Seymour Benzer (1921–2007)

The style of scientific giants differs at least as much as their interests. Seymour Benzer, who died in Pasadena on November 30, 2007, at the age of 86, was made of the stuff of the great restless explorers. But unlike the Cooks and Magellans, he never waited for a monarch's approval to sail, nor did he claim sovereignty over the new territory. With admirable drive, curiosity, and tenacity, he set out again and again on expeditions to unearth hidden treasures of knowledge. Having set foot on terra incognita, he would graciously allow his students to explore it further, without breathing down their necks or asking them to share the glory. In his marvelously idiosyncratic style, he revolutionized the science he touched: molecular biology first, neurogenetics later.

Seymour Benzer was born in 1921 in New York City's South Bronx neighborhood, to Jewish parents who immigrated from Poland about 10 years earlier. He once suggested that "Benzer" is a metamorphosis of "Ben Zoma," the name of a 2nd century Torah scholar who unfortunately published little and therefore didn't get tenure as a formal rabbi. The Mishna (a postbiblical codification of laws) says that "whoever sees Ben Zoma in his dream should expect wisdom." "Seymour" was a forename common among Jewish immigrants from the Old World who aspired to integrate into the new society; the Hebrew equivalent is Shlomo (Solomon). Hence at least the etiology of his names held some promise for the newborn. Despite the economic depression, Seymour grew up in a modest, hardworking but comfortable and protective milieu. He was the first person in his family to attend college.

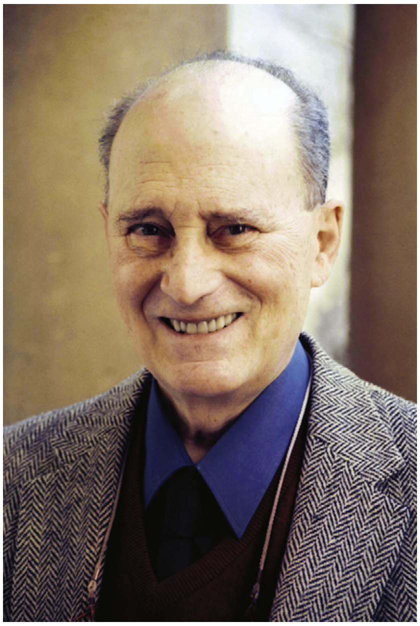
Years later, Benzer would recount dissecting frogs and setting up his first lab in the basement of his home. The centerpiece of the lab was a microscope that he got as Bar-Mitzvah present from his brother-in-law. But his attention was shifted by an influential high-school teacher from biology to chemistry, and then to physics. After graduating from Brooklyn College, and shortly after Pearl Harbor, Benzer enrolled as a graduate student in the Physics Department of Purdue University. He was drafted but was shortly afterward deferred and recruited into the war effort in the Physics Department, working on a top-secret project to develop semiconductors suitable for use in radar.

Two years after the war ended, in 1947, Benzer got his Ph.D. in physics, but his lingering interests in biology diverted him from a secure career in solid state physics. As he later recalled, two major contemporary influences were the news about genetic mapping of genes on chromosomes and Erwin Schrodinger's book *What is Life?*. He enrolled in a course on the bacteriophage organized by Max Delbrück. Delbrück was a highly successful physicist who turned biologist at the late 1930s in Caltech, introducing mathematical tools to study bacterial mutations and bacterial viruses (bacteriophages). He was later to receive the Nobel Prize in Physiology or Medicine for the year 1969, together with Alfred Hershey and Salvador Luria, for "the discoveries concerning the replication mechanism and the genetic structure of viruses." The three weeks in the summer of 1948 in Cold Spring Harbor, in the company of bright physicists, biochemists, and microbiologists, were sufficient to convert Benzer into a member of what was later dubbed in the history of biology as "The Phage Group" (Cairns et al., 2000).

The encounter with the emergent new biology in Cold Spring Harbor was followed by a year in Oak Ridge National Laboratory, experimenting on phages, and then a postdoc with Delbrück in Caltech. Benzer cleverly exploited unique properties of the *rII* mutations in the *E. coli* phage T4, which allow detection of very rare recombinants. He crossed various *rII* mutants to obtain recombination frequencies, which he then used to map mutations within the *rII* gene region in molecular detail. After years of almost manic research, he was able to present the world with the first fine-grained physical map of a gene. *Fine structure of a genetic region in bacteriophage* (Benzer, 1955) almost immediately became textbook material. Generations of students studied it, were tested on it, and considered it as a classic demonstration of the efficacy of Occam's razor in cutting into the most fundamental mechanisms of life. (For a popularized version of the philosophy, methodology, and findings of this research, see Benzer, 1962.)

