The Origins of Life: A Review of Scientific Inquiry

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1. INTRODUCTION

"It must be admitted from the beginning that we do not know how life began. It is generally believed that a variety of processes led to the formation of simple organic compounds on the primitive Earth. These compounds combined together to give more and more complex structures until one was formed that could be called living. No one should be satisfied with an explanation as general as this."

-Stanley L. Miller and Leslie E. Orgel, The Origins of Life on the Earth, 1974

This assessment by two of the leading scholars attempting to understand the origins of life, now already 45 years ago, still rings true in many ways. This is not to say that no progress has been made in this area, indeed if anything there are not only more, but more detailed, models and theories for the origins of life now, but rather that it has proven to be a difficult problem, and scientific consensus on the topic has still not been achieved with respect to many questions.

Consideration of the origins of life necessarily branches into questions of biology, chemistry, paleontology, geology, planetology, and astronomy, and perhaps now we could add questions of systems science and complexity and information theory. Very few scientists are equally at home and adept with all of these fields, or able to grasp the scope of ideas that have led to the present state of knowledge in them. Thus the best effort of any scientist to understand this question usually lacks some useful expertise and perspectives. Even when teams of experts join forces to attack these questions, they are often humbled by two other phenomenon that few enjoy acknowledging, namely, that first, to some degree this is a historical problem,¹ and from that perspective strictly speaking not reproducible, and second that the origins of life is a phenomenon that may lie at the nexus of various dynamical systems, e.g., biology, Earth science, and planetary science.

What distinguishes dynamic from dynamical systems? Dynamic systems change over time. In contrast *dynamical* systems are those whose manner of responding to changes over time itself changes over time. As one example, due to the hydrologic cycle driven by the Sun, water evaporates, returns to Earth's subaerial surface areas (land) in the form of precipitation, and runs downhill in the form of streams and rivers due to the force of gravity, interacting with surface geology as it does so. This is the way hydrogeology operated for billions of years until the evolutionary advent of mammals of the genus *Castor* approximately 50 million years ago, which, by virtue of being self-replicating systems and their ability to do work, in the thermodynamic sense, in the form of building dams, have significantly altered the way water returns to the sea. The impact of beaver evolution on Earth's hydrogeology is readily apparent in satellite images of Earth's boreal regions. A further dynamicism has arisen in this system since humans began decimating beaver populations in the second millennium AD, which has again fundamentally altered boreal watershed dynamics.

¹ In terms of the actual process that occurred on Earth billions of years ago, it is certainly possible that a living system could be recreated in the laboratory that might be considered an adequate model for this process.

It is difficult to predict how dynamical systems will evolve, or to back-extrapolate how they operated in earlier states. Such concepts have become popularized in the ideas of "chaos" (Gleick 2011), and the notion of "replaying the tape of evolution" suggested by Gould (1990). This idea underscores the difficulty in extrapolating from simpler chemical and physical sciences. Even though aggregate behaviors may be roughly predictable or generalizable (Ball 2006), there is considerable "developmental noise" in biological, Earth, and Solar System evolution.

This document describes major aspects of the current state of knowledge of the loosely defined field of origins of life studies and explores the development of the field to contextualize how it has evolved in response to discoveries in other fields.

There is currently a great deal of argument regarding how life began on Earth, and how life may originate in general. Most professional scientists agree that there has not been to date an observed artificial occurrence of a *de novo* origin of life, indeed it might even be difficult to find consensus about the existence of a dominant theory as to how this might occur. This review will attempt to define some of the issues scientists presently think are important regarding this question and describe some of the methods they have developed to understand how matter goes from a state of non-living organization to one of living organization.

This review focuses on the question of how organic compounds thought by many to be important for the origins of life could have been generated in natural planetary contexts or laboratory settings designed to mimic natural environments. This focus on the provenance of materials rather than the processes by which their emergent interactions gave rise to living phenomena belies some of the truly difficult problems in this research area, and hopefully it becomes clear during this discussion that even removing all constraints of "natural plausibility" might not bring the scientific community much closer to a consensus explanatory paradigm for the spontaneous origins of life. This is not to say it is necessarily true that the spontaneous origin of life will prove to be a difficult or rare phenomenon, only that there is little consensus currently as to how such data would present itself. This review will also attempt to outline the historical development of the field, its underlying assumptions and open questions that remain unresolved.

Although the idea of panspermia (which postulates that life was transported preformed from space to the early sterile Earth (see, for example, Ginsburg et al. 2018) cannot be completely dismissed, the majority of the scientific community seems to consider this an unnecessary assumption given the available evidence and uncertainty, and in any event would simply push the problem to some other location.

Panspermia notwithstanding, most scientists consider the question of the origins of life on Earth to be one that will be largely explicable by organic chemistry, which assumes that the transition from nonliving to living chemistry occurred in the context of carbon-based compounds. The reasons for this have been reviewed elsewhere, but briefly include the enormous complexity of organic chemical space, the energetics of carbon chemical bonds, and geochemical aspects of carbon cycling (Pace 2001). Not surprisingly, ideas regarding the origin of life have developed to a large degree concurrently with discoveries in organic chemistry and biochemistry as discussed below.

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2. TOP-DOWN AND BOTTOM-UP APPROACHES

It remains scientifically unresolved how life began on Earth. A comprehensive scientific explanation would require considerably more mechanistic nuance than is presently available. To be convincing such explanations will need to coincide with developments in other areas of science, including astronomy, biology, and chemistry and Earth and planetary science.

Each of these fields is rapidly developing, thus it is not surprising that the study of the origins of life,² which depends on all of them, is itself prone to reinterpretation over time. Consider, for instance, that while the periodic table of the elements is by and large complete with respect to the likely naturally occurring chemical elements (and has been so since around 1940),³ it was not until the mid-1960s that plate tectonics became generally accepted. Until 1992 there were no known planets beyond our Solar System (though most theory suggested there must be),⁴ while today thousands are known, to the extent general rules regarding their frequency are being constructed and the majority of such discoveries are no longer newsworthy. As another example, as late as the 1990s, introductory biology textbooks taught the "Five Kingdoms" (identifying the animals, plants, fungi, protists, and prokaryotes as fundamental clades) classification scheme, while today the "Three Domains" model (identifying the eubacteria, archeabacteria, and eukarya as fundamental clades) is canonical. The latter scheme is based on DNA sequence-based phylogenetics, which is considered to convey more detailed historical information than the previous morphology-based similarity classification schemes.

It should be clear why this question is important for humanity. Aside from whatever practical applications a deeper understanding of biological self-organization might provide to questions such as the origins of viruses, the origins of life directly addresses questions of ultimate biological ontogeny that in most cultures have traditionally been considered metaphysical. Furthermore, in the age of space exploration, humankind is on the cusp of being able to know whether there is life beyond Earth, at

 $^{^{2}}$ The community seems to prefer the term "Origins of Life" as opposed to "Origin of life" as the plural term acknowledges there may have been not only more than one origin of life on Earth, with perhaps only one surviving, but also that there may be more than one manner in which life may originate.

³ The pace of element discovery has been roughly linear since 1750, however, since the 1940s only man-made elements that are too unstable to occur in nature have added to the count.

⁴ In fact, the 2019 Nobel Prize in physics was awarded for the discovery of exoplanets. It was expected for centuries that such planets should exist, but now we know they do. The abundance and diversity of exoplanetary systems have in fact made our own Solar System suddenly seem unusual, leading scientists to question whether all our models for terrestrial evolution are in fact idiosyncratic to our solar system.

whatever form or stage of development it might be found.⁵ The expected frequency of life and intelligent life is described by the Drake Equation,⁶ which multiplies through a series of probabilities, some of which are better estimated than others. Many of the early terms in the Drake equation are now well understood, and it is becoming clear that the origin of life could prove to be the bottleneck explaining the so-called "profound silence" or apparent absence of life in the Universe (e.g., Forgan 2019). We simply do not currently know the answer to this question.

It should not be surprising that scientists often seem to seek to explain the origins of life in terms of current models in various fields, and that the most novel models should take precedence over older models that are perceived as static, nor that models that are based on techniques that rapidly produce what is perceived as more cutting-edge data become more heavily weighted, although it is sometimes the case that more cutting-edge techniques merely reproduce earlier results albeit in finer resolution. Indeed, as will be shown here, older models frequently resurface with new justifications.

It is normal in science for numerous hypotheses to be proposed over time, although few survive for long, and even the robust short-term survivors may be completely discarded after serving their purpose in scaffolding newer paradigms. Some have observed that studies concerning the origins of life resemble a "circus" (Mazur 2014), while the constant updating of hypotheses has served as fodder for some to propose that the origins of life is fundamentally intractable because it is a metaphysical problem. Another philosophical stance, taken more frequently by scientists, is that it is not a scientifically addressable problem because it is *historical* in nature.

The origins of life can be broadly split into several intersecting considerations. Some scientists take a "top down" approach (see Figure 1) that considers common core features and aspects of contemporary organisms; for example, the fact that all life is cellular, uses DNA as a long-term genetic information storage molecule, uses common energy currency molecules (e.g., ATP) and cofactors (e.g., NADH), common metabolic pathways, and uses a common genetic code and translation machinery based on RNA to produce proteins. This approach is further buttressed by reconstruction of molecular phylogenies and assumes there are vestiges not only of early organisms' biochemistry in contemporary

 $\mathcal{N} = R^{**} f_{p} * n_{e} * f_{l} * f_{i} * f_{c} * L$

⁵ There are various efforts underway to find extraterrestrial life, whether it might be microbial and in our Solar System (for example, that which might be found in a scoop of dirt on Mars or a sample from a geyser emanating from Enceladus), or microbial and beyond our Solar System (such as what might be detectably measured in an extrasolar planetary atmosphere), or advanced and discovered by the reception of some sort of intelligent electromagnetic signal from anywhere within our galaxy or beyond.

⁶ The Drake equation, first formulated by Frank Drake in 1961, is typically expressed in the form:

Where N = the number of presently communicating civilizations, R = the rate of star formation, f_p = the fraction of stars with planets, n_e = the fraction of planets that are Earth-like, f_i = the fraction of those planets upon which life arises, f_i = the fraction of those upon which intelligent life arises, f_c = the fraction of those that become capable of interstellar communication, and L = the lifetime of those civilizations.

organisms, but sometimes also vestiges of the very first organisms' biochemistry. It is often tacitly assumed that the simplest explanation for the occurrence of these structural features lies in some form of environmental chemistry ("prebiotic chemistry," which will be discussed below). These considerations suggest there should be a simple trajectory between abiological chemistry and the more complex aspects of contemporary biochemistry. This largely rejects the notion that contemporary biology is the result of an extended period of dynamical evolution and natural selection.

Figure 1. The general time scale of the origins of life in the context of Earth history.

A second approach, the so-called "bottom up" approach, considers what processes occurred in primitive environments and contributed to the complexification of chemistry, ultimately leading to systems with sufficient complexity to undergo some form of heritable evolutionary process. It should be noted that while such systems are envisioned to give rise to contemporary organisms, according to some bottom-up models the first such systems may not have been especially similar to modern organisms. In this case an appeal is implicitly made to the processes of evolution and natural selection. In other words, much of contemporary biochemistry is the result of protracted biochemical evolution, and directly dependent on the nature of chemical evolution or prebiotic chemistry. To understand the origin of modern organisms, we may need to first discover self-replicating chemical systems that are not similar to modern biology, but that are capable of open-ended evolution. The bottom-up approach is heavily dependent on knowledge of primitive Earth and Solar System environments, as well as the types of chemical and physical processes they engendered and enabled. The former are complex and the subject of ongoing study, the latter are complex in the sheer diversity of possibilities.

What Do We Need to Know to Understand the Origins of Life?

Although the origins of life lies at the nexus of many fields of study that address phenomena much larger than cells, most scientists agree that the transition from inanimate to animate matter occurs at the level of molecules, likely on a scale from angstroms to microns. As this is prior to biology, by

definition, this is squarely in the domain of chemistry, and more specifically the field of "prebiotic chemistry." Prebiotic chemistry attempts to address the origins of life theoretically, experimentally, and observationally.

Before diving too deeply into investigations and debates of how life may have begun, it is worth exploring how scientists define "life." The word "life" in English has numerous connotations, including the experience of living, the phenomenon of living, the quality of being alive, etc., which makes it an extremely knotty and circular concept. It may be that other languages have more succinct terms for the phenomenon we are concerned with here, but for the sake of discussion, one definition, produced by Gerald Joyce of the Scripps Research Institute, has received widespread dissemination, perhaps because it is so concise and easily parsed: "A self-sustaining chemical system capable of Darwinian evolution." This definition makes it clear that what is sought is likely to be instantiated chemically, while placing great weight on the concept of self-sustainability, implying that the information for the phenomenon's continuity is contained within the system, and emphasizing the importance of heritable evolvability.

That the system should be chemical, rather than digital, suggests that while it is possible that there is such a thing as machine-embodied or digital artificial life, such life would itself be the product of the more "mundane" chemical form.⁷ Thus chemical life is generally considered to be the primary form in which the level of informational sophistication allowing instantiation of living phenomena is possible. Further, most scientists have considered that life as we know it must not only be chemical, but occur in the liquid phase,⁸ be based on carbon, and use water as a solvent. The rationales behind these arguments will be addressed briefly below.

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3. HISTORICAL BACKGROUND

The historical evolution of thinking on the origins of life is intimately tied to developments of other fields, including chemistry, biology, geology, and astronomy. Early scientific thinking was wide-ranging and often surprisingly prescient of modern models. However, since this review deals primarily with modern thinking and experimentation regarding the synthesis of organic compounds on the primitive Earth, the interested reader is referred to several excellent resources detailing historical developments (Farley 1977; Fry 2000; Wills and Bada 2000).

⁷ So, for example, it may very well be that the first life we detect in the Universe is artifactual, simply because once biological organisms discover the ability to make machine-based life, it may turn out that such life is more robust than the life that originates on planets, in much the same way that we have placed rovers on Mars that have endured for years, but the technology to put humans on Mars still eludes us.

⁸ Some would argue that life does not occur in the liquid phase but rather in a colloidal phase, which was in fact Oparin's original reasoning.

Speculation regarding the origins of life has a deep history. In most cultures, there is a creation myth or set of creation myths that at the very least attempt to explain the origins of humankind (see, e.g., von Franz 2001). For thousands of years, people must have had folk concepts of plant and animal lifecycles due to the practice of agriculture and animal husbandry, as well as experience of the phenomenon of childbirth for tens or hundreds of thousands of years, though people may have lacked the notion of fertilization (Figure 2). That said, while people may have been aware of the modes of generation of higher organisms, other organisms with life cycles less open to easy observation were often believed to be generated spontaneously in the environment, to the extent we have documentation of early thinking on the topic.

Figure 2. 40,000-year-old rock art depicting childbirth from the Toca do Boqueirão site, Parque Nacional da Serra da Capivara, Piauí, Brazil.

Image http://brazilphotos.photoshelter.com/image/I0000lbyvfFEytf0.

It was not until the Renaissance that a recognizably modern scientific method was brought to bear on these questions, perhaps most famously with Redi's experiments concerning the spontaneous generation of insects.⁹ Whether the communication networks or formal scientific organizations existed for the deep dissemination of these results is debatable, nevertheless Redi's results were among the first to disprove the notion of spontaneous generation. Over the following several centuries there was considerable growth in formal biological knowledge, including the development of the science of microbiology after the invention of the microscope. While refutation of the spontaneous generation of organisms visible to the naked eye became fairly convincing during the 18th century, the spontaneous generation of microbes was less settled. In a series of high-profile experiments that were roughly contemporaneous with the publication of the first edition of Darwin's *On the Origin of Species*, Louis Pasteur was able to convincingly disprove the notion of the spontaneous generation of microbes using his famous swan-necked flask experiments (Figure 3).

⁹ This is widely considered one of the first examples of the use of a "control" experiment.

Figure 3. Pasteur's swan-necked flask experiments still lie sterile after over 150 years. As Pasteur remarked at the time, "Never will the doctrine of spontaneous generation recover from the mortal blow of this simple experiment."

