JEROME VINOGRAD

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This volume is dedicated to the memory of Professor Jerome R. Vinograd, a man who was for many years one of the intellectual leaders in the physical biochemistry and molecular biology of macromolecules and, most particularly, of the nucleic acids. The majority of the contributions which follow were directly influenced by him in that they represent developments of discoveries and of concepts which originated in his laboratory. Yet others of the contributions, although their subject matter lies farther from the areas of his own direct interests, were substantially stimulated by his ideas and encouragement. The authors themselves comprise many of his former students and close collaborators, as well as some of his contemporaries in other laboratories with whom he was in especially close contact. The breadth of their own current interests, as well as the leading role which many of his students currently play in the development of molecular biology, is itself tribute to his genius.

Jerry Vinograd began his career as a physical chemist, trained in the exacting but little-understood discipline of surface and colloid chemistry. He first received his undergraduate degree in chemistry from the University of Minnesota and then, in 1931, he went to the University of Berlin to study colloid chemistry under Professor Herbert Freundlich. In 1933 he left Germany along with Freundlich, with whom he continued to work at University College, London, for two more years. Returning to the United States in 1936, he went to UCLA and obtained a Master of Arts degree in organic chemistry under Professor W. G. Young. Jerry Vinograd's formal education was completed at Stanford under the direction of Professor J. W. McBain, and he received his Ph.D. in 1940 in physical and colloid chemistry. This solid background in physical and organic chemistry does much to explain the rigor and care which constitute the hallmark of Dr. Vinograd's published works. His deep understanding of chemistry and of molecular interactions provided his students with high standards indeed for the investigation of biological phenomena. Jerry Vinograd was a member in good standing in the select group of brilliant physicists and chemists who entered biology in the period from the thirties through the sixties and who effected a true revolution.

Jerry Vinograd published over one hundred papers in his professional

lifetime, and it is instructive to consider the development of his career in terms of their evolving subject matter. His first eight publications come from the pre-Caltech days and are devoted to studies of surface tension, of dyes in aqueous detergent solutions, and of the structure of micelles. During this period he was first a student and then, during the decade 1941-1951, a Research Chemist for the Shell Development Co.

Jerry joined the Caltech faculty as a Senior Research Fellow in 1951, progressing to Research Associate in 1956 and Professor of Chemistry and Biology in 1965. Shortly before his death he was appointed to an endowed chair, the Ethel Wilson Bowles and Robert Bowles Professor of Chemical Biology. The move to Caltech was occasioned at least in part by his desire to conduct independent basic research and to apply his knowledge of chemistry to the fascinating array of emerging biological problems. Publication number nine, submitted jointly with Dan Campbell and Phillip Sturgeon, reflects this altered emphasis: "Separation of Complete and Incomplete Rh Antibodies by Centrifugation." This was the first of a series of papers involving the ultracentrifuge which significantly influenced the course of molecular biology. In 1957 he published, with Meselson and Stahl, the now classic "Equilibrium Sedimentation of Macromolecules in Density Gradients," thus providing a method which was to become one of the two or three key techniques in the development of the molecular biology of the nucleic acids. The first major application of this method was the subsequent demonstration by Meselson and Stahl of the semiconservative nature of replication of DNA. This initial contribution was followed by a series of elegant and rigorous papers (with John Hearst, James Ifft and several others) in which the principles of equilibrium density gradient centrifugation were definitively developed. He was also, in the course of these studies, the first (with John Hearst) to demonstrate the importance of hydration in understanding the buoyant and other properties of the nucleic acids. In a second series of papers, beginning in 1963, he developed the technique of band sedimentation in a self-generating density gradient. This method represents a great advance for many purposes over the then currently used moving boundary sedimentation, both for macromolecules and for viruses. It was, in fact, the technique of band sedimentation which provided the first evidence for the existence of multiple circular forms of polyoma DNA.

