BOOKS: BEHAVIOR

It's in the Genes

Gunther S. Stent

Seymour Benzer 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. Perhaps Jonathan Weiner's biography of Benzer will make his epochal scientific contribution more widely appreciated. But its title, *Time, Love, Memory*, evokes only Benzer's lesser achievements (his studies of the role of genes in the control of fruit fly behavior), and the work that should secure for Benzer a place in the pantheon of biology—his bridging the experimental gap between formal genetics and DNA structure—occupies only a dozen or so of the book's 300 pages.

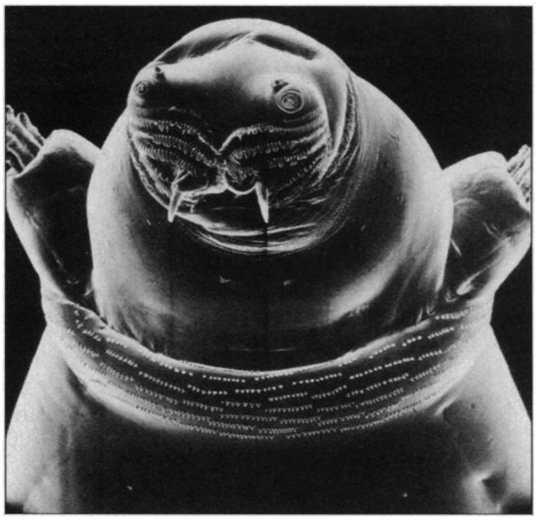
Time, Love, Memory
A Great Biologist and His Quest for the Origins of Behavior
by Jonathan Weiner

Knopf, New York, 1999. 314 pp. $27.50, C$36.95. ISBN 0-679-44435-1.

Trained as a solid state physicist at Purdue University, Benzer was well on his way toward inventing the transistor when, along with several other founders of molecular biology, he was seduced by Erwin Schrödinger's inspirational essay "What Is Life?" He switched his research interest to the mystery of the physical nature of genes, enrolled in the Cold Spring Harbor course on bacterial viruses in the summer of 1948, joined Max Delbrück's phage group (the fountainhead of molecular biology), and went on to Delbrück's laboratory at Caltech as a postdoctoral fellow in the fall of 1949.

During the growth of classical genetics, the word "gene" had gradually come to represent a conceptual chimera. It was defined as the unit of genetic material that is passed on from parent to offspring and identified operationally by its ability to mutate to alternative states, to recombine with other similar units, and to function in the endowment of the organism with some particular phenotype. Working with a bacterial virus, Benzer showed that there is no such thing as the "classical" gene. The unit of recombination is a single DNA nucleotide base pair. The unit of mutation can vary from a single base pair to hundreds of nucleotide base pairs. And the unit of function is a sequence of hundreds or thousands of nucleotides, which specify the sequence of amino acids that make up the primary structure of a polypeptide chain.

By the late 1960s, molecular biology's central problem as defined by Schrödinger—namely the structure, self-replication, and function of genes—was well in hand, and the circle of its adepts had grown from a small coterie into an incipient mass movement. Benzer, and most of the other founders, shifted research interests from the now jejune gene to what they perceived as the last thrilling biological frontier, the brain and its control of behavior. During the 20-year gestation of molecular biology these pioneers had all worked with the same organisms: bacteria and their viruses. But now they chose a panoply of different creatures as experimental materials for their brain studies, ranging from (brainless) fungi, through worms and insects, to fish and mammals.



Eat and run? "Roving" fruit-fly maggots nibble and move on; "sitting" maggots settle down and consume entire crumbs. This scanning electron micrograph could be of either form, as they differ by only a single base pair in the gene *foraging*.

CREDIT: COURTESY EDWARD LEWIS/FROM *TIME, LOVE, MEMORY*

Benzer picked the fruit fly, *Drosophila*, which didn't seem like a very promising beast. Its behavioral repertoire was considered that of a boring dullard even when compared to other flies, and its tiny size put functional studies of its brain well beyond the reach of then-available electrophysiological methods.

