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TIMELINE

The natural history of *Caenorhabditis elegans* research

Rachel A. Ankeny

The nematode *Caenorhabditis elegans* is well known to practising biologists as a model organism. Early work with *C. elegans* is best understood as part of a descriptive tradition in biological practice. Although the resources that have been generated by the *C. elegans* community have been revolutionary, they were produced by traditional methods and approaches. Here, I review the choice and use of the worm as an experimental organism for genetics and neurobiology that began in the 1960s.

The announcement of the nearly complete sequencing of the genome of the nematode *Caenorhabditis elegans* at the end of 1998 was hailed as a milestone in genomics[1]. Although the genomes of several other organisms had been sequenced by that time[2,3], *C. elegans* was the first multicellular organism to be completely sequenced. Arguably more biological information was available on 'the worm' (as it is commonly termed) than on any other relatively complex organism. This was due to the intense studies of its genetics, development and neurobiology that had been underway since the late 1960s. Here, I examine the choice and use of this nematode as an experimental organism for genetics, with particular focus on the period in the 1960s when the brain was declared to be the "last remaining frontier" for biological investigation. The worm was first chosen for investigation into the nervous system, but proved to be useful for exploring many other biological processes. I argue that early work with *C. elegans* can best be viewed as part of a descriptive tradition in biological practice, and that such descriptions are essential as the basis for successful subsequent experimental and explanatory work, as becomes evident on a close examination of the history of the field.

Choosing *Caenorhabditis elegans*

In June of 1963, Sydney Brenner (FIG. 1) wrote in a letter to Max Perutz, the then director of the Laboratory of Molecular Biology (LMB) in Cambridge, UK, that "nearly all the 'classical' problems of molecular biology have either been solved or will be solved in the next decade … the future of molecular biology lies in the extension of research to other areas of biology, notably development and the nervous system"[4]. Brenner had done extensive work primarily in bacteria and bacteriophage genetics at what came to be known as the LMB. He and Francis Crick, head of the Division of Molecular Genetics at the LMB and Brenner's long-time office partner, had a series of conversations in late 1962 to decide in which direction to take their research. These conversations were in part spurred on in early 1963 by institutional factors, such as the interest of the Medical Research Council (MRC) in expanding the LMB[5] and the trends in biology at that time, which were leading away from molecular biology. During this era and after various successes in molecular biology, notably the identification of the structure of DNA and the details of the coding mechanisms associated with it, several prominent biologists had begun to use particular organisms to study behaviour and the nervous system. These biologists shared Brenner's view that many, if not most, of the 'interesting' problems of molecular biology were solved or close to being solved. Ralph Greenspan claims that the almost unanimous convergence on the nervous system as the new problem of interest "was not by design or agreement, but reflected the sense that here lay the greatest challenge and mystery"[6]. So, what has come to be known as "the worm project" arose in the context of a framework greatly influenced not only by the successes and limitations of previous work with bacteria and bacteriophage, but also by a particular vision of biology, including what molecular

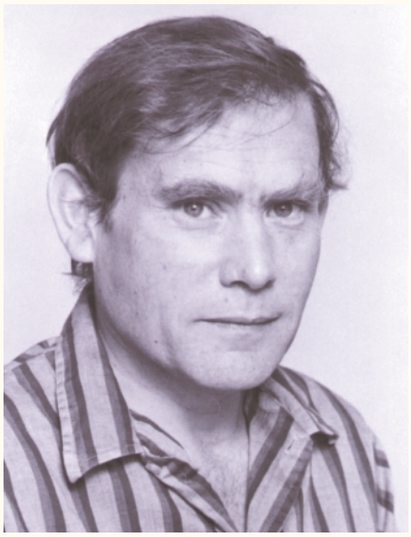


Figure 1 | **Sydney Brenner at the Laboratory of Molecular Biology in the 1960s.** (Photograph kindly provided by the MRC Laboratory of Molecular Biology, Cambridge, UK.)

biology had achieved and where it might make significant future contributions.

