon began to condense to form the moon. Fragments of debris would have condensed very close to Earth, just outside the Roche limit (2.8 times Earth's radius), a distance of only about 20,000 km away. Before too long, as the fragments in orbit began to coalesce, a new companion was circling around the young Earth (Figure 2).

Over geologic time, the Moon has receded to its present orbit some 384,400 km from Earth and is still moving away from us at the almost imperceptible rate of 3–4 cm per year. The rate was much faster, however, soon after the Moon's formation. After about 10–100 Myr, it had retreated about 50 percent of the way toward its present orbital distance.

One of the consequences of the Moon initially looming ominously close to Earth was enormous tides. Initially, tidal forces in the Earth-Moon system would have been three hundred times stronger than they are today. Tidal friction acting on the interiors of both Earth and the Moon soon dissipated the rotational energy in the system. This slowed Earth's rotation, and it slowed the less massive Moon's rotation even more until it finally turned only one face toward Earth as it does today.

These huge tidal forces would have affected the young Earth in a dramatic way. We are of course familiar with oceanic tides, but we do not realize (because we are standing on it) that tidal deformation of the crust itself takes place twice a day as Earth rotates relative to the Moon and the Sun. This daily deformation is relatively minor, amounting to only about 20 cm, but on the early Earth it was much more dramatic, since the Moon was so close and the freshly formed crust was thinner and more deformable-the crust may have risen and fallen an astonishing 60 m twice a day. The entire planet must have stretched and cracked under the fierce pull of the nearby Moon.

Earth's tides became less overwhelming as the Moon receded, but even during the period when life may have first originated, they were still substantially stronger than today's tides. As we will see, these tides may have played a key role in some aspects of the formation of life, especially by causing the periodic flooding of island lagoons and other tidal regions.

Figure 3. *Volcanic islands similar to the one depicted here were likely the only type of exposed continental areas on early Earth (painting by William Hartmann).*

The Early Oceans and Atmosphere

Life as we know it is possible on Earth because of its abundant surface water. As Stanley Miller discussed in a volume celebrating Urey's seventieth birthday (Miller, 1963), water has unique properties that are indispensable for life.

The formation of the oceans had a critical role in setting the stage for the origin of life as well as sustaining life once it appeared. Evidence now suggests that Earth may have had water oceans within a few 100 Myr after it formed. Zircons (zirconium oxide) have been found that date from around 4.3 to 4.4 Gyr ago (Wilde et al., 2001). Analyses of these ancient zircons suggest that water was plentiful on Earth's surface at that time. Whether this water was sufficient to form extensive global oceans is not known.

The volume of water in Earth's early oceans is also unknown. Today the oceans contain 10^{21} liters of water. If this water did indeed mainly come from the degassing interior of early Earth it implies that once Earth's surface was cool enough to allow the presence of liquid water, large amounts of water accumulated on its surface. Because the process of tectonics was in its infancy, there were probably few, if any, major continents on early Earth. Most of the areas of land exposed above the ocean surface would have likely consisted of small volcanic island systems (Figure 3), much like the Hawaiian Islands of today.

What about the composition of the early oceans? The ocean water 4 Gyr ago would be salty just as it is today-perhaps even more so. Today, about a third of the global near-surface inventory of sodium chloride is stored on the continents as the mineral halite and in ground water. Because large continental areas were probably absent on early Earth, the salt now stored on the continents would have been in the oceans, resulting in saltier seawater (Knauth, 1998). Early seawater may also have been highly toxic with lethal amounts of compounds such as hydrogen cyanide and formaldehyde. Drinking one drop could have killed you.

Scientists are not sure what the atmosphere of this early Earth was like, but it is possible that it initially contained gases such as methane, ammonia, and hydrogen. However, because hydrogen can escape from Earth's gravitational field, the early atmosphere was likely soon transformed into one rich in carbon dioxide, nitrogen, and water vapor. During this early period, as the frequent bombardment of Earth by comets and asteroids steadily decreased, the sun was less luminous than it is today. As Miller and I pointed out in 1994, the possibility exists that without an atmosphere rich in greenhouse gases (methane, ammonia, or carbon dioxide), Earth's oceans may have been completely covered in ice (Bada et al., 1994). In such a case, Earth would have looked much like Europa, the frozen moon of Jupiter, appears today.

The Molecules of Life

Life as we know it on Earth is based on polymers such as nucleic acids and proteins, which carry out the essential biological functions of replication and catalysis. These core molecules somehow had to be synthesized and then assembled from simple monomers into polymers with biological functions.

Today, organic material derived from once living organisms accounts for 25–30 percent of the total carbon present on Earth's surface. However, during the period immediately following the formation of Earth, there would have been no organic compounds present on the surface because of the high surface temperatures. Massive volcanic convulsions, coupled with the intense bombardment from space, generated surface temperatures so hot that any organic compounds present would have been instantly incinerated.

