Obituary

Seymour Benzer (1921–2007)

Ralph J. Greenspan

A man of genius makes no mistakes. His errors are volitional and are the portals of discovery — James Joyce

Biology lost one of its greats with the death on November 30th last year of Seymour Benzer. In the century that began with the rediscovery of Mendelian units of heredity and ended with the sequencing of the human genome, Benzer's studies of gene fine structure defined the pivotal moment in the transition from classical to molecular genetics. This quiet devoté of science, with an impish sense of humor and a taste for the phylogenetically exotic in food, then went on to found what has become the bustling field of the genetic analysis of behavioral mechanisms. It is rare enough in the history of science for someone to make a discovery as momentous and synthetic as Benzer's phage findings, let alone to go on afterwards to inaugurate a new approach that grows into a major scientific field.

Born in Brooklyn in 1921 to Jewish Polish immigrant parents, he was the first member of the family to go beyond high school. Science was his first love, and it lasted his whole life. He was interested in biology from an early age, but ended up majoring in physics and chemistry at Brooklyn College, because they were more challenging than the taxonomic approach typical of the biology teaching of the day. As a graduate student at Purdue University in the mid-1940s doing research related to the war effort (Figure 1), he discovered the key properties of germanium crystals that eventually made it the element of choice for transistors. He joined the Physics faculty at Purdue in 1947, but soon gravitated back towards biology. While a graduate student, he had read Erwin Schrödinger's *What Is Life?* [1], a seminal book which framed the question of what was the physical basis of the gene, and which was so effective in attracting physicists into the nascent field of phage genetics. If one of the giants of quantum mechanics could speculate seriously that the problem of heredity might reveal new laws of nature, then it must be challenging enough for physicists to tackle. The romantic notion of exploring totally uncharted waters appealed to Benzer then and for the rest of his life. He was undaunted by the fact that many traditional geneticists took a dim view of phage, telling Benzer that if he wanted to study genetics, he should work on a 'real organism'.

Schrödinger's book highlighted the genetic speculations of Max Delbrück, a young quantum physicist who had been bitten by the genetic bug and taken up investigations of bacteriophage as an 'elemental' genetic entity. In 1948, while an assistant professor of Physics at Purdue, Benzer took Delbrück's summer phage course at Cold Spring Harbor and parted ways with physics research for good. He joined the small international community of scientists known as the 'phage group' (led by Max Delbrück and Salvadore Luria and including Alfred Hershey, Leo Szilard, James Watson and Gunther Stent, among others) and spent as much time away from Purdue in various phage labs as he did being a faculty member. Delbrück served this group as founder, organizer, cheerleader, critic and even as scout-master for its regular camping trips in the deserts east of Caltech.

All of Benzer's papers from the phage era end with an acknowledgement to Delbrück "for his invaluable moderating influence" (when is the last time you heard of a prominent scientist exerting a moderating influence?).

With the dissemination of Watson and Crick's model for DNA structure in 1953, and its implications for linear coding, Benzer hatched a plan to use classical genetic mapping to define the functional structure of the gene. The discovery of mRNA was still eight years off in the future, and there was no way to define the gene biochemically. So Benzer used a traditional genetic approach to move genetics down to the molecular level. In a 1952 review article, entitled *"Genetic Formulation of Gene Structure and Gene Action"*, the fungal geneticist Guido Pontecorvo had framed the problem as follows:

> "[There are] various ways in which a gene can be defined; they are consistent with one another at certain levels of genetic analysis, but not at others…(1) as a part of a chromosome which is the ultimate unit of mutation; (2) as the ultimate factor of inheritable differences, *i.e.,* as unit of physiological action; and (3) as the ultimate unit of hereditary recombination." [2]