In his molecular biology years, Benzer also worked in the Pasteur Institute, Paris (1951–1952), and in the Cavendish Laboratory, Cambridge (1957–1958). But Caltech was to become his ultimate home. What do scientists do when they attain fame? Many go on to do more of the same. Not Benzer. He could have capitalized on his success and cranked out scores of citation-hits till retirement. Indeed, for a while, he drifted into the mainstream of molecular biology, working on RNA. Rather proud, he used to mail his papers to Delbrück. The latter was quick to react: "Please ask Seymour," he wrote to Seymour's first wife, Dotty, "to stop writing so many papers.... If he must continue, tell him to do what Ernst Mayr asked his mother to do in her long daily letters, namely, underline what is important." Benzer learned a lesson that should be included in the curriculum of every life-science program: "Beware of falling into the biochemical drain." Later, in welcoming new students to his lab in Caltech, he would reiterate a rule that Delbrück suggested but was never implemented, probably to the dismay of promotion committees to this day: upon receiving the Ph.D., every young investigator should be released to wander in the academic universe with a limited number of coupons, each allowing a single publication (the number ranges from 10 to 20, depending on the version of the legend). No coupons left, no papers.

All in all, the number of Benzer's own publications hardly reached 100. Only 17 are from the molecular biology phase in his career. The phase of the phage was soon to be over. Benzer decided that it was time for him to find out what really interested him—the biological roots of human behavior. But for Benzer, directly



Seymour Benzer

studying humans was the road not to be taken: they are far too complex. Instead, his basic idea was to reduce behavior and its neuronal substrates to their atoms, similar to what was done to the genes using the phage. The trick was to identify which levels of phylogeny and analysis could still provide interesting and relevant answers while at the same time being simple enough to succumb to molecular analysis. As early as 1953, Delbrück wrote to Benzer: ''I am starting a new venture tomorrow, some experiments on the phototropism of the sporangiophores of *Phycomyces*. If they work, I'll retire from phage.'' Looking back, the choice of the filamentous fungus to study sensory transduction and behavior was far from equaling that of the phage; Benzer, in contrast, aimed higher but scored better. Not devoid of doubts, he ultimately settled on the pet organism of classical genetics, the fruit fly, *Drosophila melanogaster*. Here was a locomoting creature with a complex behavioral repertoire, easy to cultivate in large numbers, with a relatively short reproductive cycle, and easily amenable to sophisticated genetic analysis. Last but not least, Caltech had been over the years the shrine of Drosophilists, so the milieu was right.

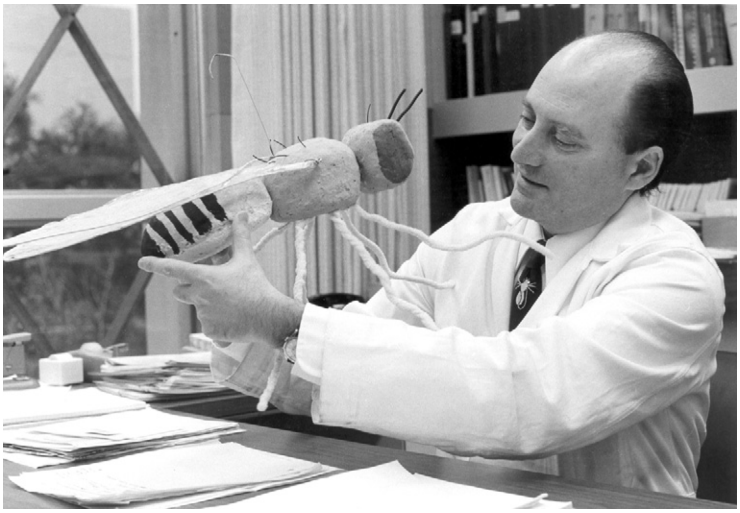
To appreciate the Benzerian revolution in neurogenetics one might wish to take into account the state of the art of neuroscience in the late 1950s and early 1960s. Biology was still celebrating the highly successful launch of the molecular era (the manifesto, Watson and Crick's *A Structure for Deoxyribose Nucleic Acid*, was published in 1953) and engaged in the molding of a new paradigmatic life-science culture. But molecular concepts and methods were slow to penetrate the discipline of brain and behavior. Reductionism did make its way into behavioral physiology, particularly with attempts made by Steve Kuffler, Jerry Lettvin, and their colleagues to identify primitives of neural responses that mediate vision. Generally speaking, however, neurophysiologists, many of whom considered themselves as keepers of the brain seal, were at that time quite resentful of molecular biologists. So were behavioral geneticists: they could have offered another path to link biology, brain, and behavior, but their trade was occupied with population genetics. They were struggling with the complexity of genetically heterogeneous pools, multigene effects, and pleiotropism, and far from displaying any interest in molecules and neurons. Watching it all were the molecular biologists, including Max Delbrück and his disciples. Their hunting instinct marked the brain as the next target. Their occasional sparks of naiveté and arrogance only irritated the physiologists and the behavioral geneticists even further.

