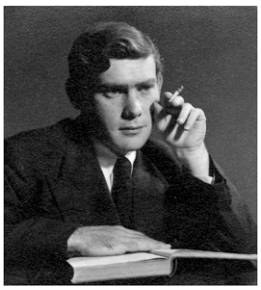
Sydney Brenner on the Genetics of *Caenorhabditis elegans*



Bob Goldstein*,†,[1]

*Department of Biology, †Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina 27599-3280

ORIGINAL CITATION

The Genetics of *Caenorhabditis elegans*
Sydney Brenner
GENETICS May 1, 1974 **77:** 71–94

Sydney Brenner decided on his lifelong scientific goals on one cold day in April 1953. He was a 26-year-old graduate student in Oxford at the time. "What I remember in Oxford is being hungry all the time, and cold," he told me. Crick and Watson had just built the double helix model, and Brenner and a few others took a road trip to Cambridge to see it before it was announced to the rest of the world. In the model, Brenner could foresee the future of biological research. "We could now find out how genes worked. On that day I knew exactly what I wanted to do" (Friedberg 2010).

Over the next 12 years, Brenner, Crick, and many others plugged away at figuring out how DNA worked. Brenner and colleagues built some of the foundations of molecular biology's central dogma with key experiments that revealed the existence of messenger RNA (Brenner *et al.* 1961), a triplet genetic code (Crick *et al.* 1961), and stop codons (Brenner *et al.* 1965).

But as early as 1962, the new field of molecular biology was getting crowded. To the founders, the endgame was in sight. "Most of molecular biology had become inevitable," Brenner said (Wood 1988). Many of the early molecular biologists chose to unleash forward genetics on more complex problems—neurobiology and development—taking the risk that the gene-by-gene reductionist approach would be effective. George Streisinger started zebrafish forward genetics. Seymour Benzer bet on fruit flies. And Brenner started tinkering with a variety of organisms.

doi: 10.1534/genetics.116.194084
Image of Sydney Brenner courtesy of Cold Spring Harbor Laboratory Archives.
[1]Address for correspondence: 616 Fordham Hall Campus Box 3280, University of North Carolina, Chapel Hill, NC 27599-3280. E-mail: bobg@unc.edu

Brenner presented his ideas for studying diverse organisms in a 1963 letter that also included a longer-term possibility: "I would like to tame a small metazoan organism to study development directly." Brenner searched for an animal that could be grown easily in the lab, that had fewer neurons than a fruit fly, and was small enough to fit in the view of a transmission electron microscope—pursuing a vision that forward genetics, detailed neural anatomy, and development might be married in a single animal.

Microscopic nematodes seemed just right. Ellsworth Dougherty in Berkeley and colleagues had already proposed the potential value of tiny nematodes to genetics research and had generated and analyzed a couple of mutants (Dougherty and Calhoun 1948; Nigon and Dougherty 1950; Fatt and Dougherty 1963). Brenner wrote to Dougherty in 1963 to ask for worms and advice, and he drafted a one-page proposal to the Medical Research Council that ended with the famously optimistic aim: "To start with we propose to identify every cell in the worm and trace lineages. We shall also investigate the constancy of development and study its control by looking for mutants." Brenner's *Caenorhabditis elegans* mutant screens began in 1967. The 1974 article in *GENETICS* reported the results of these efforts.

Brenner began by laying out the big questions of "how genes might specify the complex structures found in higher organisms." He detailed how to conduct genetic analysis on a self-fertilizing hermaphrodite that also has cross-fertilizing males, and he reported on hundreds of mutants—long worms, rolling worms, dumpy-looking worms, uncoordinated worms, blistered worms, and worms whose heads were notched or bent. Complementation and mapping identified a whopping 96 loci on six linkage groups, matching the known

number of chromosomes. The paper ended with a hint of what would follow: the preliminary analysis of mutants that would begin to identify individual gene functions, long before gene cloning.

Brenner ended his paper by suggesting an even larger effort "to look for mutants in all of the genes to try to discover how they participate in the development and functioning of a simple multicellular organism." Over the years, this effort has involved thousands of researchers pursuing their own interests along the trail that Brenner blazed, and whose discoveries have impacted the breadth of biology and biomedical science.

Communicating editor: C. Gelling

Literature Cited

Brenner, S., 1974 The genetics of *Caenorhabditis elegans*. Genetics 77: 71–94.

Brenner, S., F. Jacob, and M. Meselson, 1961 An unstable intermediate carrying information from genes to ribosomes for protein synthesis. Nature 190: 576–581.

Brenner, S., A. O. Stretton, and S. Kaplan, 1965 Genetic code: the "nonsense" triplets for chain termination and their suppression. Nature 206: 994–998.

Crick, F. H., L. Barnett, S. Brenner, and R. J. Watts-Tobin, 1961 General nature of the genetic code for proteins. Nature 192: 1227–1232.

Dougherty, E. C., and H. G. Calhoun, 1948 Possible significance of free-living nematodes in genetic research. Nature 161: 29.

Fatt, H. V., and E. C. Dougherty, 1963 Genetic Control of Differential Heat Tolerance in Two Strains of the Nematode *Caenorhabditis elegans*. Science 141: 266–267.

Friedberg, E., 2010 *Sydney Brenner: A Biography.* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

Nigon, V., and E. C. Dougherty, 1950 A dwarf mutation in a nematode; a morphological mutant of *Rhabditis briggsae*, a free-living soil nematode. J. Hered. 41: 103–109.

Wood, W. B. (Editor), 1988 *The Nematode Caenorhabditis elegans*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

Further reading in *GENETICS*

Brenner, S., 2009 In the Beginning Was the Worm. Genetics 182: 413–415.

Corsi, A. K., B. Wightman, and M. Chalfie, 2015 A Transparent Window into Biology: A Primer on *Caenorhabditis elegans*. Genetics 200: 387–407.

Ferris, H., and W. F. Hieb, 2015 Ellsworth C. Dougherty: A Pioneer in the Selection of *Caenorhabditis elegans* as a Model Organism. Genetics 200: 991–1002.

Other articles by S. Brenner in *GENETICS*

Brenner, S., W. Dove, I. Herskowitz, and R. Thomas, 1990 Genes and development: molecular and logical themes. Genetics 126: 479–486.

Herman, R. K., D. G. Albertson, and S. Brenner, 1976 Chromosome rearrangements in *Caenorhabditis elegans*. Genetics 83: 91–105.

Hodgkin, J. A., and S. Brenner, 1977 Mutations causing transformation of sexual phenotype in the nematode *Caenorhabditis elegans*. Genetics 86: 275–287.

Hodgkin, J., H. R. Horvitz, and S. Brenner, 1979 Nondisjunction Mutants of the Nematode *Caenorhabditis elegans*. Genetics 91: 67–94.

Riddle, D. L., and S. Brenner, 1978 Indirect suppression in *Caenorhabditis elegans*. Genetics 89: 299–314.

Sulston, J. E., and S. Brenner, 1974 The DNA of *Caenorhabditis elegans*. Genetics 77: 95–104.