It should be noted that although by and large Darwin left the notion of life's origins unexplained and only obliquely addressed it in his published books,¹⁰ the idea was clearly on the minds of those attempting to construct grand evolutionary scientific models of the Universe (e.g., Chambers' 1844 *Vestiges of the Natural History of Creation*) (Figure 4).

Figure 4. Tree diagram from Robert Chambers' 1844 *Vestiges* and a similar one from Darwin's personal notebooks, written during his voyage on *HMS Beagle*.

Darwin's (and Chambers') models for the evolution of biology both posited some form of branching phylogeny for living organisms, the logical extension of which would suppose a trunk and root, which presumably was a naturalistic origin of life. Thus, despite Pasteur's masterful demonstrations refuting

¹⁰ In his closing remarks in the first edition of Origin of the Species, Darwin wrote, "There is grandeur in this view of life, with its several powers, having been originally breathed **by the Creator** into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved." Following criticism by scientist colleagues he removed the bold-faced text in the second edition, and following criticism from religious figures, he added them back in subsequent editions.

spontaneous generation, during the second half of the 19th and beginnings of the 20th centuries a significant number of scientists, professional and amateur, around the world, attempted to experimentally demonstrate spontaneous generation. However, there was little organized effort, some of the work was less than rigorous, and rapid advances in more tractable scientific areas largely pushed these tinkerings to the background of scientific focus.

In part of a letter sent in 1871 to Joseph Dalton Hooker, Darwin summarized his rarely expressed ideas on the emergence of life, as well as his views on the molecular nature of basic biological processes:

It is often said that all the conditions for the first production of a living being are now present, which could ever have been present. But if (and oh what a big if) we could conceive in some warm little pond with all sorts of ammonia and phosphoric salts, -light, heat, electricity & present, that a protein compound was chemically formed, ready to undergo still more complex changes, at the present such matter wd be instantly devoured, or absorbed, which would not have been the case before living creatures were formed...

By the time Darwin wrote to Hooker, DNA had already been discovered, although its role in genetic processes would remain unknown for almost 80 years. In contrast, the role that proteins play in biological processes had already been firmly established, and major advances had been made in the chemical characterization of many of the building blocks of life.

By the time Darwin wrote this letter, the chemical gap separating organisms from the non-living world had already been bridged in part by laboratory syntheses of organic molecules. In 1827 Berzelius, probably the most influential chemist of his day, had written, "art cannot combine the elements of inorganic matter in the manner of living nature." Only one year later his former student, Friedrich Wöhler, demonstrated that urea could be formed in high yield by heating ammonium cyanate "without the need of an animal kidney." Wöhler's work represented the first synthesis of an organic compound from inorganic starting materials. Although it was not immediately recognized as such, a new era in chemical research had begun.

In 1850 Strecker achieved the laboratory synthesis of alanine from a mixture of acetaldehyde, NH_3 , and HCN. This was followed by the experiments of Butlerov, showing that the treatment of formaldehyde with alkaline catalysts leads to the synthesis of sugars. By the end of the 19th century a large amount of research on organic synthesis had been performed, leading to the abiotic formation of fatty acids and sugars, using electric discharges with various gas mixtures (Glocker and Lind 1939). This work was continued into the 20th century, for example, the synthesis of amino acids by exposing wet formamide to a silent electrical discharge (Löb 1913) or UV light (Baudisch 1913) was examined. However, since it was generally assumed that the first living beings had been autotrophs, the abiotic synthesis of organic compounds did not appear to be necessary for the emergence of life. In addition, these organic syntheses were not conceived as laboratory simulations of "Darwin's warm little pond" (this letter was not widely known until the 1960s) but rather as attempts to understand the mechanisms of nitrogen and CO_2 fixation in plants.

It is generally believed that after Pasteur disproved spontaneous generation using his famous swannecked flask experiments, the discussion of life's beginnings had been vanquished to the realm of useless speculation. However, scientific literature from the early 20th century records many scientific attempts to solve this problem. The list covers a wide range of explanations from the ideas of Pflüger on the role of HCN in the origin of life, to Troland's hypothesis of a primordial enzyme formed by chance in the primitive ocean, Herrera's sulphocyanic theory on the origin of cells, Harvey's 1924 suggestion of a heterotrophic origin in a high-temperature environment, and Muller's provocative 1926 paper on the random formation of a single, mutable gene endowed with catalytic and replicative properties (Lazcano 1995).

At the beginning of the 20th century, several less-than-mainstream scientists believed they were able to demonstrate spontaneous generation (Hanczyc 2008). Most scientists viewed these experiments with skepticism, partly due to Pasteur's masterful demonstration (Fry 2000). This left a paradox: life appeared to have a common ancestor, yet the origin of life could not be reproduced experimentally. Various explanations for this paradox were presented; for example, Arrhenius' proposed that, while it was then known that the Earth was not infinitely old, the Universe might be, and it was thus possible that, like the Universe, life was infinitely old. The spores of some type of bacterium-like "seed organism" might constantly inoculate new planets with life, which was then able to evolve into the higher forms observed today (Fry 2000).

An alternative and more experimentally addressable proposal was put forth almost simultaneously by Oparin (1924) in Russia and Haldane (1929) in the U.K., suggesting that early Earth might have provided chemical conditions facilitating spontaneous generation. Modern scientific models for the origins of life are typically traced back to Oparin and Haldane. Both of these scientists suggested the origins of life was a continuous process that started with environmental synthesis of organic compounds, which further reacted to form more and more complex assemblages until giving rise to cell- or gene-like structures that were then able to undergo something like Darwinian evolution (see the quote from Miller and Orgel above and Figure 5). In both scientists' models, chemical evolution was typically envisioned as having occurred in shallow aqueous surface environments.¹¹

Especially prescient were Oparin's suggestions that organic compounds, presumably required for the origin of the first organisms, could have been delivered to the Earth on meteorites or that they may have been generated in the early atmosphere, had it been reducing.

Oparin's proposal stood in sharp contrast with the then prevalent idea of an autotrophic origin of life. Trained as both a biochemist and an evolutionary biologist, Oparin found it difficult to reconcile his Darwinian beliefs in a gradual evolution of complexity with the commonly held idea that life had

¹¹ These ideas were not likely influenced by the above quoted letter to Hooker, which was not widely disseminated until the mid-20th century.

emerged already endowed with an autotrophic metabolism, which included chlorophyll, enzymes, and the ability to synthesize organic compounds from CO₂. Oparin reasoned that since anaerobic heterotrophs are metabolically simpler than autotrophs, the former would necessarily have evolved first. Thus, based on the simplicity and ubiquity of fermentative metabolism, Oparin (1924) suggested in a small booklet that the first organisms must have been heterotrophic bacteria that could not make their own food but fed on organic material provided by the primitive environment.

Oparin's ideas were further elaborated in a more extensive book with the same title as the pamphlet (Oparin 1938). In this new book his original proposal was revised, leading to the assumption of a reducing environment¹² in which iron carbides of geological origin would react with steam to form hydrocarbons. Their oxidation would yield alcohols, ketones, aldehydes, and so on, which would then react with ammonia to form amines, amides, and ammonium salts. The resulting protein-like compounds and other molecules would form a dilute soup, and would aggregate to form colloidal systems, or *coacervates*, from which the first heterotrophic microbes evolved. Like Darwin, Oparin did not address in his 1938 book the origin of nucleic acids, because their role in genetic processes was not yet suspected.

Oparin's proposal of a primordial reducing atmosphere was a clever inference from the then fledgling knowledge of solar atomic abundances and planetary atmospheres, as well as from Vernadsky's idea that since O_2 is produced by plants, the early Earth would be anoxic in the absence of life.

In the 1950s, Nobel Prize–winning American chemist Harold Urey also proposed that the early atmosphere would have been largely reducing, based on the preponderance of hydrogen (H₂) in the solar system (Urey 1952). Chemists use the terms "oxidizing" and "reducing" to describe the elements that carbon typically bonds with in an atmosphere. Carbon can form four bonds with other atoms: in an oxidizing atmosphere, carbon is bound via two double bonds with O to give CO_2 (an oxidized form of carbon); in a reducing atmosphere, carbon would be bound to four H atoms to give CH_4 (methane, a reduced form of carbon). The import of this is that it is considerably easier to make abiotic organic compounds from reduced gases than from oxidized ones.

¹² For Oparin, highly reducing atmospheres corresponded to mixtures of CH_4 , NH_3 , and H_2O with or without added H_2 . The atmosphere of Jupiter contains these chemical species, with H_2 in large excess over CH_4 .

Figure 5. A.I. Oparin (left image, in foreground) and J.B.S. Haldane (center image) are generally considered the "fathers" of modern theory for the origins of life. On the right a photomicrograph of coacervates is shown. These are cell-sized globule-like structures that spontaneously form from complex mixtures of heterogeneous polymers; they were a central aspect of Oparin's model.

Although experiments aimed at producing organic compounds abiologically had been attempted in the early 20th century, it was not until the 1950s that scientists began to explicitly test these models experimentally in the context of understanding the origins of life. Perhaps the first notable example of an explicit test of prebiotic organic synthesis was carried out by Calvin and colleagues at University of California, Berkeley (Garrison et al. 1951). These authors exposed ¹⁴C-labeled CO₂ and water to ionizing radiation from a cyclotron and measured the formation of trace amounts of formic acid and formaldehyde. These results, while novel, did not cause much of a stir in the scientific community. Only two years later the results of work by a young graduate student at the University of Chicago, Stanley Miller, working under the tutelage of Urey, successfully demonstrated the synthesis of a number of organic compounds starting from simple gases (H₂, ammonia (NH₃), CH₄, and water vapor), which were at the time considered to have been components of early Earth's atmosphere (Miller 1953, Figure 6). Miller's simple yet elegant experiment used electric discharges passing through this simulated early atmosphere coupled with a model hydrologic cycle to produce a complex organic mixture that upon analysis proved to include several amino acids of biological importance. These types of experiments have been repeated by numerous laboratories around the world since then to explore the effects of gas composition and energy type on the product yield and distribution. These experiments are discussed in further detail in Section 6 below.

While there had been earlier laboratory demonstrations of organic synthesis using electric discharges (see, for example, Löb 1913), this experiment is generally considered the first conducted to understand the origin of life. It is thus widely deemed to have opened the modern period of experimentation into the mechanism of the origin of life and to have been the first successful intentional example of "prebiotic chemistry." Coincidentally, Watson and Crick (1953) published their structure for the DNA double helix within a week of the publication of Miller's results. Until that time, it had been widely debated whether proteins or nucleic acids were the carriers of genetic inheritance (although the evidence was strongly in favor of the latter). The structure of DNA left little doubt. This close historical

juxtaposition of discoveries reveals a common motif in prebiotic chemistry and in origins-of-life models in general: discoveries in other fields frequently drive advances in origin of life models.

Figure 6. Stanley Miller in the 1960s with a version of his electric discharge apparatus. On the right are shown before and after images of an experiment carried out in the 1970s and later using a simplified version of the apparatus Miller employed. The light brown solution is a mixture of a wide variety of organic compounds generated in the experiment.

However, geochemists had already pointed out that the early atmosphere was unlikely to have resembled the gas mixture that Miller studied (Rubey 1951). Rather than being composed of generally reduced gases (those in which the central "heavy" atoms, e.g., C, N, or S, are predominantly bonded to hydrogen rather than oxygen). Rubey calculated the atmosphere would have been oxidizing, composed mainly of CO₂ and N₂. It was known that experiments of the Miller-Urey type using gas mixtures similar to those of Calvin and colleagues were much less productive at making organic compounds. Details regarding this issue are discussed below.

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4. OVERVIEW OF BIOLOGY

One of the greatest challenges to the study of the origins of life is the nature of biology itself and what its earliest instantiation may have been like. Presently, all terrestrial organisms are cellular, that is, they are composed of discrete bounded containers surrounded by lipid cell membranes, and sometimes other components, such as a cell wall. Enclosed in their interiors is an aqueous solution of metabolites, ions, and macromolecules. These solutions are typically about 70% water (see Figure 7).

Figure 7. Left and top right, relative composition of a microbial cell (figures from http://bionumbers.hms.harvard.edu). Lower right, a cartoon of a simple prokaryotic cell, showing the relative dimensions and organization of sub-cellular components. Purple = ribosomes, yellow strands = DNA, blue = proteins, green = cell membrane and glycocalyx.

In all contemporary organisms, the so-called Central Dogma of biology operates. According to this dogma, the cell stores hereditary information in double-stranded DNA molecules, which are in turn copied into single-stranded messenger RNA (mRNA) molecules, which are then "translated" into proteins in a process involving transfer RNA molecules (tRNA, small folded RNA adapter molecules that ensure the precise amino acid coded by a DNA strand, gets incorporated into the proper location in a protein) and ribosomes, which are large macromolecular, multi-component complexes of ribosomal RNA (rRNA) and numerous structural peptides (Figure 8). DNA is itself copied using various protein enzymes and small RNA primers.

The fact that proteins are needed to make DNA and DNA is needed to make proteins leads to a "chicken or egg paradox:" which logically would have had to arise first? The central role of RNA in this process led some to speculate that it could be the solution to the paradox (Crick 1968; Orgel 1968; Woese 1968), and this led to the notion of an "RNA World" (Gilbert 1986; Gesteland and Atkins 1993), a putative period in which RNA functioned as both catalyst and genetic molecule. Some scientists interpret the RNA World to mean that life began with a self-replicating RNA molecule, while others interpret it to mean that life passed through a period in which RNA was merely extremely important in biochemistry. The perceived simplicity of the first interpretation has driven considerable research into the prebiotic synthesis of RNA and its components.

The biochemical unity, including the Central Dogma, of modern organisms is striking, and in fact enables construction of the so-called "Universal Tree of Life."¹³ Since all organisms must have the translation machinery by definition, and since the rRNA molecules' sequences are extremely conserved between closely related species, all extant organisms can be related to each other by comparison of these, and by and large for higher organisms rRNA phylogenies reflect phylogenies previously constructed based on organismal morphology. One surprise of such modern trees, however, has been the division of all living things into three domains, two of which are prokaryotic, the Bacteria and the Archaea (or archaebacteria), and the Eucarya (Figure 8).

Figure 8. Left, the Central Dogma of biology showing how information flows at the sub-cellular level. Right, a schematic showing a modern 16S rRNA-based phylogenetic tree, and the ambiguity of locating the Last Universal Common Ancestor (LUCA) relative to modern organisms and origins of life.

Fossil and phylogenetic evidence supports the notion that the Eukarya evolved from simpler prokaryotic organisms (e.g., Knoll et al. 2006), and thus the surmise is that all modern cellular organisms are derived from a prokaryotic so-called Last Universal Common Ancestor (LUCA). Importantly, this organism or perhaps group of organisms already operated using the Central Dogma and thus was not an RNA-only based organism, and several lines of evidence suggest it was cellular.

The Archaea have several unique characteristics, including specialized forms of metabolism and membrane lipids. Some phylogenetic analyses suggest hyperthermophilic archaebacteria are the oldest organisms on Earth (Wang et al. 2007), which has been used to argue that the types of environments these organisms inhabit presently were the earliest environments for life and thus likely sites of the origin of life. This idea remains controversial (Arrhenius et al. 1999; Gupta 2000).

As Figure 8 attempts to indicate, scientists are uncertain exactly where to place the hypothetical LUCA in relation to modern organisms, and thus argue over which modern organisms are likely most closely

¹³ It should be noted that there remain various points that modern molecular biologists disagree over, thus more precisely we could say there are "Universal *Trees* of Life" that represent the true underlying phylogeny.

related to it, but it remains unknown when the archaeal and bacterial phyla differentiated, or how much time might have elapsed between the origins of life and LUCA. Indeed these two milestones could be separated by over a billion years, and some divergence estimates for these phyla even suggest this could have occurred before the Moon-forming impact (see below), a hypothesis that is often rejected (e.g., Betts et al. 2018).

