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ROBERT LEE METZENBERG JR.
1930—2007

A Biographical Memoir by

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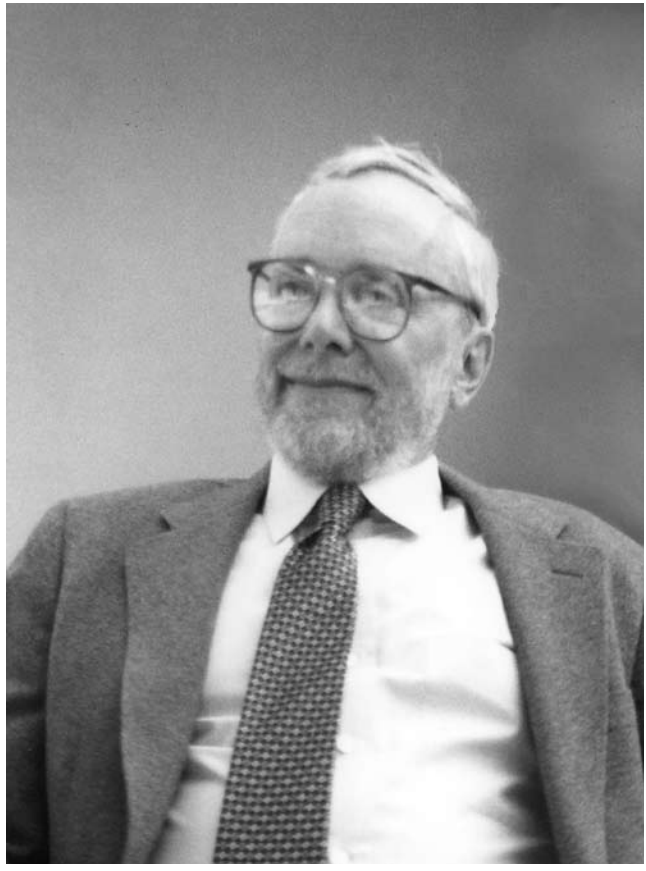
Biographical Memoir



Robert L. Metzenberg

ROBERT LEE METZENBERG JR.

June 11, 1930–July 15, 2007

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In performing over a half century of work on the genetics, biochemistry, and molecular biology of the fungus *Neurospora crassa*, Robert Metzenberg distinguished himself as an exceptionally broad and creative investigator. Neurospora was established as a model organism in the 1930s and 1940s as a result of B. O. Dodge's study of its life cycle and Beadle's and Tatum's Nobel-prize-winning work dissecting biochemical pathways (Davis and Perkins, 2002). Metzenberg was one of a few researchers who stimulated the popularity of the organism for the rest of the 20th century, making contributions that extended into many areas of modern biology.

His early studies of the pathways of sulfur and phosphate acquisition in Neurospora concentrated on mechanisms of positive control of gene activity and resulted in the discovery of complex cascade regulatory systems. Metzenberg and his colleagues also showed that the 5S rRNA genes of Neurospora are dispersed among its chromosomes rather than being clustered, as in previously described eukaryotes. He then used the dispersed 5S genes to construct molecular maps of the *N. crassa* genome, a significant step in the development of genomics for this organism, the first filamentous fungus whose DNA was fully sequenced.

His laboratory also did pioneering work on the mating-type alleles, *mat A* and *mat a*, which Metzenberg renamed "idiomorphs" in recognition of their lack of homology and their complementary function in the sexual cycle. Near the end of his career his research uncovered a new and extraordinary gene-silencing mechanism, meiotic silencing by unpaired DNA (MSUD). This mechanism, which he found to be related to RNA interference (RNAi), illuminated previously unexplained disturbances of meiosis uncovered in studies with Neurospora and other organisms.

Throughout his career Metzenberg contributed novel ideas of general significance to molecular biology, insights into the biology of the fungi, and clever, dependable techniques and resources that benefited many Neurospora workers. With his bright, modest, and magnetic personality he served as an intellectual "glue" that contributed to the cohesion of the Neurospora community.