Brenner's initial proposal to Perutz outlined a global approach that primarily focused on examining development through genetic analysis, with a long-term goal of investigating the development of the nervous system. Among other projects, including research on morphogenetic gradients that expanded Crick's earlier work on pattern formation, Brenner proposed working on several "model systems", which were to be "small metazoa, chosen because they would be suitable for rapid genetic and biochemical analysis"[7]. He also noted that there had been much success with bacteria, particularly in the analysis of lethal mutants and that this "has suggested … that we could use the same approach to study the specification and control of more complex processes in cells of higher organisms". Among the topics of investigation suggested were cell division using ciliates, control of flagellation and ciliation using "amoeboflagellates", and the study of development by "taming" a small metazoan organism, perhaps an insect.

Much work has been done on how organisms become standardized tools, particularly *Drosophila*[8] and mice[9]. The story of the standardization of *C. elegans* differs in a significant way from most of these histories. Brenner recounts scouring zoology textbooks in search of a single organism to use as a research focus, one that would match his basic, explicit criteria for a model organism. These criteria included: first, a rapid life cycle, thus allowing growth of large populations in a short period of time and increasing the likelihood of rare spontaneous mutations (a strategy that had proven highly successful in work with bacteria and bacteriophage); second, a simple reproductive cycle and genome, such that the genetics of the organism was, in principle, tractable; and last, small size, so that large populations could be generated and stored, again increasing the likelihood of mutations, and so that single animals could be examined in the window of an electron microscope to elucidate structural details.

Brenner set out with the goal of obtaining an organism to fulfil all these criteria largely by making a careful organismal choice to start with, rather than focusing on inbreeding and other typical standardization techniques. Most standardization occurred owing to the choice of a strain of an organism thought to be relatively invariant in several biological features. This strategy clearly derived from bacteria and bacteriophage work in which inbreeding is fairly trivial.

Several classes of organism were under active consideration during this period, including several protozoa such as *Dictyostelium*, *Naeglaria* and *Tetrahymena*. Brenner eventually came to focus on the lower metazoa, in part because of a book he read dedicated to these organisms (edited by an early proponent of *Caenorhabditis*[10]), and also because several of them seemed to fulfil his basic criteria. On further consideration, Brenner had concerns about working with most of these organisms; these concerns were deeply connected to his beliefs about what could serve as an appropriate model for multicellular organisms and their development. He was interested in something that was representative and on which he could work at various levels simultaneously, which many of these organisms would not have allowed.

After a brief flirtation with a related nematode, *Caenorhabditis briggsae*, Brenner obtained a culture of the Bristol strain of *C. elegans* (BOX 1) from Ellsworth C. Dougherty, who had worked extensively with the organism. Similar nematodes had been studied since the late 1800s in terms of cell lineage, and these investigations had shown that their developmental processes were relatively invariant[11]. Furthermore, Richard B. Goldschmidt had done detailed work on neural wiring in a larger but related nematode, *Ascaris*, that had also revealed invariant structures[12,13], but that had fallen into disrepute owing to its apparent lack of reproducibility. Brenner was well aware not only of these early results and the possibility of substantiating them, but also of further correlating development and structure with genetic mutations in this organism, using technologies that were unavailable to earlier researchers.

