Adrian M. Srb

1917–1997

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
June B. Nasrallah

NATIONAL ACADEMY OF SCIENCES

ADRIAN MORRIS **SRB**

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By June B. Nasrallah

Adrian Morris Srb's career in genetics spanned more than 40 years, from 1941 until his retirement in 1985. As a graduate student of George W. Beadle and as an independent researcher at Cornell University, he was involved in some of the major breakthroughs in what was called "biochemical genetics," the forerunner of modern molecular genetics. He investigated many of the genetic questions that were among the most fundamental and exciting of his time, and he was one of the most respected fungal geneticists in the world. At Cornell, he guided the transition from the Emerson-Beadle-McClintock era of classical genetics first to biochemical genetics and then to modern molecular genetics.

For most of his career, Srb's organism of choice was the red bread mold *Neurospora*, which was the preferred genetic model for biochemical genetics in the 1940s. He and his co-workers made significant contributions to the genetics, physiology, and development of *Neurospora*, covering a wide spectrum of topics including biochemical genetics, cytoplasmic inheritance, quantitative inheritance, the nature of dominance, the genetic and biochemical basis of differentiated phases of the fungal life cycle, and morphogenesis. Less often, Srb also used yeast and corn in his research. He understood and was a strong advocate for the need to develop a variety of experimental model systems, including plants.

Srb was a superb writer and his keen interest in teaching led to his co-authorship of the textbook *General Genetics*, which served for many years as the standard genetics textbook at many universities throughout the world. Srb's colleagues, co-workers, and students appreciated his extraordinary gifts as a teacher and writer, his generous mentoring of students, his scientific integrity, and his encyclopedic knowledge not only of genetics and biology, but also of literature, art, history, music, politics, sport, food, and wine.

Among Srb's other major contributions is his work as an advisor to governmental agencies and universities, where he lobbied for expanded teaching and use of genetics in agriculture, medicine, and other areas of biology.

Personal history

Adrian Srb was born in Howells, Nebraska, on March 4, 1917, to Jerome Valentine Srb and Viola Morris, who were of Czechoslovakian and Welsh descent, respectively. Srb grew up on a farm that his grandparents had originally homesteaded in the 1860s. Both his parents were educators. His mother was an English literature professor at the University of Nebraska. His father, who served for 22 years as superintendent of schools, took summer courses at the University of Nebraska, earned a master's degree in agronomy in 1937, and was subsequently hired as director of short courses and an extension specialist at the University of Nebraska College of Agriculture, working with Franklin D. Keim, a crop production specialist who was then chairman of the university's Agronomy Department.

Srb attended Howells High School, graduating in 1933. His interest in literature and his superb writing skills led him to enroll in the English literature program at the University of Nebraska in Lincoln, where he earned a bachelor of arts degree with high distinction in 1937. He supplemented his income by playing piano at local bars.

While beginning graduate work in English literature at the University of Nebraska, his interests shifted dramatically from literature to biology, allegedly as a result of an accidental visit to the science library at the university, but also no doubt after having his interest piqued by his father's activities in agronomy. Thus, he enrolled in a genetics course taught by F. D. Keim, and subsequently, under Keim's supervision, performed research on the effects of exogenously applied vitamin B1 on various phases of growth and agronomic traits in alfalfa and sorghum. He also performed field research for a hybrid corn program during the summer of 1940.

After obtaining a master's degree in agronomy in 1941, he enrolled at Stanford University to begin graduate studies with George W. Beadle in the then-emerging field of biochemical genetics.

In 1940, Srb married Jozetta Helfrich, a graduate student in economics at the University of Nebraska who subsequently obtained a master's degree at Stanford in sociology and economics. She worked for many years as research associate, publisher, and editor at the

New York State School of Industrial and Labor Relations at Cornell University, as well as a consultant to the U.S. Department of Labor in Washington, DC. The Srbs raised three children: Rosalind, Katherine, and Jerome.

Despite the shift in his professional career from literature to science, Srb maintained a lifelong interest in literature and music. In later years, he developed the hobby of collecting first-edition juvenile books and even wrote and illustrated at least one book of his own for his granddaughter.

After his retirement in 1985, Srb suffered from several health problems that lasted until his death on May 24, 1997, at the age of 80.

The Nebraska-Cornell-Stanford connection

F. D. Keim, who had obtained his PhD in 1927 at Cornell University, was in the habit of sending his best students to work with the most prominent geneticists of the day, particularly those he had known at Nebraska or Cornell. In the 1920s, he had sent his students to Cornell, urging them to work with Rollins A. Emerson, who was a graduate of the University of Nebraska and former faculty member at Nebraska before moving to Cornell in 1914.

