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Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

Robert L. Metzenberg, June 11, 1930–July 15, 2007: Geneticist Extraordinaire and "Model Human"

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The genetics world was saddened by the recent death of Bob Metzenberg. We invited Eric Selker to write an informal biography and tribute and several others to write remembrances. These illustrate the high esteem in which he was held by his colleagues. Among other honors, Bob was elected to the National Academy of Sciences and in 2005 was awarded the Thomas Hunt Morgan Medal by the Genetics Society of America.

J. F. Crow and W. F. Dove

I first met Bob Metzenberg (Figure 1) when he came to Reed College to give the Gabriel Lester Memorial Lecture in 1974. He made a convincing case for using the fungus *Neurospora crassa* to investigate gene regulation in eukaryotes. This was, of course, before DNA-mediated transformation of Neurospora and other eukaryotes, before the invention of recombinant DNA techniques, and even before a reliable method of extracting nucleic acids from Neurospora had been described. However, as anyone who has heard Bob give a presentation, formally or informally, knows, he had a knack for arranging information into tight stories and his special blend of humor and style ensured that even potentially sleepy undergraduates remained tuned in. Bob described his investigations on regulation of sulfur and phosphorus utilization at a time when little was understood about gene regulation in eukaryotes. His identification of multiple regulatory mutants and his demonstration that the underlying genes exist in a hierarchy to turn on families of unlinked structural genes was clearly a major advance. Indeed, Bob was the first to discover a cascade of positive- and negative-acting products of regulatory genes acting to govern eukaryotic gene expression. These studies foreshadowed the discovery of similar signal transduction systems in other organisms. Bob Metzenberg was not a person who tooted his own horn, however. [For example, he was not the type who "casually" mentioned that he was a member of the National Academy of Sciences, was awarded a MERIT grant, and had one of the longest-running National Institutes of Health grants ever (over 38 years) or that he had been awarded a slew of other prestigious honors, including the Thomas Hunt Morgan Medal (Selker *et al.* 2005).]

Visiting the Metzenberg laboratory 4 years later left me with two other strong impressions of Bob: his approachability and the breadth and depth of his intellectual tool chest. I discovered that he was a chemist disguised as a geneticist. The disguise was effective because he was an extraordinary geneticist, but his core of chemistry served him well: as an award-winning biochemistry professor, as a molecular biologist, and as an advisor for thousands of students and colleagues who learned to seek his advice. Those who interacted with Bob quickly discovered that the value of his extensive knowledge base was amplified by his uncommon imagination and by his legendary generosity. Gerry Fink recently noted,

> 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 glyoxalate 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 glyoxalate 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.

"DEFINING CORE," EDUCATION, AND CAREER

Robert Metzenberg was born on June 11, 1930, in Chicago, where his great-grandfather had settled. Apparently Bob's great-great-great-grandfather, the

