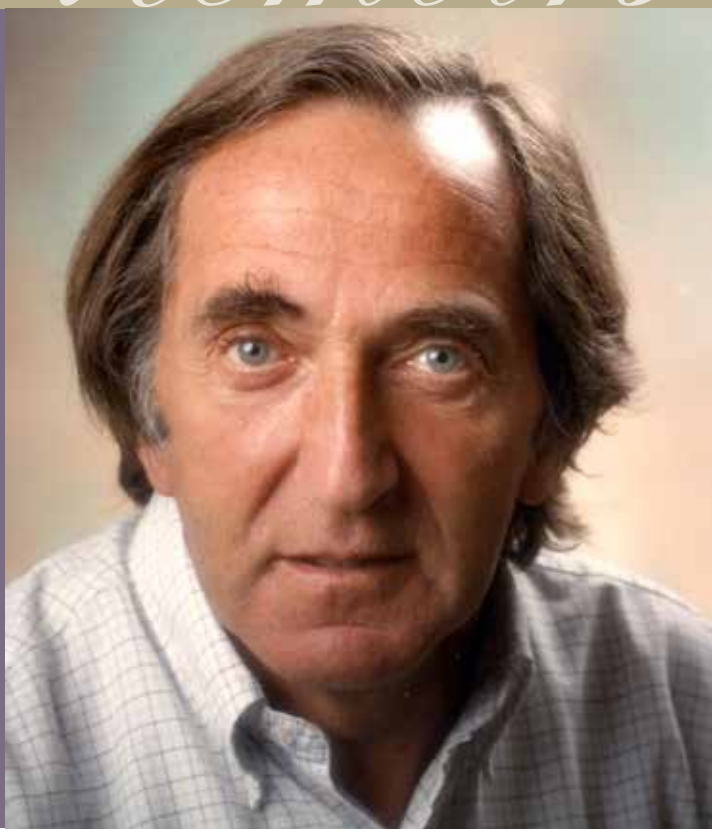
Leslie E. Orgel

1927–2007

BIOGRAPHICAL *Memoirs*



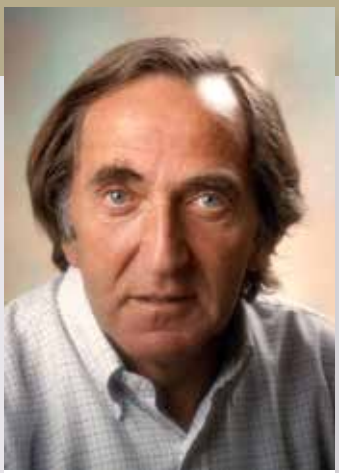
A Biographical Memoir by
Jack D. Dunitz
and Gerald F. Joyce

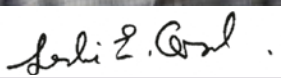
NATIONAL ACADEMY OF SCIENCES

LESLIE ELEAZER **ORGEL**

January 12, 1927–October 27, 2007

Elected to the NAS, 1990





By Jack D. Dunitz and Gerald F. Joyce

Leslie Eleazer Orgel was a theoretical chemist and investigator of the origins of life who made deep and lasting contributions in both of these scientific areas. He was born in London, England, on January 12, 1927, the second of three children of Simon and Deborah (Gnivisch) Orgel. His older brother Nevill was born on July 2, 1922, and died on December 28, 1957. His younger sister Delia was born on June 19, 1933, and currently resides in Silver Spring, Maryland. Leslie Orgel died on October 27, 2007, in San Diego, California, from pancreatic cancer. He is survived by his wife of 57 years, Alice (Levinson) Orgel; by his three children, Vivienne (b. April 4, 1955), Richard (b. November 29, 1956), and Robert (b. June 25, 1968); and by five grandchildren.

After attending Dame Alice Owen's School in London, which was evacuated during World War II to Bedford, England, Orgel studied chemistry at the University of Oxford, graduating in 1948 as BA with First Class Honours in Chemistry. He then undertook graduate research with Leslie Sutton, senior chemistry tutor at Magdalen College and himself a distinguished physical chemist.