Benzer's first paper on *Drosophila*, *Behavioral mutants of Drosophila isolated by countercurrent distribution* (Benzer, 1967), opens with a terse presentation of the new neurogenetic agenda: ''Complex as it is, much of the vast network of cellular functions has been successfully dissected, on a microscopic scale, by the use of mutants in which one element is altered at a time. A similar approach may be fruitful in tackling the complex structures and events underlying behavior, using behavioral mutations to indicate modification of the nervous system.'' (Benzer, 1967). The specific method used in this paper to isolate nonphototactic mutants was analogous to that which Benzer encountered in his earlier adventures in the RNA world: countercurrent distribution, in which molecules are separated from a mixture by their partition between two solvent phases. Only that here the molecules were replaced by behaving organisms, and the phases were the relative preference of the fly for two behavioral alternatives.

The phototactic mutants were only the first protagonists in a bustling developing narrative. Benzer's lab in Caltech became the Mecca for the new approach, harboring a mixture of enthusiasm, originality, academic freedom, and esprit de corps (Weiner, 1999). Years earlier, when Benzer had contemplated doing a postdoc with Salvador Luria instead of with Delbrück, he approached Jim Watson for advice. ''Well,'' replied Watson, ''if you come to Luria's lab, he won't leave you alone. He's very good, because every day he'll ask you what you've done. Whereas, if you go to Delbrück's lab, you may not see him for two weeks at a time, because he likes to go to the library and look up something and go his own way'' (Benzer, 2002). Benzer definitely followed the Delbrück, not the Luria mentoring style, to the delight of his research group.

Over the years, generations of students and postdocs in Benzer's lab have identified scores of behavioral and physiological mutants, either among the progeny of mutagenized flies or, occasionally, in existing fly collections. (For selected examples, see Benzer, 1973; Dudai et al., 1976; Hotta and Benzer, 1976; Konopka and Benzer, 1971; Lin et al., 1998; Wu et al., 1978; Zipursky et al., 1984.) The mutants were subjected to behavioral and physiological screening and testing protocols that were often ingenuously simple yet highly effective. All this yielded a collection of single-gene mutations affecting behaviors as complex as courtship, memory, circadian rhythms, and modifying sensory perception, nerve conduction, and neural development. The hunt for mutants also proceeded in labs established by Benzer's intellectual progeny. Some of the mutants were analyzed at the genetic and molecular level, either in the home base or in other labs. This culminated in some cases in remarkable insights into molecular mechanisms of processes such as neuronal excitability, biological clocks, or simple conditioning. Benzer himself became particularly fond of neurogenetic analysis of the *Drosophila* eye—the crystalline structure appealed to the once-physicist—and of questions related to neural development.

Exciting as they are, mutations per se could contribute only tiny bits to the



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picture, still so far from completion, of how the brain works and controls behavior. Nobody, including Benzer himself, ever thought that *Drosophila* neurogenetics would explain the human brain. Nevertheless, Benzer constantly expressed his hope that understanding *Drosophila* might indeed contribute to understanding more complex brains. He was particularly proud of research collaborations with his second wife, Carol, a neuropathologist. Together they reported on the similarities between human and fly brain molecules. Only once did he raise doubts in public about his bottom-up approach to brain and behavior. That was in the festive ceremony in which he was awarded the prestigious Wolf prize. Looking at some of the politicians seated on the podium, the low-key Benzer remarked that whereas he had started to study the fly brain with the hope of understanding the human brain, he had come to appreciate that the reverse might work even better.

Benzer received many prestigious awards in his career. The call from Stockholm, however, never arrived. He never tooted his own horn. Thousands of young neuroscientists who generate mice transgenics, knockouts and knockins, follow his path using another species, although they might not be aware of it. His earlier work on the fine dissection of the gene was by itself expected to get him the Nobel. "Seymour Benzer," remarked Gunther Stent, another founding father of molecular biology who made the transition to neuroscience, "is the most underappreciated of the founders of molecular biology. Almost all scientifically literate people have heard of Francis Crick, Max Delbrück, François Jacob, Jacques Monod, Linus Pauling, and James Watson and have at least some vague ideas about their seminal contributions to the revolution that transformed the 20th-century life sciences. But Benzer's renown is largely confined to the community of molecular biologists. Just why he has continued to be so little known to the public at large for so long remains to be accounted for by future sociologists, as does the failure of the Nobel Prize committee to honor his molecular aggiornamento of the gene." (Stent, 1999).

To the outsider, toward the latter part of his career Benzer seemed to have become an academic Antonius Block, the medieval knight in Bergman's *The Seventh Seal* who challenged death to a game of chess to buy time in face of the inevitable. Only that Benzer's chessboard was populated with genes, proteins, and peptides, rather than rooks, bishops, and pawns. He managed to find *Methuselah*, a mutant that can live 35% longer. He reported on the extension of life by a GPCR peptide inhibitor or modulation of the expression of apolipoprotein D. All in *Drosophila*, of course. This flirting with the end of the day didn't prevent him from simultaneously pursuing his legendary interest in food and reporting that the response of *Drosophila* to wasabi is mediated by *painless*, the fly homolog of the mammalian transient receptor potential ion channel TRPA1/ANKTM1. Even his last papers are thus a tribute to a bold and sincere stubbornness mixed with boundless curiosity, unique wit, and a genuine joie de vivre.

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