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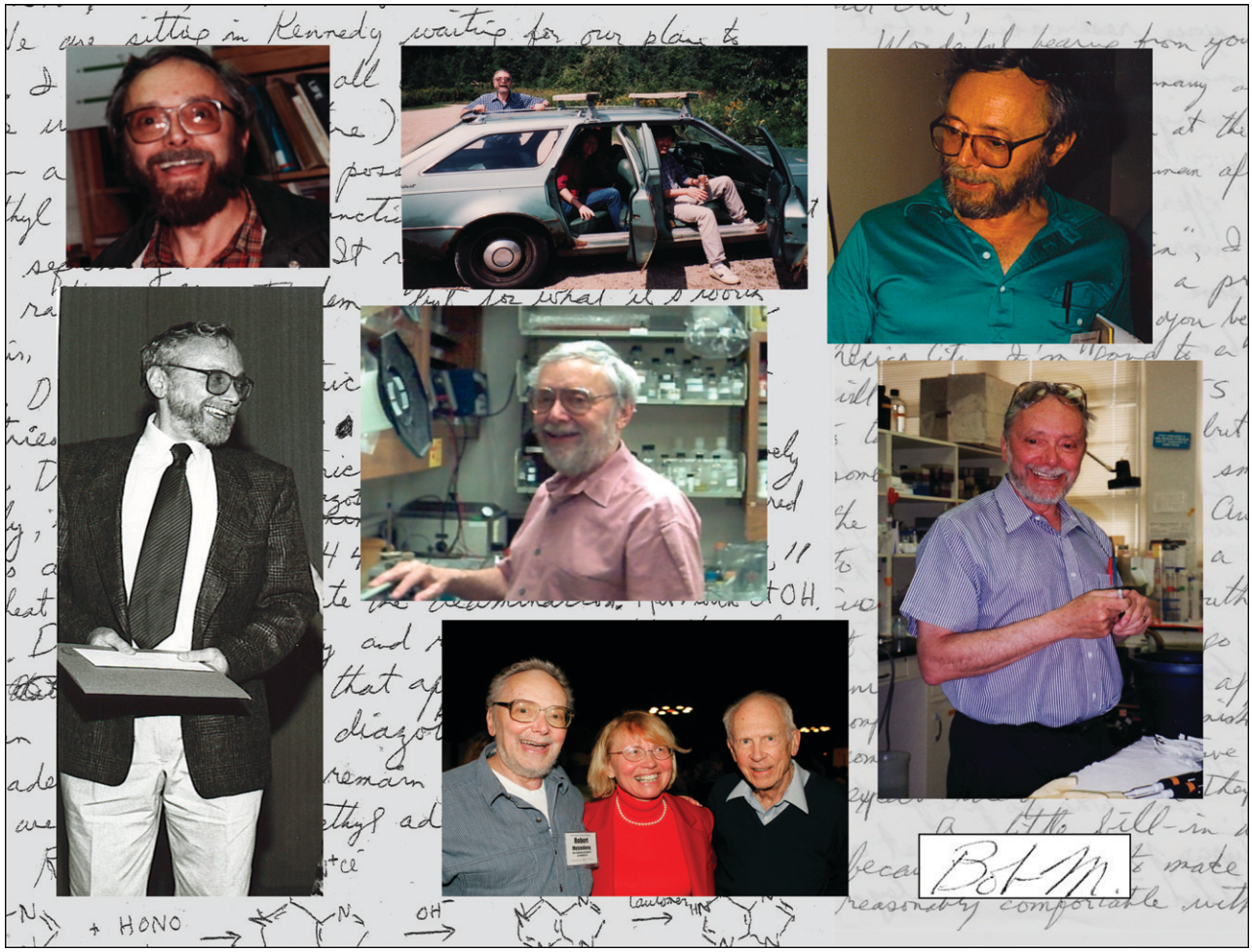

Figure 1.—Bob Metzenberg. Bob loved thinking about science in his free time. The handwriting in the background is from letters written by him while waiting for planes. In one he suggested a possible way to recognize *N*-methyl adenine in conjunction with the Church–Gilbert genomic sequencing method. The two additional people in the bottom image are Joan Bennett and David Perkins.

"Stammvater," or first Metzenberg with a surname, was a fairly successful furrier, dyer, and leather worker in Germany. Bob owed his life to the fact that one of his great-great-great-grandfather's sons decided to stay in Ireland after going there to buy a supply of leather. After I told Bob about visiting Germany to participate in a tribute to relatives of mine lost in the Holocaust, he wrote to me that he had tried to trace relatives who had lived on the Continent but his research invariably led to "*in Buchenwald gestorben*" (died in Buchenwald). He concluded,

> 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 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.

From an early age Bob lived intensely and made the most of life. Growing up, he focused on competitive swimming, photography, and baseball and excelled in arithmetic and spelling at the expense of English and art. He earned spending money mowing lawns, which financed movies, dates, etc. He cared about the world and idolized Adlai Stevenson. After graduating from high school, Bob headed west to Pomona College and made firm ties in California.

At Pomona, Bob majored in chemistry and minored in physics and biology, which he noted were "almost immiscible with chemistry" at the time. His Pomona and life-long buddy George Becker reflected,

> The Chemistry Department was anything but stuffy. Prof. R. Nelson Smith and his partner Corwin Hansch were constantly pranking one another and set the tone for their students. Partly as a result of his own DNA and certainly as a result of being in that Chemistry Department, "Metz" was emboldened to pull pranks constantly. No one enjoyed it more.

Becker also noted,

> Metz was bright, very bright and used to astonish his friends by "testing out" of classes. He seemed to be able to

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> avoid taking beginning classes and in doing so he was very self denigrating saying he was "lucky" etc.

In 1951 Bob graduated Phi Beta Kappa and enrolled in the Division of Biological Sciences at the California Institute of Technology for graduate studies. He worked with Herschel Mitchell on the synthesis of certain amino acids and interacted with an impressive group of geneticists and biochemists, including George Beadle, Ed Lewis, A. H. Sturtevant, and Max Delbrück. Matt Meselson commented, "Bob greatly helped to make CalTech the humane and intellectually exciting place it was in those days."

Bob did manage to find time for necessary fun, however. For example, Bob Lester recalls "many fine memories of extracurricular hijinks while we were still bachelors, *e.g.*, skinny dipping on a hot deserted beach in Mexico with Bob and Len Hertzenberg and paying for the sunburn where the sun doesn't usually shine."