Orgel's[1] first publication (1951) dealt with the semi-empirical calculation of electric dipole moments of conjugated heterocyclic molecules, and can be of no more than historical interest today. Notable is the expression of the authors' thanks to Charles Coulson, who was at the time a professor of theoretical physics at King's College in London. Coulson, one of the most important theoretical chemists of the time, had been lecturer at Oxford from 1945 until 1947 and then returned in 1952 as professor of mathematics. He had a great influence on Orgel and on many other budding theoreticians of the time.

1. This memoir will also appear, in slightly different format, in *Biographical Memoirs of the Royal Society*.

Already in his early years, Orgel was a prolific reader. There was a legend that although he sailed through his final degree examination with flying colors, he had attended very few formal lectures or practical laboratory exercise classes. He had learned most of what he knew through reading rather than through the formal Oxford chemistry curriculum. However, we can find no hard evidence for such a cavalier attitude on his part.

From 1951 until 1953 Orgel was a fellow of Magdalen College, Oxford. He then took up postdoctoral fellowships in America, first with Linus Pauling at the California Institute of Technology (Caltech) in Pasadena, and then with Robert Mullikan at the University of Chicago. The Caltech stay, where Orgel had little contact with Pauling but interacted closely with Alexander Rich and James Watson, was to have the greater long-term influence on his future development and career. Orgel then returned to England as assistant director of research at the Department of Theoretical Chemistry at Cambridge, directed by H. Christopher Longuet-Higgins, and as fellow of Peterhouse. Apart from a sabbatical leave at the Chemistry Department of the Hebrew University in Jerusalem in 1962, Orgel remained in Cambridge until his departure for his second career in America.

Orgel's brilliance in his first career as theoretical chemist was acknowledged by his election to the Fellowship of the Royal Society at the unusually early age of 35. The text of the proposal summarizes his achievements:

> *Distinguished for his contributions to theoretical chemistry, particularly theoretical inorganic chemistry. By applying and extending the theory of crystal fields he has interpreted and correlated a wide range of experimental data, including the thermodynamic and optical properties of transition metal complex ions, the structures of the bis-cyclopentadienyls, the observed stereochemical distortions, magnetic susceptibilities and nuclear magnetic resonance spectra of certain complex compounds, the distribution of the cations in the spinels and other problems in solid state physics. He has also contributed to the electronic spectroscopy of organic compounds and to various problems in biophysics.*

The list of names of proposers and supporters of his election reads like a directory of famous British theoretical and structural chemists of the day: Charles Coulson,

H. Christopher Longuet-Higgins, Harry Emeléus, Alexander Todd, Francis Crick, A. R. Ubbelohde, Leslie Sutton, John Linnett, Rex Richards, Dorothy Hodgkin, Edward David Hughes, Maurice Pryce, F. Charles Frank, and Kathleen Lonsdale.

Already in his early years, Orgel was a prolific reader. There was a legend that although he sailed through his final degree examination with flying colors, he had attended very few formal lectures or practical laboratory exercise classes. He had learned most of what he knew through reading rather than through the formal Oxford chemistry curriculum. However, we can find no hard evidence for such a cavalier attitude on his part.

Orgel was a prolific and persuasive writer. By the time he was 35 years old he had almost 100 scientific papers to his credit, besides a book, *An Introduction to Transition-Metal Chemistry: Ligand Field Theory* (1960), which soon became required reading for budding inorganic chemists and has established itself as something of a classic. The "Orgel diagram," a simplified graphical description of the way d-orbital energies split in fields of octahedral and tetrahedral symmetry, is still part of undergraduate education in inorganic chemistry. Although many of these early papers were products of collaboration with students and colleagues, almost half had Orgel as sole author, interpreting and re-interpreting experimental data collected from the literature regarding atomic ionization potentials, spectra, magnetic properties, crystal structures, and chemical reactivities.

