Pergamon

*Stud. Hist. Phil. Biol. & Biomed. Sci.*, Vol. 29, No. 1, pp. 81–105, 1998

Printed in Great Britain
1369–8486/98 $19.00+0.00

# Of Worms and Programmes: *Caenorhabditis Elegans* and the Study of Development

## *Soraya de Chadarevian**

In 1963, just a year after the researchers of the Medical Research Council (MRC) Unit of Molecular Biology in Cambridge, joined by some other research groups, had moved from various scattered and makeshift buildings in the courtyard of the Physics Department to a lavishly funded four-storey laboratory, B. Lush, the Principal Medical Officer of the MRC, came to inquire about their plans for future expansion. He indicated that the MRC wished to build the laboratory up to what the principal researchers considered its 'final size' until their retirement, which meant planning ahead for at least 15 years.[1] This surprising move was doubtless prompted by the recent award of the Nobel Prize to three members of the laboratory, Max Perutz, John Kendrew and Francis Crick, for their work on the molecular structure of proteins and nucleic acids. The triple award had propelled the new Laboratory of Molecular Biology into the limelight, and the MRC was interested in securing optimal research conditions for this prestigious group of researchers.

A few months later, Max Perutz, the director of the Laboratory of Molecular Biology, presented the MRC with an ambitious plan for an extension of about 20 000 square feet (in the formal proposal presented to the MRC in the autumn of the same year this shrank to half the size). The most innovative research programme suggested for the new space was not put forward by one of the laureates, but by Crick's collaborator, Sydney Brenner.

Brenner, who had a medical degree from the University of the Witwatersrand in Johannesburg and a Ph.D. from Oxford, had joined the Cambridge unit in 1957, on Crick's suggestion. He had introduced work on bacteriophages into what had

* Department of History and Philosophy of Science, University of Cambridge, Free School Lane, Cambridge CB2 3RH, England.

*Received 24 March 1997; in revised form 28 May 1997*

[1]Minutes of Meeting of Molecular Biology Board. 26.4.63 [by M. Perutz]; file on first extension, MRC Laboratory of Molecular Biology, Cambridge, England.

**PII: S1369-8486(98)00004-1**

basically been a protein crystallographic laboratory. Combining mutation studies, genetic analysis and protein sequencing techniques, he and Crick had pursued various lines of research to study the mechanism by which genetic information is translated into proteins and to decipher the genetic code. He was involved in the decisive experiments which showed that ribosomal RNA was not the information carrier in protein synthesis, but that this role was performed by an unstable RNA, later called messenger RNA.

The MRC inquiry stimulated intensive talks between Brenner and Crick about their future research. The day before Perutz was to discuss the plan for the expansion of the laboratory with Sir Harold Himsworth, Secretary of the MRC, Brenner drafted a letter to Perutz summarizing the outcome of his conversations with Crick. He recorded that it was widely realized that nearly all the 'classical' problems of molecular biology had either been solved or would be solved in the next decade. This meant that 'most of molecular biology had become inevitable' and that it was time 'to move on to other problems of biology which are new, mysterious and exciting' (Wood *et al*., 1988, p. ix). According to Brenner the most promising fields for a new attack were development and the nervous system. He acknowledged that this was not an original thought; many other molecular biologists were thinking along similar lines. However, the great difficulty with these fields was to define clearly 'the nature of the problem' and to find 'the right experimental approach'.[2] Brenner reckoned that molecular biology had succeeded in its analysis of genetic mechanisms because complicated phenomena could be reduced to simple units and because simple model systems had been devised. Building on this experience, he proposed to start attacking the problem of development by studying the process of cell division both in bacteria and in the cells of higher organisms. With respect to work with higher organisms, Brenner saw 'a great need to "microbiologize" the material' so that cells could be handled as conveniently as bacteria or viruses. As a longer term possibility he also suggested 'taming' a small multicellular organism so as to study development directly.[3]

Only a few months later, when the actual proposal to the MRC was submitted, Brenner's 'fluid' ideas regarding this last point had solidified. The plan to create a new model organism for the study of development had moved centre stage. The proposal read:

> We should like to attack the problem of cellular development… choosing the simplest possible differentiated organism and subjecting it to the analytical methods of microbial genetics. Thus we want a multicellular organism which has a short life cycle, can be easily cultivated, and is small enough to be handled in large numbers, like a micro-organism. It should have relatively few cells, so that exhaustive studies of lineage and patterns can be made, and should be amenable to genetic analysis.

[2]S. Brenner to M. Perutz, 5 June 1963; reprinted in Wood *et al*. (1988, p. x).
[3]S. Brenner to M. Perutz, 5 June 1963; reprinted in Wood *et al*. (1988, p. xi).

> We think we have a good candidate in the form of a small nematode worm, *Caenorhabditis briggsiae*…[4]

At first, the plan met with resistance from the MRC officers. They felt that this was 'pure' rather than 'molecular' biology and would lead the laboratory away from its present emphasis 'on the physics, chemistry and genetics of simple biological mechanisms'.[5] Brenner, however, insisted that his aim was to 'molecularize' the approach to development and differentiation.[6] Project and extension were approved without much further delay, although the extension took five years to be completed. Brenner started preliminary experiments which led him to settle on *Caenorhabditis elegans* as the model organism. With the new laboratories completed, the project also gained momentum.

Twenty-five years after his first proposal, introducing what was intended to be 'the sourcebook on the worm for some time to come', Brenner could rejoice that what was once 'a joke organism, often confused with the notorious flatworm of memory transfer', had become a major experimental system for the study of development and developmental genetics (Wood *et al*., 1988, p. ix). Today, more than 100 laboratories around the world work on *C. elegans*. It will be the first multicellular organism for which the complete genomic sequence is known and it is predicted a glorious laboratory future.

Having been made into a versatile laboratory tool used by a growing 'worm community', *C. elegans* can now appropriately become a tool for historical research. It can be used to address a range of questions of current interest to the historian as well as to the philosopher of science.[7] I am interested here in the early history of the construction of *C. elegans* as a model organism and laboratory tool for the study of development, and in the place of this work in the history of molecular biology.[8] I will analyse the resources Brenner and his colleagues imported from their earlier studies on gene function and protein synthesis into the study of development, and how these were challenged in the course of the work. My discussion

[4]M. Perutz, F. H. C. Crick, J. C. Kendrew and F. Sanger, 'The Laboratory of Molecular Biology. Proposal for Extension', October 1963, Appendix I; reprinted in Wood *et al*. (1988, p. xii).

[5]'Interview with Sir Harold Himsworth and B. Lush on 6 June 1963' [notes by M. Perutz]; file on first extension, MRC Laboratory of Molecular Biology, Cambridge.

[6]M. Perutz to B. S. Lush, 14 June 1963; file on first extension, MRC Laboratory of Molecular Biology, Cambridge. Perutz and the other board members of the laboratory considered the extension a vital means of inducing Brenner to stay. The new project also gave Brenner more independence from Crick, who was senior to him.

[7]For recent and current work on the worm see Doyle (1994) and Rachel Alkeny's dissertation project on the use of *C. elegans* as a model organism (University of Pittsburgh, in progress). *C. elegans* also feature on the programme of a summer school on 'Making Choices: Organisms in the History of Biology' at the Marine Biological Laboratory in Woods Hole, Massachusetts, organised by the Dibner Institute for the History of Science and Technology in the summer of 1997; see *History of Science Newsletter* **26** (1997), 28. Current interest in the history of neuro- and developmental biology will help to situate the worm project in a broader context.