While at CalTech, Bob married Helene Fox of Pasadena, and afterwards they moved to Madison, Wisconsin, so that he could do postdoctoral research in the Department of Physiological Chemistry at the University of Wisconsin School of Medicine. Bob worked with Philip Cohen on enzymatic reactions involved in urea synthesis in mammals and amphibians, but he became increasingly interested in the underlying gene regulation. He therefore took a 1-year visiting scientist position in the group of Ernst Hadorn in Zurich to do some "reading and listening" and to get "hands-on experience in developmental genetics." In 1958 Bob returned to the Department of Physiological Chemistry as an assistant professor and decided to study the regulation of enzyme synthesis in a simple eukaryote. He chose Neurospora, with which he had become familiar as a graduate student. He wanted to answer such questions as: (1) How many genes are involved in the regulation of typical families of adaptive enzymes?, (2) Do these genes act by preventing the activity of spontaneously active genes or by engendering the activity of otherwise inactive genes?, (3) If several genes are involved in the regulation of such pathways, do they exist as parallel, alternative signaling mechanisms or as a hierarchical series?, and (4) Do the structural and regulatory genes involved in a family of adaptive enzymes tend to map close together or are they scattered throughout the genome? In a tour de force, in the 1970s Bob and his colleagues answered all of these questions for genes required during deprivation of phosphorus or sulfur.

In 1977 Bob visited Stanford, where I was a graduate student, and we exchanged notes about our respective efforts to clone interesting Neurospora genes. After I extolled the virtues of building genomic libraries in phage rather than in plasmids, Bob invited me to visit his lab to help them set up some things. My visit, in May 1978, was pivotal for me, leading to decades of enjoyable collaborations and enduring friendships. Although neither of us had been successful in isolating the genes in which we were most interested, we tried to make the best of those that came relatively easily, such as rDNA genes. A joint "side project," to characterize the 5S rRNA genes of Neurospora, became central to both of our efforts (Selker *et al.* 1981). We exchanged countless letters and phone calls on everything from technical details to potential mechanisms of concerted evolution of dispersed genes. Bob's colorful writing livened up even mundane topics. Here are a few snippets from a representative letter of 1981:

> That should be impossible, I think, because there should be no RI site with lambda sequences on both sides of it. I'm trying again, and hope nothing so interesting happens next time.
>
> . . .
>
> Well, that's all woolgathering at this point, but the experiments to be done are fairly obvious. Or at least some of them are. Give me your thoughts on this too!
>
> . . .
>
> Everything seems to violate common sense, but perhaps a few solid facts will shape it up.
>
> . . .
>
> I couldn't help thinking of something wild: parsley is one of those plants, along with (at least) celery and parsnips, that contain psoralens at quite substantial concentrations. . . . It would certainly be interesting if the gene in a living plant ever turned into snapback DNA in response to infection or injury, but I admit it's a crazy idea.

Two years later, when I joined Bob's lab after a stint in Germany, I found him still working on the 5S genes. In an application for a Guggenheim Fellowship (awarded for his sabbatical in 1983), Bob commented, "In the last couple of years, accidental events have sparked my interest in a biological problem on which I had not previously done any research." To map the 5S RNA genes, Bob developed RFLP mapping for Neurospora (Metzenberg *et al.* 1984, 1985). In reference to this, Wayne Versaw, Bob's last graduate student wrote,

> During a conversation in 2000, I asked Bob which scientific accomplishment he was most proud of in his career. His answer, without even a slight hesitation, was the use of RFLPs for genetic mapping. Although Ray White and David Botstein described the use of RFLPs first (1980), Bob had independently worked out the concept of using naturally occurring polymorphisms for genetic mapping and his group published in 1984 an extensive RFLP map of *Neurospora crassa* and a detailed protocol that is still used to this day. I was struck by the fact that one of his most prized accomplishments was strictly personal—no glory or credit, just the satisfaction of doing good science.

