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J. B. S. Haldane and the origin of life

STÉPHANE TIRARD*

François Viète Center for Epistemology and History of Science and Technology, University of Nantes, Nantes, France
*E-mail: stephane.tirard@univ-nantes.fr.

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Abstract. In 1929 the British biologist John Burdon Sanderson Haldane published a hypothesis on the origin of life on earth, which was one of the most emblematic of the interwar period. It was a scenario describing the progressive evolution of matter on the primitive earth and the emergence of life. Firstly, this paper presents the main ideas put forward by Haldane in this famous text. The second part makes comparisons between Haldane and Alexander Ivanovitch Oparin's ideas regarding the origins of life (1924). These two theories, apparently very similar, presented distinct conclusions. The third part focusses on Haldane's reflections on the emergence of life during the 1950s and 1960s, and shows how they were linked to the recent developments of prebiotic chemistry and molecular biology.

Keywords. origin of life; Haldane; Oparin; prebiotic chemistry; RNA world.

Introduction

During the second part of the 19th century, the issue of the origin of life was renewed by the emergence of evolutionary theory, on the one hand, and by the refutation of spontaneous generation theory, particularly after Louis Pasteur's experiments, on the other hand. Two solutions were proposed to this issue: the first regarded the possibility of the progressive evolution of matter on the primitive earth, and the second concerned the panspermia theory claimed, for instance, by William Thomson (1872) or Svante Arrhenius (1908) (Fry 2000; Tirard 2006). Panspermia was largely abandoned at the end of the 1910s (Tirard 2013). In the 1970s, it was rarely used (Crick and Orgel 1973; Hoyle and Wicramasinghe 1979) as an assumption made to underline and discuss the improbability of the emergence of life and was not shared by the community of specialist on the origins of life (Dick 1996; Fry 2000). Therefore, during the interwar years, the several important hypotheses put forth were evolutionary. John Burdon Sanderson Haldane published one of the most emblematic hypotheses in 1929. In a short text, he brilliantly associated his reflection on the nature of life with a scenario of the origin of life on the earth (Haldane 1929). (For an overview of the history of the theories on the origin of life see Dick (1996), Farley (1997), Fry (2000), Kamminga (1991) and Tirard (2010)).

The first part of this paper reviews the main ideas put forward in Haldane's famous paper, which had a great impact on the history of ideas on the origin of life. According to the British biologist, life was able to emerge on earth through a progressive chemical evolutionary process, which he described by means of a very clear and concise scenario.

The second part of this paper makes comparisons between Haldane and Oparin's ideas regarding the origins of life (1924). For several reasons, their papers are often associated in the Oparin–Haldane hypothesis. It is important to compare them to understand the reason behind this association, as well as to underline the important conceptual distinctions between them.

The third and last part focusses on Haldane's reflections on the emergence of life during the 1950s and 1960s. Haldane's return to this issue in several papers showed his great interest in it and confirmed the originality of his thought.

1929: A scenario of the origin of life on the earth

Haldane's first contribution to the origin of life was published in *The Rationalist Annual* in 1929. When Haldane wrote it, he occupied two positions. Since 1923, he was a reader in biochemistry at Cambridge and, starting with

1927, he also had a position at the John Innes Horticultural Institution (Clark 1972). At the end of the 1920s, he was a well-known scientist, excelling in physiology, biochemistry, enzymology, genetics, and the evolutionary theory. His paper from 1929 undoubtedly benefited from his impressive knowledge. It is often considered as one of the first synthetic papers on this topic and it constitutes a milestone in the history of ideas on the origin of life. It has the double characteristic of being addressed to a large public and presenting original views. It is notably for these two reasons that it was recorded for posterity.