The viruses should also be mentioned here. Viruses, which make up approximately 0.002% to 0.7% of current terrestrial biomass, are a diverse class of replicating entity that are hosted by most cell types in one form or another. All viruses include a nucleic acid component, and variously store their genetic information in the form of single- or double- stranded RNA or DNA, and various types of virus include lipid membranes or protein coats and various accessory proteins. It is not clear which are the most ancient. Although viruses evolve via mutation and natural selection, viruses depend on host organisms for the completion of their replication cycles and generally lack translation machinery, thus most scientists do not consider them to be living organisms per se. The origins of viruses remain mysterious, although it now seems likely they may have multiple origins as either degenerate microbial cells or escaped cellular genetic elements that have attained some degree of life-cycle independence. Nevertheless many now consider that they have long played important roles in organismal evolution as vectors and incubators for novel genetic information between organisms and organismal communities, and there were likely already viruses in the biosphere before the origin of the bacterial/archeal dichotomy.

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5. OVERVIEW OF SOLAR SYSTEM AND EARTH HISTORY

Like biological systems, the Solar and Earth systems are both dynamical. Each is a complex collection of interconnected moving parts, and at any given time feedback processes have existed in them that allowed them to behave in unpredictable ways, which also makes it difficult to back-extrapolate their previous states. Additionally, like biological systems, scientists are constantly seeking new evidence to understand the early histories of the Earth and Solar System, and such evidence can be hard to come by. For example, in the case of the Solar System, because much of the material in question is difficult to access (it is in outer space), and with regard to the Earth system, because Earth is one of the few known objects in the Solar System with ongoing dynamic tectonic processes that constantly remelt and destroy earlier rock evidence.

The observation of thousands of planets beyond our solar system ("exoplanets," see, e.g., Perryman 2018) as well as several protoplanetary disks (e.g., Keppler et al. 2018), makes this an especially exciting time for scientists who study the origin of the Solar System. For the first time we are now able to compare our Solar System with thousands of others to gauge its uniqueness, as well as image newly forming solar systems to directly observe their early stages (Figure 9).

Figure 9. A. An artist's conception of the evolution of a protoplanetary disk (starting at upper left and proceeding clockwise) showing the coalescence of an initial gas/dust disk into a central star and associated planets. B. Direct image of the HL Tau extrasolar protoplanetary disk. C. Asteroid Bennu as imaged by the OSIRIS-Rex spacecraft in 2019, showing the heterogeneous nature of these bodies. D. Close up image of asteroid Ryugu imaged by the Hayabusa 2 spacecraft, showing the heterogeneity of the surface at small scale. E. Image of Ultima Thule captured by the New Horizons spacecraft, showing a primitive collision between early Solar System objects frozen in time.

The dominant model for the formation of planetary systems is the nebular or Kant-La Place hypothesis (Montmerle et al. 2006). According to this model, stars form in huge interstellar clouds of gas and dust, which become gravitationally unstable due to density inhomogeneities. This causes localized clustering of matter, and these clusters begin to assume a rotational movement as they increase further in mass by gravitational accretion, which further coordinates the rotational motion. Over time the mass of the cloud comes to concentrate into a rotating disk-shaped body known as a protoplanetary disk. As the central mass accretes more and more material from the disk, it may begin to radiate energy even before collapsing sufficiently to ignite atomic fusion to give birth to a star. In the case of our Solar System, the presolar nebula was likely composed of the remnants of a previous supernova explosion, which meant it was relatively enriched in heavy elements (those heavier than Li) compared to earlier generation star forming events.

Localized dense regions further out in the disk may accrete enough material to become planets. It is generally believed that the process from cloud to star takes about 1 Ma (mega-annum, or 10^6 years), while the overall formation of a planetary system takes 10 to 100 Ma. As discussed below, Earth is estimated to have taken an intermediary length of time to form (approximately 50 Ma).

Depending on the mass and density distribution of the initial cloud and subsequent disk, different mass and thus spectral classes of stars may result, as well as binary star systems. We will concern ourselves here mostly with objects similar to the Sun and thus the evolution of our own type of solar system.

When the central star initially ignites, it enters an active period known as the T Tauri stage. At this point, >90% of the mass of the disk has been incorporated into the central star, although the central temperature is still too low for fusion to occur. Rather, the star radiates light due to gravitational energy released as the star contracts. These young stars typically have much faster rotation rates than mature stars, radiate considerably more strongly in the energetic shorter wavelength regions of the electromagnetic spectrum and are more prone to violent solar flaring. These energetic effects tend to soften over time, but likely were consequential not only for the early Solar System, but also for the early Earth system, including life and the evolution of Earth's atmosphere.

Farther out in the evolving disk, gas and dust began to convect, and a temperature gradient developed that led certain compounds and materials to "freeze out" or condense at certain distances. Lower boiling point compounds in the disk were driven outward from the Sun, as in a distillation, each condensing at and beyond its relative condensation point. For example, the majority of the water in our Solar System condensed beyond what is known as the "snow line" or "frost line," the distance from the central star where it is cold enough for water to condense from the gas to the ice phase. Higher melting point species such as minerals condensed closer in but were also circulated farther out by various mixing processes in the disk. Together, these processes depleted the inner Solar System of these species and elements, as is observed. Thus, volatile components such as CH₄, H₂O, and N₂ coalesced into outer Solar System bodies such as the gas and ice giant planets (Saturn, Jupiter, Neptune, and Uranus) and the Oort cloud and Kuiper belt comets, while higher boiling-point compounds such as metal oxides and silicates, which make up the bulk of the inner rocky planets, condensed nearer in. The smaller resultant bodies, comets, meteors, and interstellar dust particles (IDPs) continue to impact the planets presently, and it is likely this flux was higher around the time that life formed on Earth. The presence of extraterrestrial organic molecules in meteorites, comets, and IDPs is firmly established and has led to proposals that these were sources of organic compounds possibly necessary for the origin of life (Oró 1961; Anders 1989; Chyba et al. 1990; Chyba and Sagan 1992).

The general model runs that there was an accretionary hierarchy, with gas condensing to dust and ice grains, which accreted to form larger and larger bodies, eventually reaching the size of comets and asteroids. There was initially a relatively higher concentration of radioactively unstable nuclides in the Solar System compared to today, and this radioactive decay generated heat. Bodies that grew large enough were unable to effectively dissipate this heat and as a result begin to heat internally. In addition, collisions among these nascent bodies also generated considerable amounts of heat. Thus as these bodies grew larger, they began to melt internally, which led to material differentiation via gravitational and buoyancy effects. For example, some initially homogenous objects reached internal temperatures sufficient to melt silicates and metals, causing the denser metal materials to migrate toward their cores, while the lighter materials concentrated toward their exteriors. Solid objects that attained a size of

approximately 1 km in diameter are known as planetesimals, and some of these combined to form objects on the order of 10^{22} to 10^{23} kg (roughly the sizes of the asteroid Vesta and the dwarf planet Pluto) known as protoplanets. The merger of protoplanets ultimately gave rise to the rocky planets as well as other types (e.g., gas and ice giants) of planetary cores, depending on their location in the disk.

The gas giants are thought to have accreted to their present masses over as little as approximately 10 ka (kilo-annum, or 10^3 years) and as we will see below, it is now believed that there may have been considerable migration of the planets in our Solar System since their formation.

Formation of the Earth

Scientists believe that the Earth formed through the general process of accretion of protoplanets outlined above, although Earth has numerous unique features that are the result of its specific formation history and accretionary environment. Earth's age [approximately 4.57 Ga (giga-annum, or 10⁹ years), see Figure 10] is now well constrained by measurements of isotope ratios resulting from radioactive decay chains in both meteorites and terrestrial rocks, as well as dating of rocks returned from lunar missions (Dalrymple 1994). What is meant by the age of the Earth is the age at which its stable isotope systems achieved closure, presumably coinciding with the formation of a solid body. Meteorite samples show a spread from approximately 4.53 to 4.58 Ga, which is interpreted as the duration of the solar nebula and its collapse into the solar disk to form the Solar System. Martian meteorites (e.g., pieces of Mars that have been recovered in the form of meteorites on Earth) have also been dated to approximately this age.

Figure 10. Left, historical estimates for Earth's age over time. The red point is the currently most accepted age of approximately 4.57 Ga. The discovery of radioactive decay by Becquerel (right) in 1896 ultimately enabled the modern science of radiometric dating.

The age of Earth's Moon has now been dated to approximately 4.51 Ga, having formed within a few tens of millions of years of Earth. The most widely accepted model for the formation of the Earth-Moon system involves the collision with the proto-Earth of a hypothetical roughly Mars-sized body (named Theia). Importantly, this implies that the Moon initially orbited much closer to Earth that at

present, a notion that is confirmed by contemporary measurement of the Moon's rate of recession from Earth (approximately 4 cm per year) as the angular momentum of the Earth-Moon system must be conserved over time. Back-extrapolation indicates that an Earth day would have been shorter than at present, perhaps as short as 6 hours, and the Moon would have been considerably closer, leading to massive and frequent terrestrial oceanic tides. In any event, it is generally considered that the Moonforming impact was sufficiently violent to melt the Earth's entire surface, and thus rules out a pre-Lunar impact origin of life.

In addition to a single moon, which helps maintain Earth's long-term orientation with respect to the Sun, Earth has two other special planetary features that have assisted in making it habitable over long periods of time: an active magnetic field and active plate tectonics, both of which are related to Earth's accretional history.

Earth is thought to have formed mainly from protoplanetary bodies resembling chondritic meteorites, which aside from volatile elements have a chemical composition almost identical to that of the Sun. However, as Earth accreted, the same processes responsible for the internal heating in other Solar System objects noted above, namely retention of internal heat from radioactive decay, likewise melted the bodies from which Earth formed, leading to their differentiation and segregation, with the heaviest elements (e.g., Ni and Fe) sinking in toward Earth's center, and the lighter elements (e.g., O, Al, and Si) migrating toward the surface. Over time this led to the formation of the Earth's core, mantle, and crust, and during this process different minor elements segregated according to their affinities for either the more metal-rich deeper reservoirs (so-called siderophile elements, or ones that tend to partition into metal phases in melts, and thus would have tended to co-migrate toward the core) or the more silicate-rich surface ones (so-called lithophile elements, those that combine readily with oxygen to form compounds that did not tend to sink into the core). Importantly, there is an anomalous concentration, relative to Solar abundance, of highly siderophile elements (for example, ruthenium, palladium, and platinum) in Earth's crust. These, it is believed, must have been delivered to Earth after the differentiation caused by the Moon-forming impact, otherwise they would have been sequestered into Earth's mantle and core. The importance of this will become clear below.

The formation of the core and the fact that it rotates at a different velocity than Earth's outer layers helps to create Earth's geodynamo, which in turn creates its magnetic field. Earth's magnetic field is thought to have been continuous since at least 3.5 Ga and is essential for deflecting energetic particles from the solar wind away from the Earth. These would otherwise strip away the upper atmosphere and degrade the ozone layer. Thus Earth's magnetic field shields its surface directly or indirectly from a wide variety of ionizing radiation. It should be noted that Earth's magnetic field is considerably stronger than that of any other rocky planet in the Solar System.

Earth's internal radioactive decay causes convective heat flow, which drives convective movement of mantle and crustal rocks. As these new rocks are brought to the surface by volcanism and seafloor spreading, in a compensatory fashion heavier, older rocks are subducted back into Earth's mantle where they are melted and recycled. Often, a portion of this material remains buoyant and stays at the

surface, and in this fashion the continental crust forms. It remains a matter of debate when this process started in its modern form on Earth, and how the volume and area of continental surface area has evolved over time (Figure 11). These estimates have some relevance to the discussion below regarding the plausibility of prebiotic synthesis models that depend on evaporative conditions.

Figure 11. Models for the growth of continental crust, adapted from (Korenaga et al. 2018). All these models generally agree on the notion that the amount of continental crust has increased over time. The red curves suggest there was abundant crust early in Earth history. The yellow and green models suggest a later onset of extensive continental crust. The blue curves suggest a slow and late accretion of continental land masses. Analyses of mica inclusions and oxygen isotope data in Hadean zircons suggest that the Hadean Earth had a small volume of crust with a composition similar to the modern crust (Caro et al. 2017; Hopkins et al. 2008). It should be noted that continental crust is not necessarily synonymous with subaerial land masses, and even the slow growth models could allow for significant numbers of small subaerial island arcs like the Canary or Hawaiian Islands.

Presently, the oldest oceanic crust, which most actively participates in plate tectonics, is just 250 Ma old with the majority being much younger. That is not to say that there are not older rocks on Earth's surface, indeed there are many. However, these continental crust land masses are scattered in an increasingly rare distribution across Earth's surface, with some of the oldest being found in northern Canada, Greenland, and Western Australia (Figure 12).

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Figure 12. Radiometrically dated ages of Earth's oceanic (left) and continental crust (right). Black dots indicate some of Earth's oldest geological evidence (from West to East), the Acasta gneiss (in Northern Canada), the Akilia supercrustal belt (in southeastern Greenland), and the Jack Hills formation (in western Australia). http://www.geocoops.com/theory-and-margins.html

The Early Environment and Evidence for Early Life on Earth

Earth's oldest known rocks offer some clues to what its early surface environment was like during the origin and early evolution of life. Rocks older than approximately 3.5 Ga are rare on Earth's surface and share the common problem that they have been highly metamorphosed due to Earth's ongoing tectonic recycling. In addition to the difficulty of determining the biogenicity and/or indigineity of the organic materials in such samples, it is difficult to determine the original depositional settings of their mineral contexts. This is important as it could help determine whether the putative ecosystems these samples contain represent, for example, shallow intertidal environments, and thus ones possibly containing photosynthetic organisms, or deeper hydrothermal environments that might imply chemotrophic organisms.

Evidence for life on Earth was once restricted to animals leaving visible fossils, which extend back as far as the beginning of the Cambrian period (approximately 550 million years ago). Micropaleontologists, scientists who study evidence of microbial life in ancient rocks, began to find evidence for Precambrian life in the 1960s in the form of fossilized bacteria in cherts (fine-grained silicate-dominated sedimentary rocks). Presently, the oldest commonly agreed upon fossil microorganisms (it cannot be ascertained whether these organisms were archaebacteria, bacteria, or perhaps members of another no-longer-existent line of organisms) are dated to approximately 3.5 Ga there are none with indisputable traces of life.

As modern organisms fix inorganic carbon (e.g., CO₂ during photosynthesis) from the environment, they tend to preferentially and characteristically incorporate the lighter ¹²C isotope compared to the ¹³C one, thus the resulting biological organic material tends to be "isotopically light" or *enriched* in ¹²C. There is evidence in some of the oldest known rocks for isotopically light carbon, possibly formed via biological activity, as far back as approximately 3.8 Ga (Mojzsis et al. 1996). This notion remains controversial (see, for example, Fiebig et al. 2019), and there is evidence that non-biological processes could also produce this signal (Brasier et al. 2002), or that younger biological material has leached into these rocks over their long depositional history.

Primitive Earth's water likely first outgassed as steam and slowly condensed as the crust cooled, forming the Earth's first surface waters. There is evidence from zircon minerals (remarkably weathering-resistant minerals composed of zirconium silicates that are among the oldest known on Earth) that liquid water was present on Earth as early as 4.4 Ga (Valley et al. 2002). These microscopic mineral inclusions often contain trace elements that allow them to be radiometrically dated, alongside other chemical inferences that can be drawn from their subtle chemical composition. This is in general accordance with models that suggest rapid cooling of the originally molten accreted Earth, which likely remelted as a result of the Moon-forming impact, the point being that the surface must have been cool

enough to host liquid surface water by that time. The temperature and pH of the earliest oceans remain poorly constrained, with possible values ranging between 0 and 100°C and pH 5 to 11 (Kempe and Degens 1985; Morse and Mackenzie 1998).

This is significant since whatever original characteristics the first living organisms may have had may not have carried through to the present, for example, the use of DNA or the genetic code to transfer biological information, but there are few if any scientists in this field who do not believe that the first living things were based on organic compounds and lived in water.