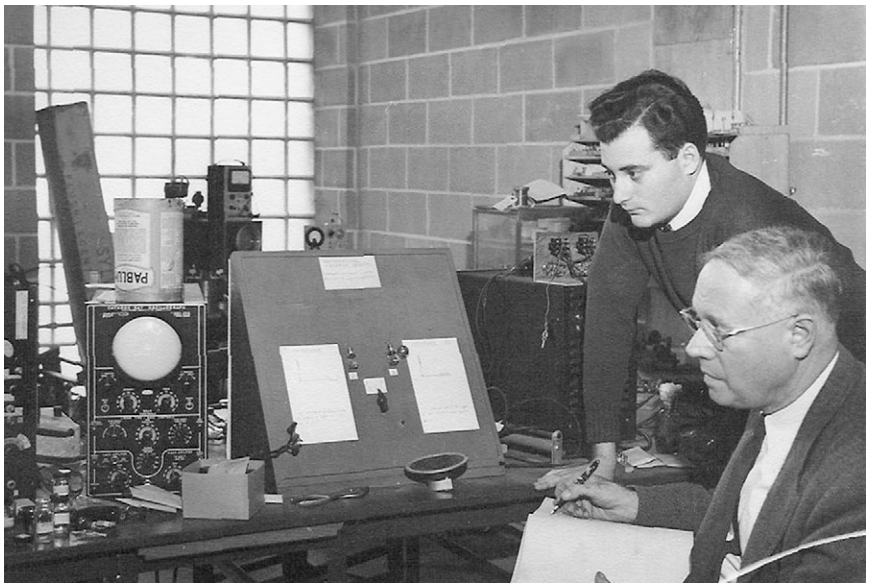

Figure 1. Benzer and Karl Lark-Horowitz at the Purdue Physics Department in 1944. (Courtesy of Seymour Benzer and the Purdue Department of Physics.)

Pontecorvo pointed out that resolution of these issues would require the ability to detect extremely rare recombination events in order to map mutations within the same gene, as well as to construct strains with two closely linked mutations on the same chromosome. The latter strategy was a prerequisite for Benzer's variation on the '*cis-trans*' test — this was Ed Lewis' complementation test [3] for assaying whether two mutations produce similar or different phenotypes when they are on the same chromosome (in '*cis*') as compared to being on opposite chromosomes (in '*trans*'). The selectability of the phenotype and the sheer number of progeny that could be generated in phage made the analysis possible down to a level of resolution and degree of saturation unthinkable in *Drosophila*. By taking advantage of the observation that with a high enough titre, it was possible to infect single bacterium with more than one phage, Benzer was able to perform *cis-trans* tests on these otherwise haploid genomes [4]. Practically speaking, the work involved doing the same experiment over and over — isolate mutations, map them with respect to each other, perform *cis-trans* tests. Working mostly by himself, Benzer described it as "Hershey Heaven", in reference to another of the early phage geneticists, Alfred Hershey, who described biological heaven as an experiment that works and goes on and on.

The result was a physical map of the *rII* region of phage T4 almost to the nucleotide level, from which Pontecorvo's three units of genetic function could be discerned. The units of mutation and of recombination were at the limit of resolution, suggesting that they were at the single nucleotide level. The unit of physiological function, on the other hand, was a long stretch of hundreds of nucleotides with distinct boundaries. These units were defined in the *cis-trans* test by the fact that two mutations in the same functional unit would fail to complement in *trans* configuration, whereas two mutations in adjacent functional units would be able to complement in *trans*. In the *cis* configuration, both types could be complemented by a wild-type chromosome. Thus was coined the term 'cistron' for the unit of genetic function.

