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Leslie Orgel 1927–2007

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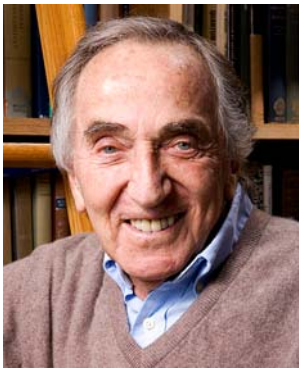

Leslie E. Orgel died of pancreatic cancer on October 27, 2007. He was 80 years of age. With his passing this journal, ISSOL, and the fields of origin of life studies and molecular biology lost one of their most creative minds. Born in London and educated at Oxford, Leslie began his career as a theoretical inorganic chemist. He is acknowledged to have been a major contributor (perhaps *the* major contributor) to the development of ligand field theory. His interest in biology was stimulated through contacts with such pivotal figures as Sydney Brenner, Jack Dunitz and Francis Crick. Leslie, independent of Crick and Carl Woese—who published similar proposals—conceived the idea that RNA must have been the first genetic material; ancestor of DNA and proteins. With the later discoveries of the catalytic properties of RNA, a complete model developed in which RNA would have been the first autocatalytically replicating molecule on earth—the idea which has come to be known as the RNA world.

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Leslie's laboratory at the Salk Institute, where he spent the major portion of his career, attacked and clarified a large number of questions which were at the heart of the problem of the origin of life. Many of these subjects were directly aimed at achieving an understanding of how the process of RNA self-replication might have begun. Important topics included, but in no sense were limited to: the synthesis of adenine and related compounds from HCN, pyrimidine synthesis, the modeling of prebiotic phosphorylation reactions, and nucleotide synthesis and oligomerization. Many of these areas were initiated at the Salk Institute, in collaboration with associates, who then served as "branching points" in continuing and expanding the studies in their own laboratories. Perhaps the most influential work of Leslie's laboratory was the creation of a synthetic system which has become known as "template-directed oligomerization of mononucleotides". The basic method utilized a pre-synthesized polynucleotide as the catalyst for the oligomerization of activated mono-nucleotides which were complementary to the template. An extensive series of investigations described the properties of the system and the results of model experiments (Orgel 2004 and references therein). The extent of the oligomerization and the regiospecificity of the linkages formed were shown to depend strongly on the nature of the activating group, the reaction conditions and the template sequence. The potential as well as the limitations of the method were explored and described in exquisite detail (Wu and Orgel 1992a, b, and c summarize the main conclusions). Certain sequences could be copied faithfully, while certain cases blocked the process (Hill et al. 1993).

Asking the right questions—an art in which Leslie was particularly skilled—sometimes produced unexpected answers. Challenging the template-directed reaction to select one chiral form out of a racemic mixture resulted in the recognition of "enantiomeric cross-inhibition" (Joyce et al. 1984). Homochirality was a unique problem, and the consequences for RNA self-replication were far-reaching. A possible way around the difficulty was the idea that another, non-chiral self-replicating system may have preceded RNA in evolution. This idea (the possible role of nucleic acid-like molecules or analogs) again gave birth to a long series of related publications, and a number of other laboratories also took up the challenge (Orgel 2004). Always generous in deferring to intellectual priority, Leslie acknowledged the precedence of Graham Cairns-Smith in suggesting the possibility of a precursor to nucleic acid replication. Nevertheless, it is clear that the stimulus for this new research direction emanated from Leslie's own laboratory. Many new nucleic acid analogs have been studied in this connection. For example, Albert Eschenmoser has analyzed a whole range of alternatives to RNA and DNA and more have been proposed by other workers. While this is not the place for a review of this field, it should be mentioned that notable results were obtained by Peter Nielsen using the non-chiral analog PNA, which also became the subject of collaborative study at the Salk Institute.

This capsule description cannot begin—and is not intended—to do justice to Leslie's scientific contributions. An appreciation of the influence of his work, and an impression of many of the studies to which it led, can perhaps be inferred from the list of contributors and topics in a recent issue of Chemistry & Biodiversity which honored his 80th birthday, as well as an earlier issue of this journal, in honor of Leslie's 70th birthday (see below). Although Leslie accepted only two candidates to pursue their Ph.D. degrees with him (Gerald Joyce and Rihe Liu), the long list of postdoctoral associates and visiting researchers at the Salk Institute reads like a who's who of origin of life research, and includes both the present and former editors of this journal. I especially remember the stimulating effect of daily interaction with Leslie, as well as the warm hospitality of Alice Orgel.

Leslie Orgel received many honors and was asked to serve on numerous advisory committees. Among other distinguished positions, he was a Fellow of the Royal Academy

of London, a member of the National Academy of Sciences of the USA, and of the Academy of Arts and Sciences. He was recipient of the Harrison Prize, the Evans Award and the H.C. Urey Medal. He was habitually courteous, considerate and possessed a fine sense of humor. All of his colleagues and friends already feel his absence and many others, who have merely experienced his congenial presence and—generally understated—contributions at a meeting, will miss him.

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Review

Orgel LE (2004) Prebiotic chemistry and the origin of the RNA world. Crit Rev Biochem Mol Biol 39:99–123 (and references therein)

Journal Issues Honoring Leslie Orgel

Chemistry & Biodiversity (2007) On Chemistry Leading to Life's Origin, 4:539–822. Dedicated to Leslie Orgel on the occasion of his 80th birthday.

Origins Life Evol. Biosphere (1997) Special Issue in Honor of Leslie Orgel on his Seventieth Birthday, 27:421–663.