In attempting to construct a timeline for the origins of life on Earth, most scientists consider the upper and lower boundaries to be sometime between 4.4 Ga, when Earth's surface was cool enough to support liquid water, and 3.5 Ga, when there is generally accepted fossil, isotopic, and contextual evidence for microorganisms on Earth. This leaves a window of approximately 800 Ma for life to have originated and evolved to the point of being able to leave behind recognizable microfossils in the geological record. Importantly, the scarcity of rocks of such age implies a global microbial ecosystem by that time. One can appreciate that the timing and tempo of the origins of life and early biological evolution are somewhat poorly constrained by geological evidence.¹⁴

Astrobiologists would like to constrain this uncertainty. Perhaps one of the first attempts to do so, which has waxed and waned in acceptance over the last 45 years or so, is the concept of the Late Heavy Bombardment (LHB). This notion, which has become integrated into more-general Solar System evolution models, is based on radiometric dating of rocks returned from the Apollo missions. These data have been interpreted to suggest there was a period of intense meteorite bombardment, approximately between 4 Ga and 3.8 Ga. As the Moon is much smaller than Earth, and thus retains less internally generated heat, it must have cooled faster, becoming tectonically inactive, and thus its surface has essentially been geologically "frozen" for billions of years. It has thus exquisitely recorded its history of meteorite bombardment almost since its formation compared to the Earth. By extrapolation of the relative masses of the Moon and Earth (the Earth is approximately 81 times as massive as the Moon), and by virtue of Earth being larger it would gravitationally attract significantly more impactors than the Moon, it is estimated Earth would have received a much higher flux of impactors than the Moon, although there is much less direct terrestrial record of this due to Earth's tectonic activity. An implication of this model is that impacts during the putative LHB would have been so intense, approximately from 4 Ga to 3.8 Ga, that the oceans would have been repeatedly sterilized (for example, by being raised to well above the boiling point of water for long periods of time) by large asteroid impacts and thus even if life had repeatedly originated before 3.8 Ga, only the last origin could be the parent of the modern biosphere. Using the lower boundary of 3.8 Ga for the origin of life leaves a rather short period of maximally 300 Ma for the origin of life given the evidence for early life that scientists currently generally accept.

¹⁴ For reference, *E. coli* growing under optimal conditions has a generation time of ~30 minutes, and 98% of published chemistry experiments since 1771 have been conducted for 48 hours or less (Keserű et al. 2014).

When the LHB-Earth sterilization concept was introduced, some scientists felt that 300 Ma was too short a time for life to have originated and evolved to the degree of complexity suggested by fossil evidence. As it is not known how long it takes for life to originate or complexify to any degree that would be ascertainable by observation with modern microscopes, 300 Ma may be more than ample time for life to originate and attain the complexity suggested by the resemblance of putative microfossils to contemporary cyanobacteria (Schopf 1983, 1993). Some authors have suggested that 10 Ma is sufficient for the transition from prebiotic chemistry to recognizable cyanobacteria (Lazcano and Miller 1994), which underscores our ignorance of the pacing of such processes. Others have criticized this analysis suggesting there are far too many gaps in our knowledge for meaningful estimates to be made (Orgel 1998). Still other scientists, prompted by the concept of the LHB model, have suggested that regardless of its intensity there would have existed refugia in Earth's crust where life could have survived, thus life could have originated earlier (Abramov and Mojzsis 2009). This is related to earlier suggestions that LUCA, which has been suggested to have been a hyperthermophile (an organism optimally living $> 60^{\circ}$ C), was naturally selected to be such because of the LHB (Arrhenius et al. 1999). This set of proposals and counterproposals is perhaps best interpreted as evidence that there is still not sufficient evidence for solid hypotheses to be concretely developed.

Approximately 20 years ago, scientists began an effort to reinterpret the evidence for the LHB. Now, what once seemed to be "settled science" is viewed by many to be poorly supported by the available evidence (see, for example, Bottke and Norman 2017; Lowe and Byerly 2018). The reasons for these doubts mainly focus on the fact that the Apollo missions may have oversampled a meteorite impact basin that gives a statistically skewed age to a single impact, which was then taken as representative of a more general process. If it becomes more generally accepted that the LHB model is incorrect this would make it more plausible that life could have originated before 4 Ga.

There is an often-referenced measurement to an isotopically light graphite inclusion in a single zircon crystal dated to approximately 4.1 Ga used as evidence for a very early, and presumably continuous, origin of life (Bell et al. 2015). This extremely small sample can be interpreted as evidence for biology by 4.1 Ga. This is certainly feasible, but most scientists consider this evidence unconvincing. It is fair to say the uncertainty in dating when life began on Earth has not changed considerably over the last 30 years, but rather a whole range of ideas, based on incomplete evidence, has emerged that allow for models postulating life to have originated in the preceding 800 Ma to be true. None of these notions impact the underlying problem that we do not have a chemical model explaining the origins of life.

The LHB concept has been considered in the context of ever-evolving Solar System formation models, among them the so called Nice or Grand Tack models that suggest that Jupiter and Saturn formed closer to the Sun, which would be in accordance with some recent measurements of extrasolar planetary systems. According to these models, these planets then later migrated outward to their present positions, in the process scattering a large variety of material around the early Solar System that was the cause of the LHB. The timing and severity of Earth's early impact history thus remains to be elucidated, and it may or not be the case that if there was a marked increase in impacts at any

given time it was caused by giant planet migration. As much as the LHB concept itself has been modified and now seems to be on the wane, giant planet migration may fall by the wayside and alternative explanations for the late veneer can be formulated. These uncertainties highlight the interconnected contingency of early Earth and Solar System evolution models and their impact on models for the origin of life.

The Early Atmosphere

The temperature at which Earth formed is important for understanding its early atmosphere, which is essential for understanding the possibility of terrestrial prebiotic organic synthesis. If Earth accreted slowly, then more of the primitive gases derived from planetesimals, likely reminiscent of the reducing chemistry of the early solar nebula, could have been retained. If Earth accreted rapidly, which is the model favored presently, the original atmosphere would have been lost and the primitive atmosphere would have been composed of retained mineral-associated volatiles or subsequent extraterrestrial delivery of volatile compounds. The late veneer hypothesis suggests that there was significant input of heavy elements after Earth had mostly formed and differentiated (which is compatible with the LHB model) and a significant inventory of reduced metals were delivered to Earth well after it formed. It has recently been suggested (Genda et al. 2017) that late input of large metallic bolides may resolve the paradox provided by zircon evidence that the upper mantle has been at or near the present oxidation state since approximately 4.3 Ga (Trail et al. 2011), but this might constrain a reducing atmosphere to well before the LHB.

 CH_4 , CO_2 , CO, N_2 , NH_3 , H_2O , and H_2 are the most abundant gas species in the Solar System, and this may have been true for early Earth as well, although it is the relative proportions of these that is of interest. It seems unlikely that Earth kept much of its earliest atmosphere during accretion, thus the primordial atmosphere would have been derived from outgassing of the planet's interior, which is thought to have occurred at temperatures between 300 and 1,500 °C. Modern volcanoes emit a wide range of gases. Most modern volcanic emissions contain CO_2 and SO_2 (oxidized species), rather than CH_4 and H_2S (reduced species, Table 1).

Location	CO ₂	CO	CH_4	$\rm NH_3$	H ₂	HCI	H_2S	SO ₂	H ₂ O
White Island, New Zealand	57.9	_	0.5	_	41.5	_	_	_	_
Nyerogongo Lava Lake, Congo	84.4	5.1	_	_	1.6	_	_	9.0	43.2
Mount Hekla, Iceland	23	3	—	—	16	52	_	6	_
Lipari Island, Italy	93.0	—	—	—	—	0.5	2.9	3.6	98.9
Larderello, Italy	92.7	-	0.92	1.72	1.76	—	—	2.45	—
Zavaritskii crater, Kamchatka	—	67	—	—	—	33	—	—	—
Same crater, B1	_	21	_	_	42	25	—	12	_
Unimak Island, Alaska	47	_	_	_	_	_	_	53	95

Table 1. Gases detected in modern volcanic emissions (adapted from Miller and Orgel 1974). Values for gases (except water) are given in volume percent. The value for water is its percentage of the total gas.

It seems likely that most of the gases released from Earth's interior today are produced from reactions of reworked crustal material and water, and do not represent components of Earth's deep interior. Thus modern volcanic gases may tell us little about early Earth's atmosphere.

The oxidation state of Earth's early mantle likely governed the distribution of gases released during early mantle outgassing. Holland (1962) proposed that Earth's atmosphere evolved through two stages, an early reduced stage before differentiation of the mantle, and a later neutral/oxidized stage after differentiation. During the first stage, the redox state of the mantle was governed by the Fe°/Fe²⁺ redox pair, also known as the iron-wustite (IW) buffer. The atmosphere in this stage would have been composed of H₂O, CO, and N₂ and approximately 0.27 to 2.7 × 10⁻⁵ atm of H₂. Once Fe° had segmented into the core, the redox state of magmas would have been controlled by the Fe²⁺/Fe³⁺ pair, also known as the fayalite–quartz-magnetite (FQM) buffer. Endogenous organic synthesis seems to depend, based on laboratory simulations, on the early atmosphere being generally reducing, which requires low O₂ levels in the primitive atmosphere.

Little is agreed upon about the composition of the early atmosphere, other than that it almost certainly contained little free O_2 . O_2 can be produced by the photodissociation of water: 2 $H_2O \rightarrow O_2 + 2 H_2$

Today this occurs at approximately the rate of 10^{-8} g cm⁻² yr⁻¹, which is rather slow, and it seems likely that the steady-state concentration of O₂ would have been low early in Earth's early history due to reaction with reduced metals such as Fe²⁺ in the crust and oceans.

Uranite (UO₂) and galena (PbS) deposits from 2 to 2.8 Ga testify to low atmospheric O_2 levels until relatively recently, since both of these species are easily oxidized. More evidence that O_2 is the result

of buildup from oxygenic photosynthesis and a relatively recent addition to the atmosphere comes from banded iron formations (BIFs). These are distributed around the world from approximately 1.8 to 2.2 Ma and contain extensive deposits of magnetite (Fe₃O₄), which may be considered a mixture of FeO and hematite (Fe₂O₃), interspersed with bands of hematite. Hematite requires a higher pO_2 to form.

On modern Earth, high O_2 levels allow for the photochemical formation of a significant amount of ozone. O_3 is the major shield of highly energetic UV light on the Earth's surface today. Even low O_2 levels may have created an effective ozone shield on early Earth (Canuto et al. 1983). The oceans could also have served as an important UV shield protecting the nascent organic chemicals (Cleaves and Miller 1998). It is important to note that while UV can be a significant source of energy for synthesizing organics, it is also a means of destroying them.

While the above discussion suggests that the early atmosphere was probably not oxidizing, it does not offer evidence that it was very reducing. It is generally accepted that free oxygen was absent from the Archean Earth's atmosphere, but there is no agreement as to the composition of the remainder of the atmosphere; opinions vary from strongly reducing $(CH_4 + N_2/NH_3 + H_2O)$, or $CO_2 + H_2 + N_2)$ to neutral $(CO_2 + N_2 + H_2O)$.

The modern atmosphere is not in thermodynamic equilibrium with respect to the biosphere, the oceans, or the continents, and it is unlikely it ever was. In the presence of large amounts of H_2 , the thermodynamically stable form of carbon is CH₄. In the absence of large amounts of H_2 , intermediate redox forms of carbon, such as formate and methanol, are still unstable with respect to CO₂. Even large sources of CO would have equilibrated with respect to CO₂ and CH₄ over short geological time spans. In the presence of large amounts of H_2 , NH₃ is the stable nitrogen species.

If a reducing atmosphere was required for terrestrial prebiotic organic synthesis, the question becomes what was the source of H₂. Miller and Orgel (1974) estimated the pH₂ as 10^{-4} to 10^{-2} atm. H₂ could have been supplied to the primitive atmosphere from various sources. For example, extensive weathering of Fe²⁺-bearing rocks, followed by photo-oxidation in water, could have generated significant amounts of H₂ (Mauzerall 1990).

The major sink for H_2 on the primitive Earth may have been Jeans escape, whereby gas molecules escape the Earth's gravitational field. The escape layer on Earth begins approximately 600 km above Earth's surface. Molecules must diffuse to this altitude prior to escape. The major conduits of H to the escape layer are CH_4 , H_2 , and H_2O , since H_2O and CH_4 can be photodissociated at this layer. Water is, however, frozen out at lower altitudes, and thus does not contribute significantly to this process.

The importance of the oxidation state of the atmosphere is linked to the production of HCN, which seems to be essential for the synthesis of amino acids and purine nucleobases, as well as cyanoacetylene for pyrimidine nucleobase synthesis (see below). In CH_4/N_2 atmospheres HCN is produced

abundantly (Chameides and Walker 1981, Stribling and Miller 1987), but in CO_2/N_2 atmospheres most of the N atoms produced by splitting N_2 recombine with O atoms to form NO.

The Early Oceans

pH is a measure of the amount of free hydrogen ions (H^+) or hydronium ions (H_3O^+) present in an aqueous solution, which describes how acidic (or basic) it is. pH and acidity strongly influence many chemical processes, and often determine whether a given environment is habitable by various types of organisms. The pH of the modern ocean (approximately pH 8.1, but slowly dropping due to recent increases in the amount of CO_2 in the atmosphere) is governed by the interplay of dissolved salts, atmospheric CO_2 levels, and clay mineral ion exchange processes. Briefly, atmospheric CO_2 dissolves in the oceans to give dissolved CO_2 , which reacts with water to give carbonic acid (H₂CO₃), which dissociates to give an aqueous mixture of bicarbonate (HCO_3) and carbonate (CO_3). The pH and concentrations of Ca²⁺, Mg²⁺, Na⁺, and K⁺ are maintained by equilibria with clays rather than by the bicarbonate buffer system. The bicarbonate concentration in the oceans is largely determined by the pH and Ca²⁺ concentrations. Limitations on paleo-pCO₂ can be derived from equilibrium considerations of clay species, which have been calculated to give a pCO₂ of 1.3 to 3×10^{-4} atm in the primitive atmosphere (Miller and Orgel 1974). For comparison, presently pCO_2 is about 4 x 10⁻⁴ atm. Clay buffering and pCO_2 have been suggested to thus leave the primitive oceans at pH approximately 8, which is coincidentally a favorable pH for many prebiotic reactions, and roughly the modern value (Halevy and Bachan 2018). The cytosol of most modern cells is maintained via complicated cellular processes near pH 8, suggesting that early cells may have evolved in an environment close to this value.

The Sun appears to be a typical G2 class star and is expected to have followed typical stellar evolution for its mass and spectral type. Consequently, the solar luminosity would have been approximately 30% less during the time period life is thought to have originated, and the UV flux would have been much higher (Canuto et al. 1983). A possible consequence of this is that the prebiotic Earth may have frozen completely to a depth of about 300 m (Bada et al. 1994). There is evidence for various completely frozen "Snowball Earth" periods later during Earth's history (Hoffman and Schrag 2002), as well as for liquid water on Archean Earth between 4.3 and 4.4 Ga (Wilde et al. 2001; Mojzsis et al. 2001), thus the jury is still out as to whether early Earth was hot or cold, or perhaps hosted a variety of regional climates or experienced wide fluctuations in climate.

The presence of liquid surface water would require that early Earth maintained a heat balance that offset the postulated 30% lower solar flux from the Faint Young Sun (FYS). Today, Earth's temperature seems to be maintained thermostatically by the so-called Berner-Lasaga-Garrels (BLAG) model (Berner et al. 1983). This model suggests that atmospheric CO_2 levels are maintained at a level that ensures moderate temperatures by controlling global weathering rates and thus the flux of silicates and carbonates through the crust-ocean interface. When CO_2 levels are high, the Earth is warmed by the greenhouse effect and weathering rates are increased, allowing a high inflow of Ca^{2+} and silicates to the oceans, which precipitates CO_2 as $CaCO_3$, and lowers the temperature. As the atmosphere cools, weathering slows, and the buildup of volcanically outgassed CO_2 again raises the temperature. On early Earth, however, before extensive recycling of the crust became common, large amounts of

 CO_2 may have been sequestered as $CaCO_3$ in sediments, and the environment may have been considerably colder.

Energy Sources on the Early Earth

Provided the early atmosphere was sufficiently reducing, energy would have been needed to dissociate atmospheric gases into radicals and other reactive intermediates capable of undergoing further reaction to form the building blocks of life.

The most abundant energy sources on Earth today are shown in Table 2. Energy fluxes from these sources may have been slightly different in the primitive environment. As mentioned earlier, the FYS would have provided a higher flux of UV radiation than the modern Sun. It is also likely that volcanic activity was higher than today, and energy from radioactive decay would have been more intense, especially from the decay of ⁴⁰K (Mosqueira et al. 1996), which is the probable source of the high concentrations of Ar in the modern atmosphere.