[8]*C. elegans* was a model organism insofar as the processes of development in the small nematode worm were viewed as a simple representation of processes which, in principle, were the same in all organisms. I speak of *C. elegans* as a laboratory tool to indicate that the work of cultivation and representation that went into *C. elegans* turned it not only into a new scientific object, but also into a means to study development. For a similar discussion in relation to other laboratory organisms see Clarke and Fujimura (1992, p. 22) and Kohler (1994, especially pp. 53–90).

will focus on the notion of a genetic programme, its role in the formulation and organization of the project, and the controversies it generated. I will also explore the shifting role of the computer as both a conceptual and a technological tool in the research on the worm. I will argue that the renegotiation of aims, tools and practices in the worm project became part of the renegotiation of what molecular biology was in the 1970s and 1980s.

## 1. Cultivating and Mapping

In the abundant worm literature of today, we find a standard description of *C. elegans*. It gives the following facts: *C. elegans* is a 1 mm long free-living (i.e. not parasitic) soil nematode. It can easily be grown in the laboratory on *E. coli* as a food source, and 100 000 worms can live in one petri dish. *C. elegans* occurs in two sexes, self-fertilizing hermaphrodites and males, and has a life-cycle of about three days. The adult (hermaphrodite) organism contains 959 cells of which 302 are nerve cells. The haploid genome contains 100 million nucleotide pairs. We learn further: 'Individual animals are conveniently observed and manipulated with the aid of a dissecting microsope. Animals are transparent throughout the life cycle, so that development can be followed at the cellular level in living preparations by light microscopy, preferably with differential interference contrast optics. Its small size allows complete anatomical description of the animal at the electron microscope level. Mutants are readily obtained following chemical mutagenesis or exposure to ionizing radiation' (Wood *et al.*, 1988, pp. 1–2). This description is usually accompanied by a micrograph of the worm or by a longitudinal diagram of its anatomy (Fig. 1).

Quite obviously, this description presents *C. elegans* as an 'experimental organism' (Wood *et al.*, 1988, p. 15) or laboratory tool. But it conceals the work which

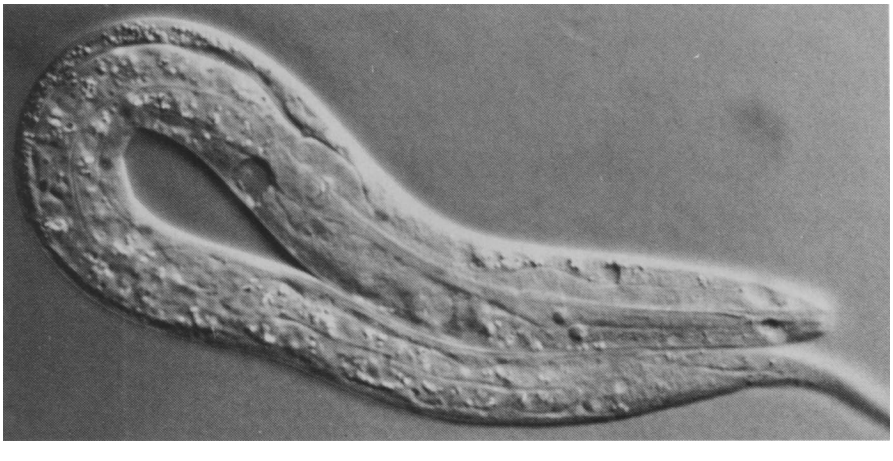

*Fig. 1. Micrograph of the nematode* C. elegans *(From* Science ***248****, (1990) 1310. Reproduced with permission of Prof. M. Chalfie, Department of Biology, Columbia University, New York).*

was necessary to turn a worm into such a tool. *C. elegans* was chosen out of around sixty nematode species, some of which were collected in Brenner's backyard or around the laboratory, and all of which were tested for their aptitude as laboratory creatures.[9] Brenner finally settled on *C. elegans* because of some properties which seemed useful at the time. An important advantage was that this particular nematode worm had been cultivated and studied by nematologists before. Previously reported problems of cultivation could be overcome by feeding on *E. coli*.[10] That the worm could either reproduce by self-fertilization of the hermaphrodite or by cross-fertilization between male and hermaphrodite, made it particularly useful for genetic analysis. Similarly, its small size meant that it interfaced well with the electron microscope. Other 'unforeseen advantages', like the transparency of the body and the extremely small genome, were exploited only later (Hodgkin, 1989).[11]

That 'taming' *C. elegans* was not easy is dramatically illustrated by the fact that, when François Jacob wanted to introduce it as a laboratory organism at the Pasteur Institute in Paris, his attempt failed.[12] Cultivating *C. elegans* in the laboratory, however, was only the first step in turning it into a tool for research on development. Brenner's plan was to produce mutants to study by deficiency the steps in the development of the worm. But in order to study the effect of mutations, it was necessary to gain detailed knowledge of the normal development and anatomy of the organism. Brenner and his colleagues embarked on what grew into an ever expanding effort to map *C. elegans*.

Brenner dedicated several years to describing the basic genetic features of the nematode (Sulston and Brenner, 1974; Brenner, 1974a, b). He estimated the size of its genome (100 million base pairs) and the number of essential genes (about 2000). He isolated around 100 mutants. Embarking on a long series of classical crossing experiments, he mapped them onto six linkage groups which corresponded to the worm's six chromosomes. By that time, Brenner's project, considered mad by many including Jim Watson, who would not have given him 'a penny' to do

[9]The nematode finally selected for use in Brenner's laboratory was the Bristol strain of *C. elegans*, originally sent from Berkeley by Prof. E. C. Dougherty, who had been investigating this particular worm since the 1940s.

[10]The irony here was that *C. elegans* fed on the organism which was the standard experimental organism of bacterial genetics.

[11]In the 1960s several molecular biologists tried to develop new model systems or adapt old ones for research on development and neurobiology. S. Benzer, for instance, worked on Drosophila, F. Jacob on the mouse, G. Stent on the leech, G. Streisinger on the zebra fish, W. Dove on slime moulds. A comparative investigation of these different systems and their success as model organisms would represent an interesting contribution to the discussion of the relations between 'jobs' and organisms; see Clarke and Fujimura (1992), Lederman and Burian (1993), and the other papers in the special section 'The Right Organism for the Job' in the same issue of the *Journal of the History of Biology*.

[12]Interview with S. Brenner, Cambridge, 30 June 1993. The explanation offered by Jacob and his team for abandoning the study of *C. elegans* referred to 'technical' difficulties regarding physiological and embryological experimentation with the organism (cf. *Annuaire du Collège de France: Résumé des cours et travaux* 1968–1969, pp. 195–196 and 1969–1970, pp. 207–209). Jacob turned to the mouse instead. His plan to build an Institut de la souris for research on developmental biology, however, did not receive the necessary funding; see Gaudillière (1991, pp. 535–540).

it, began to attract a growing number of researchers (Lewin, 1984, p. 1327). They tackled two major tasks.

John Sulston embraced the ambitious project of tracing the cell lineage of each individual cell of the developing embryo. Armed with a microscope, he sat down to observe the cells developing in the transparent body. The complete cell lineage of *C. elegans* was published in 1983 (Sulston *et al*., 1983; see Figs 2 and 3). Sulston attained 'hero status' for this feat in the community of worm workers which, by that time, was organised to the point that it produced its own newsletter (Roberts, 1990, p. 1311).[13] The cell lineage permitted unprecedented precision in experimental manipulation. A single cell, the 'fate' of which was known exactly, could be ablated with a laser beam, and the fate map allowed the effect of the manipulation to be studied in detail.