PERSONAL HISTORY

Bob Metzenberg died at the age of 77 on July 15, 2007, in Los Angeles, California, after a long struggle with cancer. He was born on June 11, 1930, in Chicago, Illinois, where his great-grandfather had settled. In 1951 he graduated Phi Beta Kappa from Pomona College in Claremont, California. At Pomona, Bob majored in chemistry and minored in physics and biology, which he noted were almost "immiscible with chemistry" at the time. Between 1951 and 1955 he earned a Ph.D. at the California Institute of Technology in the Division of Biological Sciences, studying with Herschel Mitchell.

While a graduate student at Cal Tech, he met his wife-to-be, Helene Fox, who grew up in Pasadena, California. They were married on June 26, 1954, in Vermont. In 1955 Bob and Helene moved to Madison, Wisconsin, where he

became a professor at the University of Wisconsin's Department of Physiological Chemistry (since renamed Department of Biomolecular Chemistry) in the School of Medicine. In addition to other teaching duties, from 1962 to 1996 he lectured regularly in Physiological Chemistry 704, a popular, advanced course in biochemistry required of first year medical students. In 1977 he was named a John Bascom Professor by the University of Wisconsin Board of Regents. As detailed below, Metzenberg was the recipient of a number of other honors.

In 1996 Metzenberg retired from teaching, became Professor Emeritus in the Department of Biomolecular Chemistry and moved to California, where he was appointed as a research professor in the Department of Biological Sciences at Stanford University. Bob and Helene relocated to Northridge, California, in 2002 to live near family, but he continued his active research, first as a visiting professor in the Department of Chemistry and Biochemistry, University of California, Los Angeles, and then as an adjunct professor in the Department of Biology, California State University, Northridge. In addition, Bob built a laboratory in his home, where he worked until his last day (Metzenberg, 2007).

His survivors include his wife, Helene, sons Howard and Stan, daughter-in-law Aïda, and two grandchildren.

CONNECTIONS AND STYLE

Bob's training in chemistry equipped him with a deep knowledge of the properties of matter, and he relished reducing problems to first principles. In addition, Bob had a rare knack for genetics. In graduate school he enjoyed interacting with a range of star geneticists and biochemists, including George Beadle, Ed Lewis, Norman Horowitz, A. H. Sturtevant, Max Delbrück, and Herschel Mitchell. It is

noteworthy that Herschel was known for his skepticism and empiricism, believing nothing until it survived all tests of disproof. (He distrusted speculation beyond visible facts, leading Norman Horowitz to call him a "flat earth" man.) Bob took the rigor of Herschel's approach and invested it with immense imaginative potential. He became an investigator who saw no boundary between chemistry and biology and who processed a vast array of information about biological systems. Bob's memory was an ocean of basic and arcane information, organized in a way that he could access with almost computerlike efficiency. His mind was always active, looking at how any phenomenon was related to others. He saw similarities and differences that others did not, and this led him to countless proposals for further investigation. Indeed, Bob had an extraordinary ability to make connections—connections among people, connections among disciplines, and connections among disparate phenomena and observations. Anyone falling into a conversation with him would soon be taken on a dizzying journey of new ways of thinking about the new friend's problems. Bob did not indulge himself; he gave his friends the benefit of his vision and left them with a list of experiments that could test interesting possibilities. Recent remarks by Gerry Fink cite an example:

> Bob was a wonderful scientist and intellectually adventurous person. He had a remarkable grasp of metabolism and its integration into the physiology of an organism. From the time I began an independent career, Bob was my resource for any baffling interaction that I couldn't make heads or tails of. On one occasion I mentioned a peculiar growth behavior of a mutant in the glyoxylate pathway. Bob always greeted such puzzles with an affectionate broad grin. This was the kind of problem that tickled his fancy, even though it was my problem. Without hesitation, he made a key connection between glyoxylate metabolism and gluconeogenesis that had completely eluded my students and me. The connection he made formed the basis for many important discoveries in my laboratory. Like so many of his colleagues, I found my career influenced by Bob's unique scientific style and generous spirit.

