

Prebiotic Soup—Revisiting the Miller Experiment

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“Isn’t life wonderful?” sang Alma Cogan and Les Howard in their almost forgotten 1953 hit. That same year, Stanley L. Miller raised the hopes of understanding the origin of life when on 15 May, *Science* published his paper on the synthesis of amino acids under conditions that simulated primitive Earth’s atmosphere (1). Miller had applied an electric discharge to a mixture of CH_4 , NH_3 , H_2O , and H_2 —believed at the time to be the atmospheric composition of early Earth. Surprisingly, the products were not a random mixture of organic molecules, but rather a relatively small number of biochemically significant compounds such as amino acids, hydroxy acids, and urea. With the publication of these dramatic results, the modern era in the study of the origin of life began.

Since the late 19th century, the belief in a natural origin of life had become widespread. It was generally accepted that life’s defining properties could be understood through physico-chemical characterization of “protoplasm,” a term used to describe the viscous translucent colloid found in all living cells (2). Expressions like “primordial protoplasmic globules” were used not only by scientists but also in fiction, from Gilbert and Sullivan’s *Pooh-Bah* in *The Mikado* (1885) to Thomas Mann’s somber imaginary character Adrian Leverkühn in *Doktor Faustus* (1947). But few dared to be explicit, even in novels. Questioned about the origin of life, a chemist in Dorothy L. Sayers’ novel *The Documents in the Case* (1930) states that “it appears possible that there was an evolution from inorganic or organic through the colloids. We can’t say much more, and we haven’t—so far—succeeded in producing it in the laboratory.”

Some were willing to fill in the details. At the turn of the 20th century, many sci-

entists favored the idea of primordial beings endowed with a plant-like (autotrophic) metabolism that would allow them to use CO_2 as their source of cellular carbon. However, some scientists—including A. I. Oparin, J. B. S. Haldane, C. B. Lipman, and R. B. Harvey—had different ideas (3). The most successful and best-known proposal was that by Oparin, who, from a Darwinian analysis, proposed a series of events from the synthesis and accumulation of organic

organic compounds was not considered to be a necessary prerequisite for the emergence of life.

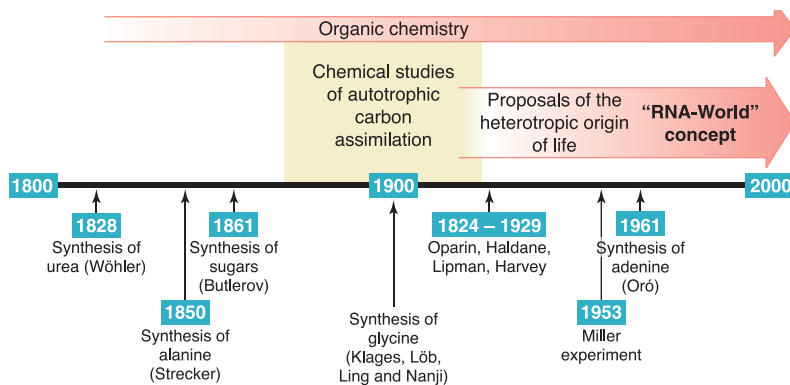
From the 1950s, chemists were drawn toward the origin of life. Driven by his interest in evolutionary biology, Melvin Calvin tried to simulate the synthesis of organic compounds under primitive Earth conditions with high-energy radiation sources. He and his group had limited success: the irradiation of CO_2 solutions with

the Crocker Laboratory’s 60-inch cyclotron led only to formic acid, albeit in fairly high yields (5). Miller’s publication 2 years later showed how compounds of biochemical importance could be produced in high yields from a mixture of reduced gases.

The origin of Miller’s experiment can be traced to 1950, when Nobel laureate Harold C. Urey, who had studied the origin of the solar system and the

chemical events associated with this process, began to consider the emergence of life in the context of his proposal of a highly reducing terrestrial atmosphere. Urey presented his ideas in a lecture at the University of Chicago in 1951, followed by the publication of a paper on Earth’s primitive atmosphere in the *Proceedings of the National Academy of Sciences* (6).