Surface temperatures slowly declined as the infall of objects from space and the intensity of volcanic eruptions decreased, and a few 100 Myr after formation, Earth's surface cooled to the point that liquid water could exist and oceans began to form. It was during this period that organic compounds could have first started to accumulate on Earth's surface, as long as there were natural pathways by which they could either be directly synthesized or supplied to Earth by the infall of objects such as comets and meteorites from space.

A central assumption that has dominated thinking about the origin of life in the research that has been conducted by NSCORT/Exobiology at Scripps and UCSD is that organic compounds, regardless of their source, accumulated in the oceans, producing a so-called prebiotic or primordial "soup." From this prebiotic soup, life somehow emerged on the planet (Bada and Lazcano, 2002, 2003).

The theory that a prebiotic soup was produced on early Earth by natural processes was first proposed by Oparin and Haldane in the 1920s (see Wills and Bada, 2000). However, how the organic compounds in the soup could have been synthesized was not experimentally demonstrated until the spring of 1953 when Miller published his classic paper on the synthesis of amino acids under simulated early Earth conditions.

The apparatus used in Miller's 1953 experiment consisted of two glass flasks connected by two glass tubes, one of which was fitted with a condenser (Figure 4). The smaller flask contained water, which was heated. The other, larger flask had two electrodes projecting from the outside into the interior, which could be used to introduce an electric spark into the gas mixture. A spark discharge was selected as an energy source because chemists had been experimenting with electric sparks in gas mixtures since the end of the nineteenth century, sometimes producing interesting syntheses (Bada and Lazcano, 2003). However, no one had considered how this might relate to prebiotic syntheses and the origin of life.

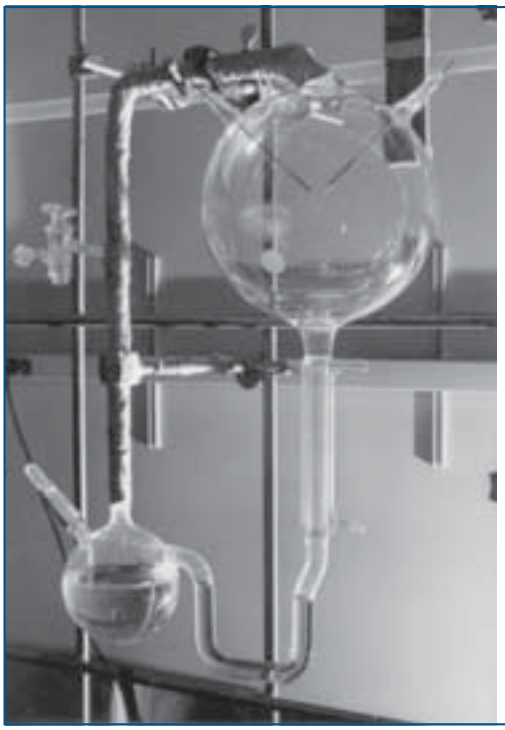

Figure 4. *The original apparatus used in the 1953 Miller experiment. (Courtesy of Stanley L. Miller)*

The spark discharge apparatus was meant to simulate the ocean-atmosphere system of early Earth. Water vapor produced by boiling the main flask simulated evaporation from the oceans. The gases and water vapor in the flasks mimicked the atmosphere, and the sparks between the electrodes simulated electric discharges, which were probably common on early Earth, occurring both in the form of lightning and auroral displays that were far more spectacular and energetic than the present-day northern lights. A condenser on one of the tubes that connected the two flasks condensed any synthesized compounds from the mini-atmosphere, allowing them to be washed into the "ocean" (the flask with the water).

Miller found that when a mixture of methane, ammonia, and hydrogen was introduced into the apparatus and the spark was run continuously for a week, the inside of the sparking flask became coated with an oily scum and the water solution turned yellow-brown. Analyses of the water showed that several amino acids were produced. Some of these, such as glycine and alanine, were common in proteins, while others like β-alanine and α-amino-n-butyric acid were only rarely found in living organisms. In all, nine different amino acids were synthesized in the first experiment. In 1972, Miller and coworkers repeated the experiment and used better analytical methods for characterization of the amino acid products (Ring et al., 1972). This time, 33 different amino acids were produced, including more than half of the 20 that are commonly found in proteins.

It was not long before other laboratories repeated Miller's experiments, using a variety of conditions and energy sources (Wills and Bada, 2000). Their results demonstrated how important it was to have reducing gases in the "atmosphere" flask of the experiment; if methane was replaced with carbon dioxide and ammonia with nitrogen, no amino acids were produced. And they showed that other energy sources such as ultraviolet light also gave the same results, though the yields of amino acids were far lower than those obtained with a spark discharge.