George W. Beadle was among these students, referred by Keim to work with Emerson. Beadle arrived at Cornell in 1927 and completed his doctorate in 1930, working on the cytogenetics of corn, one of the most exciting topics of genetics research at the time. He worked alongside an illustrious group of Emerson students that included Barbara McClintock, Marcus Rhoades, and Charles Burnham.

In 1941, Keim helped convince Srb to enroll at Stanford University for graduate work with Beadle. Srb worked alongside students and post-doctoral fellows at Stanford who are now recognized as major contributors to the field of genetics, such as Edward Tatum, Norman Horowitz, David Bonner, Herschel Mitchell, and Mary Houlahan Mitchell. The Beadle laboratory was also a destination for many of the distinguished geneticists and biochemists of the day, including Barbara McClintock, who visited Stanford in 1944, at the invitation of Beadle, to work out the basic meiotic cytology for *Neurospora*. Srb forged life-long friendships with many of these scientists. He had a particularly close friendship with Beadle, or “Beets,” as close associates called him.

During their graduate studies, Srb and his wife lived in the caretaker's quarters at the Stanford Botany Garden, where Beadle visited to check on vegetables that he grew. As recounted by Srb in his 1973 article, "Beadle and *Neurospora*, Some Recollections," Beadle would often awaken the Srbs early on Sunday mornings, ready to discuss tomatoes, squash, and corn. Beadle and Srb were avid gardeners, and Beadle would devise contests as to which one of them could grow the sweetest corn or the largest pumpkin—contests that Srb lost, more often than not.

Shortly after completing his PhD in 1946, Srb moved to the California Institute of Technology (Cal Tech), in Pasadena, with Beadle, who had accepted to succeed T. H. Morgan as chairman of the Division of Biology at Cal Tech. Srb continued his work on aminoacid metabolism as a National Research Council Fellow in Genetics. At the same time, he was appointed assistant professor at Stanford, which required him to shuttle frequently between Pasadena and Palo Alto.

In 1947, he moved to Cornell University, where he would spend the rest of his career, first as an associate professor and then professor beginning in 1951, in the Department of Plant Breeding. In the mid-1960s, his position changed to professor of genetics in the Section of Genetics, Development, and Physiology within the Division of Biological Sciences, a division of the university that he had a prominent role in creating.

Scientific contributions biochemical genetics of *Neurospora*: 1941–1957

In joining the Beadle laboratory, Srb assumed that he would investigate eye pigmentation in *Drosophila*. In collaboration with Boris Ephrussi, Beadle had developed techniques for transplanting eye discs from one larva to another with the goal of using eye color as a model for probing the nature of gene action. However, by 1941 Beadle's focus had shifted to the role of genes in metabolism, and he realized that a more suitable model system was required for understanding these genes.

Beadle had identified the red bread mold *Neurospora* as an ideal organism for genetic studies of metabolism. The sexual phase of *Neurospora*, which had been discovered more than a decade earlier, initiates by the formation of fruiting bodies in which haploid nuclei of opposite mating types, *mat A* and *mat a*, fuse to produce a short-lived diploid cell that immediately enters meiosis, after which the four meiotic nuclei divide again to form eight nuclei within a cylindrical sac, the ascus.

In the eight-spored species *N. crassa* and *N. sitophila*, each of the eight nuclei becomes enclosed in a single spore, resulting in eight ascospores that are arranged linearly within the ascus in an order that reflects the two divisions of meiosis. The ability, novel at the time, to perform tetrad analysis of the four products of a single meiosis endowed *Neurospora* with a definite advantage for genetic studies. *Neurospora* had another advantage for analysis of biochemical mutants: It could be grown in the laboratory and on a synthetic medium of defined composition.

Thus, when Srb arrived at Stanford, the Beadle laboratory was engaged in x-ray or ultraviolet-light mutagenesis of *Neurospora* and isolation of "nutritional" mutants—mutants that could only grow if a particular amino acid or vitamin was added to the synthetic minimal medium on which wild type *Neurospora* thrived.

Graduate students and more senior investigators were each involved in the analysis of particular sets of mutants. It fell to Srb and Norman H. Horowitz to study the genetic control of the ornithine cycle. They investigated 15 mutants, the growth defect of which could be rescued by addition of arginine to minimal growth medium. Based on complementation studies involving analysis of progenies from pairwise mating among the various mutant strains, as well as mating between the mutants and wild type strains, and analysis of heterokaryons formed by pairwise fusion of the mutants, they identified seven genetically distinct loci.