An example of Orgel's unique view is his 1957 paper, "Ion Compression and the Colour of Ruby." Most of us take it for granted that rubies are red, but there is a problem. A ruby is a crystal of corundum (Al_2O_3) with a small amount of the Al^{3+} ions (about 5%) replaced by Cr^{3+} ions. Corundum itself is colorless and chromic oxide (Cr_2O_3) is green, the typical color of Cr^{3+} in an oxide lattice. Indeed, corundum samples with Cr^{3+} content more than about 8% are green. So why are rubies red? The answer depends on the fact that the ionic radius of Cr^3 (0.65 Å) is larger than that of Al^{3+} (0.50Å). For small amounts of Cr^{3+} within the corundum lattice, the surrounding close-packed arrangement of oxide ions is largely unchanged, so the Cr^{3+} ions are under compression; for larger amounts the lattice expands to adapt to the larger ionic radius of Cr^3. According to crystal field theory, this compression should increase the energy difference between the ground and first excited state, and indeed, it shifts the absorption band from around 16,000 cm^{-1} (transmitted light greenish) in Cr_2O_3 to about 19,1000 cm^{-1} (transmitted light red) in ruby.

Another nice example where crystal field theory provided a convincing explanation of apparently puzzling facts in inorganic crystal chemistry concerns the spinel family

of minerals, which are $A^{3+}_2B^{2+}O_3$ minerals with a close-packed arrangement of oxide ions (1957). In this work, crystal field theory was applied to explain the distribution of the cations among tetrahedral and octahedral sites in the oxide lattice ("normal" and "inverse" spinels) and the deviations from cubic symmetry of some spinels in terms of Jahn-Teller distortions.

Another remarkable achievement of Orgel was his explanation of the stability of the new, unprecedented "sandwich" structure of the ferrocene molecule in terms of orbital symmetry considerations (1953). This was new terrain, and it seems a pity that Orgel's account was couched in such formal terms (no pictures!) that hardly anyone understood it at the time. Moreover, and sad to admit, he was deprived by his co-author (JDD) of credit for a bold prediction based on his orbital symmetry arguments. Orgel argued that the same considerations that explained the stability of ferrocene (bis-cyclopentadienyl iron) should apply with minor adaptations to the still unknown and barely imaginable molecules dibenzene chromium $(C_6H_6)_2Cr$ and dicyclobutadiene nickel $(C_4H_4)_2Ni$, and therefore predicted the stable existence of these two compounds. The co-author argued that it would be a shame to spoil a sound scientific contribution with what might be regarded as risky speculation, and he persuaded Orgel to omit his prediction, which turned out, of course, to be completely correct. A few years later, after his return from America to England, Orgel took up again his argument that the elusive cyclobutadiene molecule should be significantly stabilized by complexation with Ni (1956), a prediction that was soon borne out by the preparation of a cyclobutadiene-Ni complex with the predicted structure (Criegee and Schroeder 1959).

It is hard to say when Orgel's interest in the biosciences began, although it must have been quite early. By late 1952 there were already weekly sessions on biomolecular topics with the newly arrived South African doctoral student Sydney Brenner. In early April 1953, Orgel was one of the first to inspect the new double-helix structure of DNA and he certainly understood its significance. Following an invitation from Francis Crick to look at the new DNA model, a group of five—Dorothy Hodgkin, Beryl Oughton (a postdoctoral researcher with Hodgkin), Sydney Brenner, Leslie Orgel, and Jack Dunitz—drove over from Oxford. They all knew enough about the problem to recognize almost immediately that the proposed DNA structure must be correct in its essential features. The base pairing explained, at least in principle, how information was transmitted from generation to generation. This visit turned out to have some historical importance, as it was the first occasion that Crick met Orgel and Brenner, both of whom became his close associates in later years.

Leslie Orgel and other members of the RNA Tie Club, photographed in 1955 at the Crick residence, Cambridge, UK. Left to right: Francis Crick, Alexander Rich, Leslie Orgel (not wearing his club tie) and James Watson. (Photo credit Alexander Rich.)

By early 1954 and the time of his arrival as guest scientist at Caltech, the DNA double-helix structure had already become the basis for two further problems. One was the genetic code: how could the sequence of amino acids in a protein be coded by the four-letter sequence of the nucleic acids? The other was the structure and function of RNA. At Caltech, Orgel became involved in both problems. Whereas the first problem was at that time a purely intellectual puzzle, the RNA question was open to experimental study. It was already known that RNA production in the living cell was associated with protein synthesis, and there were hopes of obtaining RNA samples that might yield interpretable diffraction patterns, such as those that had been produced by Rosalind Franklin for DNA. At Caltech, Orgel collaborated with James Watson and Alexander Rich on both problems.

