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EDITORIAL

Revisiting the Origins of Life Experiment

Biology is a discipline that has two distinct faces. There is a remarkable diversity of form and function amongst living organisms. There is also an underlying unity of the molecular mechanisms that are responsible for the maintenance of life. Modern biology rests on a few major pillars; Darwin's evolutionary synthesis driven by the ideas of natural selection, Schwann's ideas of cells as a basic unit of biological structures, Mendelian rules of inheritance and the principles of coding and transmission of genetic information based on the Watson–Crick double helical structure of DNA. Biology is a wonderfully fertile field for research, with mathematicians, physicists, chemists, computer scientists, materials researchers and engineers entering the field, hoping to understand and sometimes exploit nature, using tools and techniques that have been successful in other fields. There is a messy side to biology, where elegant theories and unifying concepts seem to make little headway; the subdiscipline of biochemistry remains a formidable maze of complex, interlinked chemical reactions. The advance of molecular biology has not simplified matters. Indeed, regulation and control of chemistry in biological systems is turning out to be mired in complexity. The developing area of systems biology may offer hope, but its promise remains to be realized. Physicists, mathematicians and surprisingly even geneticists dismiss the complexities of biochemistry as an unnecessary distraction in understanding biology. At the level of molecules there is again a diversity of form and function. The modern day 'structural biologist' sometimes bears a striking resemblance to the practitioners of classical systematic biology. The former applies the principles of classification, 'taxonomy', to molecules while the latter surveys nature's organisms. At a recent discussion I heard the dismissive characterization of those who work to catalog structural detail in biological molecules as 'people who have mistaken the trees for the forest'. As one who has undoubtedly lost his way amongst the 'trees', I was nonplussed. The criticism was probably valid. But, were the signposts pointed in the wrong direction in the reductionist approach to biology? Not too long ago it was popular to talk about the 'molecular basis of life'; a term that promised deep insights if the trail of reductionsim was followed to the very end. Biology is, however, a subject that has not yielded entirely to a reductionist strategy. Classicists often take shelter behind Dobzhansky's famous dictum: 'Nothing in biology makes sense except in the light of evolution'.

The Darwinian view has dominated discussions of biological evolution. For the reductionst there is a related issue. How did the enormous diversity of molecules, that are central to the chemistry of life, evolve? Darwin, of course, cautiously avoided a consideration of the origins of life, a chapter in evolutionary history that must surely precede speciation and the evolution of diversity. His oft-quoted allusion to a 'warm little pond' in which life originated was a passing acknowledgement of an unsolved problem. Chemical evolution must surely have taken place in a distant past, when the Earth's surface and atmosphere were far from conducive for life. Some answers are to be found in a classic paper, unpretentiously titled, 'A production of amino acids under possible primitive earth conditions' by Stanley Miller, published over half a century ago (*Science*, 1953, **117**, 528). Miller, then a graduate student at the University of Chicago devised an apparatus in which a mixture of water vapour (H_2O), ammonia (NH_3), methane (CH_4) and hydrogen (H_2) was subjected to an electric discharge. The residues formed revealed the presence of a variety of amino acids, small molecules that go on to form the polymeric chains of which proteins are composed. This was the first demonstration of the formation of the elementary molecules of biochemistry from a mixture of gases that might have constituted a primitive atmosphere on Earth. The Miller experiment, which was based on the ideas of Oparin, Urey and Haldane captured the public imagination and was quickly dubbed in the popular press as an experiment that revealed the 'origins of life'. Miller's little, matter of fact note, which occupies slightly more than one printed page, is modest in its claims, eschewing speculation. He provides a clear and succinct description of his experiment and the results, avoiding any reference to the origins of life.