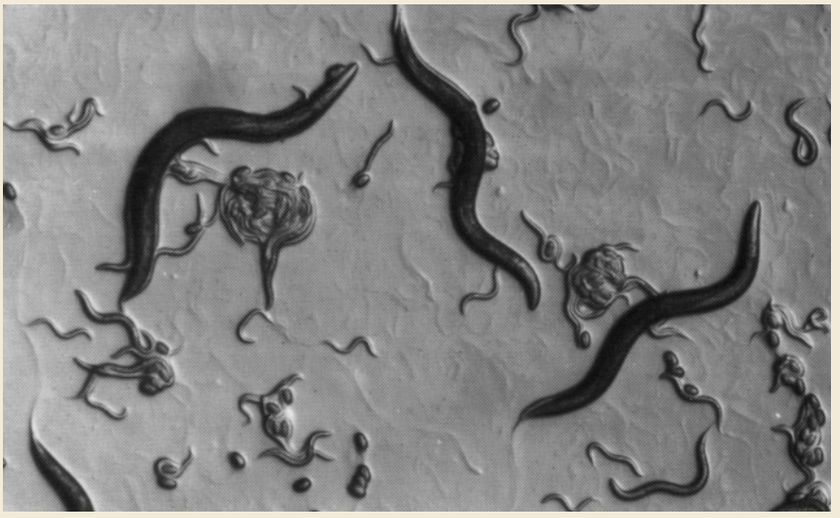
The 1960s neurobiological revolution

Brenner was not alone among molecular biologists in viewing neurobiology as the new frontier for research. One of the earliest attempts to connect genetics and behaviour had been made by Julius Adler, who in ~1960 began to study chemotaxis — the movement of cells in response to a chemical stimulus — in the bacterium *Escherichia coli*[14]. He had searched for a simple system in which to study a basic behavioural process "in the hope [that] some underlying principles might be discovered that are applicable at many different levels of biological complexity"[15]. By the mid-1960s, Adler and others working with him had isolated several mutants, some of which failed to recognize certain attractive agents and others which were generally non-chemotactic[16,17].

In the mid- to late 1960s, several other scientists turned to the study of behaviour and the nervous system, and to a more limited extent to the study of development, through the use of different model organisms. Other projects that also used genetic methods to understand behaviour, and that are frequently cited as peers of the worm project, included the study of: the rotifer and *Daphnia* (among other organisms) by Cyrus Levinthal[18]; the leech by Gunther Stent[19]; and *Drosophila melanogaster* by Seymour Benzer, which was probably pursued most extensively. Benzer selected *Drosophila* in ~1965, after a failed attempt at working on the flatworm *Planaria*[20], because detailed genetics of the fly were already available, and as a compromise between the human and *E. coli* in terms of mass, number of neurons, genome size and generation time[21]. He was able to isolate a set of phototaxic mutants by simply allowing flies to run towards a light source and by separating the population according to their responses[22]. His assumption was that such mutants could be genetically analysed to reveal sensory mechanisms. As Greenspan has put it: "what made his approach so irresistible to some, and so infuriating to others, was its technological simplicity and its indifference to current trends in neuroscience"[23], as it ignored the traditional approaches of neurobiology, which were largely anatomical and biophysical.

By contrast, reports communicated between the MRC and the LMB in 1966 began to stress the investigation of the anatomy and development of the nervous system

Box 1 | Worm farming



Caenorhabditis elegans is a free-living nematode, ~1 mm in length, with relatively simple behaviours and structures. A complete life cycle takes three days, during which the worm goes through four larval stages. There are two dimorphic sexual forms — a self-fertilizing hermaphrodite and a smaller male, which is rarer and can fertilize hermaphrodites. The sexual forms make inbreeding and the control of genetic types extremely simple. The organism is transparent throughout its life cycle, making observation of its structure and many biological processes possible by microscopy. (Photograph by Henri van Leunen, kindly provided by Jonathan Hodgkin, Genetics Unit, Department of Biochemistry, University of Oxford.)

in nematodes among the aims of the lab[24,25]. The emphasis on the nervous system at that time revealed Brenner's strong interest in it, as well as his underlying belief that the nervous system was the most elaborately developed system, as it involved not only basic biochemical functions but also more complex mechanisms for the differentiation of neuronal connections and physical structures. The presence of rigidly defined neural connections from individual to individual in invertebrates, and especially in nematodes, indicated to Brenner that such connections might be produced genetically, making the descriptive mapping of the nervous system an ideal way to gain insight more generally into development.

This conceptualization of the project had been crystallized by 1967, when Brenner was invited to give a talk to the Biological Research Board of the MRC about the future of molecular biology. In accepting the invitation, he wrote in a letter to the principal medical officer of the MRC, who was coordinating the talk, that "I have changed my interests from molecular genetics to a rather vague field of the development and structure of the nervous system"[26]. In his talk, entitled "Molecular Biology and the Nervous System", Brenner used the lab's preliminary work on the worm to show how simple organisms might be used to determine the precise development and structure of at least parts of the nervous system, as well as possibly allowing investigation into the genetic determination of the nervous system[27].