Almost a year and a half after Urey’s lecture, Miller, a graduate student in the Chemistry Department who had been in the audience, approached Urey about the possibility of doing a prebiotic synthesis experiment using a reducing gas mixture. After overcoming Urey’s initial resistance, they designed three apparatuses meant to simulate the ocean-atmosphere system on primitive Earth (3). The first experiment used water vapor produced by heating to simulate evaporation from the oceans; as it mixed with methane, ammonia, and hydrogen, it mimicked a water vapor-saturated primitive atmosphere, which was then subjected to an electric discharge (see the figure on p. 746). The second experiment used a higher pressure, which generated a



Highlights in organic synthesis in conjunction with theories of the origin of life.

compounds to primordial life forms whose maintenance and reproduction depended on external sources of reduced carbon.

The assumption of an abiotic origin of organic compounds rested on firm grounds. In 1828, F. Wöhler had reported the first chemical synthesis of a simple organic molecule (urea) from inorganic starting materials (silver cyanate and ammonium chloride).

After a large body of research on the synthesis of simple organic compounds accumulated in the 19th century (see figure above), W. Löb achieved the chemical syntheses of simple amino acids such as glycine by exposing wet formamide to a silent electrical discharge and to ultraviolet light (4).

These efforts to produce simple organic compounds from simple reagents heralded the dawn of prebiotic organic chemistry. However, there is no indication that the scientists who carried out these studies were interested in how life began on Earth, or in the synthesis of organic compounds under possible prebiotic conditions. This is not surprising, because the abiotic synthesis of

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hot water mist similar to that of a water vapor-rich volcanic eruption into the atmosphere, whereas the third used a so-called silent discharge instead of a spark.

Miller began the experiments in the fall of 1952. By comparison with contemporary analytical tools, the paper chromatography method available at the time was crude. Still, after only 2 days of sparking the gaseous mixture, Miller detected glycine in the flask containing water. When he repeated the experiment, this time sparking the mixture for a week, the inside of the sparking flask soon became coated with an oily material and the water turned a yellow-brown color.

Chromatographic analysis of the water flask yielded an intense glycine spot; several other amino acids were also detected. Experiments with the second apparatus produced a similar distribution and quantities of amino acids and other organic compounds, whereas the third apparatus with silent discharge showed lower overall yields and much fewer amino acids (primarily sarcosine and glycine).

After Miller showed the impressive results to Urey, they decided to submit them to *Science*. Urey declined Miller's offer to coauthor the report because otherwise Miller would receive little or no credit. Knowing that a graduate student could have a difficult time getting a paper like this published, Urey contacted the *Science* editorial office to explain the importance of the work and ask that the paper be published as soon as possible. Urey kept mentioning the results in his lectures, drawing considerable attention from the news media.

The manuscript was sent to *Science* in early February of 1953. Several weeks went by with no news. Growing impatient, Urey wrote to Howard Meyerhoff, chairman of AAAS's Editorial Board, on 27 February to complain about the lack of progress (7). Then, on 8 March 1953, the *New York Times* reported in a short article entitled, "Looking Back Two Billion Years" that W. M. MacNevin and his associates at Ohio State University had performed several experiments simulating the primitive Earth—including a discharge experiment with methane wherein "resinous solids too complex for analysis" were produced. The next day, Miller sent Urey a copy of the clipping with a note saying "I am not sure what should be done now, since their work is, in

essence, my thesis. As of today, I have not received the proof from *Science*, and in the letter that was sent to you, Meyerhoff said that he had sent my note for review."