A few years later, John White, an electrical engineer who had worked on computers before joining the worm project, together with Nichol Thompson, a technician specializing in electron microscopy, and Eileen Southgate, a second technician, presented the complete 'wiring diagram' of the worm's nervous system. Analyzing 20 000 electron micrographs and matching the different series, they traced the approximately 8000 connections of the 302 nerve cells of the worm. Again, this was an unprecedented feat which was feasible only because of the small size of the organism. 'The mind of a worm' was published in a single 340-page article in the *Philosophical Transactions of the Royal Society* (White *et al*., 1986).[14] The material was displayed in a way that 'facilitated quick access', diagrammatically representing each single nerve cell with all its connections next to a series of electron micrographs on which the evidence was based (Fig. 4). What was in fact a mosaic of several nervous systems was presented as a '"canonical" nervous system' (White *et al*., 1986, p. 4).[15]

The mapping efforts of the worm workers did not end here. No sooner had Sulston completed the cell lineage, than he started work on a complete physical map of the worm's genome, again pioneering such a venture. The physical mapping effort grew into a British–American collaboration to sequence the genome. The work now ranks as a pilot of the Human Genome Project, the most ambitious mapping effort ever. It became the flagship project of the newly founded Sanger Centre in Cambridge, one of the largest genome centres in the world, of which Sulston was appointed director (Sulston *et al*., 1992; Aldhous, 1993; Cook-Deegan, 1994 especially pp. 48–55 and 333–335). The complete sequence of *C. elegans* will be available later this year.

Each of the mapping efforts just described not only pioneered new technologies,

[13]On the growth and organization of the community of *C. elegans* researchers see below.

[14]'The Mind of a Worm' was the running title of the article.

[15]The paper also introduced a uniform system of nomenclature for naming the neurons of *C. elegans*. An appendix listed the equivalences between the new system and the various nomenclatures previously in use (White *et al*., 1986).

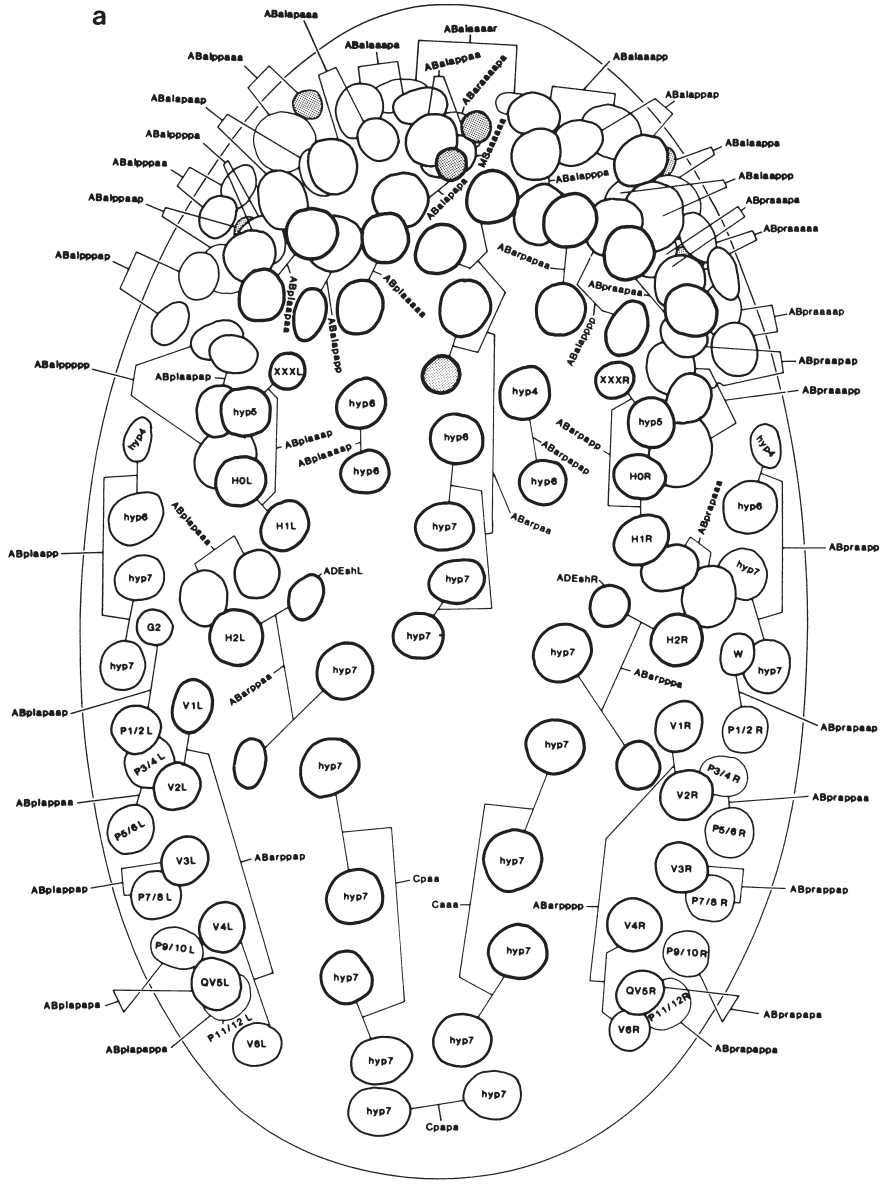


*Fig. 2.* C. elegans *embryo, 260 min. old. Dorsal view. Camera lucida drawing of superficial cell nuclei (From* Developmental Biology ***100****, (1983) 84. Copyright 1982 Academic Press, Inc. Reprinted with permission).*

but also created a new description of *C. elegans*. The series of representations produced by the various technological approaches did not map onto each other (they could not be combined to a map of maps), they rather created *C. elegans* as a laboratory tool open to a series of interventions. Yet how was this mapping

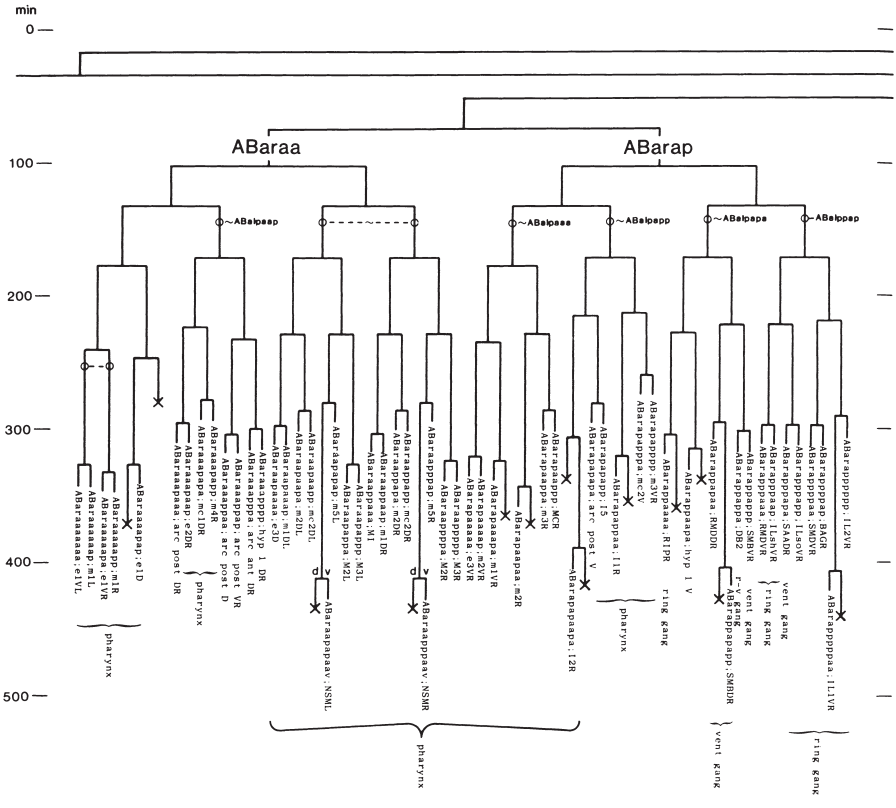


*Fig. 3. Part of the cell lineage of* C. elegans. *From camera lucida drawings of various developmental stages the lineage of every single cell could be reconstructed (From* Developmental Biology ***100****, (1983) 70. Copyright 1982 Academic Press, Inc. Reprinted with permission).*

activity connected to Brenner's original project of studying development in *C. elegans* as model organism?