In addition to his intellect, important aspects of Bob's character were his modesty, his generosity, and his humor. Louise Glass, one of his postdoctoral students mentioned, "In addition to being the most inspirational scientist that I have known, Bob, along with David Perkins, was also the most selfless. He habitually gave out strains and ideas prior to publication and refused to be an author on publications unless he actually contributed experimental work." Bob became one of the two "go-to guys" at the center of the Neurospora community. The other guy, as Louise said, was David Perkins, the keeper of Neurospora resources, strains, methodologies, and traditions, with whom Bob maintained extensive collaborations to the end of both their lives in 2007. Jay Dunlap wrote in a recent memorial, "Bob could be very direct, but was never unkind. But for anyone new to a field, he was just the kind of senior person who personified a field with which you'd want to be associated."

Bob's imagination and humor made his lectures in courses and meetings enjoyable and memorable. He was widely known for formulating sharp metaphors in his lectures to clarify complex issues: "metabolic impasses" for biosynthetic paths that seemed to cancel each other's output; "turner-onners" and "turner-offers" for regulatory genes; a duplicate enzyme as a "pinch-hitter;" and his argument that apparent "junk" DNA was not necessarily "the navel lint" of the genome. An imaginative but rigorous justification of positive control mechanisms in eukaryotic cells lay in a calculation of the extreme cost of effective concentrations of negative controlling proteins in terms of their osmotic potential.

Like any person of depth and sensitivity, Bob had a reserve that contained his darker thoughts, more candid opinions of others, strong feelings about the evil in this world, and a fatalistic but not unhopeful attitude toward the possibili-

ties of life on this Earth. In an e-mail to one of us (E.U.S.) Bob wrote,

> It seems that nobody in my patronymic family survived the Holocaust. I have no living relative on the Continent on my mother's side either. . . . The Holocaust was much talked about in my family when I was a small child. I have no doubt that the horror of it was, and is, the defining core of my life. I have never lost my gratitude for having been born in this country, nor have I ever taken my luck for granted.

Thus he was a man of complex feelings, and despite his reserve we, as colleagues, knew that by inference. All of us could have profited from knowing more of him.

In a "Grandfather Remembers" book that he filled out for his granddaughter he completed the statement, *A simple statement that sums up my attitude about life is*: "that it should be enjoyed, and lived with a little enthusiasm and flair. We should be ready to leave when it's over. When that time comes, we fall back into the arms of the universe. That's not so bad!" On his last day he organized Neurospora stocks in his home-based laboratory for the benefit of younger workers who would use them to continue and follow up projects that he had largely inspired. Bob enjoyed both the intellectual and physical aspects of doing science and was exceptionally altruistic. He mentioned to his last graduate student that his most important scientific contribution was his development of RFLP mapping for the Neurospora community, rather than one of his magnificent basic discoveries.

SCIENTIFIC CONTRIBUTIONS

Bob had an unusual breadth of biological knowledge. Before he settled on the fungus *Neurospora crassa*, he acquired experience working on development in *Drosophila melanogaster* and performing the rigorous biochemistry of a newly discovered urea cycle enzyme (carbamoyl phosphate synthetase)

of frogs (1958). His broad acquaintance with the literature in other fields enabled him to relate his Neurospora studies to many other biological systems, including prokaryotes, and thus to generalize the significance of his findings.

REGULATORY SYSTEMS

Bob's initial work with fungi concerned carbohydrate metabolism, but he found that the pathways of sulfate and phosphate acquisition were more amenable to regulatory studies. The studies of his laboratory on the sulfur pathway (1966, 1968) defined a set of activities coregulated by a group of regulatory loci. This extended the regulon concept and the operation of positive control genes to a eukaryotic system, one elaborated in work by two of his scientific descendants, George Marzluf and John Paietta.

Bob soon achieved a major intellectual advance in his studies with the even more complex phosphate acquisition system—one that influences all current thinking about complex regulatory systems. This work began with a study of the regulation of enzymes such as alkaline phosphatase and membrane proteins devoted to phosphate transport. Bob then searched for mutants lacking these functions, and this eventually led to the isolation of pleiotropic regulatory mutants, both "constitutive" and "null," as he called them. In 1973 his work culminated in an ingenious model that accounted for the behavior of his double and triple mutants (1973). Based on his observation that two null mutants could be distinguished by their genetic interactions with a constitutive mutant, he deduced the existence of a chain of interactions between the various gene products. One gene product activated the structural genes, a second blocked the action of the first, a third blocked the action of the second, and phosphate concentrations controlled the action of the third. This cascade of regulation was worked out purely on the basis

of genetic and phenotypic analyses and was accomplished before similar regulatory systems were established in yeast for the galactose and amino acid cross-pathway control systems. Metzenberg's intellectual contribution to this now-vast field was key. His sense of the universality of his findings is embodied in an influential review in *Microbiological Reviews* (1979). Work on the control of phosphate metabolism continued in Metzenberg's laboratory and subsequently elsewhere (1990, 1993), and the basic form of his model has held up.