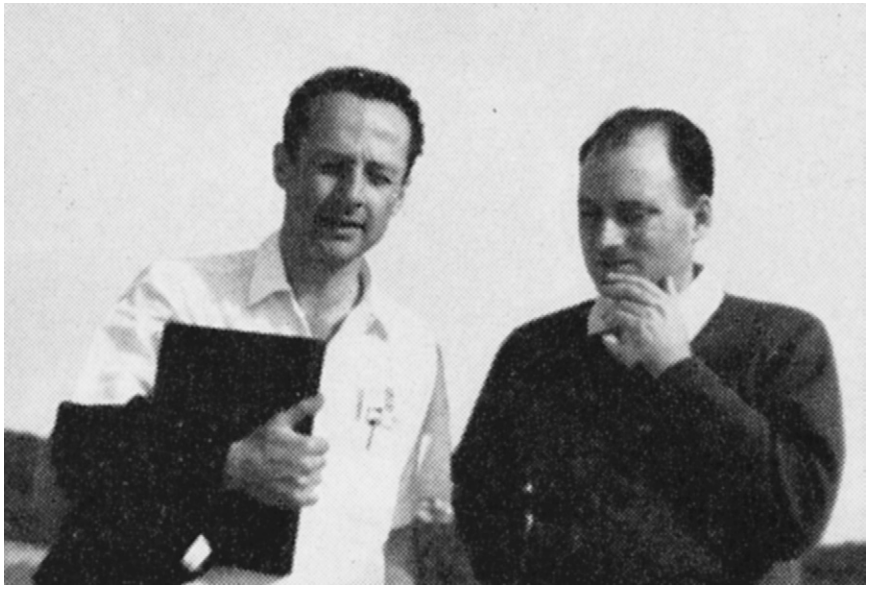

Figure 2. Benzer and Matthew Meselson at the Cold Spring Harbor Symposium in 1961. (Courtesy of the Cold Spring Harbor Laboratory Archives.)

Further analysis of chromosomal deletions of various sizes inside, outside and across the *rII* region, including one that resulted in a fusion of the two adjacent cistrons of *rII* into what he inferred to be a chimeric gene product, allowed Benzer to perform a topological analysis of the arrangement of all of these factors [5]. The result supported the conclusion that a functional gene was a linear stretch of DNA with definable boundaries, and that these stretches of DNA are all linked to each other as adjacent pieces of chromosome. (See [6] for a full account of Benzer's phage experiments.)

These mid-century findings reverberated forty years back to the early days of genetics when Alfred Sturtevant first discovered that the stable Mendelian units of heredity were arranged linearly along the chromosome in *Drosophila* [7]. Benzer had forged the link between the macro level of Sturtevant's map and the micro level of the linear structure of DNA. The road to relating the biochemical properties of genes to their physiological functions was now open, all accomplished by the simple act of performing genetic crosses — beautifully conceived and analyzed genetic crosses.

The work was received as earth-shaking from the outset and the awards began to roll in. These would eventually include the Ricketts Award of the University of Chicago, election to the National Academy of Sciences USA, the Canadian Gairdner Award, the Lasker Award, the T. Duckett Jones Award of the Helen Hay Whitney Foundation, the Prix Charles Leopold Mayer of the French Academy of Sciences, the Louisa Gross Horwitz Prize of Columbia University, and election to the Royal Society. By the end of his life, the list of awards for all of his work covered almost every prize in existence, including the National Medal of Science, the Thomas Hunt Morgan Medal of the Genetics Society of America, the Wolf Prize for Medicine, the Crafoord Prize of the Royal Swedish Academy of Sciences, the Gruber Award and the Albany Medical Center Prize. His impish humor would leak out occasionally during his many speaking engagements. In one such incident, he described the discovery of a new drug, bubbamycin, that reversed the flow of genetic information: from protein to RNA to DNA. 'Bubba meises' is a phrase in Yiddish that literally means grandmother's stories, and is figuratively used to refer to 'old wives' tales'. (This joke preceded by ten years the discovery of reverse transcriptase, thus proving the law that parody is conserved.)

As the magical decade of early molecular biology (1953–1963) unfolded (Figure 2), Benzer's

research became more biochemical and resulted in additional seminal contributions. One of these was the demonstration that it is the aminoacyl tRNA synthetases, the enzymes which attach the correct amino acid to each tRNA molecule, that actually 'translate' the genetic code [8]. This was shown by chemically modifying cysteine to alanine, after it was already linked to its tRNA, and observing in an *in vitro* translation system that alanine was now incorrectly inserted into a hemoglobin polypeptide where cysteine should have been. Another of his studies from this period demonstrated the degeneracy of the genetic code by correlating the different insertion sites of leucine into hemoglobin (again *in vitro*) with specific leucine codons [9]. During this period, Benzer's publication rate rocketed from less than one paper per year to nearly four per year.