In the late 1980s and early 1990s, Bob and members of his laboratory made important contributions in other areas, including characterizing the structure and func-

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Figure 2.—Bob and his home laboratory. Clockwise from top left: Bob, January 2007; "stockroom"; microscope and work table; "autoclave."

tion of mating genes of Neurospora (Glass *et al.* 1988, 1990a,b; Metzenberg 1990; Metzenberg and Glass 1990; Nelson and Metzenberg 1992; Randall and Metzenberg 1995; Ferreira *et al.* 1998), discovering a premeiotic process resulting in drastic changes in the number of tandem rDNA repeats in the genome (Butler and Metzenberg 1989) and isolating and characterizing the phosphorus family genes (Mann *et al.* 1988; Kang and Metzenberg 1993; Peleg *et al.* 1996) that Bob had identified genetically in the early 1970s (for review, see Metzenberg 1979). He also continued to design and share imaginative technical advances, such as a method to use "sheltered RIP" (repeat-induced point mutation) to identify and study essential genes (Harkness *et al.* 1994) and a new chemical method to couple DNA to glass slides for microarray experiments (Dolan *et al.* 2001). Mary Case noted,

> Bob had an overall knowledge of Neurospora. He was interested in the whole organism from new methods to isolate tetrads, new mapping procedures, biochemical genetics, molecular biology and new techniques in working with DNA. He was a frequent contributor with his ideas to the Neurospora Newsletter and later to the Fungal Genetics Newsletter. His ideas were always useful and unique. He was a wonderful person to talk to you about your research. He always had good questions and ways to help you achieve the results you wanted. . . .

Bob's generosity and creativity together yielded countless contributions to the community. A typical multi-page letter from Bob in 1991, describing a new idea for identifying recessive mutations in essential genes, started with, "I have no special reason to think you need this procedure, but I wanted to give you, Mary Anne and Louise copies of this in case it proves useful."

Immediately before "retiring" in 1996, Bob and his postdoctoral fellow discovered a remarkable and unexpected new epigenetic phenomenon in Neurospora, initially called meiotic transvection and later renamed "MSUD" for *m*eiotic *s*ilencing by *u*npaired *D*NA (Aramayo and Metzenberg 1996; Shiu *et al.* 2001). Elegant work, largely devised and carried out by Bob independently, showed that any sequence that is unpaired during meiosis elicits an RNAi-like mechanism that silences all homologous sequences in the genome, paired or unpaired, for the duration of meiosis. The finding that MSUD is mechanistically related to RNAi came from one of Bob's characteristically imaginative genetic schemes for selecting suppressor mutations.

As detailed below in the remembrance by Namboori B. Raju and David J. Jacobson, while fighting cancer, Bob worked his last 10 years as an emeritus professor, first at Stanford, followed by UCLA, California State University at Northridge, and, finally, up until his final day, in his home laboratory (see Figure 2).

In his marvelous style, in January of 2007, Bob wrote a piece entitled "Research in your retirement house" (p. 7 of http://www.genetics-gsa.org/pdf/newsletter_jan07.pdf), which starts out:

> Retirement can be one of the most productive and satisfying times of your scientific career. All you need is a spare, dedicated room, an understanding and patient companion, neighbors who don't suspect you of brewing up anthrax bacilli, and a small amount of money.

He goes on, suggesting,"do not be shy about doing a bit of dumpster-diving at an institution near you" and

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notes that "younger people will see you as a harmless eccentric." He then proceeds to explain that when normal job constraints are suddenly removed, "one discovers how severely they limit our ability to follow up high-risk, high-payoff ideas."

STYLE AND HUMOR

Bob's enjoyable and interesting style was not only evident in his writing and speaking—it came through in all aspects of his life. He made the extra effort to add flair, consistent with his entry in a "Grandfather Remembers" book that he filled out when his granddaughter was born in 1985. He said that a simple statement that sums up his attitude about life is: "it should be enjoyed and lived with a little enthusiasm and flair. We should be ready to leave when it's over."

Clearly, Bob had no shortage of "enthusiasm and flair." Craig Wilson, who was curator of the Fungal Genetics Stock Center, contributed the following from a typical Metzenberg postcard:

> I apologize for calling you Doctor, and didn't know whether it applied or not. When people ask me if I like to be called Dr. or what, I tell them my real preference would be to be called "Oh, Venerable One," but too often it comes out "Venereal One." My second favorite name is "Bob."

Probably everyone who interacted with Bob has at least one example of his humor coupled with his humility. I selected the following examples from e-mails that Bob sent me over the last few years, written while already fighting for his life:

> Thank you for your kind words. I still think they made a clerical error and some poor secretary is going to be fired.
>
> . . .
>
> Sorry it's taken me several days to answer your letter. My mind seemed to be going ta-pocketa on one cylinder, but this morning a second cylinder seems to be coughing fitfully into action. Let me try to state the problem to see if I have got it right.
>
> . . .
>
> Some or all of you may tell me I have devised the Neurospora equivalent of an appendix transplant. I await your criticisms! Alternatively, would anybody be willing to pick a few interesting, obviously essential genes and try a proof-of-principle? I would try to be helpful.
>
> . . .
>
> I finally clicked into Genetics, and, lo and behold, there I was. At last I understand how a "woman of a certain age" feels when she gets an extreme makeover at a top-of-the-line spa and likes the stranger she sees in the mirror. I haven't forgotten that, despite your kind profile, I'm still me, warts and all. Nevertheless, it was more than generous of you to airbrush them out.
>
> . . .
>
> As far as I am concerned, fruitcakes are one of the crowning achievements of Western civilization, and will persist after the Sistine Chapel has crumbled into ruins and the late Beethoven Quartets have been forgotten. Well, almost, anyway.
>
> . . .
>
> With a little luck, I will be around for a long time to bedevil my friends and family, but if that's not in the cards, I want things to be left reasonably shipshape.
>
> . . .
>
> I'm sorry it took me five days to respond to your letter. It was my druggy week, and I have been sleeping most of every day and spending my waking hours wandering on a strange, cratered planet on which I am the only life form. Finally yesterday I started to return to earth, and today I even drove into UCLA and got some samples ready for Patrick to work on tomorrow. The next two weeks will be fine—then it all starts over again, unfortunately. I should count my blessings: hardly anyone has it so easy.
>
> . . .
>
> Thank you so much for the letter, which is full of interesting ideas that I want to study further. It cheered me up to be hearing and thinking science again!
>
> . . .
>
> You were correct in guessing that I might be full of poisons that would keep me from responding promptly or even lucidly. It has been a less than perfect month, which finally culminated in a substantial stay in the hospital with a pulmonary embolism. Since I have only three of my original five lobes, losing function in one of them was very unwelcome. I am, thank goodness, now discharged from the hospital. However, no more bungee-jumping, sky-diving, or street-fighting allowed; I will be on blood-thinners from here on out.

After nearly succumbing to pneumonia in January 2006, Bob wrote,

> . . . a few people have told me from time to time that I have walked the earth with no baggage, and that I am a completely uncomplicated person. I wish it were true, but the right moment to correct this impression has never presented itself. But after I go to that Big Lab Bench in the Sky, someone may say so again. I don't want to have my character prettied up any more than my physical remains. I've elected you to say "It ain't so!"

The fact is that Bob's character and credentials are not at all in need of being "prettied up": they are impressive in their native state. Bob was a model scientist, continuously doing research with his own hands and overflowing with ideas, energy, and flair. He was a natural tinkerer and educator who also inspired others to try "wild" things. Moreover, he was a model human being: caring and generous with a great sense of humor. And in spite of his talents, Bob was exceptionally modest. He was complex, but only in a positive way. We will continue to miss him tremendously.

REMEMBRANCES FROM THE WISCONSIN COMMUNITY

The following remembrances are from colleagues at the University of Wisconsin, where Bob Metzenberg

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joined the faculty in 1958 as an assistant professor of physiological chemistry. Bob's role on the faculty of that department in the medical school is expressed by his colleague Larry Kahan:

When I joined the Physiological Chemistry Department in 1973, I was given the opportunity of sitting in on Bob's lectures to the medical students. I did this with more than a little interest since I was slated to take over some of those lectures the following year. I was surprised and impressed by the way in which Bob could take as relatively dry a subject as the biochemistry of blood clotting and weave in everything from European history to the similarities between genetic dissection of a pathway and biochemical dissection of a pathway in ways that captured the interest of the medical students. His lectures had everything—basic biochemical and genetic principles, clinical examples, and a good deal of very dry humor. Bob made it clear to the students that he was not just teaching them biochemical facts: he was also preparing them to understand and incorporate the biochemistry that they would encounter in the several decades of their careers as physicians.

Behind the scenes I had some long discussions about teaching philosophy with Bob. At the time, the medical school was starting up a new, independent study curriculum. Bob had some very definite ideas about teaching, particularly about the value of integrating the basic science courses of the first semester by studying the subjects concurrently rather than serially, the unique learning gained from hands-on laboratory experiences, the value of the lecture as a teaching method, and the proper way to test students, which were at odds with the then-current philosophy of the medical school. He was instrumental in arriving at a compromise that maintained some of these elements even in the new independent study curriculum (eventually abandoned several years later).