## 2. The Logic of the Genetic Programme

Brenner's original plan was to study development by genetically 'dissecting' the steps involved in the process (Brenner, 1973, p. 269). His efforts to describe the genetic make up of *C. elegans* laid the groundwork for these investigations. By the early 1970s, he had developed a more specific project to study the genetics of behaviour in *C. elegans*.[16]

[16]For this approach Brenner referred to the work of Seymour Benzer, who was pursuing a similar project at Caltech studying behavioural mutants of the fruit fly Drosophila (Benzer, 1971, especially p. 1022). In his critical assessment of the genetic approach to the study of development and especially to the development of the nervous system, Stent distinguished between an 'ideological' and an 'instrumental' aspect. The ideological aspect concerned the view that the structure and function of the nervous

For Brenner, the behaviour of an organism was 'the result of a complex set of computations performed by the nervous system' (Brenner, 1973, p. 269). Behaviour was thus removed from the direct action of the genes. This pointed to the complexity of a genetic understanding of behaviour, but also indicated a route to it. He announced: 'What has to be done is clear in general outline: i.e. isolate mutants affecting the behaviour of an animal and see what changes have been produced in the nervous system' (Brenner, 1973, p. 269). Studying behavioural mutants thus implied, and became the gateway to, studying the development of the nervous system.

Brenner was well aware, or so he thought, of the challenges this project presented. Understanding the connection between genes and behaviour, he reckoned, 'might well involve solving all the outstanding questions of biology' (Brenner, 1973, p. 269). I gather that for Brenner this was a reason to embrace the project, rather than to shrink from it. With *C. elegans* he was convinced that he had found a simple model organism which allowed him to accept the challenge. There was another reason which, I would like to suggest, was crucial to Brenner's conviction that the problem he had chosen was a 'doable' one (Clarke and Fujimura, 1992). His work was based on the expectation that development was controlled by a 'genetic programme' which possessed a logical structure (Brenner, 1973, p. 271). This expectation, which guided the way Brenner set out his project, built on the earlier achievements of molecular biologists. It was further fuelled by the use of computers as models for thinking about development. Let me explain.

That there was a rule or a universal structure (a logic), according to which genes controlled development, was an expectation Brenner and other molecular biologists extrapolated from their studies of gene function. The genetic code represented such a universal structure, and the central dogma, according to which information could only flow from nucleic acids to proteins, applied also to the study of development. The notion of a genetic programme was imported into molecular genetics from electronic computing as part of a more general information discourse which was introduced into biology, and specifically into genetics, in the aftermath of World War II.[17] As François Jacob pointedly put it: 'The programme is a model borrowed

system, and thus behaviour, were controlled by the genes. According to this view, which Stent attributed to both Brenner and Benzer, analysis of gene function represented the key issue in developmental biology. In contrast, the instrumental aspect used mutants to study developmental processes, without considering genes as controlling elements. Stent sharply criticized the first, but praised the second aspect of the genetic approach to the study of development (Stent, 1980, p. 51 and 1981). On Stent's critique of Brenner's approach, see also below. The place of both Brenner's and Benzer's projects in the new field of neurogenetics and the initial resistance of neurobiologists to these new approaches are discussed by Greenspan (1990).

[17]As Lily Kay has recently argued, this happened even before DNA had replaced proteins as the hereditary material. The pioneers of information technologies, like Norbert Wiener and John von Neumann, themselves ventured into the field of biology, importing their new tools; see Kay (1995, 1998). Evelyn Fox Keller distinguishes two separate borrowings from 'cyberscience' (including information theory, cybernetics, system analysis, operations research and computer science) into biology after World War II. Developmental biologists built on cyberscience to handle the complexities of embryonic development. Molecular biologists who aimed at reducing the complexity of organisms to simple causal relationships also borrowed the cybernetic term of information, but used it in a colloquial sense. Infor-

from electronic computers. It equates the genetic material of an egg with the magnetic tape of a computer' (Jacob, 1989, p. 9). Nowhere does Brenner systematically develop his use of the notion of a genetic programme. This confirms that the term, like information, code or message, had become currency among molecular biologists. However, Brenner's use of the notion of a genetic programme was more than 'just a way of talking'. For Brenner, studying the worm and learning about computers went hand in hand.

Prior to fully embarking on the nematode work, Brenner in his own words 'disappeared into a computer for about 18 months' (Brenner, 1984, p. 172). By the end of the 1960s he had his own computer and pioneered the use of this new tool in biological research. Thus, in the reconstruction of the nervous system of *C. elegans* from serial electron micrographs, much effort was devoted to computerizing the work. The micrographs were digitalized and stored in a computer. The data base was used for the three-dimensional reconstruction of the nervous system on the screen as well as for more selective retrieval, such as of branching patterns or wiring diagrams of the nerves (White, 1974). Brenner and White themselves wrote the graphics programmes necessary for these operations.[18] But the computer was more than just a technological tool. It became a model in terms of which to think about development and, accordingly, to organize research.

Brenner hoped to find a set of instructions, laid down in the genes, which would govern development. How the effects of the genes were mediated, was to Brenner 'an entirely separate question' (Brenner, 1973, p. 271). The distinction he made was between the 'software of organisms' and 'their hardware'. He explained that questions regarding the former were 'not strictly molecular'. He reckoned that 'in the long run' the 'molecular implementations' had to be found, but judged that the then current methods of protein investigation were 'too crude and cumbersome' to undertake such a task (Brenner, 1974a, p. 787).

Brenner's first experimental results with behavioural mutants of *C. elegans* seemed to confirm that there was a logic to the way genes control development. Many of the mutants he isolated seemed to alter the development of the nervous system in a very specific way. The mutation would affect a subset of neurons, but leave the rest unaltered. Brenner expected that a thorough study of the effects of such mutations could throw light on the genetic programme that regulated the process. The same results also suggested to Brenner that, like computer pro-

mation received meaning and was interpreted as instructions coming from the genes (Fox Keller, 1995, pp. 79–118). Gaudillière's account of two distinct cultures of information and regulation amongst French molecular biologists at the Pasteur Institute seems to undermine Keller's neat disciplinary distinction, at least for the French case (Gaudillière, 1994b). In the 1960s the notion of a central computer which controlled all cell functions was widespread among molecular biologists; see e.g. Blow (1962, especially p. 177).

[18]In the study of the nervous system of *C. elegans*, the use of the computer turned out not to be essential. Patient labelling proved more effective than digitalizing (interview with J. Hodgkin, Cambridge, 28 June, 1994). Yet the experience with the computer was not lost. Later mapping and sequencing projects became increasingly computer-borne. Other sophisticated uses of the computer in the study of *C. elegans* included the computerized video tracking of behavioural mutants.