THE 5S RRNA GENES AND RFLP MAPPING

With others, Metzenberg explored the relationship of 5S rRNA genes to the other ribosomal RNA genes and found that the 5S genes are dispersed in the Neurospora genome (1979,1981). This novel arrangement evoked questions regarding concerted evolution of dispersed genes and the regulation of their products in ribosome biogenesis. About 10 years later Metzenberg's laboratory also discovered that the tandemly arranged genes responsible for production of the large rRNAs in Neurospora are subject to huge changes in copy number at the same time that repeat induced point mutation (RIP) occurs (i.e., in the interval between karyogamy and meiosis) (1990, 1993; Selker, 1990).

Restriction fragment length polymorphism (RFLP) mapping of the *N. crassa* genome originated with the 5S RNA work (1985). This technical contribution significantly advanced studies on the molecular biology of the organism in part because it allowed cloned DNAs to be quickly mapped. Homologous targeting of transforming DNA is typically rare in filamentous fungi, unlike the situation in common yeasts. Thus RFLP mapping served as a valuable method to establish the identity of cloned genes of interest. Metzenberg made and freely distributed an RFLP mapping kit for *N. crassa* consisting of two parents with diverse backgrounds together with

their progeny, all carrying already scored, standard genetic markers. The result was a dense map that could be probed easily, with landmarks for every region of the genome. This facilitated rapid progress toward determining the complete sequencing of the Neurospora genome in 2001.

MATING TYPES

Metzenberg's next major contribution was the isolation and characterization of the mating-type *A* allele of *N. crassa* (1990). The mating-type gene, with *mat-a* and *mat-A* alleles, had long fascinated mycologists. However, they were poorly accessible to mutational approaches and acted quite differently than the yeast mating-type genes. Bob's laboratory, in a model of cooperative behavior, coordinated work on Neurospora mating type with related work in the Yanofsky laboratory at Stanford. Together they revealed that the mating-type genes of *N. crassa* consisted of nonhomologous sequences, which Bob named "idiomorphs" (1990). Subsequent work on these genes (1998) allowed his students and collaborators to quickly define the important elements of the gene, and to perform a comparative study of mating-type genes in related fungi. The *N. crassa* mating-type system became a prototype for workers in at least five other well-studied fungal species. Using DNA flanking the idiomorphs, Bob's lab followed the evolution of the region in and among *Neurospora* species (1995, 1998). They found that in many cases the *A*-flanking regions of distantly related species were more similar to one another than to the *a*-flanking regions of the same species, a striking example of independent evolution of these chromosomal regions.

MEIOTIC SILENCING BY UNPAIRED DNA

A late high point of Bob Metzenberg's research career was the discovery and artful analysis of a meiotic silencing

mechanism initially suggestive of transvection in Drosophila (1996, 2001, 2002, 2006). Metzenberg called the process "MSUD (meiotic silencing by unpaired DNA)" after demonstrating that unpaired DNA, in an early stage of meiosis, led to failure of meiosis or death of progeny. He showed that unpaired DNA of a gene activates an RNAi-based system that blocks mRNA expression from its homologs, paired or unpaired. If the affected gene is vital for the progress of meiosis or the germination of the ascospore, meiosis or germination is blocked. The initial experiments demonstrating this phenomenon were genetic *tours de force*. They made use of ectopic integrants (lack of pairing unless both parents have the insertions at the same place), point mutations of one copy (allowing pairing with the normal copy), deletions (obviating pairing), and a strain that had both a copy that could pair and another that could not (used to show that pairing of alleles was not sufficient to prevent MSUD by an unpaired homologue). He then looked for and identified suppressors of this mechanism (*sad-1*, *sad-2*), leading to the realization that MSUD is related to RNAi processes in Neurospora and other organisms.