Bob was truly a dedicated teacher. He loved being in the laboratory with students during the enzyme kinetics laboratory, walking around and pointing out that they could see the tubes changing color as the reaction proceeded. His lectures were classics. When introducing the subject of prenatal diagnosis, Bob began with the following:

> "A Whimsical Example Illustrating the Principle." I have chosen prenatal diagnosis of Transylvanian Vampirism to emphasize that we don't need to know the relation between the gene and phenotype to apply this method. The analysis is made possible by linkage of the gene governing this trait to the gene which determines round *vs.* square toenails. Vampirism is caused by homozygosis for the recessive allele, *vp* (genetic constitution *vp/vp*). Heterozygotes and homozygotes (*Vp/vp* and *Vp/Vp*, respectively) are not vampires. In the romance of the century, Melanie Moozendoodle and Gary Gazinkus courted, wed, and started procreating. Unbeknownst to them they were both descendants of the infamous Vlad Tepes the Impaler (Count Dracula) and were heterozygotes of constitution Vp/vp. This came to light when their firstborn turned out to be a vampire.... When Melanie became pregnant again, she decided that nursing one child from her jugular vein was enough. Gary, who was taking half the night feedings, agreed. Yet they knew that there was one chance in four the fetus she was carrying would be a homozygote, like its older sibling. The hollow saber incisors characteristic of vp/vp homozygotes appear only at birth, so there is no way this can be directly observed in the fetus. Can any predictions be made?

Bob then proceeded by analysis of linkage of the vampirism gene to the toenail-shape gene to the conclusion that:

> The new Gazinkus child is the joy of her parents' lives. The only sign of her heterozygous condition is that, like the parents themselves, she gets a craving for blood sausage when the moon is full.

After capturing the students' interest, Bob then went on to introduce the students to prenatal diagnosis through the use of closely linked RFLPs.

Bob's knowledge was truly encyclopedic. It was well known and appreciated that if you had a really strange question you could not answer that Bob was the person to ask, no matter how unrelated the question might be to his teaching or research. I took frequent advantage of this, and he never disappointed. He was always willing to take on extra teaching to help out a colleague, sometimes giving a lecture literally on a moment's notice.

Finally, Bob really cared about the students. He was willing to spend hours going over the material with students who were having difficulty. He delighted in working with students who wanted to extend the material that he had covered.

Within the mega-university of Wisconsin, as in many a research university, a faculty member could fully occupy himself with his research program and his departmental responsibilities. Not so, Bob Metzenberg, as explained in the following by Bill Dove:

Bob and I first came together as pioneers. Working with Walter Plaut (zoology) and Millard Susman (genetics), we (physiological chemistry and cancer biology) crossed the college and departmental matrix of the mega-university that is Wisconsin. We were driven only by our shared enthusiasm for the emergent fields of molecular genetics and molecular cell biology and by our enjoyment of the spectrum of undergraduates in this land-grant university who chose to join us to explore new fields of inquiry without boundaries. Our guiding educational principle was the importance of "The Experiment." For a full year, we four designed a set of novel experiments in cell biology, biochemistry, and genetics. For decades afterward, Bob continued to design experiments for Biocore as it grew from a cottage industry to one of the bulwarks of undergraduate education in biology at Wisconsin. Indeed, The Experiment was Bob's lifeblood—for his own science and then for his teaching of others.

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Another example of Bob's talent for explanation of seemingly subtle ideas is offered here by Millard Susman:

> In the Biocore course, Bob wanted to make the point that the various scientific disciplines were distinguished by the methods that they used and by the kinds of questions that they asked. He told the students that a biochemist who wanted to understand a motor car would grind it up, reducing it to a pile of little chunks, and then would separate the chunks from one another, studying each chunk separately to try to figure out what it did and how it did it. An anatomist would get a huge band saw and slice the car like a salami. The anatomist would then study the slices individually and in sequence to try to figure out the contours of the individual parts and to determine which parts were connected to one another and how they are connected. A geneticist would work with the whole car, removing one bit at a time—a valve here, a gear there—and see how the removal of that one part affected the operation of the car. It was an immediately comprehensible and memorable analogy.

Bob's life at Wisconsin, in the university and in the community, knew no boundaries. During the three decades following our foray into the wilderness of Biocore, many of our encounters involved mutually enjoyed musical events. Bob had a finely tuned sensitivity to the differences among people—beyond the student body at Wisconsin. We would often exchange postcards from new travel discoveries. We and our wives jointly came forward to help preserve Wisconsin's classical American Player's Theater (APT), where Bob again demonstrated his ability to cross disciplines. Discovering with Louise Glass and others that the different alleles of the highly polymorphic mating-type loci of fungi each arose from a distinct sequence origin, Bob consulted with the classics professor of Beloit College who was directing one of the plays at APT. From that consultation was born the neologism "idiomorph."

Bob Metzenberg's quick sense of humor was enhanced by his ability to recall facts and events that allowed him to view events in unusual ways. Both within and outside of the laboratory and classroom he was well known for his encyclopedic knowledge of tastes and smells. Jim Dahlberg has noted how these latter abilities made him a very popular expert at wine-tasting gatherings. He was said to have a "gas-chromatographic nose" for ketones and esters. He was a cofounder and an active member of a tasting group that still meets regularly, and his wry comments kept the group from becoming too serious about itself.