One can hardly claim that these Caltech efforts led to any notable success, but they brought Orgel into the circle of scientists concerned with such problems. Indeed, he was elected to membership in the exclusive and slightly lunatic RNA Tie Club, founded by the remarkable polymath astrophysicist George Gamow. Each of the twenty regular members was associated with one of the proteogenic amino acids and permitted to wear a woolen necktie embroidered with a green-and-yellow helix (designed by Gamow). Orgel was assigned threonine, Crick was tyrosine, Watson was proline, Brenner was valine, Rich was arginine, and so on. The story of the creation, development, and ultimate demise of the RNA Tie Club deserves a scholarly account.

After his return from America to take up his appointment in Cambridge, Orgel went back to transition metal chemistry as the main focus of his scientific interests. In the course of the next few years, however, he was turning more and more towards problems of molecular biology and evolution. Besides discussions with his colleagues, such as Longuet-Higgins and John S. Griffith, for whom theoretical physics and chemistry overlapped with theoretical biology; and besides continued involvement with transition metal chemistry, Orgel enjoyed frequent discussions with Francis Crick and Sydney Brenner.

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By the early 1960s, amongst publications on ligand field theory and such matters, there are papers on the maintenance of accuracy in protein synthesis (1963) and on adaptation to disturbance of enzyme function (1964), clear indications of a switch in the direction of Orgel's scientific interests.

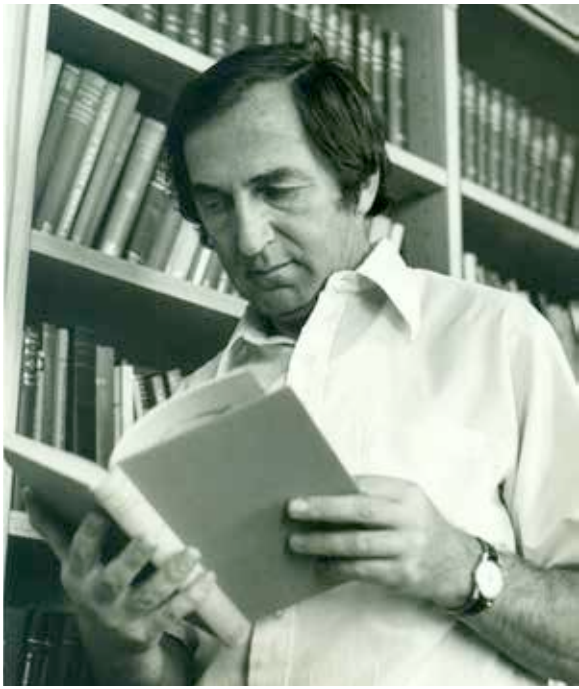
By the mid-1960s, Orgel increasingly felt that his future contributions to science were to be in the direction of molecular biology, especially in problems concerning the origins of life on Earth. He could see that future progress in theoretical chemistry was destined to depend on progress in computational solutions to quantum mechanical problems and no longer on application of model considerations to the interpretation of experimental data. After all, John Pople had been one of his colleagues at Cambridge, and Orgel could see the way the wind was blowing. He was well aware that the chemical and biological problems to which he was attracted and to which he wished to devote his future could not be solved by theory. They required an experimental approach along directions that were still undefined into a new and unexplored continent. He also saw that the switch from recognized expert and authority in theoretical chemistry to intruder in the biosciences was not going to be an easy one, especially in the UK, where university departments tended to support existing lines of research and where funding for new scientific projects was scarce. Although there were, of course, many exceptions to these limitations, Orgel saw better possibilities in America for starting a new career.

In 1964 Orgel was appointed as a senior fellow and director of his own Chemical Evolution Laboratory at The Salk Institute for Biological Studies in La Jolla, California. He was among the first group of faculty appointees at the Salk when its laboratories opened in 1963, also including Jacob Bronowski, Melvin Cohn, Renato Dulbecco, Edwin Lennox, and Jonas Salk. There, Orgel directed his attention to the origins of life and how self-replicating, evolving molecules could have first arisen on the Earth.