Brenner's first line of attack at the start of the worm project in the mid-1960s was to establish the genetic wild type and to create biochemical (primarily nutritional) mutants. The earliest stages of the *C. elegans* work were focused on purely genetic inputs and outputs, the so-called 'black box' approach that had proven successful with bacteriophage. Although nutritional mutants were initially of interest because they were more likely to be biochemically tractable, attention quickly shifted to morphological and motility mutants, with the latter proving more straightforward to manipulate and exploit experimentally (and of course more directly related to Brenner's neurobiological interests). Brenner began to treat cultures of *C. elegans* hermaphrodites with a solution of ethyl methanesulphonate (EMS) — an alkylating agent known to be a mutagen — which had been used on other organisms, including bacteriophage and *Drosophila*, in the hopes of creating morphological mutants. He varied the concentrations of EMS and the length of time that worms were exposed to it to assess phenotypic effects and survival rates. Eventually, an individual was identified that was considerably reduced in length. When the isolate was allowed to reproduce through self-fertilization, its progeny were also short and 'dumpy' compared with the wild-type worms. Therefore this new strain, named E1, was identified as the first true-breeding mutant in *C. elegans*. Backcrosses to the wild-type background determined that the dumpy phenotype was due to an autosomal-recessive mutation, which eventually became known as allele *e1* of the gene *dpy-1* (REF. 28).

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From 1967 until the early 1970s, over 300 EMS-induced mutations were identified, most of them recessive (see TIMELINE). The bulk of mutations were those that affected behaviour, primarily resulting in worms that were defective in movement ('uncoordinated'); other mutations altered the size and shape of the worms, including the dumpy mutant, as well as other aspects of its morphology. These mutants allowed the characterization of ~100 genes, which were mapped into six linkage groups — the six chromosomes that had been previously identified[29]. This approach relied on describing and maintaining an independent concept of what counted as wild-type *C. elegans*. In this way, genetics provided mutants that were defective in movement and that might reveal information about the nervous system, something that previous nematological and parasitological work had not provided in enough detail, especially for the phenotypes that came to be of particular interest to Brenner and his group.

Although at least the first five years of work on *C. elegans* focused on developing the genetics of the organism, Brenner maintained his long-term interests in exploring the nervous system, emphasizing that it was