Yet the fruit fly had one tremendous advantage. After being chosen by T. H. Morgan in 1907, it became the organism with which he and his school developed "classical" genetics (whose gene concept Benzer had just reformed), and more was known about its genetics than about that of any other metazoan. So Benzer decided to dissect its behavior by genetic rather than electrophysiological means. He isolated *Drosophila* mutants having abnormal behavior, mapped the mutant alleles to their chromosomal loci, identified the molecular basis of the phenotypic change, and then inferred the normal mechanism of behavioral control from mutant phenotypes. To isolate rare fly mutants with aberrant behavioral phenotypes, Benzer invented ingenious selective procedures inspired by the methods that he had previously devised for finding very rare mutants of bacteria and their viruses.

Benzer founded a school at Caltech whose members undertook the genetic dissection of the *Drosophila* behaviors alluded to in the title of Weiner's book. In regard to "time," they addressed the fly's innate control of the phases of its diurnal activity cycle, as well as of the endogenous clocking of its precisely scheduled sequence of developmental stages, from fertilized egg to adult. In regard to "love," they studied the fly's surprisingly elaborate courtship rituals, which involve singing and dancing by males and the expected reactions to these displays by females. And in regard to "memory," they demonstrated that the fly has the capacity to "learn" to modify its spontaneous movements under a regime of classical Pavlovian conditioning. Working hard for the past thirty or so years, Benzer's school managed to isolate a large, diverse collection of behaviorally aberrant mutant flies, whose sophisticated genetic analysis leaves no doubt about the gene-directed developmental origin of these innate routines.

It would seem, at least according to Weiner's account, that to date the genetic dissection approach has generated relative-

The author is in the Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720–3200, USA. E-mail: stent@uclink4.berkeley.edu

ly few insights into the detailed physiological mechanisms actually responsible for the implementation of behavioral routines related to time, love, and memory. By contrast, studies carried out in other laboratories, on larger animals that are more accessible to physiological (especially neurophysiological) experimentation than *Drosophila*, have already provided a somewhat deeper understanding of mechanisms that generate animal behavior.

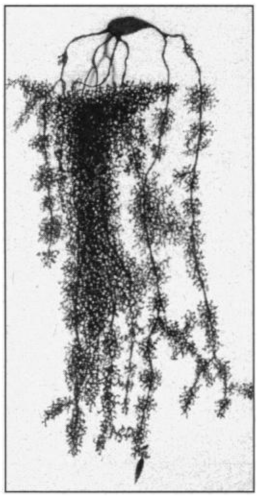
The chief merit of *Time, Love, Memory* is its empathetic description—neither panegyric nor carping—of the remarkable personalities of the story's protagonist and his disciples. Benzer is convincingly portrayed as one of those few people who really does merit the appellation "scientist's scientist," one who presents that rare conjunction of genius, lucidity, fairness, maximal self-confidence, and minimal self-promotion. Weiner thus provides his readers with an enjoyable yet realistic account of the working interactions among a top-of-the-line, end-of-the-millennium, life-science research coterie and its distinguished leader.

BOOKS: PRACTICE OF SCIENCE

Seasoned Suggestions for Success

Jon H. Kaas

In 1887 Santiago Ramón y Cajal, Spain's most distinguished scientist and a founder of modern neuroscience, gave up a promising career in bacteriology when he first saw sections of brain tissue stained with Camillo Golgi's then-new silver chromate technique. The Golgi method had the great advantage of staining only a scattering of the densely packed nerve cells in the brain, so that "the trees could be seen in the forest." Cajal soon realized that the method is most effectively applied to embryonic material, and the complexity of the brain is best understood by studying smaller animals at early, simpler stages of development. Cajal went on to publish impressive drawings and descriptions of neurons throughout the nervous system. He became known for his successful defense of the neuron doctrine, the now basic idea that the nervous system is constructed of separate neurons that conduct information from the cell body along axons that contact and activate the dendrites and cell bodies of other neurons. In contrast, Golgi and others held the "false theory" that neurons are joined to form a continuous net without polarity. Cajal also discovered the growth cone (the growing tip of developing and regenerating axons), and he formulated a theory of neurotropism (the attraction of growing axons by distant targets). He strongly believed in the plasticity of even the mature nervous system, an area of considerable research today. In 1906 Cajal shared the Nobel Prize in Medicine with his scientific rival, Golgi. Ramón y Cajal remains perhaps the best known and most influential neuroanatomist of all time. He continues to be frequently cited in scientific publications, and students of neuroanatomy have long been reminded that much of what we know now was described in detail by Cajal nearly 100 years ago.