Orgel studied all aspects of the chemical origins of life, although he was especially intrigued by RNA. As the 1960s progressed, it became increasingly clear that RNA plays a central role in biology, serving as both the carrier and translator of genetic information.

Yet it was understood that proteins are the chief agent of biological function, with a role in replication of the genetic material. Orgel, together with Francis Crick and the microbiologist Carl Woese, were among the first to consider the possibility that early life was based entirely on RNA, without encoded proteins, with RNA bringing about its own replication. In a 1968 article titled "Evolution of the Genetic Apparatus," Orgel wrote:

> *To decide whether or not life based on nucleic acids alone might have evolved to any considerable degree of complexity in the absence of a well-defined relation between nucleic acids and protein synthesis, one must consider two problems, replication without (protein) enzymes and evolution without proteins.*



Leslie Orgel in his study at The Salk Institute in approximately 1965. (Photo by Optico Inc. Custom Photography, San Diego; courtesy of Alice Orgel.)

Orgel set out to demonstrate what he considered "quite plausible:" that reasonably accurate replication of RNA could be achieved in the absence of enzymes through the template-directed polymerization of activated nucleotides. If an RNA template could be made to direct the synthesis of its complement, and if the complement could do the same, then replication with exponential growth might be achieved. Furthermore, if a variety of different template sequences behaved in this manner, then natural selection would begin to operate, and what Orgel called "replicative doodling" (acellular Darwinian evolution) might be achieved. He postulated that this doodling would give rise to primitive "replicases" and to various synthetic "enzymes" composed of RNA. Thus, in 1968, he laid out the manifesto for what later came to be known as the "RNA world" hypothesis (Gilbert 1986). This hypothesis was not broadly accepted until the discovery of RNA enzymes in

the early 1980s, and for some skeptics not even until the crystal structure of the ribosome revealed that it is an RNA enzyme that catalyzes peptide bond formation.

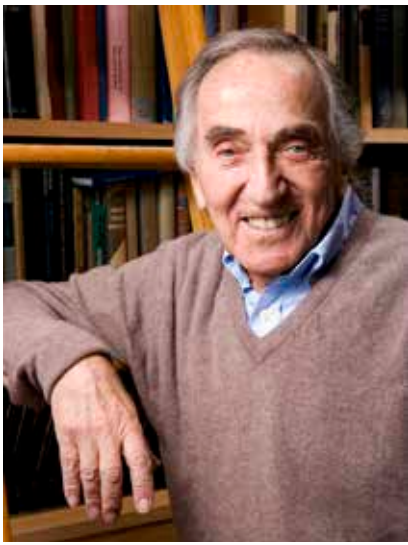
For Orgel, the RNA world hypothesis immediately gave rise to an experimental research program. He was confident that the chemical replication of RNA could be achieved, although he was less confident that RNA alone might have extensive catalytic ability. Thus his program explored the prebiotic synthesis of the building blocks of RNA, the assembly of those building blocks into mono- and polynucleotides, and the ability of a polynucleotide template to direct the synthesis of its complement. He made considerable progress in each of these areas and generally set the agenda for the study of prebiotic chemistry of nucleic acids for the next 30 years.

In the area of prebiotic chemistry, Orgel explored the synthesis of purines and pyrimidines from simple building blocks that are likely to have been available on the primitive Earth. As early as 1957, he was thinking about these problems. In a February morning walk through Kensington Gardens with Jack Dunitz, the two discussed the occurrence of adenine in the key molecules of both genetics and metabolism. Orgel remarked that what makes adenine so special is that it is the first insoluble polymer of hydrogen cyanide. Four years later, Joan Oró showed that adenine can be formed in remarkably high yield from ammonia and hydrogen cyanide (Oró 1961). Orgel subsequently explored mechanisms for concentrating these reactants under plausible prebiotic conditions, most notably through eutectic freezing (1966). He also made advances regarding the prebiotic synthesis of the other purine bases and of the pyrimidines, and demonstrated the coupling of purine bases with either ribose or ribose-phosphate to form purine nucleosides or nucleotides, respectively. Orgel considered alternatives to RNA, such as nucleic acid analogues based on arabinose rather than ribose, or with phosphoramidiate rather than phosphoester linkages joining the nucleoside subunits.

