Sidney W. Fox

My father was one of the pioneers of laboratory based research into the origins of life. Today, and for some time, in certain quarters his work is attacked and then disregarded (Stanley L. Miller and Leslie E. Orgel, *The Origins of Life on Earth*, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1974, pp. 143-145). Sid focused on thermal syntheses as distinct from electrical discharge, and emphasized the principle of *emergence*, a byproduct of self-assembly. That he was a difficult person late in his life is acknowledged by me. However, one should at least look at the proteinoid microsphere model that *has a life of its own*, so to speak and separate the model's attractive properties from Sid, the personality. This is not easy to do as can be seen from the contents of the Miller-Orgel book, and as has been discussed in detail by James Strick in his article: (*Creating a Cosmic Discipline: The Crystallization and Consolidation of Exobiology, 1957–1973*). The Strick article can be read here: [Strick]. I grew up with the model in the 1950's and even did my own experiments with proteinoid microspheres. Unless one has looked at microspheres under the microscope there is no other way to convey in mere words some of the attractiveness of this model. Uniform populations of micron diameter spheres are seen with an oil immersion, optical microscope. It is possible to watch Brownian motion vigorously animate the spheres in a way not easily distinguished from looking at some types of live bacteria.

Using a thermally controlled microscope stage, it is possible to observe microsphere formation as the boiled aqueous solution cools. Once a sphere has nucleated, subsequent sphere formations can be buds or even divisions. *De novo* generation of spheres also continues. As a 10-14 year old I made such preparations and observations. Dividing microspheres were a highlight among what could be seen. The division was assisted by the Brownian motion, at the end of which two daughter spheres would go off at random from each other. It is unexplained why the population of spheres is so uniform in diameter, in contrast to preparations of lipid bilayer membranes. The physical acts of budding and of division serve to preserve the size. Could modern cell division have some of its origin in the natural physical tendency of microspheres to divide, and is the size of simple bacteria a result of the same physical properties that determine the size of these microsphere preparations? (On this score, Miller and Orgel are summarily dismissive, *op. cit.* p. 144.) The microspheres exist and offer many experiments yet to be done. They present an attractive alternative basis for many of the quite recent experiments proposed and tried in the laboratory of Jack Szostak.

A string of amino acids is not a string of colored, identical beads. The chemical differences among the residues are substantial. In real syntheses, preferences exist between linking pairs. Some amino acids are incorporated more than others and some preferred pair wise associations also exist. In reality nothing like the totality of combinatorially possible types of sequences actually occurs, and what does occur is not uniformly distributed among the possible sequences. The true distribution of amino acids in a proteinoid is far from the proportions in the initial amino acid mixture. The proteinoid product can be fractionated, and the fractions can be sequenced. These sequences have a variety of catalytic and structural properties. Racemization of amino acids occurs with heating and some peptide bonds involve residue carboxyl groups (e.g. glutamic acid and aspartic acid) and residue amino groups (e.g. lysine). Normally DL mixtures of amino acids are used to make proteinoids. Chirality in the origin of life is still an open question (now L amino acids and D ribose, almost exclusively). Many plausible explanations can be entertained (see Miller-Orgel, *op cit*.).

Aspartic acid and glutamic acid are more frequent than average in many proteins. When enough of them, and/or basic amino acids, compared to the amount of the other amino acids, is in the mixture, a fine white (or light brown) powder of proteinoid can be isolated. Not enough aspartic acid, glutamic acid and/or basic amino acids and a dark unworkable tar results instead. Aspartic acid and glutamic acid are abundant in Miller-Urey type experiments as well, and in extraterrestrial sources.

Microspheres form by self-assembly from aqueous solution of proteinoid powder. They actually make double membranes. They are permeable to small molecules. This is actually desirable for a compartment very early on in the evolution of life as will be explained in the main text.

Sid died in 1998 at the age of 86. He had survived quintuple bypass surgery 9 years earlier. This fact is salient when trying to understand some of the animosity towards Sid and his work. The Miller-Fox relationship was tense for many years before that (see Strick) and each individual is credited with a degree of irascibility by those who knew them personally. When Sid had the bypass surgery he did not awaken from the anesthesia after the operation. For 13 weeks he remained in a coma. Interactions between various administered drugs seem to be responsible and it was my brother Larry who finally got the drugs changed. Sid woke up and, to everyone's surprise, seemed mentally unimpaired. However, there were initially unappreciated subtle side-effects, including increased irascibility and bouts of irrationality. These effects were manifested at scientific meetings, so I am told by friends who were attendees. I experienced it first hand on several occasions and toward the end of his life, Sid openly expressed the desire to disown me because I would not accept that he had already solved the problem of the origins of life. I wrote a few theoretical papers (and books) on the open problems as I saw them and this infuriated him because he saw the problem as solved. Nevertheless, his proteinoid microsphere model is still the most comprehensive *experimental model* for very early, pre-RNA World stages of the origin of life. As the reader will see, I put stock in many of its features.

Footnote, 9/14/08

That Sidney Fox existed at all is a rare chance circumstance. His Mother, Louisa (Lisa) Fox *nee* Berman, came to the United States at age 11 hidden in a crate aboard a ship to Boston, Massachusetts. She started out in Ukraine. It was standard practice to run long sharp blades into the crates to check for stowaways. She could easily have met her demise in this way but managed to avoid the blades by her own account. Aboard ship she scurried about. It is said she was very mature for 11, physically, mentally and emotionally. A man aboard ship "adopted" her and protected her during the journey. He helped her search for her older sister once they were in in Boston. Her sister already had seven children and basically could not help her. At 15 Lisa was married to a man 20 years her senior, Sid's father Jacob. Since Sid was 10 years younger than the elder of two sisters, Lisa was at least 25 in 1912 when Sid was born in Boston (Roxbury). Sid soon moved to Los Angeles, California. His early education was in LA, college was at UCLA and graduate school was at Caltech. Lisa Berman's journey made the existence of Sid the result of a long lineage of chance events. If not for the kindness of a total stranger, she may not have safely crossed the Atlantic Ocean. Isn't the history of each of us the result of sequences of rare chance events like this, at least at some time(s) in our ancestry?

Footnote, 9/15/08

Ironies:

By now the reader may have recognized that fefox is a chemical joke :-) Fe is the scientific notation for the element iron. Thus we have fefox → ironfox → I Ron Fox, a self-referential construct. Sid created such jokes. When I was in college, he would write letters with the salutation HFe. (For those of you who are too slow, that's Hi Ron.) Sid, himself, has a similar self-referential structure. Since he believed he had solved the problem of the origin of life on the early Earth, he was into other projects. The concept he found most profound and which received more of his time than others was the idea of the *id*. Sid wanted to extract his *id* before he died. Sort of like Sid → *id* . He believed it was an entity he might be able to isolate. I would object jocularly, *Id est* the *id* is just a manifestation of the living brain, and "dies" with the brain. For the same reason, I find the word chosen by Francois Jacob, *integron*, especially appealing. Yet, all of this has to do with the chance event of chosing a name. There is no *id* in it.