Srb and Horowitz examined the response of each of the mutants to the addition of various compounds structurally related to arginine, and they found that normal growth was restored by arginine alone in one mutant; by arginine or citrulline in two mutants; and by arginine, citrulline, or ornithine in four mutants. They concluded that each of the genetically distinct mutants was blocked in a separate enzymatic reaction of the arginine-biosynthetic pathway. Moreover, by determining which compound accumulated in the culture medium for each of the mutants, they inferred a biosynthetic pathway in which a precursor compound is converted to ornithine, then citrulline, and finally arginine, with four enzymatic reactions required for the production of ornithine from the unknown precursor.

It is now known that four of the five reactions leading to the formation of ornithine are specified by the four genetic loci that Srb and Horowitz identified. Their work, together with the analysis of various biochemical mutants by others in the Beadle group, led to formulation of the "one gene-one enzyme" hypothesis of gene action, for which Beadle, During World War II, the Committee on Medical Research of the Office of Scientific Research and Development declared Beadle's *Neurospora* program essential to the war effort for its potential value in developing bioassays for vitamins and amino acids in food.

together with his research associate Edward Tatum and Tatum's student Joshua Lederberg, was awarded the 1958 Nobel Prize in Physiology or Medicine.

During World War II, the Committee on Medical Research of the Office of Scientific Research and Development declared Beadle's *Neurospora* program essential to the war effort for its potential value in developing bioassays for vitamins and amino acids in food. As a result, neither Srb nor other members of the Beadle group were drafted for service in the war. Towards the end of the war, during 1944 and 1945, Beadle was asked by them War Production Board to investigate the possibility of obtaining strains of *Penicillium* with increased yields of penicillin. Srb worked on this Stanford Penicillin Project as a civilian with the Office of Scientific Research and Development, but his efforts and those of other students engaged in the penicillin project did not produce the desired outcome.

In the 11 months between 1946 and 1947 that Srb spent at Cal Tech performing post-graduate study under a National Research Council fellowship in genetics, he studied the effects of canavanine on *Neurospora* and demonstrated that canavanine and arginine act as metabolic antagonists. This work was carried out under the supervision of Norman Horowitz and Cornell graduate Sterling H. Emerson, another Nebraskan and the son of Rollins A. Emerson who had worked with his father on the genetic relationships of andromonoecious mutants of corn.

Srb joined the faculty at Cornell and continued his studies of the arginine biosynthetic pathway, primarily in Neurospora but also in plants and yeast, the latter during a sabbatical in 1953 and1954 as a Guggenheim and Fulbright Research Fellow with Boris Ephrussi at the University of Paris. His continued analysis of mutant strains of *Neurospora* revealed the complexity of the pathway and its intersection with other amino-acid biosynthetic pathways.

His genetic studies also uncovered the importance not only of biosynthetic genes, but also of unlinked genetic modifiers that affect a strain's sensitivity to amino-acid deficiencies. He initiated experiments to study the effects of these modifiers on the evolution of biochemical pathways. He also extended the canavanine and arginine work to corn embryos cultured on artificial media and inferred that arginine biosynthesis used the same precursors in corn as in *Neurospora*.

A major unanswered question at the time related to the nature of mutagens and mutations. To address this issue, and as a result of his study of spontaneous and induced mutations, from canavanine sensitivity to canavanine resistance, Srb proposed the use of canavanine sensitivity as a means to screen various agents for mutagenic activity.

He also collaborated with his colleague Harold H. Smith, a plant geneticist in the Department of Plant Breeding at Cornell, on a project aimed at identifying the types of chemicals that have mutagenic activity. The goal was to use the resulting information for deducing the types of reactions that will cause genetic alterations, and possibly to understand the nature of the mutation process under these conditions. Various chemicals were tested for mutagenic effect on a variety of biological materials, including corn pollen, onion and bean root tips, and *Neurospora* spores, and several alkylating agents were found to be effective mutagens in both plants and fungi.

From biochemical genetics to cytoplasmic inheritance and developmental genetics: 1958–1985

Srb never lost interest in the genetic basis of metabolism, but starting in the late 1950s, he tackled a range of other topics that were then at the forefront of genetic research. During his first sabbatical in Paris, he had developed an interest in non-Mendelian inheritance. Cases of extra-chromosomal inheritance were beginning to emerge in several organisms, and basic questions were being asked as to whether extra-nuclear heredity really existed, and if so, in how many forms it existed.