Orgel's most significant contributions pertaining to the origins of life concerned the templated synthesis of RNA, employing a preformed RNA template to direct the polymerization of activated mononucleotides, a process that is at the heart of RNA replication. Just as he had hypothesized in 1968, Orgel showed that an RNA template could be made to direct the synthesis of its complement. Initially this reaction could be carried out only in modest yield, employing a very restricted set of templates, and resulting in a mixture of 2′,5′-, 3′,5′-, and 5′,5′-phosphodiester linkages among the products (1976). However, he continued to make improvements in every aspect of the reaction, and eventually it became possible to copy a variety of template sequences to their complementary

products (1983). Orgel never achieved, and to this day no one has achieved, the residue-by-residue copying of RNA in a sequence-general manner. Thus, his vision of "replicative doodling" has yet to be realized experimentally.

Orgel's work on the origins of life sometimes had practical applications, which he did not hesitate to pursue. For example, his investigation of alternatives to ribonucleosides led him to devise a novel and straightforward way to synthesize cytosine arabinoside (1970), a compound that is widely used to treat leukemias and lymphomas. Orgel derived modest patent income from this invention, which he put to good use supporting afternoon tea and occasional parties for members of his laboratory. He also devised methods for cross-linking proteins and nucleic acids, which were patented and have had applications in clinical diagnostics.



Leslie Orgel in his study at The Salk Institute in 1998. (Photo Credit: Sarah Loffler, The Salk Institute.)

Although Orgel did as much as anyone to advance the RNA world hypothesis, he also was one of its sharpest critics. He never hesitated to point out aspects of the prebiotic synthesis of RNA that remained unresolved, especially the difficulty in forming RNA without generating complex mixtures of related compounds that would interfere with RNA replication. Particularly troubling for him was his experimental finding that the template-directed polymerization of D-mononucleotides is severely disrupted by the corresponding L-enantiomer (1984). On the racemic prebiotic Earth, this would have been a serious obstacle to the emergence of RNA-based life. Accordingly, Orgel explored potential alternatives to RNA as the first genetic molecule, especially compounds that are simpler, more readily accessible through prebiotic synthesis, and not susceptible to enantiomeric inhibition (1987). He also studied the transfer of information through template-directed synthesis from these potential RNA predecessors to RNA (1995, 1999).

In his later years, Orgel saw substantial progress from other laboratories on the problems he had long studied, which gave him hope that the origins of life would become more completely understood. For example, John Sutherland demonstrated a fruitful new approach to the prebiotic synthesis of nucleotides involving the concerted, rather than

separate, synthesis of their component building blocks (Anastasi et al. 2006). Donna Blackmond showed that, through entirely chemical processes, there may have been a high degree of enantiomeric enrichment in particular locales on the primitive Earth (Klussmann et al. 2006). Albert Eschenmoser developed what Orgel regarded as plausible precursors to RNA based on simpler analogues that have excellent templating properties (Schöning et al. 2000). Despite these advances, Orgel did not believe that the origin of life of Earth would ever be understood in its entirety because he regarded it as an inherently historical event. One may be able to understand the rules that governed life's origins, but not the details of each successive molecular transformation that culminated in our particular form of life.

Orgel regarded Darwinian evolution as being the central, unifying principle of biology, and he felt that if one could explain the chemical origins of Darwinian evolution on Earth, "the rest is just history." He viewed Darwinian evolution as a chemical process that can be realized with molecules, cells, or multicellular organisms. In 1967, Sol Spiegelman conducted the first extracellular Darwinian evolution experiment, employing the genomic RNA of Qß bacteriophage, which he replicated in the test tube using Qß replicase protein and the four nucleoside-triphosphates (Mills et al. 1967). Spiegelman was a visiting investigator in Orgel's laboratory in 1969, and although the two had a pricklish relationship, they conducted a remarkable experimental demonstration of evolution in action in which Qß RNA was made to evolve resistance to the intercalating molecule ethidium bromide (1970). The starting RNA molecules could not be replicated in the presence of 60 μM ethidium, but the evolved molecules amplified readily in the presence of 100 μM ethidium, and had become dependent on ethidium for optimal amplification efficiency.