Shock waves from extraterrestrial impactors and thunder were also probably more common during the late stages of planetary accretion. Presently, large amounts of energy (though meager in comparison with the solar flux) are discharged atmospherically in the form of lightning; it is difficult to estimate the lightning flux early in Earth's history. The energy flux associated with the van Allen belts and static electricity discharges is also significant.

Some energy sources may have been more important for some synthetic reactions. For example, electric discharges are effective at producing HCN from CH_4 and NH_3 or N_2 , but UV radiation is not. Electric discharge reactions also occur near the Earth's surface (in the troposphere), while significant amounts of UV light are absorbed higher in the atmosphere. Any molecules created would have to be transported to the ocean and might be destroyed on the way. Thus transport rates must also be taken into account when considering the relative importance of various energy sources in prebiotic synthesis.

Source	Energy (cal cm ⁻² yr ⁻¹)	Energy (J cm ⁻² yr ⁻¹)
Total radiation from sun	260,000	1,090,000
Ultraviolet light < 300 nm	3400	14,000
Ultraviolet light < 250 nm	563	2360
Ultraviolet light < 200 nm	41	170
Ultraviolet light < 150 nm	1.7	7
Electric discharges	4.0 ^a	17
Cosmic rays	0.0015	0.006
Radioactivity (to 1.0 km)	0.8	3.0
Volcanoes	0.13	0.5
Shock waves	1.1 ^b	4.6

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Table 2. Energy sources on the modern Earth (adapted from Miller and Orgel 1974). a) 3 cal cm⁻² yr⁻¹ of corona discharge and 1 cal cm⁻² yr⁻¹ of lightning; (b) 1 cal cm⁻² yr⁻¹ of this is the shock wave of lightning bolts and is also included under electric discharges.

6. PREBIOTIC CHEMISTRY AND MODELS FOR THE ORIGINS OF LIFE

The accumulation and organization of organic material leading to the origin of life must have occurred sometime during the period between when Earth had cooled sufficiently after the Moon-forming impact and accepted evidence for life approximately 3.5 Ga ago. While some have attempted to define a reasonable time frame for biological organization based on the short time available (Lazcano and Miller 1994), the actual time required could be considerably longer or shorter (Orgel 1998). In any event, life would have had to originate in a relatively short period, and the synthesis and accumulation of the organic compounds for this event must have preceded it in even less time. The synthesis and survival of organic compounds on primitive Earth would have depended on the prevailing environmental conditions. To a large degree these conditions are poorly defined by geological evidence.

If the origin of life depends on the synthesis of organic compounds, then the source and nature of these is crucial. The origin of terrestrial prebiotic organic compounds may depend to some degree on the primordial atmospheric composition. This in turn is determined by the oxidation state of the early mantle, which depends on how the Earth formed. Discussions of each of these processes are compromised by the paucity of geological evidence remaining from the time period under discussion, and are therefore somewhat speculative. While a complete discussion of each of these processes is outside the scope of this review, they are crucial for understanding the uncertainty surrounding modern thinking regarding the origin of the prebiotic compounds thought by many to be necessary for the origin of life.

Life, Carbon, and Water

One might ask why the field of prebiotic chemistry has limited itself to aqueous reactions that produce reduced carbon compounds. Such studies are heavily biased by the nature of modern organisms: there is only one known example of a functioning biology, our own, and it is governed by the reactions of reduced carbon compounds in aqueous media. Might there be other types of chemistry that could support a functioning biology? Hydrogen is the most abundant element in the universe, having formed shortly after the Big Bang. Besides helium and small amounts of lithium, the synthesis of the heavier elements had to await later cycles of star formation and supernova explosions. Due to the abundance of oxygen and hydrogen in the early Solar System, most other atomic nuclei ended up as either their oxides or hydrides. Water, which can be considered as the hydride of oxygen or the oxide of hydrogen, is one of the most abundant compounds in the Universe. Life in a solid state of water would be difficult, as diffusion of metabolites would occur only very slowly. It is likewise improbable that life in water's gas phase would be able to support the stable associations required for the propagation of genetic information, and large molecules are generally non-volatile. According to this logic, life would need to exist in a liquid medium.

The question then becomes what solvent molecules are prevalent and able to exist in the liquid phase over the range of temperatures where reasonable reaction rates might proceed while at the same time preserving the integrity of the solute compounds. The high-temperature limit is set by the decomposition of chemical compounds, while the low temperature limit is determined by the reactivity of the solutes. Water has the largest liquid stability range of any known common molecular compound at atmospheric pressure, and the dielectric constant of water and its high heat capacity are uniquely conducive to many geochemical processes.

There are no other elements besides carbon that appear to be able to furnish the immense variety of chemical compounds that allow for a diverse biochemistry. Carbon combines with a large variety of other elements to generate stable heteroatomic bonds, as well as with itself to give a huge inventory of carbon-based molecules. In addition, carbon has the exceptional ability to form stable double-bonded structures with itself, which are necessary for generating fixed molecular shapes and planar molecules that appear to be necessary for molecular recognition. Most of the fundamental processes of life at the molecular level are based on molecular recognition, which depends on the ability of molecules to possess functional groups that allow for weak interactions such as hydrogen bonding and π -stacking. While silicon is immediately below carbon in the periodic table, its direct polymers are generally unstable, especially in water, and silicon is unable to form stable double bonds with itself.

Organisms presently use energy, principally sunlight, to transform environmental precursors such as CO_2 , H_2O , and N_2 into their constituents. While silicon is more prevalent in the Earth's crust than carbon, and both are generated copiously in stars, silicon is unable to support the same degree of molecular complexity as carbon. Silicates are in general less soluble in water than organic compounds, and silicon does not have an appreciably abundant gas phase form such as CH_4 or CO_2 , making a metabolism based on silicon likely more difficult for a nascent biology.

Sources of Organic Compounds

This section will briefly summarize historical and recent findings regarding the potential environmental sources of organic building blocks thought to be important for the origins of life on Earth. In addition to the background readings regarding historical perspectives suggested above, the interested reader is referred to several additional excellent texts that remain scientifically relevant (Miller and Orgel 1974; Schopf 1983).

Prebiotic chemistry attempts to not only produce organic compounds that could have been used to assemble the first living organisms, but also to explain the self-assembly of the first living organisms. For many researchers, the goal of prebiotic chemistry is the synthesis of a simple living system with some of the common attributes of modern cells, i.e., a lipid membrane, RNA and/or DNA, and small protein-like peptides.

The apparent ease of formation of bioorganic compounds under "plausible" prebiotic conditions¹⁵ as demonstrated by Miller suggested that organic compounds were present in the primitive terrestrial

¹⁵ What constitutes "plausibility" is often a matter of opinion among origins-of-life scientists, which is a considerable hindrance to consensus in this field.

environment. These models also suggested how these compounds could have been made mechanistically.

For the approximately 60 years since Miller's pioneering experiment, the synthesis of the components of modern cells has been the somewhat less ambitious goal. While the list of compounds that can be synthesized in the lab is impressive, not all modern cell constituents have been proven to be synthesizable under plausible prebiotic conditions, nor have all of them been found in meteorites. One possible explanation for this discrepancy is that some modern components are products of evolved biochemistry and were not added to the biochemical inventory until well after organisms had developed a considerable degree of complexity (Cleaves 2010).

Although we do not know which compounds were available or required for the origin of life, prebiotic chemists tend to focus on compounds that are present in modern biochemistry, ignoring the large fraction of compounds found in meteorites or produced in simulations that are not found in biology. A recent study of the Murchison CC using sophisticated analytical instruments revealed the presence of as many as 14 million distinct low-molecular-weight organic compounds (Schmitt-Kopplin et al. 2010). This can be contrasted with the approximately 1,500 common metabolites found in contemporary cells (Morowitz 1979) and the 600 or so small molecules positively identified in the Murchison meteorite to date (Table 2).

In addition to synthesis in the Earth's primordial atmosphere and oceans, it is likely that the infall of comets, meteorites, and interplanetary dust particles, as well as submarine hydrothermal vent synthesis, may have contributed to prebiotic organic evolution. The primordial organic soup may have been quite complex, but it did not likely include all the compounds found in modern organisms. Regardless of their origin, organic compounds would need to be concentrated and complexified by environmental mechanisms. While this review is by no means exhaustive, many of the issues central to the state of the art of prebiotic chemistry are reviewed here.

"Prebiotic chemistry" can be understood to mean several things: chemistry that occurred before life began or the chemistry that led to life on Earth or other planets. Scientists in this field practically define it as naturally occurring chemistry in planetary environments that may contribute to the origin of life on planets such as Earth. The terms "abiotic chemistry" (chemistry that takes place in the absence of biology) and "prebiotic chemistry" are in some senses synonymous, but it is recognized that there is chemistry that occurs on Earth today that is not biologically mediated, and this chemistry need not be involved in generating life *de novo*. It is generally assumed that the Universe is not goal directed, and since it is not known what processes led to the origin of life, the study of prebiotic chemistry almost certainly includes chemical processes with little direct relevance to the origins of life.

This section covers the synthesis of small organic compounds; however, it should be borne in mind that major uncertainties still surround how these compounds self-organize into self-replicating systems.

As it is widely believed that life requires an aqueous environment, and it is a cornerstone of many ideas regarding the origins of Earth's early organics that the early atmosphere was reducing, it is worth discussing the origin of Earth's oceans, atmosphere, and crust, how they interact dynamically over geological time scales, and the effects of these interactions affect their ability to influence the production of organic compounds. During Earth's early differentiation, when siderophile and lithophile¹⁶ elements were distinctively partitioned, the migration of significant amounts of reduced iron to the Earth's core and mantle took with it a great deal of the planet's reducing equivalents. Much of the lighter material, including elements such as C, N, and H, migrated toward the surface, with the oxidation state of these elements determined by the equilibration conditions they were exposed to during migration.

Whether Earth's early atmosphere was ever reducing remains contentious (Tian et al. 2005), but it seems unlikely that it was for long. This matters because gas-phase abiotic synthesis of organic compounds depends on the redox states of the gases involved (Figure 13).

Figure 13. Amino acid yields from electric discharge experiments conducted using different initial oxidation state gas mixtures. The efficiency of such syntheses depends markedly on the ratio of H/O, with more H-rich mixtures being orders of magnitude more productive than more O-rich ones. Adapted from Stribling and Miller (1987).

In the absence of a significant source of molecular hydrogen, N_2/CO_2 -dominated atmospheres may be the most stable, especially in the absence of biology. The O_2 in the present atmosphere is almost entirely generated from biological photosynthesis. In the absence of biology, the lifetime of O_2 would be extremely short due to its reaction with elements such as iron in the crust (for example, 1.5 O_2 +2

¹⁶ Geologists often use the Goldschmidt classification to define four major types of elements among the periodic table, siderophile, chalcophile, lithophile, and atmophile elements. Siderophile elements tend to partition into metal phases in melts, chalcophile elements tend to form compounds with sulfur, lithophile elements tend to combine with oxygen, and atmophile elements tend to form gases which segregate into the atmosphere.

 $Fe^{2+} \rightarrow Fe_2O_3$). A consequence of the lack of O_2 in the early atmosphere is that there would have also been little UV-absorbing ozone (O₃), which would have allowed highly energetic bond-breaking UV radiation to reach the Earth's surface (Cleaves and Miller 1998), which was likely exacerbated by the likely fact that the early Sun produced a far larger amount of radiation in the UV region and energetic particles (Kasting and Siefert 2002) than at present (see discussion of T Tauri stars above) and that Earth's magnetosphere-generating geodynamo may not have been entirely active early in Earth history.

The oxidation state of the early mantle likely governed the distribution of outgassed species. Holland (1962) proposed, based on the idea of Earth accreting homogenously and cold that Earth's atmosphere went through two stages: an early reduced stage before differentiation of the mantle and a later neutral/oxidized stage after differentiation. During the first stage, the redox state of the mantle was governed by the Fe°/Fe²⁺ redox pair. The atmosphere in this stage would be composed of H₂O, H₂, CO, and N₂, with approximately 0.27 to 2.7×10^{-5} atmospheres of H₂.

Once Fe° segregated into the core, the redox state of magmas would have been controlled by the Fe^{2+}/Fe^{3+} pair or fayalite-magnetite-quartz buffer. If the core differentiated rapidly (via rapid sinking of Fe° into Earth's interior), the early atmosphere likely resembled the composition of modern volcanic gases (Rubey 1951). Rubey estimated that a CH₄-dominated atmosphere could not have persisted for more than 0.1 to 100 Ma due to photolysis. The Urey/Oparin atmosphere (CH₄, NH₃, H₂O) model is thus based on astrophysical and cosmochemical constraints, while Rubey's model is based on extrapolation of the geological record. It should be noted that 0.1 to 100 Ma is still an enormous amount of time in terms of organic chemical reactions,¹⁷ and it is unknown how long it takes to go from planet formation or organic formation to living systems.

Modern thinking on the origin and evolution of the Solar System, Earth, and its atmosphere and oceans has not been shaped largely with the origin of life in mind. Rather, current origin-of-life theories are usually modified to fit evolving geochemical models. Light atmospheric gases such as H₂ would have been prone to rapid escape to space due to their low escape velocities, while others such as NH₃ are expected to be rapidly atmospherically decomposed by UV photolysis (Ferris and Nicodem 1972; Kuhn and Atreya 1979). Nevertheless, low levels of these compounds could have been maintained at steady state, and significant amounts of NH₃ could have dissolved in the oceans if the pH of the early oceans was lower than the pK_a of NH₃ (approximately 9.2 at 25°C) (Bada and Miller 1968). Indeed, recent estimates support the idea of an early oceanic pH well below this value (Halevy and Bachan 2017).

If a reducing atmosphere was required for terrestrial prebiotic organic synthesis, the crucial question is the source of H₂. Miller and Orgel (1974) estimated the pH₂ as 10^{-4} to 10^{-2} atmospheres, depending

¹⁷ Bibliometric analysis of chemical databases curated since 1771 show that some 97% of studied reactions were conducted over periods of 48 hours or less (Keseru et al. 2014), thus reactions beyond this time scale are very poorly surveyed.

on the various sources and sinks. H₂ could have been supplied to the primitive atmosphere by several sources (Tian et al. 2005), and it is unclear what would have governed this balance. The oxidation state of the atmosphere is important for the production of HCN, an important reactant in the prebiotic synthesis of purines and amino acids (see below). In CH₄/N₂ atmospheres, HCN is produced abundantly (Chameides and Walker 1981; Stribling and Miller 1987), but in CO_2/N_2 atmospheres, most of the N atoms produced by splitting N₂ recombine with O atoms to form NOx species (Chameides and Walker 1981). Although reduced gas mixtures are generally more conducive to organic synthesis than oxidizing or neutral gas mixtures, even mildly reducing gas mixtures produce large amounts of organic compounds, and it seems likely that energy was not the limiting factor (Stribling and Miller 1987).

Extraterrestrial Sources of Organics

Regardless of what the early Earth's atmosphere was like, the planet was undoubtedly bombarded then, as it is now, by extraterrestrial material such as meteorites and comets. The presence of extraterrestrial organic compounds had been recognized since the mid-19th century, when Berzelius analyzed the Aläis meteorite, a carbonaceous C1 chondrite, and confirmed a few years later when Wöhler studied the Kaba meteorite, a C2 carbonaceous chondrite. Today the presence of a complex array of extraterrestrial organic molecules in meteorites, comets, interplanetary dust, and interstellar molecules is firmly established, and has led some to propose them as exogenous sources of prebiotic organic compounds for the origin of life (Oró 1961; Anders 1989; Chyba 1990; Chyba and Sagan 1992). One reason for proposing an extraterrestrial origin of the components of the prebiotic soup is the CO₂-rich model of the primitive Earth's atmosphere (Kasting 1993), which would not be as conducive to atmospheric organic synthesis.

The Apollo missions revealed few if any organic materials on the Moon; however, doubts as to the occurrence of organic materials in the Solar System were laid to rest in 1969 when a meteorite fell in Murchison, Australia. This meteorite was seen to fall and was rapidly collected, thus minimizing field contamination, and analyzed in the laboratory.