PRESSURE COOKER FOR AN AUTOCLAVE

In addition to the substantial influence of Metzenberg's work in the corresponding fields, it also served as models for work of others and generated projects for developing scientists. His direct, clever experimentation and articulate presentations served as excellent examples for others. Moreover, when his students and postdocs left his laboratory for independent positions, Bob, unselfish to a fault, encouraged them to work on projects that he had helped develop. He had no shortage of ideas, and he characteristically continued his own pathbreaking work on related projects with his own hands in his small laboratory, while maintaining contact with

his "descendants." He then set up his home laboratory with a pressure cooker for an autoclave and other equipment salvaged from a variety of sources, including—according to Bob—from some "dumpster diving" around university buildings (Selker, 2008). Metzenberg was funded by the National Institutes of Health and the National Science Foundation continuously from 1961 to the end of his days.

MENTORING AND CITIZENSHIP

Bob Metzenberg trained many of the next generation of Neurospora workers. Perhaps even more important, however, Bob's work and example enriched the entire fungal genetics community. From the start of Neurospora conferences in 1961, Bob was a highly visible and important participant at virtually all meetings of the Neurospora community, as well as at numerous broader meetings. He attended concurrent sessions on subjects far from his own research, making insightful comments in a variety of areas. As noted above, he inspired beginning investigators at meetings, giving them ideas generously and inspiring them to do their best work when they returned to their laboratories. Bob contributed numerous imaginative tools for fungal researchers, such as introducing the use of partial diploids for regulatory analysis and developing an early, simple method to extract DNA from Neurospora. He designed and built numerous ingenious genetic stocks for special applications, transferred mating-type genes from other *Neurospora* species into *N. crassa*, and devised methods by which one can recover strains with null mutations in indispensable genes by sheltering them in nuclei with chromosomal gene duplications (1994).

After the famous pioneering experiments with Neurospora by Beadle and Tatum, Bob played a major part in the relatively small, cohesive second-generation Neurospora community. As this generation aged, Neurospora became less visible

and influential until it was reinvigorated by the advent of molecular biological techniques. Even then its visibility was overshadowed by the voluminous output of the yeast community. This problem became less serious after Neurospora researchers invited all those working on filamentous fungi to join them for regular meetings. Bob was a prime mover in bringing about this change, as he recognized that tools of genetics and molecular biology were broadly applicable. The result was the assembly of a group 10 times the size of the original Neurospora community, essentially establishing a new field, fungal genetics and biology. He became one of the first scientific chairs of the new biennial meetings of the broader fungal biology group, which covered immense taxonomic and disciplinary distances. The new grouping had a transforming effect upon plant pathology, medical microbiology, fungal evolution, industrial mycology, and pharmacology.

Metzenberg served as a member of the Genetics Study Section of the National Institutes of Health, a member of the editorial boards of *Genetics*, *Molecular and Cell Biology,* and *Experimental Mycology* (now *Fungal Genetics and Biology*). He cochaired the 1990 Gordon Conference on Fungal Metabolism and the 1997 Fungal Genetics Conference. He served as president of the Genetics Society of America in 1990. These roles demonstrate not only his willingness to serve his scientific communities but also the respect that scientists in these communities had for his probity in scientific and institutional affairs. It is also noteworthy that Bob was very popular as a keynote and after-dinner speaker.

HONORS

Metzenberg's honors include his graduation summa cum laude and Phi Beta Kappa from Pomona College in 1951, a Thomas Hunt Morgan Award from Caltech for graduate

work in 1954, and American Cancer Society and John and Mary Markle postdoctoral awards for his postdoctoral research. He was given a U.S. Public Health Service Research Career Development Award for the period 1963-1973 and a Guggenheim Fellowship in 1983. He was elected as a fellow of the American Academy of Microbiology in 1996 and a member of the National Academy of Sciences in 1997. He was awarded the Thomas Hunt Morgan Medal by the Genetics Society of America in 2005. An award given in Bob's honor, the Metzenberg Prize, was established by the Neurospora community in 2004 to recognize his contributions to science and to promote the work of others in his spirit. It is given to a Neurospora worker whose innovative achievements or contributions have significantly advanced our understanding of biology.

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