The decade in California, described below, generated the end of this story. We continued to exchange messages about new ideas, and in 2005 Bob stepped forward to write a masterly essay on one of his Caltech mentors, Norman Horowitz, for the *Perspectives* article in Genetics (Metzenberg 2005). Our last encounter was in January 2006 when Alexandra and I briefly visited Bob and Helene in Northridge. Again, The Experiment took first place. Bob announced that he was publishing with Patrick Shiu and others a study on the perinuclear localization of the RNA-directed RNA polymerase involved in meiosis in silencing the expression of unpaired genomic sequences (Shiu *et al.* 2006). This article was important enough to elicit a "Comment" (Kelly 2006). "I chose to submit this to the Proceedings by Track II," said Bob, eschewing the option of coordinating its review himself as an Academy member. This message was cut from the same cloth as the final word of Bob's tribute to Horowitz (Metzenberg 2005, p. 1448):

> Somehow, Norm always managed to tell the truth without becoming a scold. There can never be enough of such people, and his legacy must be kept alive.

Operating outside the traditional academic borders, enriching the scientific communities of Caltech, Wisconsin, Stanford, and Neurospora, engaging disciplines beyond science, Bob Metzenberg created a remarkable life from three elements: experiment, communication, and truth.

REMEMBRANCES FROM THE CALIFORNIA COMMUNITY

Rowland Davis (University of California at Irvine):

I met Bob in 1961 at the very first Neurospora Information Conference in La Jolla, California. The meeting was free for all, in both senses of the phrase, and Bob and I began talking at the free bar after the last-night banquet. Characteristically, he drank Coke, and I drank Canadian Club. Even as I became less articulate, he became more so, and I remember only one thing from that night: I had made one of the best scientific friends of my life.

Bob was then at Wisconsin. I had taken a job at the University of Michigan. I kept seeing Bob at meetings, and in the early 1970s, our labs exchanged visits. In Ann Arbor, Bob inspired one of my most daring experiments—one I had thought impossible if he had not said, "Why not?" At that point, almost whimsically, he rattled off a protocol that might do the job, and within a month we accomplished the task. This was his habit: using his multi-tasking imagination to explore, at the speed of light, landscapes of possibilities in ways that Mozart might have used to choose harmony and orchestration. As we, his friends, coupled our imaginations to his, we felt that even his hypothetical dead ends were more illuminating than a close scrutiny of quantitative data. He proved repeatedly Francis Bacon's point that the truth is better served by error than by confusion. He remains a model of how much sheer fun science—and talking about science—could be.

Out of context, one of his remarks about himself might sound ridiculous: "I had no talent!" But the context is illuminating. Having taken instruction in musical composition earlier in life, he had completed several string quartets. He related this to me over lunch

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one day at Stanford, saying, "They were competent, but they simply followed the rules. Derivative of Haydn and all. But I discovered I simply had no *talent*!" This illustrates not only Bob's aesthetic refinement, but also his curious blend of modesty and ambition, an ambition to use his mind to the fullest. It also explains his symphonic understanding of the complex biochemical systems that he probed with a sensitivity to detail, subtle complexity, and the surprising formal beauty of cascade regulatory systems.

Finally, Bob became one of the best friends of all of us in our scientific community. Always good humored and anxious to help, he willingly suffered fools, hoping at first that he might show them the light. A lack of success would then bring out advice in an advanced play on words that at least he could enjoy. Finally, the fools would retire, yielding Bob's attention to others better equipped to enjoy it. I believe Bob made few enemies, largely because he retained a reserve that few people—myself included—fully penetrated. But what overlay that reserve amounted to an incomparable friend and scientist, one who will glow in the dark for years to come.

Namboori B. Raju and David J. Jacobson (Stanford University) interacted with Bob after he retired from Wisconsin and provided the following comments on his time in California:

Bob Metzenberg was no stranger to California; he was here first as a student and later as a retiree. When Bob retired from the University of Wisconsin in 1996, he returned to California to be closer to his family. His two sons live in California: Howard in San Francisco and Stan in Northridge near Los Angeles. Bob chose Stanford for continuing his Neurospora research, mainly because of David Perkins and Charley Yanofsky in the Department of Biological Sciences. This was Bob's second sojourn at Stanford, the first being a 6-month sabbatical in the Perkins laboratory in 1983. Bob's research interests had long overlapped with those of the Perkins lab, especially in the areas of Neurospora sexual biology (Metzenberg 1995), mating-type genes, rRNA genes, and, more recently, meiotic silencing (Shiu *et al.* 2001). He was at ease with classical genetics as well as with molecular biology, and he practiced both at Stanford. In early collaborations, Bob provided molecular data for the analysis of a chromosome rearrangement, which has a breakpoint in the nucleolus organizer region that is composed of 150–200 rDNA repeats (Perkins *et al.* 1986).