How were the various amino acids and other compounds made in Miller's spark discharge experiment? Miller was aware of the nineteenth century experiments of Alfred Strecker who had synthesized alanine from hydrogen cyanide, acetaldehyde, and ammonia and he thought that a similar synthetic process might be taking place in his experiment. If this was the case, then sparking methane, ammonia and, hydrogen should have generated hydrogen cyanide (HCN), aldehydes (the simplest being formaldehyde), and ketones (such as acetone). As long as these simple compounds were in the vapor phase no further reactions took place. However, when they were flushed out of the gas phase and accumulated in the flask containing

Figure 5. *Lightning associated with the 1963 eruption of the submarine volcano that created the island of Surtsey, Iceland (cover of Science, 28 May 1965; Anderson et al., 1965).*

water, they could react. Indeed, analysis of the contents of the water flask found abundant amounts of HCN, aldehydes, and ketones (Miller, 1957).

Thus, a key aspect of the Miller experiment was the formation of "reagents" such as HCN, aldehydes, and ketones during the sparking of reduced gases such as methane, hydrogen, and ammonia. If this type of process also took place on early Earth, then these reagents would have accumulated in the oceans, where they could have directly reacted to produce amino acids and other compounds. HCN could have accumulated to levels in the early oceans that would be highly toxic to modern organisms.

What about other components of polymers essential to living organisms today such as DNA and RNA, which are made up of the five nucleobases adenine, guanine, cytosine, thymine, uracil, phosphate, and the sugars ribose and deoxyribose? The presence of HCN in Miller's experimental mixture set the stage for further experiments. In 1961 Juan Oró showed that by gently heating a highly concentrated HCN solution, adenine was produced (Oró, 1961). Again the reaction chemistry was very simple; five HCN molecules combine together to produce adenine. This is an immensely important reaction, for not only is adenine a component of DNA and RNA, it is also an important part of the most common high-energy compound in the living cell, ATP. Oró and others showed that very high concentrations of HCN were necessary to drive the polymerization of HCN to adenine. The reason that Miller did not originally detect any adenine in his spark discharge experiment was that the HCN concentration in the water solution was too low. However, even dilute solutions of HCN in the oceans could have easily been concentrated by evaporation of tidal lagoons and freezing (Bada and Lazcano, 2002).

Besides the nucleobases, another important component of nucleic acids-sugars-could also have been readily formed on the primitive Earth from simple components. In 1861, Russian chemist Alexander Butlerov showed how many different sugars, including sugars found in DNA and RNA, could be synthesized from concentrated formaldehyde solutions containing mineral catalysts such as carbonate and alumina (Lazcano and Bada, 2003). The number of sugars is astonishing, which can generate an overabundance, because the number of sugars used in biochemical reactions in living things is limited to only a few. In addition, sugars in nucleic acids are linked to phosphate to form the backbone of the molecules. At first it seemed that the combination of sugars with phosphate would yield a bewildering number of products. However, Scripps geochemist Gustaf Arrhenius, in collaboration with researchers at the Scripps Research Institute, has shown that in the presence of various mineral catalysts, a much more limited variety of combinations is obtained, including the types of sugar-phosphate molecules that might have been incorporated into early nucleic acids (Krishnamurthy et al., 1999).

Another important aspect of the Miller experiment that should not be overlooked is that the main product was an oily goo. This type of material may also have been produced in large quantities on early Earth, forming an vast oil slick1-10 m thick that could have been produced on early Earth in only a few Myr (Lasaga et al., 1971). Although this would be an environmental catastrophe today, on early Earth it might have formed a protective layer that allowed for molecules to be protected from destruction by the sun's ultraviolet light, and may have also been important in promoting the condensation of simple monomeric compounds into polymers (Cleaves and Miller, 1998; Nilson, 2002).

Contemporary geoscientists tend to doubt that the primitive atmosphere had the highly reducing composition like that used by Miller in 1953, and many have suggested that the ultimate origin of organic compounds needed for life may have come from extraterrestrial sources such as meteorites (Chyba and Sagan, 1992). However, evidence strongly indicates that amino acids and other biochemical monomers found in meteorites were synthesized in parent bodies by reactions remarkably similar to those in the Miller experiment (Peltzer et al, 1984). Moreover, it is possible that localized reducing environments existed on the primi-

tive Earth, especially in the vicinity of volcanic plumes (Anderson et al., 1965) where associated electric discharges may have driven prebiotic synthesis (Figure 5). Thus, instead of global Miller-type syntheses taking place on early Earth, there could have been localized syntheses that contributed to the inventory of organic molecules in the ocean's prebiotic soup.