Infuriated by this news, Urey had Miller withdraw the paper and submit it to the *Journal of the American Chemical Society*. Ironically, at the same time (11 March), Meyerhoff, evidently frustrated by Urey's actions, wrote to Miller that he wanted to publish the manuscript as a lead article and that he wanted Miller—not Urey—to make the final decision about the manuscript. Miller immediately accepted Meyerhoff's offer, the paper was withdrawn from the *Journal of the American Chemical Society* and returned to *Science*, and was published on 15 May 1953.

On 15 December 1952, well before the Miller paper was sent to *Science*, K. Wilde and co-workers had submitted a paper on the attempted electric arc synthesis of organic compounds using CO₂ and water to the same journal. They reported that no interesting reduction products, such as formaldehyde, were synthesized above the part-per-million level. This result supported the surmise of Miller and Urey that reducing conditions were needed for effective organic syntheses to take place. Surprisingly, when the paper by Wilde *et al.* was published in *Science* on 10 July 1953, it did not mention Miller's paper, although the authors did note that their results had "implications with respect to the origin of living matter on earth."

Miller's paper was published only a few weeks after Watson and Crick reported their DNA double-helix model in *Nature*. The link between the two nascent fields began to develop a few years later, when Juan Oró demonstrated the remarkable ease by which adenine, one of the nucleobases in DNA and RNA, could be produced through the oligomerization of hydrogen cyanide (8). It would eventually culminate in the independent suggestions of an "RNA world" by Carl Woese, Leslie Orgel, and Francis Crick in the late 1960s and by Walter Gilbert in 1986.

The impact of the Miller paper was not limited to academic circles. The results captured the imagination of the public, who were intrigued by the use of electric discharges to form the prebiotic soup. Fascination with the effects of electricity and spark discharges on

biological systems started with the work of L. Galvani in 1780 with frog legs and the discovery of "animal electricity." And an everlasting impression was left in the public's imagination by Mary W. Shelley's *Frankenstein* (1818), in which Erasmus Darwin gained a place for his advocacy of therapies based on electric discharges.

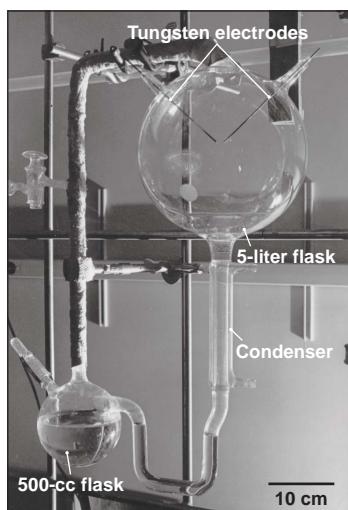
Although in 1953, few envisioned the possibility of Frankenstein monsters crawling out of Miller's laboratory vessels, the public's imagination was captivated by the outcome of the experiment. By the time that the results were corroborated by an independent group 3 years later (9), the metaphor of the "prebiotic soup" had found its way into comic strips, cartoons, movies, and novels, and continues to do so. In Harry Mulisch's novel *The Procedure* (1998), one of the central characters encounters disaster while paving his way to the glittering halls of Stockholm for achieving the artificial synthesis of life from a primitive soup.

But is the "prebiotic soup" theory a reasonable explanation for the emergence of life? Contemporary geoscientists tend to doubt that the primitive atmosphere had the highly reducing composition used by Miller in 1953. Many have suggested that the organic compounds needed for the origin of life may have originated from extraterrestrial sources such as meteorites. However, there is evidence that amino acids and other biochemical monomers found in meteorites were synthesized in parent bodies by reactions similar to those in the Miller experiment. Localized reducing environments may have existed on primitive Earth, especially near volcanic plumes, where electric discharges (10) may have driven prebiotic synthesis.

In the early 1950s, several groups were attempting organic synthesis under primitive conditions. But it was the Miller experiment, placed in the Darwinian perspective provided by Oparin's ideas and deeply rooted in the 19th-century tradition of synthetic organic chemistry, that almost overnight transformed the study of the origin of life into a respectable field of inquiry.

References and Notes

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Apparatus used in the original Miller experiment.