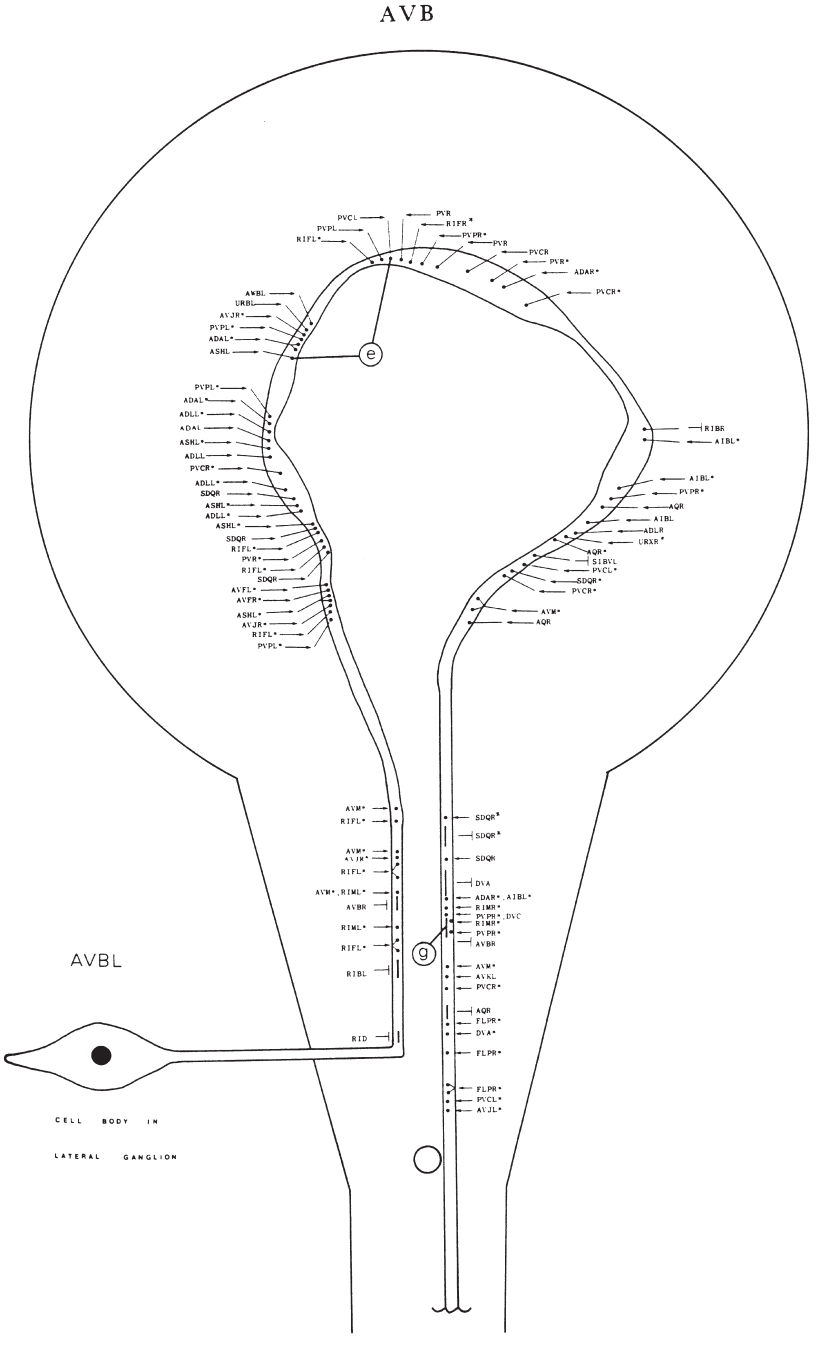


*Fig. 4. Connectivity diagram of a nerve cell of* C. elegans *(From* Philosophical Transactions of the Royal Society of London B ***314****, (1986) 123. Reprinted with permission).*

grammes, the programme that controlled development was partitioned and would thus be easier to analyse.

Even before starting serious research, Brenner declared: 'The general belief is that developmental biology will not be solved at one stroke but its problem will be partitioned into subproblems each of which could be tackled separately, preferably in a model system' (Brenner, 1974a, p. 786). The view that the genetic programme was partitioned into subsystems reinforced this point. It allowed work on the development of the worm to be subdivided into different subprojects which could be entrusted to different researchers. One researcher who joined Brenner's group as a doctoral student at the beginning of the 1970s recalled:

> [The worm] was subdivided. For example, the gut was given to one worker to work on, the head to another, the tail to another, the muscles to another, and by the time I arrived there were a few portions left. I was given the eggs to work on (Pickvance, 1976, 18; see Fig. 5).

The subdivision of the worm according to organ systems was nowhere explicitly justified and appears to me a relic of older anatomical traditions.[19]

## 3. 'Describing What There Is'

Brenner was not the only one to embrace the notion of a genetic programme as the key to the problem of development in the 1960s and early 1970s. In fact, the notion gave rise to sharp debates over opposed research strategies and to authority disputes among and between molecular biologists and embryologists. In the course of his research, Brenner himself became increasingly critical of the same notion.

For the French molecular biologists at the Pasteur Institute, the notion of a genetic programme that controlled development moved centre stage as part of their attempt to define a new approach to biology. Since the end of the 1960s this group of researchers had been engaged in a major project intended to apply the 'operon' model, formulated in their laboratory to describe the regulation of gene activity in bacteria, to problems of development in higher organisms. Development here became understood as differential gene activity. The notion of a 'programme' indicated the integrated and logical structure of the process.

In his *The Logic of Life. A History of Heredity*, Jacob aimed at providing wider legitimation for this Pasteurian approach, deploying epistemological and historical arguments. Jacob affirmed that the reduction of the problem of heredity to the transmission and translation of a genetic programme written in molecular language made old contradictions disappear. It explained both the history and the logical structure of organisms, their memory and their design (see Jacob, 1989, p. 2, and

[19]Yoxen (1982) stressed the connections between a biology which conceived of life in terms of a programme and the managerial research system which became dominant in the decades following World War II.