The proliferation of these papers, and their distinctly non-romantic nature, prompted a rebuke from his erstwhile mentor, Max Delbrück. In a letter from his wife Manny to Seymour's wife Dotty, Delbrück added a note saying, "[P]lease tell Seymour to stop writing so many papers. If I gave them the attention his papers *used* to deserve, they would take all my time. 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*" (quoted in Benzer, 1966 [10]). The comment hit home and reinforced a nascent interest that Benzer had been cultivating on the side in his Purdue lab — the brain. For the previous few years, he and his technician, Mary Lou Pardue, had been dissecting and sectioning brains from various animals, from fruit flies to cows. (As part of Seymour's phylogenetically promiscuous taste for food, some of these were taken home and cooked for dinner afterwards.)

Benzer's interest in genetic influences on the brain was prompted by several events. He had been intrigued with the findings of one James McConnell in 1962, a former advertising executive who claimed that RNA isolated from trained Planaria could be administered to untrained Planaria and transfer the behavior to them. This finding spawned a bubble of experiments in rats and reports in top journals, all of which confirmed McConnell's basic findings, until the bubble burst when it was shown that all of the results had been unduly influenced by wishful thinking [11]. The excitement at the time, however, is readily understandable as a possible molecular mechanism for learning and memory and there was much speculation as to whether there might be a 'neuro-genetic code'. Benzer even tried his hand at conditioning Planaria, but gave up when he found that an electric shock split the worms in two. A second influence was reading *The Machinery of the Brain* by Dean Wooldridge [12]. Wooldridge had been director of electronics research at Hughes Aircraft and then one of the founders of the aerospace company TRW. In his 1963 book, Wooldridge laid out a Schrödinger-like challenge to explain the workings of the brain in terms of physics and chemistry. The third influence was Benzer's observation that his second daughter, Martha, totally differed in personality from his first, Barb, despite the apparent lack of change in his and Dotty's behavior as parents.

The catalytic event in Benzer's change of research was a sabbatical year in Roger Sperry's lab at Caltech in 1965. His initial project was to test the effect of his phage mutagens on the wiring projection of the frog's retinal ganglion cells onto its optic tectum. The specificity of neuronal wiring was Sperry's signature system at the time, based on the evident fidelity with which a rotated eye would reconnect with the brain. The prospect of using mutagens in this system appeared to Benzer to be an avenue into molecular mechanisms underlying brain function. Unfortunately, the dose required to see an effect was also that at which death ensued. But Benzer was undaunted (see quote at beginning). With some encouragement from Ed Lewis, he began experimenting with fruit flies and their phototactic behavior.

Fruit fly phototaxis had a long research history, going back to the original pre-Morgan fly lab of William Castle at Harvard, where F. Carpenter [13] had documented the fly's responses to light and gravity. A decade later in Morgan's lab, R.S. McEwen [14] had shown that fly mutants such as *tan* were defective in phototactic behavior. In the 1950s, Jerry Hirsch had taken up this neglected field and shown that fly behavior could be dramatically altered after selective breeding for divergent phototactic or geotactic behavior [15,16]. Hirsch's work was directed at showing that behavior has a basis in genetics, but his flies could not be further analyzed for which genes were responsible, let alone the mechanisms responsible. Benzer's approach was to take the power of genetic analysis as practiced in phage and bacteria and bring it to bear on the problem of behavior in *Drosophila*. He published his first paper on fly behavior in 1967, the same year he joined the faculty at Caltech, and the field of fly neurogenetics was launched [17]. It had the requisite romantic appeal for Benzer: a problem for which the contours of a solution could not yet be seen. And in a further echo of his earlier romantic quest, traditional neurobiologists told him he was crazy to think that genetics would have anything to contribute to the study of the brain.

For the next forty years, until his death, Benzer would attract bright young scientists to his lab to explore new areas of fly behavior, neurobiology, and (later on) aging (Figure 3). Among them were most of the founders of what now constitutes the field (reviewed in [18–20]. No behavior was too far out to be tried, no idea too crazy to entertain. Is there a neurogenetic code? Is there one gene per synapse? Are there such things as 'behavioral' genes? (Recall that this was the pre-cloning, pre-sequencing era, and the identities of most genes were still a mystery.) Some of these questions still provoke argument. If Benzer's phage work was laser-like in its penetrating focus, his fly work had the character of a fountain with streamlets flying off in all directions. In 1973, he wrote an article for *Scientific American* entitled "Genetic Dissection of Behavior" [21], which helped lure many (including this author) into the nascent field.