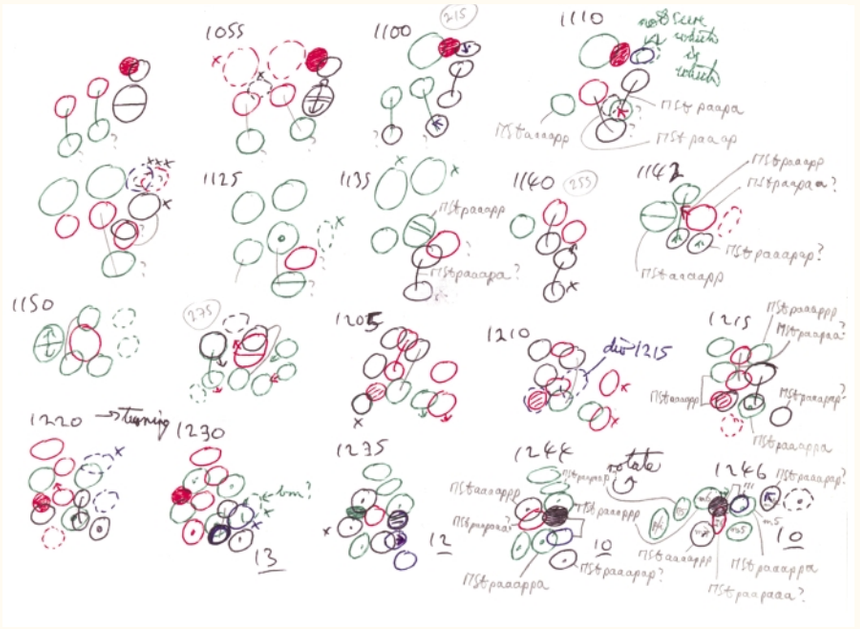


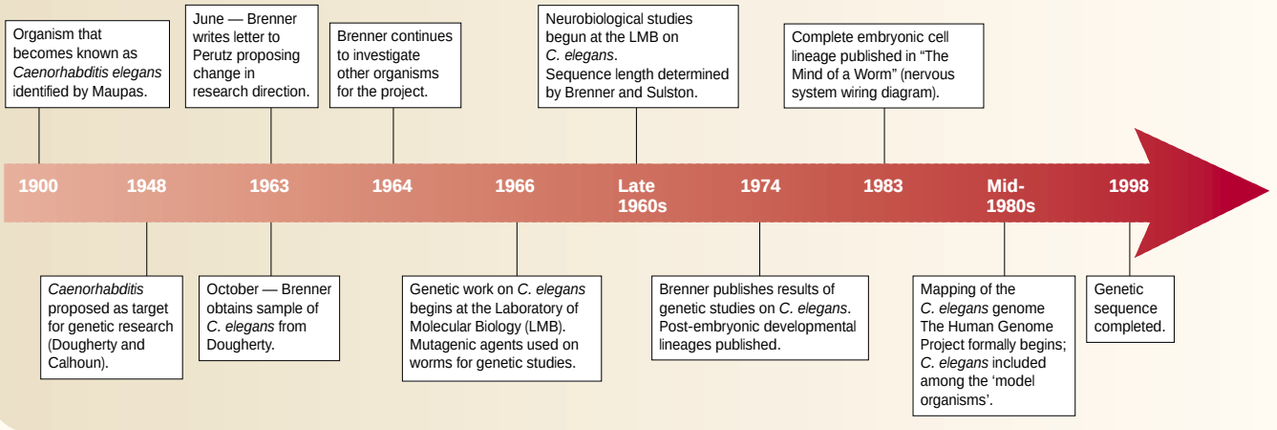
Figure 2 | **Copy of original laboratory notebook drawings by John Sulston.** Drawings of the observations of cell division taken from a dorsal view of the pharynx on May 6, 1980. Hundreds of such drawings were made to record the complete cell lineage for *Caenorhabditis elegans*. (Kindly provided by John Sulston, The Sanger Centre, Cambridgeshire, UK.)

amenable to molecular attack. The underlying hope was that detailed knowledge of the nervous system, together with relatively simple patterns of motion and behavioural response in *C. elegans*, would lead relatively easily to determining the functions of various parts of the nervous system. In what was perhaps the earliest published article that discussed the worm project, Brenner stated that "[i]n principle, it should be possible to dissect the genetic specification of behaviour much in the same way as was done for biosynthetic pathways in bacteria or for bacteriophage assembly"[30]. This type of bravado on Brenner's part generated what has been characterized as "overt hostility" by those already working in the field of neurobiology, partly because his announcement of his project was "… perceived by many neurobiologists, not unreasonably, as an indictment of their field. According to one prominent neurobiologist, the message they heard was, 'If you only had your heads screwed on right, you could clear up the mess in this field. It's only your ignorance that has prevented it'"[31].

However, causal explanations were difficult to obtain for neurobiological processes, particularly given the available techniques. So, it became clear that among the questions that needed to be answered before the relationship between the genetic 'programme'[32] and behaviour could be examined was whether every nerve cell is unique from every other and how precisely the cells and their connections are specified. The detailed drawings of the neural connections in the larger related nematode *Ascaris*, produced by Goldschmidt using conventional microscopy, were difficult to interpret, although Goldschmidt had concluded from these diagrams that neuron processes formed a syncytial network. Because he had not unambiguously resolved individual processes in nerve bundles, the connections shown in his diagrams were thought by some to be artefacts of the relatively low resolution he was able to obtain. Consequently, Brenner felt this task could be best accomplished in the even smaller worm, *C. elegans*, by using serial electron micrograph sections to determine neural connections, the so-called 'wiring diagram'. So, the study of behaviour and neurophysiology was de-emphasized in favour of establishing a description of neural structure as a necessary step towards understanding genetics and behaviour.