The organic material on early Earth before life existed, regardless of its source, would have likely consisted of a wide array of compounds, including essential biological compounds such as amino acids and nucleobases. How these abiotic organic constituents were assembled into the first living entities is presently one of the main areas of research into the origin of life. In modern biological systems, amino acids are the monomeric building blocks for proteins and enzymes, the structural and catalytic units without which life as we know it cannot exist. In addition, DNA and RNA, the molecules that encode and transcribe genetic information in all terrestrial organisms, are made up of mononucleotides, which contain nucleobases such as adenine, guanine, thymine, cytosine, and uracil, attached to a sugar-phosphate backbone. Thus simple abiotic compounds were only the starting points for the chemical evolution that followed.

When the transition from abiotic chemistry to biochemistry took place on early Earth is not known. But once life arose it changed the planet forever.

The Emergence of Life

As molecules in the prebiotic soup were generated with increasing degrees of complexity, some acquired the ability to catalyze reactions. Eventually, some type of molecule formed that had some of the properties or characteristics we identify with life. This would have been the point of the transition from prebiotic chemistry to biochemistry, the transition from a lifeless to a living Earth.

What distinguishes life, or biochemistry, from nonliving chemistry? Certainly it is easy to see the differences between rock and plant, animal and bacteria. But what about life at the simple molecular level?

At a minimum, the first living entities must have been able to:

- make copies of themselves (though the replication need not have been exact),
- make "activated" molecules that could be used in the replication process, and
- "live" long enough to ensure survival of their fittest "offspring."

One of the more widely accepted scenarios for the transition from abiotic to biotic chemistry is that the simple monomeric compounds present in the prebiotic soup somehow underwent polymerization, perhaps with the assistance of clays and minerals, and formed longer and longer chains of polymers which over time became increasingly more complex with respect to their structures and properties. Eventually, some of these polymers acquired the capacity to replicate, one of the fundamental and most important properties of living organisms. This would have marked the appearance of the first molecular entities capable of multiplication, heredity, and variation, and thus the origin of both life and evolution (Bada and Lazcano, 2002).

In order for monomers in the early oceans to have undergone polymerization, a thermodynamically unfavorable process, concentration of the soup constituents by some mechanism would have been required (Bada and Lazcano, 2002). Experimental evidence suggests that clays, metal cations, along with other organic components, may have catalyzed a wide variety of prebiotic reactions, including polymerization. The selective absorption of molecules onto various mineral surfaces has been suggested as a means of promoting polymerization and this process has been demonstrated in the laboratory using a variety of activated monomers. Because absorption involves the formation of weak noncovalent bonds, the mineral-based concentration process would have been most efficient at cool temperatures. Concentration could also have been accomplished by the evaporation of areas such as tidal lagoons and by eutectic freezing of dilute aqueous solutions. The latter process has recently been shown to be particularly effective in the nonenzymatic synthesis of nucleotide chains.

What the first molecular self-replicating entities consisted of and how replication was accomplished is not known, but threose-based RNA analogs and peptide nucleic acid (PNA)-type molecules are considered possible contenders (Nielsen, 1993; Joyce, 2002). Miller and coworkers found that the monomer building blocks of PNA molecules could be synthesized under likely prebiotic conditions and thus could have been constituents of the prebiotic soup (Nelson et al., 2000). Still to be worked out are mechanisms for the effective polymerization of the monomers. However, even with PNA-like genetic informational molecules, stability may be a problem. Other possibilities need to be considered because there may be other backbones and bases that were more abundant and more efficient for early biotic replication.

The first living molecular entities eventually evolved into the "RNA world," a period in the history of Earth when life consisted of nothing more than catalytic RNA molecules that could promote their own self-replication (Joyce, 2002). The RNA world in turn evolved into the "protein/DNA world," which had all the characteristics of modern biochemistry. By 3.5 Gyr ago, life had apparently evolved into single-cell organisms that resemble modern day cyanobacteria (Schopf, 1999), although whether the structures observed in rocks from this period are indeed ancient fossils has recently been questioned (Brasier et al., 2002).

Conclusion

When the transition from abiotic chemistry to biochemistry took place on early Earth is not known. But once life arose it changed the planet forever. For example, today's abundant atmospheric oxygen is a product of photosynthesis, a process the appeared early in the history of life on Earth.

Regardless of what the first self-replicating entities consisted of, however, they would have had a challenging existence. Earth was still likely being traumatized by large, planet-sterilizing asteroid and comet impacts, some of which were large enough to have completely vaporized the oceans (Maher and Stevenson, 1988). The first life that arose, regardless of the process that brought it about, may not have survived subsequent sterilizing impacts. Life may have originated several times before surface conditions became tranquil enough for periods long enough to permit the survival and evolution of the first living entities into the first cellular organisms, whose remnants may be present in ~3.5 Gyr-old rocks.

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