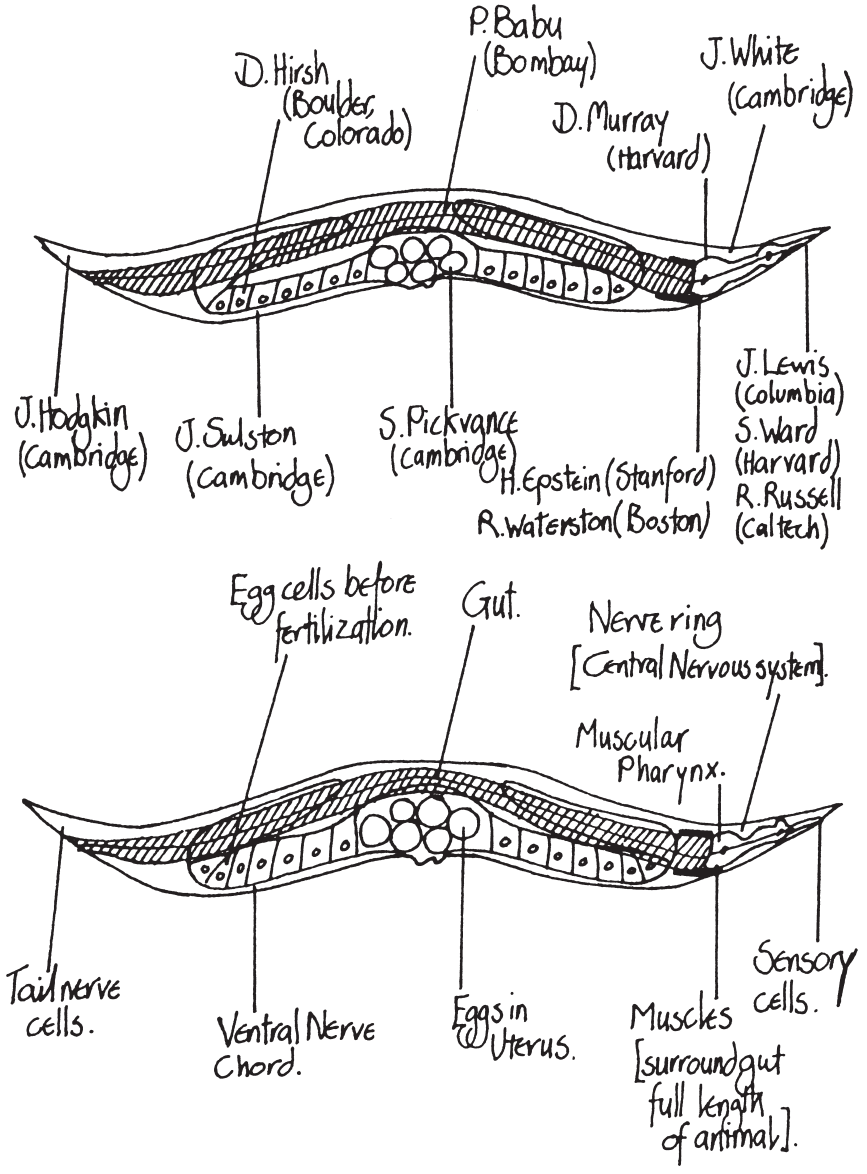


*Fig. 5. The subdivision of* C. elegans *(From* Radical Science Journal **4***, (1976) 20. Reprinted with permission).*

more generally pp. 1–17 and 247 ff).[20] The integration of genetics and embryology became an important, even if not the most successful, strategy in the State-supported attempt to consolidate molecular biology as the 'new biology' in France (Gaudillière, 1991, pp. 438–551; Gaudillière, 1994a).[21]

[20]The original French version of Jacob's book appeared in 1970. Jacob, however, continued to be confident of the existence of a genetic programme well into the late 1980s, when Brenner had long abandoned the notion; see his *The Actual and the Possible*, first published in English in 1982, and the combined re-edition of both his books (Jacob, 1989). For the notion of a genetic programme in *The Actual and the Possible* see *ibid*., pp. 398–399.

[21]The British embryologist Conrad Waddington, after briefly embracing the operon model for the study of development, took on the role of a spokesperson against reductionist molecular biological approaches to development. In his 'theoretical biology' he pointed out the limits of genetic approaches

When first moving into the field of development, Brenner seized on the Pasteurians' approach to the problem of development and reckoned that Jacob and Monod's operon model could be the 'central clue'.[22] Yet when he came to formulate his research agenda for a 'genetics of behaviour', he took a much more critical stance regarding the usefulness of the model for explaining development. He now declared: 'It is not good enough to answer [questions regarding development] by saying it is simply a matter of turning some genes on and others off at the right times. It is true that molecular biology provides numerous detailed precedents for mechanisms by which this can, in principle, be done, but we demand something more than these absolutely true, absolutely vacuous statements' (Brenner, 1974a, p. 786).[23] But, as indicated, this critique did not challenge the notion that there was a genetic programme controlling development, the logical structure of which could be elucidated.

From the beginning, however, Brenner also acknowledged the existence of 'a fairly large antigenetic school of molecular biologists' who believed that the study of development should proceed from the biochemistry rather than from the genes (Brenner, 1974a, p. 787). Gunther Stent from the University of Berkeley in California became the most outspoken critic of the attempt to reduce the question of development to the instantiation of a genetic programme.

In the late 1960s, Stent agreed with Brenner that molecular biology had entered an 'academic phase', whose sole agenda remained to 'iron out the details' (Stent, 1968, p. 394). Like Brenner, Stent was looking for 'new frontiers', but their views differed as to where these frontiers lay. Stent listed the problem of development, the field chosen for study by Brenner, as one of the details to be filled in with the newly acquired knowledge of molecular biology. For Stent the only major frontier still open in biological inquiry was the study of the nervous system, and for this molecular mechanisms still could not be imagined (Stent, 1968, pp. 394-395).[24] Following this analysis, Stent embarked on a major project on the nervous system of the leech, which he chose for its repetitive, and therefore simple body plan. Investigations in his laboratory centred on complex behaviour like the swimming mechanism of the leech. The ojective was to identify the nerve cell circuits involved in these movements. The techniques employed in these studies included anatomical investigations and electrical recording.

In the course of a few years, Stent radically revised his position regarding the question of development. His own research project soon embraced developmental questions. Significantly, however, his aim was not to study how genes regulate development, but to pursue specific questions regarding the phenotypic develop-

[22]S. Brenner to M. Perutz, 5 June 1963; repr. in Wood *et al*. (1988, p. xi).

[23]See also Joshua Lederberg's cautioning remarks in his introduction to Moscona and Monroy (1966, p. x).

[24]For Stent, who, like Delbrück, was in search of 'paradoxes', this offered the hope that 'some other laws of physics' could still turn up.

ment of nerve cells and circuits. These questions derived from detailed knowledge of the functioning of the adult nervous system. For their investigations researchers in his laboratory developed new cell tracing techniques and combined anatomical with electrophysiological and chemical studies of the developing nerve system.[25] At the same time, Stent embarked on a sharp critique of the application of the concept of genetic information to the problem of development.[26] Molecular biology, he now declared, had a 'noxious impact' on developmental biology, retarding rather than advancing progress (Stent, 1985a, p. 1). Brenner's project formed a main target of his critique.

Stent started with a conceptual clarification. He maintained that the view that development was controlled by a genetic programme was rooted in a 'semantic confusion' about the concept of programme (Stent, 1980, p. 51).[27] Development, Stent elaborated, belonged to the class of regular phenomena which from a particular initial situation led, via a more or less invariant sequence of events, to a particular final situation. But regular phenomena were not necessarily regulated by a programme.

Programmes, Stent explained, were isomorphic to the phenomena they were programmes of, or, in other words, a one-to-one correspondence existed between programmes and their products. Taking molecular biologists' most celebrated achievement, Stent affirmed that the assembly of amino acids into a polypeptide chain was in fact a programmatic process, since the sequence of the corresponding gene was isomorphic to the amino-acid sequence. According to Stent, however, this was one of the very few regular biological phenomena that could be called programmatic. He suspected that molecular biologists had been led astray by this exception. Already, the folding of the polypeptide chain into its specific tertiary structure represented a non-programmatic event, since folding depended on the 'contextual situation'. Regarding development, Stent held that it was 'most unlikely' that the sequence of developmental events was 'isomorphic with the structure of any second thing, especially not with the structure of the genome'. No plausible hypothesis had been advanced to explain how this could be feasible (Stent, 1980, p. 51).[28]

The notion of a genetic specification of the nervous system was for Stent erroneous not only on the conceptual level. It also represented a misinterpretation of the available knowledge. For Stent, the fact that mutation of a gene could alter

[25]Whether or not the leech would have represented a useful tool for genetic analysis is a separate question. It had certainly not been selected according to this criterion and no genetic study of the leech existed. For a synoptic account of research on the development of the leech nervous system in Stent's laboratory, see Stent and Weisblat (1982).

[26]This critique did not involve the use of mutants as means of studying the normal development or behaviour of organisms, or what Stent called the 'instrumental' in contrast to the 'ideological' aspect of genetic analysis. See above, note 16.