The eventual result of this project was the mapping of the architecture of the nervous system by reconstructing (largely by hand) 8,000 prints from serial-section electron micrographs, done by John White together with Eileen Southgate, J. Nichol Thomson and Brenner. This project was completed in ~1984, resulting in an enormous article published several years later, known in short as "The Mind of a Worm"[33].

Timeline | Major events in *Caenorhabditis elegans* research



It included diagrams that represented each nerve cell with its connections, side by side with the electron micrographs from which the diagrams had been abstracted. These diagrams were actually a mosaic of the nervous systems of many worms, but were presented as a 'canonical nervous system'. It was concluded that *C. elegans* has 302 neurons, which are grouped into 118 types on the basis of various anatomical and histochemical criteria. The neurons form a total of ~8,000 synapses throughout the hermaphrodite (a complete map of the male neural connections has never been made). By comparing the nervous systems of genetically identical individuals, the researchers found essentially the same connections, with minor differences in cell morphology, position and connectivity. In short, the task that had been abandoned just after the turn of the century by Goldschmidt had now been completed, and had laid the foundation for the correlation of genes, developmental processes and structure.

The worm's legacy

Brenner's choice of *C. elegans* seems to have been partially influenced by the desire to do something no one had been able to do (or that none of his peers was likely to be able to do with the organisms they had selected): to achieve a complete understanding of a simple organism. He quickly noted that the organism he had selected had certain attributes that allowed what some have viewed as an extreme approach (Horace Judson has termed it the "brute force" approach[34]), namely the complete description of all detectable genetic mutants, as well as of the structure of the nervous system. Others in the LMB group soon took a similar tack with the developmental processes in the organism, observing and documenting the complete cell lineages in the worm. The first of this kind of study was done by John Sulston on the post-embryonic developmental lineages in the ventral cord[35]; this work, together with subsequent studies that culminated in the complete lineage[36,37] (FIG. 2), is considered by those in the worm community (and other biologists) as a *tour de force* in the tradition of classic lineage studies. It has recently been compared to Charles Darwin's observations on the differences in finch beaks in an article that lamented the lack of funding for "basic research", particularly of the descriptive kind[38]. This comparison is less telling for research funding as it is for what it reveals about the need for descriptive biology as the epistemic basis for revolutionary research.

"[i]n principle, it should be possible to dissect the genetic specification of behaviour much in the same way as was done for biosynthetic pathways in bacteria or for bacteriophage assembly"

The elucidation of the cell lineages laid the groundwork for what has became a rapidly expanding field of study. Knowledge of the cell lineages provided the basis for correlating mutations and developmental processes. Cell-ablation studies, in particular, allowed more precise examination of aberrant development. New genetic mapping and sequencing techniques were applied to the worm, resulting in more information at the molecular level and eventually the entire genome sequence for the organism. The latest research focuses on knocking out particular genes to determine their precise functions and interrelations, and studies on development, neurobiology, ageing and learning, to name only a few areas.

Many model organisms now provide unprecedented resources owing to the availability of data, not only on their genetic sequences but also on other biological processes that can be correlated with sequences and protein products. The history of the development of *C. elegans* as a model organism reveals the need to articulate extensive descriptions of the material to be used before the development of particular hypotheses or theories. This is not to say that biological work with model organisms does not depend on a range of background theories and assumptions. Instead, the claim is that there must be a proto-explanatory phase in which a descriptive model of an experimental organism is developed. Such models seem to occur more frequently and play more fundamental roles in biological sciences but they certainly are not unique to these disciplines. Because they are inherent to scientific practice and epistemology, they are potentially more interesting to investigate than the more abstract models that are typically explored in the philosophy of science. Indeed, the genome sequence itself is a form of description, a preliminary step on the way to a potentially deeper understanding of biological processes. Far from being mere "molecular stamp collecting", as some have derogatorily termed it, at least when much is known about an organism (such as in the case of *C. elegans*), the sequencing of model organisms is yet another vital resource with important historical precedents.

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Links

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