A host of organic compounds was revealed to be present that were indubitably of extraterrestrial origin. These organics strongly resemble those produced in laboratory syntheses under presumed prebiotic conditions (Wolman et al. 1972, Table 5). Questions remain regarding the survival of the organic material from extraterrestrial bodies, although obviously those in the Murchison meteorite did survive. There is also an abundance of extraterrestrial amino acids in the geological record associated with the 65-million-year-old impact event, implicated in the decline of the dinosaurs (Zhao and Bada 1989).

Chyba and Sagan (1992) estimated the flux of extraterrestrial organics to the Earth based on the lunar cratering record. They then extrapolated an organic content and a yield based on the survival of these organics during entry, and estimated that extraterrestrial delivery would have made a significant contribution to the primitive Earth's organic inventory. Survival of extraterrestrial organic material would have been higher if the Earth's atmosphere were denser. The estimated flux of HCN equivalents compared with that estimated to be produced in a reducing atmosphere is shown in Figure 15. Thus

even if the early Earth's atmosphere were oxidizing or neutral, the case can be made that significant amounts of prebiotic organic compounds resembling the types made in terrestrial atmospheric synthesis would have been delivered to the Earth (Chyba and Sagan 1992; Thomas et al. 1996).

The compositions of some of these objects are discussed briefly below.

Comets

Comets are mixtures of dust and ice that accreted early in the history of the Solar System (Festou et al. 2004). In addition to water ice and various inorganic components, the volatile organic components of several comets have been measured spectroscopically (Ehrenfreund and Charnley 2000). Reactive organic compounds such as hydrogen cyanide (HCN) and formaldehyde (HCHO), among others, although variable from comet to comet, are often observed in high abundance (Table 3).

Compound	Abundance
H ₂ O	100
CO	23
CO ₂	6
CH ₃ OH	2.4
H ₂ CO	1.1
NH ₃	0.7
CH ₄	0.6
HCN	0.25
HCONH ₂	0.02
CH ₃ CHO	0.02

Table 3. The abundance of small molecules relative to water in comet Hale–Bopp as measured spectroscopically. Adapted from Bockelée-Morvan et al. (2000).

Measurement of the H isotope ratios of cometary water suggests that some of the Earth's oceans may derive from comets (Chyba 1990; Meier et al. 1998). If true, comets would also have delivered significant amounts of organics, although the survival of these would depend on the nature of the delivery process (Oró 1961; Oró et al. 1980). Assuming cometary nuclei have a density of 1 g cm⁻³, a 1-km-diameter comet would contain 2×10^{11} moles of HCN, or an amount sufficient to provide 40 nanomoles cm⁻² of the Earth's surface. This is comparable to the yearly production of HCN in a reducing atmosphere from electric discharges and would be important if the Earth did not have a reducing atmosphere, assuming complete survival of the HCN on impact.

While comets are extremely cold, it appears that some aqueous-phase organic reactions have occurred in them, as evidenced by the detection of the simplest amino acid, glycine, in particles returned from comets (Elsila et al. 2009); thus comets could have delivered more complex compounds as well.

Meteorites

Meteorites represent generally less volatile remnants of the early Solar System, i.e., objects that formed closer to the Sun and underwent more significant thermal processing (Lauretta and McSween 2006). Their compositions range from metallic to stony. The latter category includes a class with which prebiotic chemists are particularly fascinated, the carbonaceous chondrites (CCs), which contain a significant organic component, usually 1% to 2% by mass (Alexander et al. 2007). Besides a few recovered cometary grains, CCs remain the best-studied bona fide examples of "prebiotic chemistry," represented by several hundred exemplars in various curated collections. CC organic material is variable in composition, but typically 70% to 99% is a complex high-molecular-weight kerogen-like material, with the remainder being small soluble organic compounds (Pizzarello et al. 2006). A variety of organic compounds have been identified in CCs, including many also found in modern biochemistry (Pizzarello et al. 2006). That these compounds are indigenous to the meteorites, and not terrestrial contamination, is supported by their unusual isotopic ratios, the presence of types of compounds not found in biochemistry, and because compounds with stereocenters are found in nearly equal quantities with respect to their optical isomers, with some notable exceptions (Glavin and Dworkin 2009). A condensed summary of the types and relative abundances of compounds identified to date is shown in Table 4.

Class	Concentration (parts per million)	Compounds identified
Aliphatic hydrocarbons	>35	140
Aromatic hydrocarbons	22	87
Polar hydrocarbons	<120	10
Carboxylic acids	>300	48
Amino acids	60	74
Hydroxy acids	15	38
Dicarboxylic acids	>30	44
Dicarboximides	>50	2
Pyridine carboxylic acids	>7	7
Sulfonic acids	67	4
Phosphonic acids	2	4
N-Heterocycles	7	31
Amines	13	20
Amides	Nd	27
Polyols	30	19
Imino acids	nd	10
Total	778	565

Table 4. Organic compounds detected in the Murchison carbonaceous chondrite. Adapted from (Pizzarello et al 2006).

Furthermore, there is a distinct similarity between the amino acids detected in carbonaceous meteorites and those detected in MU experiments (Table 5), suggesting there may be a general similarity between the two in terms of their mode of generation.

Amino acid	Murchison	Electric discharge
Glycine	****	****
Alanine	****	***
α -Amino- <i>n</i> -butyric acid	***	***
α -Aminoisobutyric acid	****	**
Valine	***	**
Norvaline	***	***
Isovaline	**	**
Proline	***	*
Pipecolic acid	*	<*
Aspartic acid	***	***
Glutamic acid	***	**
β -Alanine	**	**
β -Amino- <i>n</i> -butyric acid	*	*
β -Aminoisobutyric acid	*	*
γ-Aminobutyric acid	*	**
Sarcosine	**	***
N-Ethylglycine	**	***
N-Methylalanine	**	**

It should be noted that a less targeted re-examination of the Murchison meteorite using high-resolution Fourier-Transform Ion Cyclotron Resonance Mass Spectrometry (FT-ICR-MS) has revealed an enormous molecular diversity, and in fact it is likely that >99% of the small organic molecule inventory of carbonaceous meteorites may be unaccounted for, and thus scientists may be overestimating such meteorites as efficient sources of biomolecules for prebiotic chemistry (Figure 14).

Figure 14. Left, a sample of the Murchison meteorite. Right, FT-ICR-MS spectrum of a methanol extract of the Murchison meteorite (Schmitt-Kopplin et al. 2010), showing the enormous diversity of intermediate weight organic compounds present.

Interstellar Dust Particles

Exogenous organic input from interstellar dust particles (IDPs) may have been more important than that of comets or meteorites. Their present infall rate is large (approximately 100,000 kg per day, though only a fraction of this is organic), and it may have been greater by a factor of 100 to 1,000 on primitive Earth (Love and Brownlee 1993). The organic composition of IDPs is poorly understood (Maurette 1998); the only molecules that have been identified to date are polycyclic aromatic hydrocarbons and α-aminoisobutyric acid (Gibson 1992; Clemett et al. 1993). Heterogeneous organic polymers loosely termed tholins (also produced by electric discharges, ionizing radiation, and UV light) could be major components of IDPs. Amino acids are released from tholins on acid hydrolysis (Khare et al. 1986; Cleaves et al. 2014); tholins could thus also be a source of organics. On entry to Earth's atmosphere, IDPs could be heated and their tholins pyrolyzed, creating HCN and other molecules, which could then participate in terrestrial reactions (Mukhin et al. 1989; Chyba et al. 1990).

Comparison of Terrestrial and Extraterrestrial Organic Sources

As models for the origin of life based on environmentally pre-synthesized organics depend on those organics' abundance (as well as their type), it has been of interest to explore the consequences of the Earth being a poor source of them. Models exploring this suggest extraterrestrial input can compensate for a poorly reducing upper mantle and early atmosphere (Figure 15).

Figure 15. Estimated inputs of HCN from various energy sources and organic compounds from comets. The cometary inputs are from Chyba and Sagan (1992). The area is shaded because of the uncertainty of the fall-off of dust input on the early Earth. The cometary input has been converted to nmoles cm⁻² yr⁻¹ assuming a molecular weight of 100. The HCN production rate is discussed in Stribling and Miller (1987).

6.1 Prebiotic Syntheses of Biochemicals

The top-down approach to origins of life operates on the premise that the earliest organisms were composed of the same, or similar, biochemicals as modern organisms. Here we consider modern biomolecules and experimental results demonstrating how these may have come to be synthesized on primitive Earth via plausible geochemical processes.

Amino Acids

It is unlikely that all the modern amino acids were present in the primitive environment, and it is unknown which, if any, would have been important for the origin of life. The first successful prebiotic amino acid synthesis was carried out with an electric discharge (see Figures 6 and 16) and a strongly reducing model atmosphere of CH₄, NH₃, H₂O, and H₂ (Miller 1953).

Figure 16. The apparatus used in the first electric discharge synthesis of amino acids and other organic compounds in a reducing atmosphere. It was made entirely of glass, except for the tungsten electrodes (Miller 1953).

The result of this experiment was a large yield of racemic amino acids, together with hydroxy acids, short aliphatic acids, and urea (Table 5).

Compound	Yield (µmoles)	Yield (%)
Glycine	630	2.1
Glycolic acid	560	1.9
Sarcosine	50	0.25
Alanine	340	1.7
Lactic acid	310	1.6
N-Methylalanine	10	0.07
α-Amino- <i>n</i> -butyric acid	50	0.34
α -Aminoisobutyric acid	1	0.007
α -Hydroxybutyric acid	50	0.34
β -Alanine	150	0.76
Succinic acid	4	0.27
Aspartic acid	4	0.024
Glutamic acid	6	0.051
Iminodiacetic acid	55	0.37
Iminoaceticpropionic acid	15	0.13
Formic acid	2330	4.0
Acetic acid	150	0.51
Propionic acid	130	0.66
Urea	20	0.034
N-Methyl urea	15	0.051

Table 5.	. Yields of sm	all organic	molecules fro	m sparking	a mixture	of methane	e, hydrogen,	ammonia,	and	water	yields
given bas	ed on input ca	arbon in th	e form of met	hane). Adap	ted from M	filler (1955).				

A variety of prebiotic processes can form amino acids, for example, Miller-Urey (MU)-type electric discharge experiments (Miller 1953) and reactions of HCN in water (Ferris et al. 1974), among others, and amino acids are found in a variety of carbonaceous chondrites (CCs) (Martins et al. 2007). One of the likely principal mechanisms of formation of amino acids in these samples is the Strecker synthesis (Figure 17A), named for Adolf Strecker, a 19th century chemist who was the first to artificially synthesize an amino acid. Evidence for this mechanism in MU experiments comes from measurements of the concentrations of HCN, aldehydes, and ketones in the water flask produced during the course of the reaction (Figure 17B), which are derived from the CH₄, NH₃, and H₂ originally introduced into the apparatus. This suggests that amino acids are not formed directly in the electric discharge but are the result of synthesize involving aqueous-phase reactions (Miller 1955). Both amino and hydroxy acids can be synthesized at high dilutions of HCN and aldehydes in a simulated primitive ocean (Miller 1957). Reaction rates depend on temperature, pH, and HCN, NH₃, and aldehyde concentrations but are rapid on geologic time scales. The half-lives for the hydrolysis of the amino- and hydroxy-nitrile intermediates (the rate-limiting steps in these reactions) are less than 1,000 years at 0°C (Miller 1998).

Figure 17. A. The Strecker and cyanohydrin mechanisms for the formation of amino and hydroxy acids from NH₃, aldehydes and ketones, and HCN. B. Time course for production of NH₃, aldehydes and ketones, HCN, and amino acids during the course of a reducing electric discharge experiment. Adapted from (Miller 1957).

Corroborating this notion of rapid synthesis, the amino acids found in the Murchison meteorite were apparently formed in less than 10⁵ years (Peltzer et al. 1984). The Strecker amino acid synthesis requires the presence of NH₃. As mentioned above, gaseous NH₃ is rapidly decomposed by UV light, and during Archean times, the absence of a significant ozone layer would have limited the atmospheric concentration of NH₃. However, NH₃ is extremely water soluble and similar in size to K⁺, thus, it easily enters exchange sites on clays. A considerable amount of NH₃ may have been dissolved or adsorbed on submerged mineral surfaces.

Spark discharge experiments using CH₄, CO, or CO₂ as a carbon source with various amounts of H₂ show that methane is the best source of amino acids, but CO and CO₂ are almost as good if a high H/C ratio is used. Without added H₂, amino acid yields are quite low, especially when CO₂ is the sole carbon source (see Figure 13). Recent results, however, suggest that amino acid yields from neutral atmospheres may be higher than previously thought. Buffering reaction pH near neutral (as dissolution of gaseous CO₂ tends to lower the pH) and adding oxidation inhibitors (which may counteract the oxidative effects of NO_x species generated in the reaction) increased the amino acid yields from $CO_2/N_2/H_2O$ electric discharge reactions several fold (Cleaves et al. 2008). Alternatively, amino acids can be synthesized from the reaction of urea, HCN, and an aldehyde or a ketone (the Bucherer–Bergs synthesis). This reaction pathway may have been significant if little free ammonia were available.

A wide variety of direct sources of energy must have been available on primitive Earth (Table 2). It is likely that in the prebiotic environment, solar radiation, and not atmospheric electricity, was the major source of energy reaching Earth's surface. However, it is unlikely that any single one of the energy sources listed in Table 2 can account for all organic compound syntheses. The importance of a given energy source in prebiotic evolution is determined by the product of the energy available and its efficiency in generating organic compounds. Given our current ignorance of the prebiotic environment, it is impossible to make absolute assessments of the relative significance of these different energy sources.

For instance, neither the pyrolysis (800 to 1200° C) of a CH₄/NH₃ mixture or the action of UV light acting on a strongly reducing atmosphere give good yields of amino acids. However, the pyrolysis of methane, ethane, and other hydrocarbons gives good yields of phenylacetylene, which upon hydration yields phenylacetaldehyde. The latter could then participate in a Strecker synthesis and act as a precursor to the amino acids phenylalanine and tyrosine in the prebiotic ocean. The available evidence suggests that electric discharges were the most important source of HCN, which is recognized as an important intermediate in prebiotic synthesis. However, the hot H atom mechanism suggested by Zahnle (1986) could also have been significant.

In addition to its central role in the formation of amino nitriles during the Strecker synthesis, HCN polymers have been shown to be a source of amino acids. Ferris et al. (Ferris et al. 1978) have demonstrated that, in addition to urea, guanidine, and oxalic acid, hydrolysis of HCN polymers produces glycine, alanine, and aspartic acid, though the yields are not particularly high except for glycine (approximately 1%).

It should be noted that organic compounds often also display stereoisomerism, a form of isomerism in which molecules have the same molecular formula and atom connectivity, but that differ in the threedimensional orientations of their atoms in space. Most of the 20 coded biological amino acids can occur in two stereoisomeric forms, and modern organisms almost exclusively construct their proteins from amino acids of the L enantiomer. In contrast the amino acids produced by prebiotic syntheses are often racemic.

Lipids and Membrane-Forming Compounds

All modern life is cellular. Eukaryotic and bacterial cell membranes are composed of largely straightchain fatty acid acyl glycerols while those of the Archaea are composed of isoprenoid glycerol ethers (Ourisson and Nakatani 1994) (Figure 18a, b). Either type could logically have been the primordial lipid component of cells, given uncertainties in rooting the Tree of Life.

Long-chain fatty acids and their derivatives spontaneously form vesicles and micelles under appropriate conditions, and these can transiently trap various organic species and maintain proton gradients (Deamer et al. 2002). Most prebiotic simulations don't generate large amounts of fatty acids (Allen and Ponnamperuma 1967), with the exception of some hydrothermal vent simulations (McCollom et al. 1999). Heating glycerol with fatty acids and urea produces acylglycerols (Hargreaves et al. 1977). A prebiotic synthesis of long-chain isoprenoids lipids has been suggested based on the Prins reaction of formaldehyde with isobutene (Ourisson and Nakatani 1994); thus, there are plausible prebiotic routes to these types of compounds. The Murchison CC contains small amounts of fatty acids, though some of these may be contamination (Yuen and Kvenvolden 1973). Other amphiphilic components have been observed in the Murchison meteorite and in various laboratory simulations of prebiotic chemistry (Dworkin et al. 2001) (Figure 17c), although the composition of these remains undetermined.