Work on yeast in the Ephrussi laboratory had established some basic principles of extra-nuclear inheritance and its interactions with the nuclear genetic system. Srb was interested in the potential role of cytoplasmic inheritance in evolutionary processes. Reciprocal crosses between different species of *Neurospora* and strains of *N. crassa* from different geographical locations revealed strong interactions between the nuclear and cytoplasmic genetic systems. These results supported the hypothesis that cytoplasmic genetic systems diverge during speciation in a manner similar to their nuclear counterparts.

These studies and Srb's thoughts on cytoplasmic inheritance were further refined during his second sabbatical in 1960 and 1961 as a National Science Foundation senior post-doctoral fellow working at the University of Paris with Boris Ephrussi and at the Centre National de la Recherche Scientifique at Gif-sur-Yvette with Piotr Slonimski. Slonimski's studies in yeast had demonstrated that genetic information resides outside the nucleus in mitochondria, a finding that established the field of mitochondrial genomics.

While performing his experiments in the Ephrussi laboratory during 1953 and 1954, Srb had identified not only the biochemical mutants he sought, but also spontaneous morphological mutants of yeast. This finding provided the initial impetus for the work that would occupy him for the rest of his career: understanding the genetic and cellular basis of morphogenesis.

However, his interest in morphogenesis was largely based on his conviction that the study of differentiation and development was an important emerging field at the intersection of cell biology, physiology, evolutionary biology, systematics, and the emerging field of molecular biology. And he had ample material for these studies in the form of many morphological mutants that had been recovered as a by-product of his research with mutagens. Among these mutants, several exhibited compact or "colonial" growth instead of the spreading filamentous mycelial growth typical of wild type. Srb related this mutant morphology to dichotomous branching of vegetative hyphae, and in collaboration with F. C. Steward, a plant physiologist at Cornell, the new method of polyacrylamide gel electrophoresis of proteins was applied in an attempt to correlate this variation with biochemical changes in protein composition. This electrophoresis approach, a precursor of the molecular biology technique that eventually dominated the field of developmental genetics, was later expanded by Srb's students to include the study of fruiting body development and identification of proteins made at specific stages of *Neurospora* sexual development.

Analysis of one class of colonial mutants, the peak mutants, was the springboard for a major thrust in Srb's laboratory, the analysis of ascus and ascospore development. He and his students had observed that pairwise mating of different peak mutants produced aberrant asci that were balloon shaped and had a non-linear arrangement of ascospores instead of the linearly arranged ascospores found in the cylindrical asci of wild type strains. These results demonstrated that the properties of an ascus are under genetic control of the zygote that initiates its development. Thus, the methods of diploid genetic analysis, including dominance-recessive interactions and zygote complementation tests, could be used for identifying the genetic components of the sexual reproductive apparatus of *Neurospora*, investigating the effects of these genetic components, and establishing their interactions with one another.

To isolate the large numbers of ascus/ascospore mutants required for this analysis, Srb devised a simple enrichment scheme. Based on the assumption that colonial morphology mutants other than peak mutants might also exhibit altered development of the ascus, the scheme involved repeated filtration through cheesecloth to trap wild type filamentous hyphae while allowing the passage of the microspherical colonies formed by colonial mutants.

Several thousand morphological mutants were recovered, among which were mutants that produced balloon-shaped asci, indurated asci that were characterized by lack of ascospore walls and ascospore delimitation as well as hardening and melanization of the ascus wall, and asci that contained an abnormal number of ascospores.

Also recovered were mutants that exhibited aberrant spore size or shape. Some mutants produced giant spores that often filled the entire volume of the ascus. Others produced round spores or triangular spores instead of the lemon-shaped ascospores produced by wild type strains.

These mutants provided students in the Srb laboratory with ideal materials for genetic analyses of dominance and epistatic interactions, and in a nod to Srb's early interest in biochemical mutants, for identifying nutritional deficiencies that phenocopy the mutant phenotypes (e.g., biotin deficiency producing indurated asci). These studies were accompanied by detailed cytological analyses using light and electron microscopy, which described the details of meiotic and mitotic spindle orientation in the developing ascus of wild type strains and the cytological defects in mutant strains.

While Srb's retirement preceded the development of transformation methods for *Neurospora* and the sequencing of its genome, the ascus and ascospore mutants identified by him and others (especially David Perkins at Stanford University) represent a treasure trove of biological materials to which application of molecular methods will no doubt help explain the complex molecular and cellular processes that control sexual development in this model fungus.