To introduce the issue, Haldane first drew attention to the fact that, even if the old idea of spontaneous generation had been abandoned in the 19th century, it was still possible to accept that such an evolutionary process occurred in the past. Second, he questioned the possibility of viruses being alive. He was indeed very interested in the debate on this issue. At that moment, viruses were only known as agents of infectious diseases. They were invisible and had the property of being able to pass through the tiniest filter used in microbiology laboratories. In his paper, Haldane focussed on d'Herelle and Bordet's opposing views. The former, who discovered bacteriophages, which infect bacteria, claimed that these viruses were living organisms. The latter believed them to be a ferment. Haldane preferred to follow the intermediate view of the American geneticist Muller (1926), who compared 'the bacteriophage to a gene—that is to say, one of the units concerned in heredity' (Haldane 1929). Finally, Haldane claimed that 'The bacteriophage is a step beyond the enzyme on the road to life, but it is perhaps an exaggeration to call it fully alive' (Haldane 1929). Undoubtedly, his reflection on viruses was very heuristic in terms of the issue of the limits of life (Podolsky 1996) and particularly of the origin of life.

Regarding the scenario of the origin of life on the earth, Haldane began his description after the cooling of the earth, when it developed a solid crust and when water was condensed. He insisted on the primitive conditions and, according to him: 'The primitive atmosphere contained little or no oxygen and was rich in carbon dioxide (…). The sun was perhaps slightly brighter than it is now, and as there was no oxygen in the atmosphere the chemically active ultraviolet rays…'

His assumption could be considered as a phototrophic pathway of synthesis of organic molecules. He claimed that: 'when ultra-violet light acts on a mixture of water, carbon dioxide, and ammonia, a vast variety of organic substances are made, including sugars and apparently some of the materials from which proteins are built up'. He added that: 'before the origin of life such substances must have accumulated till the primitive oceans reached the consistency of hot dilute soup'. This metaphor of the 'soup', invented by Haldane, was continuously and widely used in literature. It certainly contributed to the posterity of this text. Haldane continued with the explanation of his conception of the first living things, and insisted on the possibility of an intermediate state: 'The first living or half living things were probably large molecules synthesized under the influence of the Sun's radiation, and only capable of reproduction in the particularly favourable medium in which they originated. Each presumably required a variety of highly specialized molecules before it could reproduce itself, and it depended of chance for a supply of them.' Then he continued with the emergence of a cell: 'The cell consists of numerous half-living chemical molecules suspended in water and enclosed in an oily film. When the whole sea was a vast chemical laboratory the conditions for the formation of such films must have been relatively favourable; but for all that life may have remained in the virus stage for many millions of years before a suitable assemblage of elementary units was brought together in the first cell. There must have been many failures, but the first successful cell had plenty of food, and an immense advantage over its competitors.'

These previous quotations show how Haldane organized a hypothesis on the origin of life constituted by three main stages depending on the conditions of the primitive earth. Firstly, organic molecules were synthesized under the action of ultra-violet light on primordial mixture of water, carbon dioxide, and ammonia. Secondly, under the action of the sun's radiation on this hot dilute soup, large molecules capable to reproduce themselves emerged. Thirdly, cells were formed.

Oparin and Haldane: two parallel ways

Oparin and Haldane are very often associated in historiography and their hypotheses are evaluated as very similar. This can be explained by a variety of reasons. Firstly, their publications were quasi simultaneous. Haldane's text came five years after Oparin's (Oparin 1924). However, it is important to note that he did not know about the Soviet scientist when he wrote his own paper. Therefore, it is an interesting case of simultaneity, which amplified their common posterity. Secondly, their two texts described, step-by-step, using a very similar method, the progressive emergence of life on the primitive earth. Thirdly, the possible influence of Marxist ideas on Haldane and Oparin was often discussed (Graham 1973; Gouz 2012; Lazcano 2016). It is important to underline that, in their first texts on the origin of life, there was no reference to Marxism or to political influences. At that time, Haldane had political ideas which were more to the left, but he had not yet joined the Communist Party; he did it at the beginning of the Spanish war. It seems possible to claim that Haldane wrote this text without any political or philosophical influences other than simple materialism. When it comes to Oparin, it also appears that, at the beginning of the 1920s, he was motivated by his own interest in evolution and that Marxist ideology did not appear in his work. Fourthly, a last common point must be underlined even if it is rarely signalled. Both Oparin and Haldane insisted on the historical character of the process of the origin of life, which was unique in the past and did not leave any geological traces. In this regard, they noticed the particular position of scientists when confronted with such a problem and Haldane did not hesitate to write: 'The biochemist knows no more, and no less, about this question than anyone else. His ignorance disqualifies him no more than the historian or the geologist from attempting to solve a historical problem' (Haldane 1929).