[27]Stent reiterated his critique on various occasions and in various contexts; see for example Stent (1981, 1985b). In the following, I derive some examples and quotations from his later presentations; the basic tenets of his critique, often including the very wording, were, however, the same in all publications.

[28]Stent himself does not make the point, but his critique seems to imply that the idea of a developmental programme involved some abstract kind of preformation theory.

the normal course of development showed that genes were part of the 'causal antecedents' that led to the adult animal, but did not in any way indicate that the mutant gene was part of a programme (Stent, 1980, p. 51). Rather, studies on the development of the nervous system indicated that the processes involved were not programmatic, but stochastic: one event led to the next in a historical sequence.

To illustrate the difference between programmatic specification and stochastic history as alternative accounts of regular phenomena, Stent used the example of the establishment of ecological communities upon colonization of islands or growth of secondary forests. In both these cases

> …a more or less predictable ecological structure arises via a stereotyped pattern of intermediate steps, in which the relative abundances of various types of plants and animals follow a well-defined sequence. But the regularity of these phenomena is obviously not the consequence… of an ecological program encoded in the genome… of the colonizing species. Rather,… the regularity is a consequence of a historical cascade of complex stochastic interactions between… various creatures and the world as it is (Stent, 1985b, p. 213).

Stent concluded that, rather than uncovering a genetically controlled programme, the goal of developmental neurobiology should be 'the discovery of the functional relations, or algorithms, that govern the nonprogrammatic, contextually determined intra- and intercellular interactions underlying the historical phenomenon of metazoan ontogeny' (Stent, 1985b, p. 213).

Twenty years after setting out his project on the development of the worm, Brenner came to share a very similiar position to the one espoused by Stent. While celebrating the achievements of the worm project, Brenner, in an interview with *Science*, conceded that the original expectation that there would be a logic of development encoded in a genetic programme had had to be abandoned. The notion of a programme, Brenner now warned, must be handled with care, 'even when used metaphorically'. Especially the study of the cell lineage of the worm, which showed an invariant but completely illogical pattern of development, had taught Brenner and his colleagues that 'there is hardly a shorter way of giving a rule for what goes on than just describing what there is' (Lewin, 1984, p. 1328). The 'grammar of development' which Brenner now invoked lay in the principles of molecular assembly and interactions (Lewin, 1984, p. 1327).[29]

Brenner still believed that, ultimately, the organism had to be explicable in terms of its genes, but he now held that the representation of 'genetic space' onto 'organismic space' would not be a direct and explicit one, or, as he also put it: 'It is not a neat, sequential process, like the linking together of amino-acids in a protein. It is everything going on at the same time… ' (Lewin, 1984, pp. 1327 and 1328).

[29]Brenner does not further explicate his use of 'grammar' as a term, but in contrast to the 'logic' of a programme, the notion of 'grammar' invokes the rules of natural languages. To Richard Doyle, who takes *C. elegans* as paradigmatic for the 'narrative of radical simplicity' of which he accuses molecular biologists, it could be objected that work on the worm itself had undermined this narrative and opened up a new 'dislocated' narrative of the kind Dolye is after (Doyle, 1994). The current importance attributed to genetic sequencing data as well as the insistence on a 'complete' description of the worm, however, seems to challenge this response.

What was missing in the original formulation of the research programme therefore, was the realization that cells were the units of development. The key question for Brenner now was 'how genes get hold of the cell' (Lewin, 1984, p. 1329). What was needed was 'a way of getting to the biochemistry of gene products' (Brenner, 1984, p. 172). New techniques, in particular recombinant DNA technologies and DNA sequencing methods, offered powerful tools for this kind of analysis and had in fact already been applied in a detailed genetical and biochemical study of muscle proteins in *C. elegans*, initiated in Brenner's lab (Brenner, 1984; see Fig. 6).[30]

The computer still functioned as a point of continuous reference for Brenner, yet significantly now mainly to illustrate the differences between computer and organism: writing a computer programme that tells the machine to draw an icosahedron was different from the self-assembly of the icosahedral head of a bacteriophage; unlike computers, cellular processes were based on diffusion processes and, unlike computer programming, natural selection was cheap and had plenty of time to work (Lewin, 1984).

The rejection of the notion of a genetic programme meant a clear shift in the focus of the project to understand the development of the worm. That the effects were not more dramatic and the shift in emphasis from the logic of a genetic programme to the biochemistry of the cell could take place at all, indicates that the notion of a genetic programme did not determine or exhaustively describe the project. For example, from the beginning, the work included a strong descriptive component aimed at mapping not only genetic mutations but also the normal development of the single cells. As Brenner put it in his first proposal: 'To start with we propose to identify every cell in the worm and trace lineages'.[31] In this sense, twenty years later, Brenner could announce the completion of the original project. The available maps of the worm, together with new research technologies and a large community of worm researchers, allowed new questions to be approached. Only if this renegotiation of material and conceptual tools, organizational structures and social relations is possible, is a research programme productive—as the worm project proved to be.[32]

## 4. Complete Solution

When setting up his project on the worm, Brenner was ambiguous as to wether he intended to leave molecular biology or to expand its domain. Arguably, for many years, work on the worm followed more the lines of 'classical' than molecu-

[30]Ironically, these same tools would later also lead to the description of a group of genes which control certain aspects of development in *C. elegans*, as in other organisms. Some researchers see in these genes and their function the 'logic of development' which Brenner originally set out to find. On this point see Morange (1995, 1996).

[31]M. Perutz, F. H. C. Crick, J. C. Kendrew and F. Sanger, 'The Laboratory of Molecular Biology. Proposals for Extension', October, 1963, Appendix I; reprinted in Wood *et al.* (1988, p. xiii).

[32]Compare here also Rheinberger's definition of experimental systems as 'future-generating devices' or 'generators of surprises' (Rheinberger, 1992, pp. 321–324, and Rheinberger, 1994).