The lab itself was like a carnival with a sideshow in every room. Unsuspecting visitors entered the assembled lunch room at their own peril, as likely to encounter peals of laughter from the constant joking (much of it sophomoric), as probing questions. Many mutants and genetic approaches that anticipated or started new fields came out of this first decade at Caltech: the

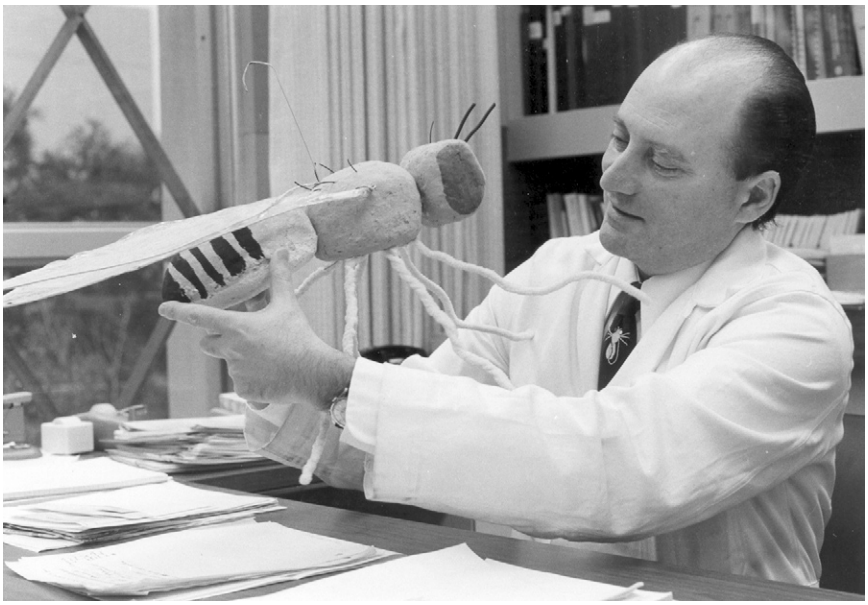

Figure 3. Benzer and friend at Caltech in 1974. (Courtesy of the Archives, Caltech.)

circadian rhythm mutant *period* [22]; the neurodegeneration mutant *drop-dead* [23,24]; the learning mutant *dunce* [25]; the cell fate mutant *sevenless* [26]; the mapping of behavioral effects to specific sites and cells in the nervous system [27–29], and the neurophysiological analysis of mutants [30–32]. During this extraordinarily fertile period, Benzer's publication rate hovered around one paper per year, but not because of lack of attention to the science. Benzer was notorious for his inclination to finesse other professorial duties, nor was he a political operator in the larger world of science. He founded this field but never warmed to the role of an institutional leader of it.

In the lab's second decade, eye development became the principal topic of research, following a seminal study of the dynamics of retinal development in the fly [33]. Benzer's publication rate crept back up after 1976, peaking at eight papers in 1993 and then plateauing at roughly four papers per year for the duration. Delbrück died in 1981, so there was no one to repeat the earlier rebuke about publishing too many papers. But no reminder was necessary at this point. Benzer made fun of himself for publishing so much and acknowledged that the world had changed. He mused that the greatest danger to a field was its successful establishment, as measured by the founding of a 'Journal of …' and an 'International Congress of …'. This decade, however, also saw the loss of Benzer's wife to cancer, but then subsequent meeting and remarriage to Carol Miller, a neuropathologist from USC with whom he collaborated on several papers and a son.

As the new millennium dawned, the lab transmogrified again into the study of neurodegeneration and aging, where it continued to explore new territory. But behavior and fly psychology were never abandoned. Mutants affecting thermo- and hygro-sensation were isolated [34], as was a nociceptive mutant dubbed *painless* [35], and studies were initiated on feeding behavior [36]. Benzer was an active and insatiably curious scientist to the end. His example reminds us of the philosophy that we should die young — as late as possible.