Professional honors, service, and mentoring

At Cornell, he was instrumental in the creation of the Division of Biological Sciences, which brought most of the biologists on campus into one unit, allowing for more cohesive and interactive training of students in various aspects of biology.

Srb received many honors for his research. In addition to his election to membership in the National Academy of Sciences in 1968, he was elected a fellow of the American Academy of Arts and Sciences, the American Association for the Advancement of Science, and the American Society of Naturalists. He was also named an honorary foreign fellow of the Botanical Society of Edinburgh and an honorary member of the Chilean Genetics Society. In 1969, he was awarded an honorary DSc degree by his alma mater, the University of Nebraska.

Srb served on countless committees at Cornell University and elsewhere, tirelessly advancing the cause of basic biology, genetics in particular, and the need for developing strong training programs in this field. In 1971, he co-authored an NIH report about the future of training in genetics.

At Cornell, he was instrumental in the creation of the Division of Biological Sciences, which brought most of the biologists on campus into one unit, allowing for more cohesive and interactive training of students in various aspects of biology. He stressed the need to develop a variety of experimental model systems including, yeast, ciliates, fruit flies, and plants.

He was a strong advocate for the application of modern genetic approaches in agriculture, both with respect to plant breeding and animal husbandry. He was also quick to see the potential of plant tissue culture, regeneration, and somatic hybridization to revolutionize agricultural genetics, and he made the case for the application of selective techniques to vegetative cells in tissue culture in order to recover whole plants with desired traits.

With his usual foresight, he recognized the tremendous social and economic importance of this agricultural genetics, and he lobbied for its incorporation in training programs supported by the National Institutes of Health. Srb was also a strong proponent of teaching science, and particularly experimental science, to nonscientists. He understood the critical need for spokesmen for and interpreters of science who could clearly communicate science to lay audiences. Thus, after many years of teaching a course in basic genetics for biology majors and a graduate-level course in physiological genetics, he taught an undergraduate course on human genetics to non-biology majors and students intending to enter medical school. This course introduced students to advances in genetics that have far-reaching sociological and ethical implications.

He was an ardent supporter of women in science, and he went out of his way to facilitate their careers. In his own laboratory, he provided them with a flexible work schedule that allowed them to juggle family and work, thus ensuring that they could continue productive scientific careers.

Despite their rigor, Srb's courses were very popular because he was a superb teacher and lecturer. And, like his courses, his writings were exemplary for their lucidity. In March 1952, he published with Ray D. Owen the first edition of the textbook *General Genetics*, and in 1965 he co-authored a second edition with Owen and Robert S. Edgar. This textbook was used in more than 100 American colleges and universities for nearly two decades, and it served for many years as the standard genetics textbook that other authors sought to emulate. The textbook was also widely adopted throughout the world and was translated into Japanese, Spanish, and Polish. Even in 1980, an advertisement for a new genetics textbook still made comparisons to the original textbook by Srb and Owen.

Srb was also an excellent mentor. He was an ardent supporter of women in science, and he went out of his way to facilitate their careers. In his own laboratory, he provided them with a flexible work schedule that allowed them to juggle family and work, thus ensuring that they could continue productive scientific careers.

Srb provided his students with a highly interactive and productive laboratory environment, which was enriched by discussions with illustrious scientists who visited Srb, such as Barbara McClintock, Boris Ephrussi, and Max Delbrück.

Srb was always available to students for discussing results or providing advice on experimental strategies, but he did not manage their work on a day-to-day basis. He supported his students and their work with funds from an uninterrupted continuing award from the National Institutes of Health, but he gave them the freedom, and even expected them, to develop their own ideas and research projects.

Upon joining the laboratory, a graduate student might be assigned the task of mapping a particular mutation, largely as a learning experience on how to grow *Neurospora*, perform crosses, and dissect ascospores from single asci for tetrad analysis. Whether the mutation was mapped or not was immaterial, as long as the student devised a realistic and potentially productive research project. Consequently, Srb's students learned how to take responsibility for their research, to defend their interpretations, and to realize the implications of their work—in short, to become independent researchers.

Many of Srb's students and post-doctoral fellows had productive careers of their own. Some went on to be successful university teachers or administrators at colleges. Others developed independent research programs, not only in fungal genetics, but also in several fields of plant research such as disease resistance, self-incompatibility, biochemistry, breeding, biotechnology, and international agriculture. The majority, if not all of these students, will no doubt agree that their success was in no small part due to the excellent mentoring they received from Srb. While his contributions to the field of genetics are indisputable, it is Srb the man—cordial, warm, generous, inspiring, teacher, and mentor—who will persist in the memories of those who knew him.

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