In January 1996, Bob and his postdoc Rodolfo Aramayo settled into the Perkins lab. Here, Bob continued his seminal research on a new phenomenon first called transvection, and since renamed *m*eiotic *s*ilencing by *u*npaired DNA (MSUD) (Aramayo and Metzenberg 1996; Shiu *et al.* 2001). After Rodolfo left for a faculty position at Texas A&M in 1997, Bob, together with Patrick Shiu, Namboori Raju, and Denise Zickler in France, greatly extended meiotic silencing studies by ectopically inserting single genes (at the *his-3* locus), whose function is essential for meiotic progression. When such strains are crossed with wild type, the unpaired DNA sequences trigger RNAi-mediated silencing processes involving the RNA-directed RNA polymerases and dicers, in addition to several other components. Consequently, ascus development is abnormal in heterozygous crosses because of meiotic silencing of unpaired genes, but their development is completely normal in homozygous crosses. Bob isolated two suppressor mutants of meiotic silencing, *Sad-1* and *Sad-2*, whose wild-type gene functions are essential for meiotic silencing (Shiu *et al.* 2001, 2006; Shiu and Metzenberg 2002). The availability of GFP-tagged histone H1 and β-tubulin genes greatly facilitated the visual demonstration of meiotic silencing and its suppression during ascus development (Freitag *et al.* 2004; Raju *et al.* 2007; Jacobson *et al.* 2008). Shiu and Raju had the privilege of collaborating with Bob on several of these research projects. The last of five joint articles with Raju was published in May 2007, barely 2 months before Bob passed away (Raju *et al.* 2007). Bob was extremely pleased that the article was among the "Issue Highlights" and that our Neurospora image was featured on the cover of Genetics.

Bob's arrival at Stanford was warmly celebrated during a local Neurospora information conference on the Stanford campus in March 1996. His presence at Stanford also brought together Neurospora workers for 1-day "joint lab meetings" from the nearby University of California campuses of Berkeley and Santa Cruz. Bob especially enjoyed interactions with students and postdocs and often gave them valuable advice for solving their technical problems. During the 7 years at Stanford, Bob made many friends both in his host department and in the medical school. He also taught a biochemistry course. Lunchtime conversations in the Perkins lab were very lively, with Bob doing most of the talking. He was always bubbling with new ideas and hypotheses, which he often tested within the next few weeks. It was during his time at Stanford that Bob started to suffer his own health problems, although this did not affect his productivity, as evidenced by his election to the National Academy of Sciences and being awarded the Genetics Society of America's Thomas Hunt Morgan Medal.

In 2003, Bob moved to Northridge mainly to be close to and help his son's family. In southern California, he spent some time as a guest in the Department of Chemistry and Biochemistry at the University of California, Los Angeles, and afterward in the Department of Biology at California State University at Northridge. However, he spent most of his work hours in his converted home laboratory. Bob's enthusiasm for research was clearly seen in an essay on how to conduct research after retirement (http://www.genetics-gsa.org/pdf/newsletter_jan07.pdf). He was actively thinking

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about various experiments and writing his final paper just a couple of weeks before he passed away.

Bob's energy for work was surpassed only by his dedication to others. He was devoted to his family, friends, and colleagues. His years in California were spent as much helping others as doing research. Bob's sacrifices were legendary, even close to his own end. On learning that his close friend David Perkins was critically ill at the end of 2006, Bob, very ill himself, drove with his son the 7 hr from Northridge to Palo Alto to see David in the hospital. Although David was heavily sedated and unresponsive, Bob spent more than an hour at David's side, analyzing the situation and making sure the best possible care was being provided. He flew home the next day, catching pneumonia on the plane, but with the satisfaction that he was able to do what he could for his friend.

Eric Selker thanks Joan Bennett, Stan Metzenberg, Mary Anne Nelson, Patricia Pukkila, and Matthew Sachs for contributing some of the photographs reprinted here. He also thanks Helene Metzenberg and friends and colleagues of Bob Metzenberg who contributed remembrances and he regrets that not all could be included in this brief tribute. A more complete collection of pictures and remembrances can be found at http://pmb.berkeley.edu/~glass/Glasslab_site/Glass_lab_research/bob%20website/bob%20memorial%20webpage.html. Above all, he wants to express his appreciation for Bob, who enriched his life and made this article relatively easy to write.

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