The foregoing recounts the many scientific 'firsts' for which Benzer was responsible. By the same token, there are several scientific 'lasts' that accompany his passing. He is the last (or nearly so) of the generation of children of eastern European Jewish immigrants to Brooklyn and New York's Lower East Side who helped propel U.S. science to the forefront of the world, and one of the last of the original molecular biologists. He is one of the last of the scientific romantics who not only pursued science for its own sake (when it paid so poorly that there was no other reason to go into it), but also pursued questions whose answers were not at all visible, and for which there was no guarantee of obtaining any results at all. And finally, he was surely the last of an era in which a scientist did not have to be fast-talking, slick, or self-promoting.

Benzer's accomplishments are emblematic of the half-century during which he worked, an era that saw the problem of the physical basis of the gene solved and the tangled relationship between gene and behavior seriously addressed. He approached science with rare fearlessness, imagination, and insight, and his legacy will survive all of us.

Acknowledgments

Sources for this article, unless otherwise cited, are personal conversations with S. Benzer and with various former members of his lab. I thank Jeff Hall, Chun-Fang Wu and Jim Haber for additional comments. R.J.G. is the Dorothy and Lewis B. Cullman Fellow in Experimental Neurobiology at The Neurosciences Institute, which is supported by the Neurosciences Research Foundation.

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Primer

Executive function

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Executive functions are the high-level cognitive processes that facilitate new ways of behaving, and optimise one's approach to unfamiliar circumstances. As many situations in everyday life are not exactly the same as ones that we have encountered before, it follows that the operation of executive processes accompanies a very wide range of behaviours. But we particularly engage such processes when, for instance, we make a plan for the future, or voluntarily switch from one activity to another, or resist temptation; in other words, whenever we do many of the things that allow us to lead independent, purposeful lives. These processes are thought to be supported, at least in part, by structures within the frontal lobes of the brain. But they are understood far less comprehensively than some of the functions supported by other brain regions. Indeed, a review published as recently as 1996 described this domain as a "somewhat embarrassing zone of almost total ignorance" (Monsell, 1996). But cognitive neuroscience has recently made significant strides in characterising the nature of these processes, and their underlying brain mechanisms. This Primer surveys some of the theoretical frameworks commonly used for understanding executive functions, and their relationship with the frontal lobes.

Role of executive processes in the organisation of cognition

At the heart of most (but not all) theories of executive function is a distinction, or gradation, between routine (or 'automatic') and non-routine (or 'controlled') processing. Routine processing refers to mental operations that are well rehearsed or overlearned, for example reading out a word. By contrast, non-routine processing most commonly refers to mental operations that are used in situations when there is not a well-established stimulus-response association, or where a behavioural impasse has occurred (for example one notices an error, or realises that one is behaving in a sub-optimal fashion). The term 'executive functions' has become synonymous with those behaviours and abilities.

At an abstract level of processing, least tied to routine behaviour, are flexible representations of goals and intentions. Such 'higher-level' representations are often contrasted with 'lower-level' cognitive processes involved in analysing specific perceptual inputs (such as visual processing of stimuli such as 'BLUE') and generating specific motor outputs (such as vocal responses). According to most theories, executive function entails the modulation of lower-level processes by those at a higher level. Depending on our current goal, we are able to modulate lower-level perceptual-analysis and speech-output processes in order to produce appropriate behaviour. In different contexts we might ignore the word, read it out, or name its colour, even though we are presented with the same perceptual input in each case. Thus, executive functions allow us to behave flexibly, rather than being slaves to our environment and always behaving in a stereotyped manner when particular events occur. This equips us with the ability to adapt to novel, or changing, situations.

The modulation of various cognitive, perceptual, and motor processes according to abstract goals and intentions is commonly referred to as 'top-down control'. However, this should not imply a strict unidirectional influence from higher-level to lower-level processes. Instead, the role of executive function in cognition is probably more accurately considered in terms of continual interaction between higher- and lower-level processes. Higher-level processes are commonly triggered in everyday life by conflicts between representations or inputs at lower levels, for instance when something unexpected occurs or when behaviour does not have the usual consequences.

Paradigms in executive function research

Historically, a major obstacle to progress in research into executive function has been the difficulty of quantifying the processes supported by the human frontal lobes, a problem compounded by the variety of cognitive, social, and emotional changes that have been reported to occur as a consequence of damage to this region. Methodological and