Brain wiring. Drawings of nerves from the brains of a fly by the pioneer neuroanatomist Santiago Ramón y Cajal.

CREDIT: COURTESY CAJAL INSTITUTE/FROM *TIME, LOVE, MEMORY*

Remarkably, Cajal took time to write a small book of advice to young scientists. The book, based on a 1897 speech, was subsequently revised several times. Neely Swanson, a translator, and Larry Swanson, a neuroscientist, have now produced a very readable, modern (rather than literal) rendition based on the fourth edition, which was published in 1916, and a previous English translation of the sixth edition (*1*). Cajal wrote the book for Spanish scientists of his time. Thus some of the advice is specific or dated, but much is more universal and still applicable. The advice was intended for serious young scientists, with the hope that it would "increase their love for laboratory work." Most of Cajal's pronouncements were based on strong opinion and most were clearly and amusingly expressed. More than anything, Cajal believed that devotion to laboratory work would bring rewards. As he noted, "the turtle may pass the hare."

Advice for a Young Investigator
by Santiago Ramón y Cajal
translated by Neely Swanson and Larry W. Swanson
MIT Press, Cambridge, MA, 1999. 172 pp. $22.50. ISBN 0-262-18191-6.

Cajal wrote that almost anyone of normal intelligence could become a productive scientist. He believed the plasticity of the brain allowed for improving and refining its machinery so that with experience one would become better and better at scientific thinking. He felt that work "creates talent." Furthermore, one should focus one's efforts on one or two interests, rather than many. Cajal concluded that "multifaceted investigators have disappeared, perhaps forever." He likened focused interest in a single research issue to sharpening a single-edged sword until it cuts efficiently. Adding more cutting edges would progressively diminish such a sword into "a dull bludgeon." Cajal recognized that it is best to start sharpening the mind while one is young, for "the youthful brain is wonderfully pliable." Late in life, the "plasticity of nerve cells is greatly reduced."

Concentration and laboratory work not only improve the mind for further discovery, but produce "the fruit of patience and perseverance." Cajal concluded that the theoretical scientist with an aversion to the laboratory "is a lazy person masquerading as a diligent one." He reminded us that discoveries are made by people and not by scientific instruments or overflowing libraries. The misguided addict of instruments is "as fascinated by the gleam of metal as the lark is with its own reflection in a mirror," and the reader of books needs to contribute as well as acquire knowledge. To allow scientists to focus on research, Cajal thought that the "ideal university would be a monastery with monks consecrated for life to the study of nature." Cajal, however, recognized that the life of a monk would be an "intolerable sacrifice for the majority of scholars." Thus, some of his advice was on how to limit the impact of social distractions. He advises the young male scientist never to marry a wealthy woman, for "a wife's riches are fatal to one's work." After such a marriage, evenings in the laboratory would be replaced by "useless hours spent at parties or the theater." In regard to writing, he simply stated, "have something to say, say it, and stop."

For practical advice on how to write a first grant or address the concerns of manuscript reviewers, we will need to look elsewhere. Cajal's conclusions were meant to encourage and motivate. The book is short, enjoyable, and valuable as a view of a great scientist of another time.

The author is in the Department of Psychology, Vanderbilt University, Nashville, TN 37240 USA. E-mail: jon.h.kaas@vanderbilt.edu

References

1. S. Ramón y Cajal, *Precepts and Counsels in Scientific Investigation: Stimulants of the Spirit*, J. Ma. Sanchez-Perez, Transl., C. B. Courville, Ed. (Pacific, Mountain View, CA, 1951).