My attention was drawn to this old experiment by the appearance of a recent report entitled 'The Miller Volcanic Spark Discharge Experiment', in which Miller's original samples were reanalysed using modern instrumentation – 'high-performance liquid chromatography and mass spectrometry that allows for identification at the sub-picomolar ($<10^{-12}$ M) level' (Johnson, A. P. *et al.*, *Science*, 2008, **322**, 404). The group led by Jeffrey Bada, a former student of Miller, writes: 'After Miller's death in May 2007 we found several boxes containing dried residues. Notebooks indicated that the vials came from the 1953–54 University of Chicago experiments that used three different configurations'. Modern day geoscientists have been skeptical that the Earth's primitive atmosphere had the reducing conditions that Miller had used. Bada and his colleagues now establish that one of Miller's original experimental configurations 'possibly simulates the spark discharge synthesis by lightning in a steam-rich volcanic eruption'. In this scenario the first building blocks of biochemistry may have been born in an environment that forced molecules into existence, while biology might still await Darwin's 'warm little pond'; a description that seems more conducive for life. A few years ago Bada and Lazcano wrote a historical essay, 'Prebiotic Soup – Revisiting the Miller Experiment', looking back on the 50th anniversary of the paper that launched the field of chemical evolution (*Science*, 2003, **300**, 745). They begin with lines from an old and forgotten song: 'Isn't life wonderful' and provide a marvellous account of Miller's work and its impact on the public imagination. Science as practised in the Miller's experiment, provided the 'metaphor of the "prebiotic soup" ' which later 'found its way into comic strips, cartoons, movies and novels and continues to do so'.

The genesis of the Miller experiment can be traced to a remarkable book written in Russian by A. I. Oparin in 1936 titled 'Origin of Life', with the English translation appearing two years later (Macmillan, 1939; Dover Publications, New York, 1953). Oparin's opening sentences summarize the importance of the area of inquiry: 'The question of the origin of life, of its first appearance on Earth, still occupies the human mind, as it has done since antiquity. It may be safely said that it is one of the most important problems of natural history'. Oparin surveyed chemical and biochemical knowledge, then available, in masterly fashion. He also noted in his conclusion, after 250 pages of discussion, the effects of biological evolution: 'Natural selection has long ago destroyed and completely wiped off the face of the Earth all intermediate forms of organization of primary colloidal systems and, wherever the external conditions are favourable to the evolution of life, we find countless numbers of fully developed highly organized living things. If organic matter would appear at the present time it could not evolve for very long because it would be quickly consumed and destroyed by the innumerable microorganisms inhabiting the earth, water and air'. Oparin clearly saw biology obliterating all traces of its chemical origins. Despite his reference to natural selection, the sole mention of Darwin (p. 45) is related to his dismissal of a view that 'living things' originated from inorganic substances without the intervention of any specific vital force. Oparin discussed the steps by which organic substances might evolve and reached a pessimistic conclusion: 'The tremendously long intervals of time separating the single steps in this process make it impossible to reproduce the process as it occurred in nature under available laboratory conditions' (p. 251). Less than twenty years later, Miller demonstrated the feasibility of Oparin's models for abiotic synthesis.

Miller began his research career as a graduate student in Harold Urey's laboratory at Chicago. Urey won the Nobel Prize in Chemistry in 1934 for his work on deuterium at Columbia University. When he moved to Chicago in 1946 his interests were turning to geochemistry. He reached a conclusion, not too different from that of Oparin, that a primitive atmosphere would be reducing, a view not supported entirely, today. In a memorable seminar, he suggested that such conditions might be favourable for producing organic compounds. Miller, who originally began working with Edward Teller and then changed advisors, sensed an opportunity to try an experiment. In later years he was to say that when he arrived in Chicago he was convinced that 'experiments are time-consuming, messy and not as important . . . as theoretical work'. He was quickly rewarded when he 'produced an oily scum and a yellow brown water solution' that yielded compounds of importance in biochemistry. In an appreciation of Miller, written after his death, A. Lazcano and J. L. Bada describe reactions when Miller presented his results at a seminar, 'with Urey in the front row'. The results were clearly important. 'In the question period Enrico Fermi turned to Urey and said, "I understand that you and Miller have demonstrated that this is one path by which life might have originated. Harold, do you think it was *the* way?" Urey replied, "Let me put it this way, Enrico. If God didn't do it this way, he overlooked a good bet!" ' (*Orig. Life Evol. Biosph.*, 2008, doi 10.1007/s11084-008-9145-2; Arnold, J. R. *et al.*, *Biogr. Mem. Natl. Acad. Sci. USA*, 1995, **68**, 363).

Decades after the Miller experiment, the origins of life and the evolution of the complex organic molecules essential for its sustenance remain shrouded in mystery. There is a remarkable simplicity and directness with which Miller approached an apparently intractable problem. Few Ph D students, before or after Miller, have begun their careers with an experiment that launched a new field. The results of his analysis have been borne out by the recent reinvestigation of the residues of his experiments. The new technologies of chemical analysis have revealed far more than Miller could have seen in the 1950s. Can there be a better example of the importance of preserving samples and records?

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