Experiments like these led to the development of "Orgel's Rules" of evolution. Orgel's First Rule is: "Whenever a spontaneous process is too slow or too inefficient, a protein will evolve to speed it up or make it more efficient." This is a statement about necessity driving evolutionary invention. Orgel's Second Rule, which is the more widely cited, is: "Evolution is cleverer than you are." In other words, evolution is a better "designer" than any so-called "intelligent designer." The twists and turns of evolution are difficult to predict, let alone outwit. In the modern era of directed evolution technology, a common explanation for an experiment gone awry is, "You get what you select for." This is really just a corollary of Orgel's Second Rule because if you were as clever as evolution you would always know how to go about selecting for what you want.

Orgel had a sharp intellect, a broad range of interests, and he read widely in many disciplines. He was interested in anything that provided intellectual challenge and was an excellent discussion partner because he listened attentively, weighed up the merits or flaws of any new suggestions, often saw new aspects of the matter under consideration, and was never slow to voice his opinions. There was often a particular expression in his eyes when he became involved in intellectual discussion: attentive, questioning, sometimes almost teasing. On rare occasions he could be brusque, even rude, turning his back and walking away when he felt at a loss as to how to continue a conversation. Orgel could hold his own in discussion even with such spectacularly brilliant personalities as Francis Crick and Sydney Brenner, his companions at Cambridge and his colleagues in La Jolla. Those who had the privilege of witnessing this trio in action will remember it all their lives.

Orgel could be patient with stupidity or slow wittedness, which were characteristically met with raised eyebrows and an ominous silence. He seldom lost his temper, and then only with regard to what he considered intellectual dishonesty. On those occasions when he felt compelled to set things straight, he did so with the dagger of his intellect, rather than the bluster of his emotions. His substantial intellectual gifts provided a kind of hyper-rationality that served him well, including helping him face without sentimentality the fateful diagnosis of metastatic pancreatic cancer. Told that he had only a few months left to live, he saw no reason to believe that he would be a statistical outlier with regard to the time of survival after diagnosis. Further, he admonished: "You shouldn't expect any deathbed conversions from me!" Orgel found comfort in looking at things objectively, even his own mortality, and he found comfort in the purity of rational thought. Indeed, his final weeks were devoted to the completion of his last paper, published posthumously, on "The Implausibility of Metabolic Cycles on the Prebiotic Earth" (2008).

In addition to his scientific interests, Orgel was a keen, often obsessive, collector in several areas: Oriental carpets, Andean rugs, books important in the history of science, objets d'art, and French wines. His collection of Persian saddle bags was one of the two largest in the United States, which he described in an article for *Oriental Rug Review* titled, "An Obsession for Bags" (1990). These pursuits occasionally took him into experimental efforts, for example, validating the authenticity of antique textiles by electron microscopy and other analytical methods.

One of Orgel's journeys from collector to scientist concerned the development of what he called "eutectic wine." This was perhaps inspired by his reading about Robert Boyle's interest in freezing aqueous solutions and Boyle's account of early Dutch navigators

stranded in the ice near Nova Zembla who sampled the results of the partial freezing of beer and other alcoholic beverages (Boyle 1661). Orgel's idea was to cool wine to the eutectic temperature, at which point most of the water could be removed as a frozen solid, leaving behind liquid alcohol that contained, hopefully, all of the flavors. Transport of such a concentrate would be much more economical than that of the original product.

Orgel, his wife Alice, and friends frequently engaged in camping trips, especially to Baja, California, during which the evening meal around the campfire was not complete without fine wine. These expeditions provided a good excuse for an experimental investigation. One could save weight and bulk by bringing along the equivalent of a 750 ml bottle of wine in a 50 ml pouch. Addition of water in the correct proportion should then recreate the original wine. With the permission of then Salk President Frederick De Hoffman, Orgel's graduate student (GFJ) was set to work on this side project. The experiments were a technical success, but a critical tasting revealed that, except for the wines Orgel called "plonk," too much flavor had been lost to the aqueous phase. The control wines, of course, were perfectly drinkable and provided some consolation for the failed theory. Cheers to a remarkable scientist and dear friend.

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