Figure 18. Ether (a) and ester (b) lipids of biological membranes (R can be various small molecule constituents including phosphate). (c) Micrograph of cell-like boundary structures formed spontaneously from organic extracts of the Murchison meteorite. Fig. 5c image courtesy of NASA.

Nucleic Acids and Their Components

Modern organisms store their genetic information in DNA and transcribe it into RNA. The difference between these molecules is the use of deoxyribose and thymine in DNA and ribose and uracil in RNA. Although some now doubt that RNA itself is prebiotic, numerous laboratory experiments have shown pathways for its components.

Nucleosides and Nucleotides

RNA is composed of a long chain of building blocks known as nucleotides. Nucleotides, in turn, are made up of a nucleoside and a phosphate group. The earliest attempts to produce nucleosides prebiotically involved simply heating purines or pyrimidines in the dry state with ribose, which gives a few percent yield of mixed nucleoside isomers (Fuller et al. 1972). Direct heating of ribose and U or C has thus far failed to produce uridine or cytidine. Pyrimidine nucleoside syntheses have been demonstrated that start from ribose, cyanamide, and cyanoacetylene; however, α -D-cytidine is the major product (Sanchez and Orgel 1970). This can be photo-anomerized to β -D-cytidine in low yield. Sutherland and coworkers (Ingar et al. 2003) demonstrated that cytidine-3'-phosphate can be prepared from arabinose- 3-phosphate, cyanamide, and HCCCN in a one-pot reaction.

More recently, reactions using more complex reagents added in precise orders, with the products isolated and carried through to the next step, have been shown to produce significant yields of ribotides (Powner et al. 2007). These reactions give good yields of the pyrimidine ribotides (Powner and Sutherland 2008), and a related series of reactions could produce the purine ribotides (Powner et al. 2010) (Figure 22).

Figure 22. Some recent multi-step prebiotic syntheses of the biological nucleosides and nucleotides.

It is not clear that these syntheses solve previously raised objections to the plausibility of prebiotic nucleoside and nucleotide synthesis (Shapiro 1984). Prebiotic phosphorylation of nucleosides has also been demonstrated (Schwartz 1969; Rabinowitz and Hampai 1978; Yamagata et al. 1991), but again with caveats. Small amounts of condensed phosphates are emitted in volcanic fumaroles (Yamagata et al. 1991), and heating orthophosphate at relatively low temperatures in the presence of ammonia results in a high yield of condensed phosphates (Osterberg and Orgel 1972).

However, it has also been suggested that condensed phosphates are not likely to be prebiotically abundant materials (Keefe and Miller 1995). Early attempts to produce nucleotides using organic condensing agents (Lohrmann and Orgel 1968) were generally inefficient, but nucleosides can be phosphorylated with acidic phosphates when dry heated (Beck et al. 1967).

Nucleosides can also be phosphorylated in high yield by heating ammonium phosphate with urea at moderate temperatures, as might occur in a drying lagoon (Lohrmann and Orgel 1971). Heating uridine with urea and ammonium phosphate gave yields of nucleotides as high as 70%, however, the reaction with purine nucleosides also leads to considerable glycosidic cleavage. Thus, another problem with the "prebiotic" RNA world is that the synthesis of purine nucleosides is somewhat robust, but nucleotide formation may be difficult, while nucleotide formation from pyrimidine nucleosides is robust, but nucleoside formation may be difficult.

Common calcium phosphate minerals such as apatite are themselves reasonable phosphorylating reagents (Lohrmann and Orgel 1971). Heating ammonium phosphates with urea leads to a mixture of high-molecular-weight polyphosphates (Osterberg and Orgel 1972).

The difficulties with prebiotic ribose synthesis and nucleoside formation have led some to speculate that perhaps a simpler genetic molecule with a more robust prebiotic synthesis preceded RNA (Joyce et al. 1987). Substituting sugars besides ribose has been proposed (Eschenmoser 2004). Oligomers of some of these also form stable base-paired structures with both RNA/DNA and themselves, opening the possibility of genetic takeover from a precursor polymer to RNA/DNA. Such molecules may suffer from the same drawbacks as RNA with respect to prebiotic chemistry, such as the difficulty of selective sugar synthesis, sugar instability, and the difficulty of nucleoside formation. It has been demonstrated that backbones based on acyclic nucleoside analogs may be more easily obtained under reasonable prebiotic conditions, for example, by the reaction of nucleobases with various small prebiotic compounds (Cleaves 2002; Rodriguez et al. 2019; Teichert et al. 2019).

More exotic alternatives to nucleosides have been proposed, for example, peptide nucleic acid (PNA) analogs (Nielsen et al. 1994). Miller and coworkers demonstrated the prebiotic synthesis of the components of PNA under the same chemical conditions required for the synthesis of the purines or pyrimidines (Nelson et al. 2000). Most possible alternative structures have not been investigated with respect to prebiotic plausibility (Cleaves et al. 2019).

Purines

Now that we have explored the synthesis of nucleotides and nucleosides, let's consider two of their constituent parts: purines and pyrimidines. The first evidence that purines could be synthesized abiotically was provided when Oró and Kimball (1961) reported the formation of adenine (formally a pentamer of HCN, $C_5H_5N_5$) from concentrated solutions of NH₄CN refluxed for a few days. It is surprising that a synthesis requiring at least five steps (see Figure 19) should produce such high yields of adenine. Other purines, including guanine, can be produced by variations of this synthesis (Sanchez et al. 1967, 1968). The mechanisms shown in Figure 19 are likely an oversimplification, and synthesis may also involve the formation and rearrangement of other precursors (Voet and Schwartz 1983).

The steady-state concentration of HCN in primitive terrestrial waters would have depended on the pH and temperature of the oceans and the input rate of HCN from atmospheric synthesis. Even assuming favorable HCN production rates, steady-state concentrations of HCN in the primitive oceans would likely have been very low (Miyakawa et al. 2002). In this case, mechanisms for concentrating HCN would have been required. One way this could have occurred is in ice brines, in eutectic solutions of HCN–H₂O, which would require that some regions of the Earth froze from time to time. High yields of DAMN are obtained by freezing dilute HCN solutions to -10 to -30° C for a few months (Sanchez et al. 1966a, b), and various purines including adenine and guanine are also made during freezing (Levy et al. 1999, 2000). Production of adenine in HCN polymerizations is accelerated by the presence of aldehydes, and thus heterogeneous chemical mixtures may have still allowed for this type of synthesis (Schwartz and Goverde 1982).

In addition to producing the biological purines, HCN oligomerization also produces non-biological purines such as 2,6-diamino- and dioxopurines. This same suite of purines has been identified in CCs (Callahan et al. 2011), making a compelling case that similar mechanisms are responsible for their syntheses in CCs. Formamide (HCONH₂), the hydrolysis product of HCN, has also been shown to produce purines, albeit under more extreme conditions (Bredereck et al. 1961; Saladino et al. 2007).

Figure 19. Mechanisms of formation of DAMN, AICN, AICA, and purines from HCN.

Pyrimidines

The first "prebiotic" synthesis of pyrimidines investigated was that of uracil (U) from malic acid and urea (Fox and Harada 1961). The prebiotic synthesis of cytosine (C) from cyanoacetylene (HCCCN) and cyanate (NCO⁻) was later described (Sanchez et al. 1966a, b; Ferris et al. 1968) (Figure 20). The reaction of dilute cyanoacetaldehyde (CAA, produced from the hydrolysis of HCCCN) with urea or guanidine in laboratory simulations of drying beaches gives large yields of pyrimidines (Robertson 1995, Robertson et al. 1996).

A reaction producing the biological pyrimidines via freezing has also been demonstrated (Cleaves et al. 2006). U and its biosynthetic precursor orotic acid were also identified as products of HCN polymer (Ferris et al. 1978; Voet and Schwartz 1982), and U has been identified in carbonaceous meteorites (Stoks and Schwartz 1979).

Figure 20. Suggested prebiotic syntheses of the pyrimidines used in RNA, starting from cyanoacetylene.

Sugars

Many biological sugars have the empirical formula $(CH_2O)_n$, a point underscored by the discovery of the formose reaction, in which sugars can be formed by the reaction of formaldehyde (which has the formula CH_2O) under basic conditions (Butlerow 1861). The Butlerov synthesis is complex and incompletely understood. It depends on the presence of catalysts such as $Ca(OH)_2$. In the absence of base catalysts, little or no sugar is obtained. Clays such as kaolin catalyze the formation of sugars, including ribose, in small yields from dilute (0.01 M) HCHO solutions (Gabel and Ponnamperuma 1967; Reid and Orgel 1967; Schwartz and Degraaf 1993). The formose reaction is autocatalytic and proceeds through glycoaldehyde, glyceraldehyde, and dihydroxyacetone. The reaction is also catalyzed by glycolaldehyde, acetaldehyde, and various other organic catalysts (Matsumoto et al. 1984). A simplified schematic for the reaction is shown in Figure 21.

Figure 21. A simplified scheme of the formose reaction.

The reaction tends to stop when the formaldehyde has been consumed. The reaction produces all of the epimers and isomers of the small C2–C6 sugars, some of the C7 ones, and various branched sugars, as well as polyols such as glycerol and pentaerythritol, and is generally not particularly selective, although methods of overcoming this have been investigated. Of special interest is the observation that borate, which occurs widely in evaporitic environments, can skew the product mixture in favor of certain sugars, including ribose, and the borate adducts are more stable than the free sugars (Prieur 2001; Ricardo et al. 2004). Inclusion of acetaldehyde in the reaction produces deoxyribose (Oró 1965). Problems with the formose reaction as a source of sugars on the primitive Earth have been noted. One is the complexity of the product mixture.

More than 40 different sugars were identified in one reaction mixture (Decker et al. 1982). Another problem is that the conditions of synthesis are also conducive to the degradation of sugars (Reid and Orgel 1967). Sugars undergo various reactions on short geological time scales that are seemingly prohibitive to their accumulation in the environment (Larralde et al. 1995). Additionally, when aqueous solutions of HCN and HCHO are mixed, the major product is glycolonitrile (Schlesinger and Miller 1973), which could preclude the formation of sugars and purines in the same location (Arrhenius et al. 1994). Nevertheless, both sugar derivatives and nucleic acid bases have been found in the Murchison meteorite (Cooper et al. 2001; Callahan et al. 2011), and it seems likely that the chemistry that produced the compounds found in the Murchison meteorite was from aqueous reactions of simple species such as HCN and HCHO. This suggests that the synthesis of sugars, amino acids, and purines from HCHO and HCN may co-occur under certain conditions. More recently, it has been found that sulfite may help concentrate formaldehyde and allow it to react to selectively yield carbohydrates (Kawai et al. 2019).

Cofactors and Other Small Molecules

It might be assumed that most of the inorganic cofactors (Mo, Fe, Mn, etc.) were present as soluble ions in the prebiotic seas to some degree. Many of the organic cofactors, however, are either clearly byproducts of an extant metabolism or have syntheses so complex that their presence on the early Earth cannot reasonably be postulated. Most enzyme-catalyzed reactions use a cofactor, and these are often members of a small set of small biochemicals known collectively as vitamins. The most widely used is nicotinamide, and several prebiotic syntheses of this compound have been devised (Dowler et al. 1970; Cleaves and Miller 2001). Other vitamins that have prebiotic syntheses include components of coenzyme A and coenzyme M (Miller and Schlesinger 1993a,b; Keefe et al. 1995) and analogs of pyridoxal (Austin and Waddell 1999). There have been reports of flavin-like compounds generated from dry-heated amino acids, but these have not been well characterized (Heinz et al. 1979).

It may be that many compounds that do not have prebiotic syntheses were generated later once a functioning biochemistry was in place (White 1976). Interestingly, many of these can carry out their catalyses, albeit to a lesser degree, in the absence of the enzyme. Non-enzymatic reactions that occur in the presence of vitamin cofactors include thiamin-mediated formose reactions (Shigemasa et al. 1983) and transamination with pyridoxal (Snell 1945). These may have some relevance to prebiotic chemistry, or perhaps to the early development of metabolism. It is unclear whether porphyrins were necessary for the origin of life, although they are now a part of every terrestrial organism's biochemistry as electron carriers and photopigments. Prebiotic syntheses have been demonstrated for these (Rothemund 1936, Hodgson and Baker 1967).

There are numerous biochemicals that do not appear to be prebiotically accessible, despite some interesting prebiotic syntheses that have been developed. Tryptophan, phenylalanine, tyrosine, histidine, arginine, lysine, and the cofactors pyridoxal, thiamin, riboflavin, and folate are notable examples. These may not be necessary for the origin of life and may be instead byproducts of a more evolutionarily sophisticated metabolism.

6.2 Environmental Considerations

Whether in meteorites or on Earth, prebiotic chemistry may have occurred largely in an aqueous environment, as water is a ubiquitous component of the solar system and the Earth's surface. Among the variables of the local environment that could affect the way this chemistry occurs are pH, temperature, inorganic compounds such as metals, mineral surfaces, the impact of sunlight, etc. The potential role of mineral surfaces on prebiotic chemistry is an especially complex and underexplored aspect of this chemistry (Cleaves et al. 2012). Although we do not presently know which compounds were essential for the origin of life, it seems possible to preclude certain environments if even fairly simple organic compounds were involved (Cleaves and Chalmers 2004).

Stability of Biomolecules at High Temperatures

A thermophilic origin of life was first suggested by Harvey (1924), who argued that the first life forms were heterotrophic thermophiles that had originated in hot springs such as those found in Yellowstone

National Park. As underlined by Harvey, one advantage of high temperatures is that they speed up chemical reactions and primitive enzymes could have been less efficient. However, high temperatures are also destructive to organic compounds. Hence, the price paid is loss of biochemical compounds to decomposition. Although some progress has been made in synthesizing small molecules under hydrothermal vent-type conditions, the larger trend for biomolecules at high-temperature conditions is decomposition.

As has been demonstrated by various authors, many biological molecules have half-lives to hydrolysis on the order of minutes to seconds at the high temperatures associated with hydrothermal vents. Ribose and other sugars are quite thermolabile (Larralde et al. 1995). The stability of ribose and other sugars is problematic, but pyrimidines and purines, and many amino acids, are nearly as unstable. At 100°C the half-life for deamination of cytosine is 21 days, and 204 days for adenine (Garrett and Tsau 1972; Shapiro 1995). Some amino acids are stable, for example, alanine with a half-life for decarboxylation of approximately 19,000 years at 100°C, but serine decarboxylates to ethanolamine with a half-life of 320 days (Vallentyne 1964). White (1984) measured the decomposition of various biological compounds at 250°C and pH 7 and found half-lives on the order of seconds to hours for most. It should be borne in mind that the half-lives for polymers are even shorter as there are so many potential breakage points in a polymer. While hydrothermal environments may serve as synthesis sites for simpler compounds such as acetate or more refractory organic compounds such as fatty acids, it is unlikely they played a major role in synthesizing most biochemicals or their polymers. Submarine vents at 350°C do not seem to presently synthesize organic compounds, more likely they decompose them in a time span ranging from seconds to a few hours.

This does not imply that hydrothermal springs were a negligible factor on the primitive Earth. If the mineral assemblages were sufficiently reducing, the rocks near the vents may have been a source of atmospheric CH_4 or H_2 . As stated earlier, the concentrations of biomolecules that could have accumulated on the primitive Earth are governed largely by the rates of production and the rates of destruction. Submarine hydrothermal vents would have also been important in the destruction rather than in the synthesis of organic compounds, thus fixing the upper limit for the organic compound concentration in the primitive oceans.