However, beyond the common characteristics of their models, some differences existed in their respective conceptions of primitive life. Oparin's paper, which was longer than Haldane's, insisted more on the formation of the earth. However, they agreed on the absence of O_2 and the presence of CO_2 in the primitive atmosphere. According to them, the first organic synthesis occurred in the primitive atmosphere and continued in seawater. However, an important difference existed regarding the final products imagined by the two scientists. According to Oparin, the organic compounds aggregated, producing some little 'bits of gel', which prefigured the primitive cells. Oparin always focussed on metabolism and, starting in 1936, he used coacervates which, according to him, 'may be compared to the properties of protoplasm'. He claimed that 'the coazervate represents a special type of concentrated colloidal sol, in which the water molecules are rigidly oriented with regards to the colloidal particle. A real separation is thus brought about between the shell of oriented water molecules and the free molecules of the equilibrium liquid' (Oparin 1938).

In contrast, the successive hypotheses proposed by Haldane in 1929 focussed increasingly on molecules responsible for heredity. Contrary to Oparin, Haldane followed the same lines as Muller who claimed, in 1926, that the gene was the basis of life (Muller 1926; Fry 2000; Falk and Lazcano 2012). He notably referred to genes when he focussed on the issue of the growth and reproduction of large molecules, claiming: 'They occur, it would seem, in certain polymerizations which are familiar to organic chemists. In my opinion the genes in nuclei of cells still double themselves in this way. The most familiar analogy to the process is crystallization.'

It is necessary to also underline the differences regarding the issue of the primitive metabolism. The progressive complexity of organic matter described by Oparin argued for a heterotrophic process. Haldane, taking a contrary stance, as seen above, insisted on the role of light in chemical synthesis, and preferred an autotrophic process.

The last point to be underlined regards the place of the origin of life in their respective careers. As mentioned above, Haldane was already an accomplished scientist in 1929, with a large panel of specialities. Thereafter, the origin of life was only one among his many subjects of study, and he returned to this topic only in the 1950s. In contrast, Oparin, who first specialized in plant physiology, actively pursued the field of the origin of life throughout his career. He published an important book in 1936, which was translated into English in 1938 with the title *The origin of life*, and, as biochemist, he became the leader of the Soviet school of the origin of life. After the WWII, Oparin devoted his career to the origin of life. In the Soviet context led by Lysenko, he was constrained to neglect the development and consequences of molecular biology and particularly the roles of nucleic acids. However, despite the Cold War, Oparin stayed in contact with Western specialists on the origin of life and focussed his own work and that of his school on the metabolic and energetic aspects of the issue.

The extensions of Haldane's thought on the origin of life

During the 1950s, Haldane returned to the issue of the origin of life in several papers, in which he revisited his own views and those of his colleagues. Pirie illustrated very well how Haldane was able to connect the more up-to-date scientific thought (Pirie 1968). This was undoubtedly the case in the 1950's.

He was very stimulated by the recent changes occurring in the scientific context. Firstly, the 1950s stood out as the beginning of a new period for the study of the origin of life, with the first experiments of prebiotic chemistry. This method was used to study possible chemical pathways in experimental conditions respecting the supposed conditions of the primitive earth. Calvin inaugurated this direction in 1951. He exposed CO_2 in solution to gamma rays and obtained formic acid (Garrisson *et al.* 1951). Two years later, Stanley Miller tested a hypothesis suggested by Harold Urey. In a famous experiment, he exposed a mixture of CH_4, NH_3, H_2O and H_2 to electric discharges for one week, showing the production of amino acids (glycine, α-alanine and β-alanine) (Urey 1952; Miller 1953). Therefore, these two experiments were emblematic of a new and very active field with chemical investigations and scientific debates on the origin of life (Ponnamperuma and Gabel 1968). Secondly, the 1950's were remarkable due to the development of molecular biology, which revealed the roles of nucleic acids and their relationship with proteins.