Jerry's other interests during the late fifties and early sixties included protein chemistry, especially the study of myxomycin and of

hemoglobin. The buoyant technique was expanded to include proteins, and a series of experiments was undertaken to investigate the nature of the subunit interactions in hemoglobin. In a short-lived return to his earlier interests, Jerry also published (with J. Bello and others) a series of papers elucidating the mechanism of gelation of gelatin.

Jerry Vinograd is, of course, best known for his enormously significant work involving first the discovery (in polyoma virus) and later the exposition of the principal properties of closed circular DNA. The first paper in this domain, coauthored by Roger Weil, came in 1963, appearing in the same issue of the Proceedings as a comparable study by Dulbecco and Vogt. This paper showed that the DNA of purified polyoma virus yields three components upon band sedimentation, and these were given the now-familiar appellations components I, II and III. The true stroke of brilliance was, however, reserved for the next publication (in 1965): "The Twisted Circular Form of Polyoma Viral DNA." Here it was first proposed that Component I contains two covalently continuous strands. The terms "topological restraint" and "tertiary turns" were used for the first time, and the revolutionary consequences of these concepts for DNA structure were clearly recognized.

The great contributions of Jerome Vinograd to understanding closed circular DNA are so well-known that no detailed discussion is required here. A list of his major discoveries during the subsequent years would include, as highlights, the first mathematical formulation of the topological constraint ($\alpha = \beta + \tau$); development of most of the methods, still in use, for counting the number of twists in a closed DNA; the discovery of catenanes and of circular oligomers; the origination of the concept that free energy is associated with superhelix formation, and its estimation; and the first application of intercalative dyes to the detection, isolation, and characterization of closed circular DNA.

Beginning in about 1970, Jerry became actively interested in two new topics: the replication of closed circular DNA and the use of this molecule as a substrate for various enzymes. The structure of a stable replicative intermediate, termed D-loop DNA, was first reported in 1971 (with H. Kasamatsu and D. L. Robberson) in extracts of the mitochondrial DNA from mouse L cells. This work was later extended to include the characterization of intermediates in more advanced stages of replication and the demonstration of the unidirectionality of replication in mouse mitochondrial DNA. Among his last contributions was the application of closed circular DNA

to the study of the eukaryotic DNA nicking-closing enzyme, work which led to an elegant paper in the 1975 Proceedings describing the ability of this enzyme to catalyze the formation of a Boltzman distribution of closed, twisted DNAs from a closed DNA substrate of any extent of super-coiling. It is clear, in retrospect, that Jerry Vinograd was responsible for initiating a new and existing area of research. This distinction belongs to few individuals indeed. In a very real sense, every paper involving circular DNA is a tribute to the wit and originality of Jerome Vinograd.

Official recognition was amply provided for Jerry's many accomplishments, not only by his academic appointments but by his election to the National Academy (in 1968). He was appointed to numerous special lectureships and was the recipient of a variety of other honors, including the Kendall Award (1970) and the Helen Hay Whitney Foundation T. Duckett Jones Award (1972). In spite of the increasing public recognition he remained throughout a modest man. He was a friendly and generous person, noted for his honesty, politeness, respect for others, and devotion to careful and correct procedure. He worked long hours in the laboratory, with a devotion that can only originate from a keen appreciation of the excitement of discovery. This in spite of two major heart attacks (in 1954 and 1969), which he allowed to restrict his activities less than was perhaps wise. His unbounded enthusiasm would however, permit no other course.

In retrospect, Jerry Vinograd's seemingly varied career shows what is perhaps a remarkable consistency. He fully appreciated the great usefulness of chemistry in understanding seemingly anomalous biological phenomena. He had the knack to recognize when an unexplained observation was significant and the tenacity to follow through with a correct explanation. He progressed intellectually from micelles to proteins to ultracentrifugation to DNA to closed circles to replication, building each new discovery upon those which had gone before, yet continually reaching out into new and fascinating problem areas. His approach to understanding phenomena was rigorously objective and, to the assertion that some observation or other could not be explained, his characteristic reply was "There's no such thing as magic." In this he was, perhaps, somewhat mistaken. There was indeed a sort of magic, expressing itself in the life of Jerry Vinograd, which will not come again.

William R. Bauer