Concentration Mechanisms

When aqueous solutions are frozen, as the ice lattice forms, solutes are excluded and extremely concentrated brines may be formed. In the case of HCN, brine may contain up to 75% weight percent (about 25 M) HCN. In principle any degree of concentration up to this point is possible. Salt water, however, cannot be concentrated to the same degree as fresh water in a eutectic; for example, from 0.5M NaCl, similar to the concentration in the modern ocean, the eutectic of the dissolved salt is the limit, which is only a concentration factor of about 10. Eutectic freezing has been shown to be an excellent mechanism for producing biomolecules such as amino acids and adenine from HCN (Levy et al. 2000). This requires that some regions of early Earth were cold enough to freeze, which requires that atmospheric greenhouse warming due to CO_2 , CH_4 , and NH_3 or organic aerosols was not so great

as to prohibit at least localized freezing. Concentration by evaporation is also possible for non-volatile compounds, as long as they are stable to the drying process (Nelson et al. 2001).

Some prebiotic organic syntheses may have depended on the availability of dry land areas. Although the timing of the growth of continental crust remains open to debate (see Figure 11), the geological record contains some evidence of sedimentary rocks that must have been deposited in shallow environments on primitive Earth. It is not unreasonable to assume that some dry land was available on primitive Earth in environments such as island arcs.

There is the possibility that hydrophobic compounds could have been concentrated in lipid phases if such phases were available. Calculations and some experiments suggest that an early reducing atmosphere might have been polymerized by solar ultraviolet radiation in geologically short periods of time. It has been suggested that a thick oil slick could have been produced in this way and could have been important in the concentration of hydrophobic molecules (Lasaga and Holland 1971).

Clays are complex mineral assemblages formed from dissolved aluminosilicates. Such minerals form templates for the formation of subsequent layers of mineral, leading to speculation that the first organisms may have been mineral-based (Cairns-Smith 1977). Clays are also capable of binding organic material via ionic and van der Waals forces, and may have been locations for early prebiotic synthesis. Early ion exchange processes would also have concentrated ⁴⁰K⁺, which would have exposed early prebiotic organics to high fluxes of ionizing radiation (Mosqueira et al. 1996).

Minerals

There are approximately 4,400 known naturally occurring minerals on Earth today (Hazen et al. 2008). This number was likely smaller on early Earth, as many minerals are produced by oxidation with environmental O₂, biological deposition, or the vast amounts of time that have passed since Earth formed. Minerals may have complex effects on prebiotic organic synthesis (Lahav and Chang 1976) by concentrating reactants and by lowering activation barriers to bring compounds into more rapid equilibrium (Marshall-Bowman et al. 2010).

Hydrothermal Vents

The discovery of hydrothermal vents at mid-ocean ridges and the appreciation of their significance in the element balance of the hydrosphere were a major advance in oceanography (Corliss et al. 1979). Since the process of hydrothermal circulation began early in Earth's history, hydrothermal vents and their associated chemistry were also likely present. Large amounts of ocean water presently pass through mid-ocean spreading-center vents, with the whole ocean going through them approximately every 10⁷ years (Edmond et al. 1982). This flow was probably greater during Earth's early history Earth, because the heat flow from the planet's interior was greater. There are various types of hydrothermal environments on the modern Earth, including subaerial hot springs and submarine hydrothermal vents. In the latter, temperatures range from about 4°C to 350°C, with pH values ranging from 0 to 11 (Martin et al. 2008). Various minerals precipitate as the heated vent water enters the surrounding ocean water, leading to the formation of baroque rock formations. It has been

speculated that the pores in such minerals may have served to concentrate organic species via thermophoresis (Baaske et al. 2007).

Such vents have received a great deal of attention in the context of the origins of life, partly because of uncertainty regarding the oxidation state of the early atmosphere. Soon following the vents' discovery, a hypothesis suggesting a hydrothermal emergence of life was published (Corliss et al. 1981), which suggested that amino acids and other organic compounds could be produced during passage of the effluent through the temperature gradient from about 350°C to about 0°C, roughly the temperature of modern ambient ocean waters.

Polymerization of the organic compounds thus formed, followed by their self-organization, was also proposed in this environment. At first glance, submarine hydrothermal springs appear to be ideally suited for organic synthesis, given the geological plausibility of a hot early Earth. Vents exist along the active tectonic areas of the Earth, and in at least some of them, potentially catalytic minerals interact with an aqueous reducing environment rich in H_2 , H_2S , CO, CO₂, CH₄, and NH₃. It is difficult to corroborate these speculations with the composition of the effluents of modern vents, as much of the organic material released from modern sources is simply environmentally processed biological material (e.g., Fiebig et al. 2019). Modern hydrothermal vent fluids contain some organic compounds, although it remains unclear what percentage are derived from extant biology, and what percentage are derived from abiotic processes. For example, for amino acids, the bulk of the evidence available supports a biological origin (Bassez et al. 2009). Presently, the amount and type of organic matter found in hydrothermal vent environments unequivocally thought to be of abiotic origin is limited to a few parts per million of small hydrocarbons such as CH₄ and ethane (McCollom et al. 2010).

One of the most articulate autotrophic vent origin-of-life hypotheses stems from the work of Wächtershäuser (1988, 1992), who argued that life began with the appearance of autocatalytic, twodimensional chemolithotrophic metabolic system based on the formation of pyrite (FeS₂). The FeS/H₂S combination is a strong reducing agent and has been shown to reduce some organic compounds under relatively mild conditions. Wächtershäuser's scenario fits well with the environmental conditions found at some deep-sea hydrothermal vents, where H₂S, CO₂, and CO are abundant; however, the FeS/H₂S system does not reduce CO₂ to amino acids, purines, or pyrimidines, although there is more than enough free energy to do so (Keefe et al. 1995b).

Pyrite formation can produce H₂ and reduce nitrate to NH₃, and HCCH to H₂CCH₂ (Maden 1995). Other experiments have shown that the activation of amino acids with CO and (Ni, Fe)S can lead to peptide bond formation (Hüber and Wächtershäuser 1998), although the degree to which these experiments mimic geochemical environments is debatable. In general, organic compounds are decomposed rather than created at hydrothermal vent temperatures, although temperature gradients exist. Sowerby and co-workers have shown (Sowerby et al. 2001) that concentration on mineral surfaces would tend to concentrate organics created at hydrothermal vents in cooler zones. The presence of reduced metals at high temperatures could facilitate Fischer–Trospch-type (FTT)

syntheses. FTT catalysts are poisoned by water and sulfide, though some of the likely catalysts such as magnetite may be immune to such poisoning (Holm and Andersson 1998).

6.3 Prebiotic Chemistry Beyond Earth

Of the eight accepted planets in our Solar System and their moons, several appear compatible with the synthesis of organic compounds, and several are known to contain them. Fewer appear to be compatible with the existence of liquid water or the more complicated evolution of these compounds. For example, the extreme temperatures of Venus or Mercury's sunlit side are likely too hostile for the synthesis of complex organics. The immediate sub-surface of Mars appears to harbor both liquid and solid water (Rennó et al. 2009), and it is widely believed that liquid water once flowed on Mars' surface. Meteorites likely impacted Mars' surface abundantly in its early history, and it is reasonable to expect that some of these were CCs. The nature of Mars' early atmosphere remains unknown, but Mars and Earth may have been similar early in their histories.

Proceeding outward from the Sun, the conditions on the solid surfaces of Saturn and Jupiter are thought to be too hostile for more complex organic chemistry. Nevertheless, the presence of various organic species has been confirmed in their atmospheres (Lodders 2010).

Several of the outer planets' moons have intriguing environments that appear to foster prebiotic chemistry and could conceivably be capable of sustaining biology. Saturn's moon Titan is now known to harbor a rich organic chemistry (Waite et al. 2007), and more recently organics have also been detected in geyser plumes emitted from Saturn's icy moon Enceladus. Jupiter's moon Europa is covered with a thick ice layer that likely harbors a water ocean several kilometers thick (Manga and Wang 2007). Its organic content remains unknown.

Extrasolar Planets

For centuries, the existence of planets beyond our solar system has been the subject of philosophical and scientific speculation (Urey et al. 1963; Dick 1999). The first extrasolar planets were detected in the late 1980s and early 1990s (Hatzes et al. 2003). Recent astronomical observations have since yielded hundreds of planets orbiting other suns (<u>http://www.exoplanet.eu/</u> and <u>http://nsted.ipac.caltech.edu/</u>). Methods to date have favored the detection of large planets with orbits very close to their parent stars, but new techniques are already allowing detection of smaller planets with orbits compatible with the existence of liquid surface water.

Our Solar System contains three rocky Earth-like planets, two of which are almost in the "habitable zone," the disk-shaped region sufficiently near and far from the Sun to support planetary surface temperatures compatible with liquid water. Our Solar System may be somewhat anomalous, although given the fact that it seems most stars have planets, it may not be unique either. Given the billions of Sun-like stars in any galaxy, there may be many rocky Earth-like planets in stellar habitable zones in the Universe (Laughlin 2010), some of which may have undergone similar development compatible with the origin and evolution of life. The detection of such planets and possible signatures of alien

biochemistry may not be far off, assuming that the origin of life is facile. The detection of even one such planet would strongly reinforce the idea that it is.

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7. PROGRESS FROM RECENT JTF-FUNDED PROJECTS

The John Templeton Foundation has had major impacts on various aspects of the study of the origins of life in recent years, both through a variety of individual grants made to teams and individual researchers, but also to two larger consortia in particular, the Earth-Life Science Institute (ELSI) Origins Network (EON) hosted at ELSI at the Tokyo Institute of Technology and the Chemistry to Life (CtL) initiative hosted by the Foundation for Applied Molecular Evolution (fFAME) in Florida.

The CtL aimed to define which problem areas were most amenable to experimental and observational constraint, especially by focusing on various "paradoxes" that have been noted in leading OoL models (Benner 2014). Such paradoxes were attributed to formal logical arguments that proceeded from culturally indisputable premises that led to unacceptable conclusions. Specifically to the impossibility of the origins of life.

Among the major efforts supported by the CtL were projects ranging from the formation of habitable environments on Earth to the creation of a Darwinian chemical system based on RNA. This work was in support of an "RNA-First Model" for the origin of life, which as noted above arose by analysis of contemporary molecular biology.

The geology projects attempted to connect unknowns in Earth history with organic chemistry projects supported by the program. The University of Colorado team combined radiochemical analysis and orbital mechanics to construct a scenario in which a Moon-sized impactor delivered Earth's "late veneer" sometime around 4.47 Ga (e.g., Genda et al. 2017). According to this model, metallic iron delivered to the early environment could have transiently created the reducing atmosphere thought to be so important for abiotic organic synthesis, while still allowing for the relatively oxidized early mantle previously postulated from examination of Hadean zircons.

A second project examined how large amounts of precursors for RNA building blocks could have accumulated on early Earth. This model leveraged the early oxidized mantle to propose that sulfur dioxide, a relatively oxidized sulfur-bearing volcanic gas, could have helped stabilize formaldehyde and other carbohydrates (Kawai et al. 2019). These sulfonic acid–carbohydrate derivatives were further shown to form nucleosides, to be regio-specifically phosphorylated to form nucleoside phosphates and diphosphates, and condensed to give short RNA molecules.

Yet other CtL teams showed how short RNA fragments could be recombined to give longer oligomers (e.g., Mizuuchi and Lehman 2019), and developed tools to explore the selection of RNA aptamers with catalytics activities or the propensity to bind small peptides (e.g., Tirumalai et al. 2018).

EON attempted to spur interdisciplinary and international collaboration to address a diversity of problems regarding the origins, emergence, and evolution of biological phenomena (e.g., Scharf et al. 2015). To this end, in addition to hosting a large number of workshops and visitors from around the world and training a new cadre of origins scholars and faculty, EON-supported scientists made significant discoveries in the nature of the Ediacaran fauna (Cuthill and Morris 2017), how viruses drive evolutionary innovation (Petrie et al. 2018), how horizontal gene transfer can help explain the origins of the genetic code (Froese et al. 2018), the non-enzymatic functioning of sequences of the reverse Krebs cycle (Muchowska et al. 2017), as well as developing experimental and computational tools for the exploration of prebiotic chemistry (Meringer and Cleaves 2017).

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8. UNKNOWNS AND THE FUTURE

A basic tenet of the heterotrophic theory of the origin of life is that the origin of the first living systems depended on environmentally supplied organic molecules. As summarized here, there has been no shortage of discussion as to how the formation of such molecules can occur. Organic compounds may have accumulated on the primitive Earth via numerous mechanisms, including contributions from endogenous atmospheric synthesis, deep-sea hydrothermal vent synthesis, and exogenous delivery. Although this raises the issue of the relative significance of the various sources, it also recognizes the wide variety of potential sources of organic compounds.

Given adequate expertise and experimental conditions, it is possible to synthesize almost any organic molecule in the laboratory under simulated prebiotic conditions. However, the fact that a number of molecular components of contemporary cells can be formed non-enzymatically in the laboratory does not necessarily mean that they were essential for the origin of life, or that they were available in the prebiotic milieu. The primitive soup, however thin or thick it may have been, may have been a complex mixture, but likely did not include all of the compounds or molecular structures found today in even the simplest prokaryotes, and may well have contained many other unique ones.

The existence of different abiotic mechanisms by which biochemical monomers can be synthesized under plausible prebiotic conditions is well established, although of course vast amounts of sideproducts remain uncharacterized and the enormous number of ways in which the yields of any given compound could be maximized remain unexplored.

Not all prebiotic pathways are equally efficient, but the wide range of experimental conditions under which organic compounds can be synthesized demonstrates that organic compounds are prebiotically "robust," that is, the abiotic reactions leading to them do not take place under a narrow range defined by highly selective reaction conditions, but rather under a wide variety of environmental settings, though this is likely untrue for any tightly defined type or class of compound. Although our ideas on the prebiotic synthesis of organic compounds are based largely on experiments in model systems, the robustness of this type of chemistry is supported by the occurrence of diverse organic compounds in carbonaceous meteorites and comets, as well as elsewhere in the Solar System. It is therefore plausible, but not proven, that similar synthesis took place on the primitive Earth. For all the uncertainties surrounding the emergence of life, it appears that the formation of a "prebiotic soup" is one of the most firmly established aspects of the primitive Earth, though its recipe remains difficult to decipher.

The origins of life is perhaps an unusual field among the sciences in that it has resisted significant resolution over a century of admittedly weakly concerted effort. It is worth comparing OoL with various major scientific enterprises that were deemed worthy of almost bottomless funding during the 20th century, such as the War on Cancer, the Manhattan Project, Project Apollo, or the efforts to discover subatomic particles or gravitational waves, all successful efforts whose price can be assessed. Project Apollo cost approximately \$700 billion in 2019 dollars to go from no effort at all to a man walking on the Moon over the course of approximately 10 years. It is somewhat more difficult to gauge the progress of the War on Cancer, seeded with \$100 million in 1971 dollars (about \$635 million in 2019 dollars), which has consumed on the order of a trillion 2019 dollars now in total. While many human lives have been saved over this time, millions of people still die annually from cancer. The Manhattan Project, in contrast, is an extremely compressed example of a scientific concept that went from infancy to instantiation in only a few years with a relatively small budget (estimated as \$23 billion in 2018 dollars).

Can we do a similar cost accounting for scientific efforts to study the origins of life? It is probably safe to say that formal funding for the question began sometime in the 1960s. This funding has perhaps amounted, over the years and on average, to a few million to tens of millions of dollars per year. This would lead to a rough estimate of perhaps a few hundred million to approximately a billion dollars spent on this question in 2019 dollars since then. This is a paltry amount of money compared to these previous projects, although the comparison is perhaps unfair as Project Apollo and the Manhattan Project were in a sense fairly straightforward applications of engineering. The origins of life question is possibly more akin to the War on Cancer in that it involves the study of complex systems whose workings we do not yet wholly understand and for which the tools required for study may not yet exist.

It is impossible to predict how soon the problems prebiotic chemistry addresses will be solved. It seems plausible, if not very likely, that in the near future, chemists will assemble living organisms entirely *de novo*. An entire synthetic genome has been constructed (Gibson et al. 2008), a ribozyme capable of assembling 80% of its sequence has been developed in the laboratory (Wochner et al. 2011), and a self-sustained and autocatalytic set of self-propagating RNA molecules has been culled from laboratory experiments (Lincoln and Joyce 2009). What remains more problematic is a comprehensive understanding of how such systems may have arisen from environmentally plausible reactions on primitive Earth. Despite considerable progress, much work remains, and undoubtedly, many surprises are in store.

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