Therefore, it was in this new context, characterized by the double emergence of prebiotic chemistry and molecular biology, that Haldane confirmed his interest in global reflections on the origin of life. His claim from 1929 regarding half-living molecules found a new meaning in this new conceptual context, due to the fact that molecules were now identifiable with nucleic acids. Contrary to Oparin, he clearly adopted the new concepts of molecular biology. His main lines of vision on the origin of life stayed the same as in 1929, with a progressive evolution of matter from molecules to cell (Haldane 1954, 1957). However, it referred to recent biochemical data. It was based on a first stage of simultaneous syntheses of three fundamental categories of complex organic molecules: polysaccharides, proteins and nucleic acids, which were capable of replication. Then he imagined that a monolayer of protein could enclose some of these molecules. However, he changed his mind on primitive atmosphere and claimed that it contained methane rather that CO_2.

Haldane completed his hypotheses nourished by new concepts on molecular biology and biochemistry. However, his work on the emergence of life appeared to be closely linked to his reflection on minimal life. The following quote is a perfect illustration of his approach: 'I believe that life demands not only self-reproducing molecules but a self-reproducing system of such molecules' (Haldane 1957). Beyond this first principle, he claimed: 'The minimum living organism which I can imagine would contain a copyable nucleic acid spiral, whose structure enabled it to make at least the following enzymes' (Haldane 1957). He provided a list: a nuclease, a proteinase, phosphokinases, a nucleosidase. He added that 'It would also contain a supply of a self-reproducing pyrophosphoric ester, possible ATP. Such a system would automatically synthesise adenosine. It would be surrounded by a monolayer of protein, possibly consisting of the enzymes named. Such a primitive cell would [...] be able to grow in a medium containing sugars, basis, and amino-acids' (Haldane 1957). Therefore, his theoretical approach to the origin of life, which he named, at this stage, emergence of life, provoked thought on the nature of a minimal living system, more than a description of a scenario.

In 1963, Haldane participated in an important symposium on the *Origins of prebiological systems and their molecular matrices* took place in Florida (Fox 1965). On this occasion, he met Oparin for the first time. As the chairman of Oparin's lecture, Haldane addressed these words to his colleague: 'I have very little doubt that Professor Oparin has the priority over me. I am ashamed that I haven't read his early work, so that I don't know. As far as I know, I didn't publish until 1927 [sic] and he did in 1924, and there was precious little in my small article which was not to be found in his books. I think if his first book was in 1924, the question of priority doesn't arise. The question of plagiarism might' (Fox 1965).

During this symposium, in his own lecture, Haldane was one of the first to consider the possibility of a central role of RNA in the origin of life, an idea that became central during the 1980s (Haldane 1965). His hypothesis was related to his interest in viruses, and he claimed this model: 'I suggest that the first synthetic organisms may have been something like a tobacco mosaic virus, but including the enzyme or enzymes needed for its own replication' (Haldane 1965). A few lines further he added: 'If there is any sense in this view, some RNA configurations may be a great deal more probable than others formed from the same components, and this owing to properties of the whole which, if they are beyond our grasp at present, are, in principle, calculable, like energy levels of a benzene molecule from atomic parameters. Thus, the probability of spontaneous formation of a biologically relevant RNA pattern might be very greatly increased, without any supposition that a vital force or soul was guiding the molecules into the right configuration' (Haldane 1965).

Conclusion

Haldane is often presented, together with Oparin, as the author of one most important hypotheses of the mid-war period on the origin of life. Throughout his life, he maintained an interest in this issue and, more generally, in fundamental issues such as nature and the definition of minimal living organism.

He was also able to participate in the renewing of the reflection on origin of life during the 1950s and 1960s and incorporated the newest data of molecular biology in his own original approach. His last contribution to the issue was the very interesting assumption that RNA was important at the origin of life.

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