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EDITORIAL

Cells, Molecules and Evolution: Historical Issues in Molecular Evolution

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When the book *The Life of Erasmus Darwin* written by Ernst Krause was translated into English in 1879, Charles Darwin was asked to add a preliminary note based on letters and notebooks kept by his family. "In his Temple of Nature", wrote Charles Darwin, "there is a curious instance of his prophetic sagacity with respect to 'microscopic animals'…Therefore the following sentence of my grandfather, considering how little was then known on the subject, appears to me remarkable. He says", added Charles Darwin, 'I hope that microscopic researchers may again excite the attention of philosophers, as unforeseen advantages may probably be derived from them like the discovery of a new world".

Although along his life Charles Darwin owned several microscopes and enjoyed using them, he did very little to fulfill his grandfather's hunch. Microbes are conspicuously absent in *The Origin of Species* and in his other books, and for some time the discussions on evolution and natural selection were at limited to animals, plants, their distribution and their paleontological records. And yet, as the development of cell theory and the process of molecularization of life sciences ripened, Ernst Haeckel and few others explicitly advocated the application of evolutionary analysis to these new fields.

By the turn of the 20th century the idea of evolution had gained considerable acceptance, but prior to the development of neodarwinism many favored symbiosis, orthogenesis or mutationism over natural selection. It will come as surprise to many to know that in this intellectual environment, as summarized by Edna Suarez in her paper on the history of molecular evolution included in this special issue, that molecular approaches to taxonomic and evolutionary questions were born, and that in 1904 the American-born British physician George H. F. Nuttall published a book summarizing the results of the detailed comparisons of blood proteins that he had used to reconstruct the evolutionary relationships of animals. As she writes, thanks to this and other pioneering efforts led to the use of molecular techniques such as amino acid sequencing, nucleic acid hybridization, and zone gel electrophoresis, among others, which allowed the recognition of that evolution takes place via different mechanisms and at different pace at molecules and organisms and opened new debates, such as the heated discussions on the relationship between humans and other primates, or the development of the neutral theory of molecular evolution.

The theoretical foundations of molecular evolution have been based on a number of central concepts, many of which were inherited from older disciplines such as physiology, anatomy and neodarwinism. As discussed in fascinating detail by S. A. Inkpen and W. Ford Doolittle in their contribution to this special issue, homology, which is one of the key concepts in evolutionary biology that was first used by Goethe, Owen and other 19th century thinkers to describe structural resemblance to an archetype. The concept was rapidly incorporated to classical Darwinian theory and, later on, became an integral part of molecular phylogenetics. These passages did little to clarify it. Homology has been repeatedly confused with sequence similarity, and although orthology, paralogy and xenology are loosely used, its precise definition and use poses methodological and theoretical issues far from solved.

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Following the publication of *The Origins of Species,* evolutionary biology became intertwined with the process of secularization of life sciences, and provided a framework for materialistic explanations of biological phenomena. As Juli Peretó shows in his paper "Erasing borders: a brief chronicle of early synthetic biology", Jacques Loeb, like other scientists, conceived cells as chemical machines, an approach that led to research programs on experimental abiogenesis that can be seen as a direct predecessor of current efforts on synthetic biology. As summarized by Peretó, the observation of lifelike behavior of microscopic droplets of different compositions led Jerome Alexander, Stephane Leduc and Alfonso L. Herrera to strenuous efforts to define life in purely physical terms, based on magnetism, surface tension or radioactivity. Although the Belgian biochemist Marcel Florkin once described these approaches as part the ''dark age of biocolloidology", Peretó demonstrates how driven by their anti-vitalistic philosophy Loeb and others to attempted to achieve the laboratory synthesis of artificial cell as the only way to understand in full the nature of living systems.

As summarized by Ismael Ledesma and H. James Cleaves, one such scientist was the Mexican Alfonso L. Herrera, a prominent naturalist well-known for his liberal political views and the first popularizer of evolutionary ideas in the country. The task was not easy, but it was certainly facilitated by the secular atmosphere that prevailed in Mexico after the religion wars and the hold that positivism had rapidly acquired in Latin America. As summarized by Ledesma and Cleaves, Herrera played a key role in incorporating Darwin's ideas in schools and in research programs. A multi-faceted and energetic character, Herrera also devoted major efforts to the development of a mechanistic theory of life in which he attempted to synthesize autotrophic artificial cells.

Oparin's ideas followed a different direction. As Antonio Lazcano discusses in his paper on the history of the heterotrophic theory of the origins of life, Oparin was based on a Darwinian framework, and published in 1924 a small pamphlet where he argued that living organisms were the historical outcome of a gradual transformation of lifeless matter. Eighty years ago his second book was published in Moscow. Although it had the same title of the 1924 monograph, the depth and the extent of the new book were substantially different. In his new volume, Oparin presented a surprisingly coherent picture of evolution that started with the synthesis of organic compounds in a highly reducing primitive Earth, followed by a process of precellular evolution that led to the emergence of primordial anaerobic heterotrophs. This idea was strongly opposed by the geneticist H. J. Muller, who argued that single genes or DNA molecules represented primordial living systems. Their debates represent not only contrasting views of the nature of life itself, but also demonstrate how attempts to understand the emergence of life were affected, in socio-political terms, by the harsh Stalinist period and the Cold War atmosphere.

Herrera, Leduc, Loeb, Oparin and many others considered cells as the basic unit of life. As discussed by David W. Deamer in his article "Membranes and the origin of life: a century of speculation", many have underlined the role that membranous boundaries may have played in the emergence of living systems. Was compartmentalization essential for the appearance of life? lipidic molecules are essential components of cells, and amphiphilic molecules have been formed abiotically. As summarized by Deamer, biological membranes are involved in the appearance of transduction systems and energy-producing mechanisms, i.e., the bioenergetics processes which lie at the very basis of metabolism. Pioneering efforts by Oparin and others led to current efforts to encapsulate ribozymes within lipidic membranes, and to develop laboratory models of chemical networks, and approach that has shown that liposomes and micelles are in fact chemical microreactors.

The RNA World concept is a hypothesis firmly rooted in empirical data and part of a long and storied scientific perspective that goes back more than 50 years when the discovery of the centrality of RNA in protein synthesis took place. As our understanding of RNA biology progressed, several independent proposals of protein-free primordial life forms were made in the 1960s by Rich, Crick and Orgel. The unexpected discovery of ribozymes by the groups of Thomas Cech and of Sidney Altman, gave considerable credibility to the proposal that the first living entities were based on RNA as both the genetic material and as catalyst, a hypothetical stage called the RNA world by Walter Gilbert, who coined the term. In her paper "The RNA World at thirty: a look back with its author", Neeraja Sankaran summarizes and analyzes the outcomes of a lengthy interview with Gilbert, who revisits his hypothesis and how he was led to propose it.

As the collection of papers presented here shows, the relationship between molecular biology and evolutionary theory is a long, storied process. With the development of rapid genome sequencing, faster computers, the development in vitro RNA evolution techniques, and the development of systems chemistry, the issues discussed in this *special issue* of the *Journal of Molecular Evolution* will continue to develop and are likely to undergo major changes in the near future. There is an increased awareness that the processes underlying the generation of evolutionary novelties can be extended to the subcellular levels and cannot be restricted to classical neodarwinian explanations. For all the debates and heated discussions that are currently take place, these are the best of times.