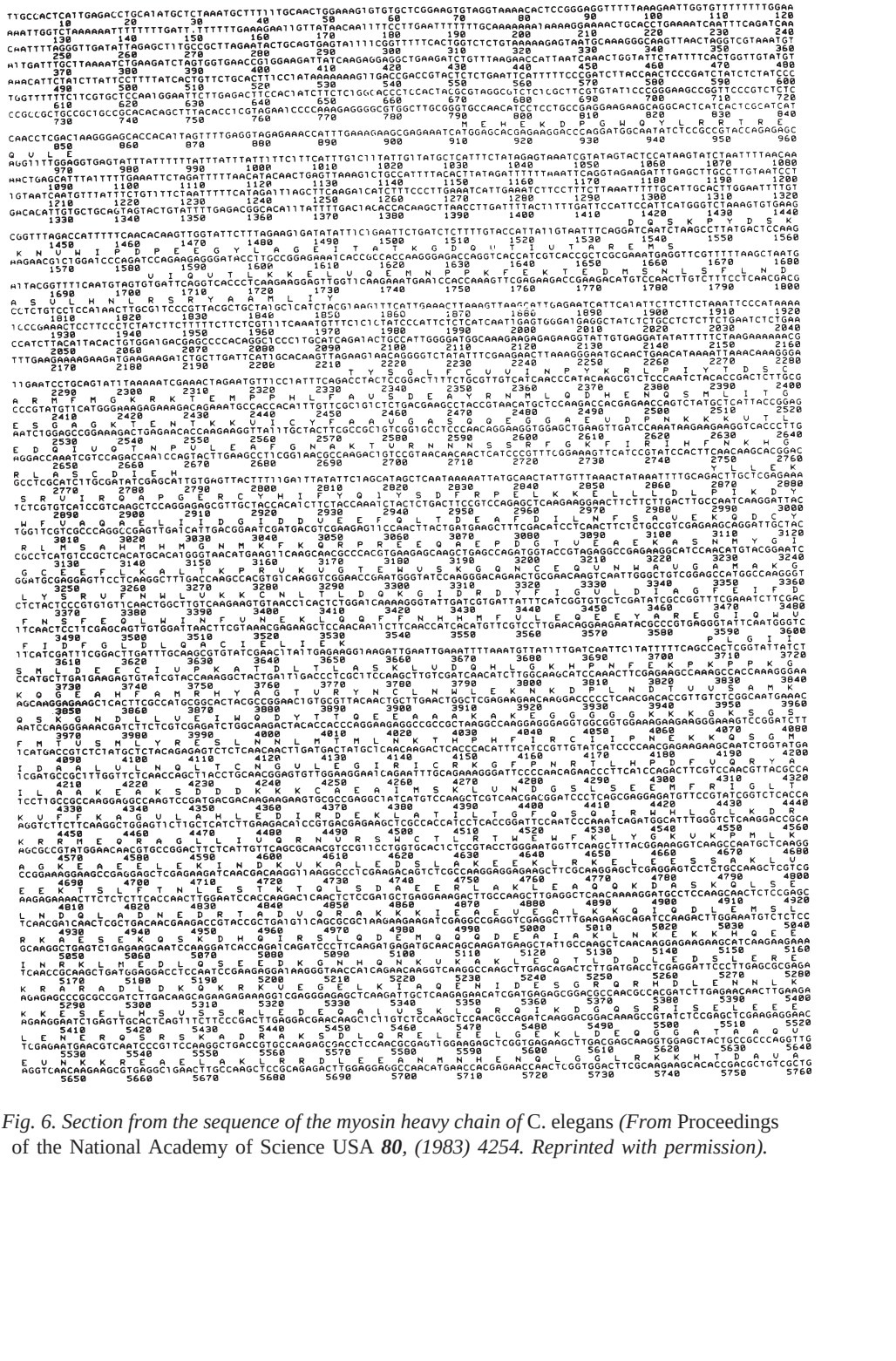

*Fig. 6. Section from the sequence of the myosin heavy chain of* C. elegans *(From* Proceedings of the National Academy of Science USA ***80****, (1983) 4254. Reprinted with permission).*

lar biology.[33] But, throughout, there were also important links to and imports from molecular biology. What molecular biology was, was as much under negotiation in the 1960s and 1970s as it is today, in the discussion wether the plan to sequence the human genome is merely a technological project or itself part of molecular biology.[34] The worm project, I would like to suggest, became part of this re-negotiation in the 1970s and 1980s.

The 'taming' of *C. elegans* for the study of development proved a long and laborious process. It depended crucially on generous and long-term funding. This privilege Brenner had acquired for himself and his group through his own and the Laboratory of Molecular Biology's earlier achievements in the field of molecular biology. Without the 'large amount of basic backbreaking work done by us who had no short-term commitments', Brenner reckoned, nothing would have come out of the *C. elegans* project.[35] In this respect there was a clear continuation from the earlier work in molecular genetics to the later study of development. Moving to his new field of investigation, Brenner, like other molecular biologists who moved to study development or the nervous system, did not relocate to one of the biological departments where development was traditionally studied, but continued to work in his old institution and to circulate in his old networks. Significantly, the plan to hire Horace Barlow, a trained neurobiologist from the Physiology Department in Cambridge, to work in the laboratory was soon abandoned.[36] Barlow was a member of the Hardy Club, a Cambridge biophysics club created in the late 1940s, in which the molecular biologists interacted with a select group of young zoologists and neurophysiologists. The Club convened regularly until the mid-1960s, when the meetings became less successful. Paradoxically, this happened at a time when Brenner, and with him other molecular biologists, were moving into fields which, potentially, offered more scope for interaction with the other club members.[37]

Brenner brought to his new project the experience of his earlier work in molecular genetics. With others, he held that the winning strategy of molecular biology had consisted in the choice of simple model organisms and in the reduction of

[33]This was the term with which molecular biologists used to refer—mostly in disparaging ways—to non-molecular approaches to biology. Molecular biologists' own use of these approaches necessarily shifted the meaning of this demarcation. As I have argued elsewhere, molecular approaches often relied in crucial, if unacknowledged, ways on (natural history) collections and non-molecular functional knowledge (de Chadarevian, 1998).

[34]For discussion on a new 'paradigm shift' in molecular biology, see Fujimura and Fortun (1996).

[35]Interview with S. Brenner, Cambridge, 30 June 1993.

[36]Interview with S. Brenner, Cambridge, 30 June 1993.

[37]The Minute Book of the Hardy Club is kept in the Churchill Archives, Churchill College, Cambridge. Among the Club members were many who in the 1950s became Fellows of the Royal Society and Nobel Laureates, notably Alan Hodgkin and Andrew Huxley from the Physiological Laboratory in Cambridge. The laboratory gained world fame in the 1950s for their and others' work on the electrophysiology of nerves. Members of the laboratory attributed the later decline of their department to failure to 'have gone molecular'; interview with R. Darwin Keynes, physiologist and long-term Secretary of the Hardy Club, Cambridge February 1993.

complex phenomena to basic principles. For Brenner, this way of going about things defined molecular biology, as much as its specific achievements. When embarking on his new project, Brenner aimed to follow the same strategy. The notion of a genetic programme and the expectation that there was a logic of development were part of the same baggage that Brenner brought with him. In this respect also, the worm project clearly built on his earlier work.

Work on the worm made Brenner revise many of his expectations about development. When Brenner now declared: 'We came to realize… that the molecular biology of development is the molecular biology of the cell,' this implied a redefinition not only of development, but also of what molecular biology was about (Lewin, 1984, pp. 1328–1329). Molecular biology did not consist only of general rules, but also comprised exhaustive descriptions of 'how genes get hold of cells' or of gene products and their reactions in the cell. The use of new technologies which made such analysis possible had bound the *C. elegans* project back to molecular biology. Yet in the worm these technologies were put to new use, considerably expanding molecular biologists' field of action. Developmental biologists, who had taken the place of embryologists, also increasingly adopted molecular biological approaches to the study of development.[38]

The worm project not only opened up a vast field of inquiry to molecular biology, ranging from studies of genome structure, development and the nervous system to the biology of aging (Fig. 7), it also and importantly introduced new work organizations, linked to the aim of a *total* description of the nematode worm.

Brenner's project on the worm was not necessarily planned to become 'big'. Brenner at first hoped that looking at one ganglion might be enough to understand some of the principles involved in the development and function of the nervous system. At that point, Brenner was also ambivalent about other people working on 'his' project. In the 1970s, however, he began actively recruiting new people. Many of these came as postdoctoral fellows to the prestigious Laboratory of Molecular Biology in Cambridge to work on other projects, but were then attracted to working on the worm. When moving back to their home countries, they set up their own worm groups. This was particularly true for the American fellows, who represented the largest group of postdocs and on their return to the United States had better chances than their European colleagues of building up new and independent research groups. By this mechanism the community of worm workers grew.[39]

The subdivision of the worm not only made research projects manageable, it also became a strategy to avoid competition among the growing number of worm workers. At the same time, the *C. elegans* researchers represented a tightly knit community. As one of them commented:

[38]The relations of developmental biologists and molecular biologists require separate treatment. See note 21 for relevant references.

[39]Interview with S. Brenner, Cambridge, 30 June 1993, and with J. Hodgkin, Cambridge, 28 June 1994.

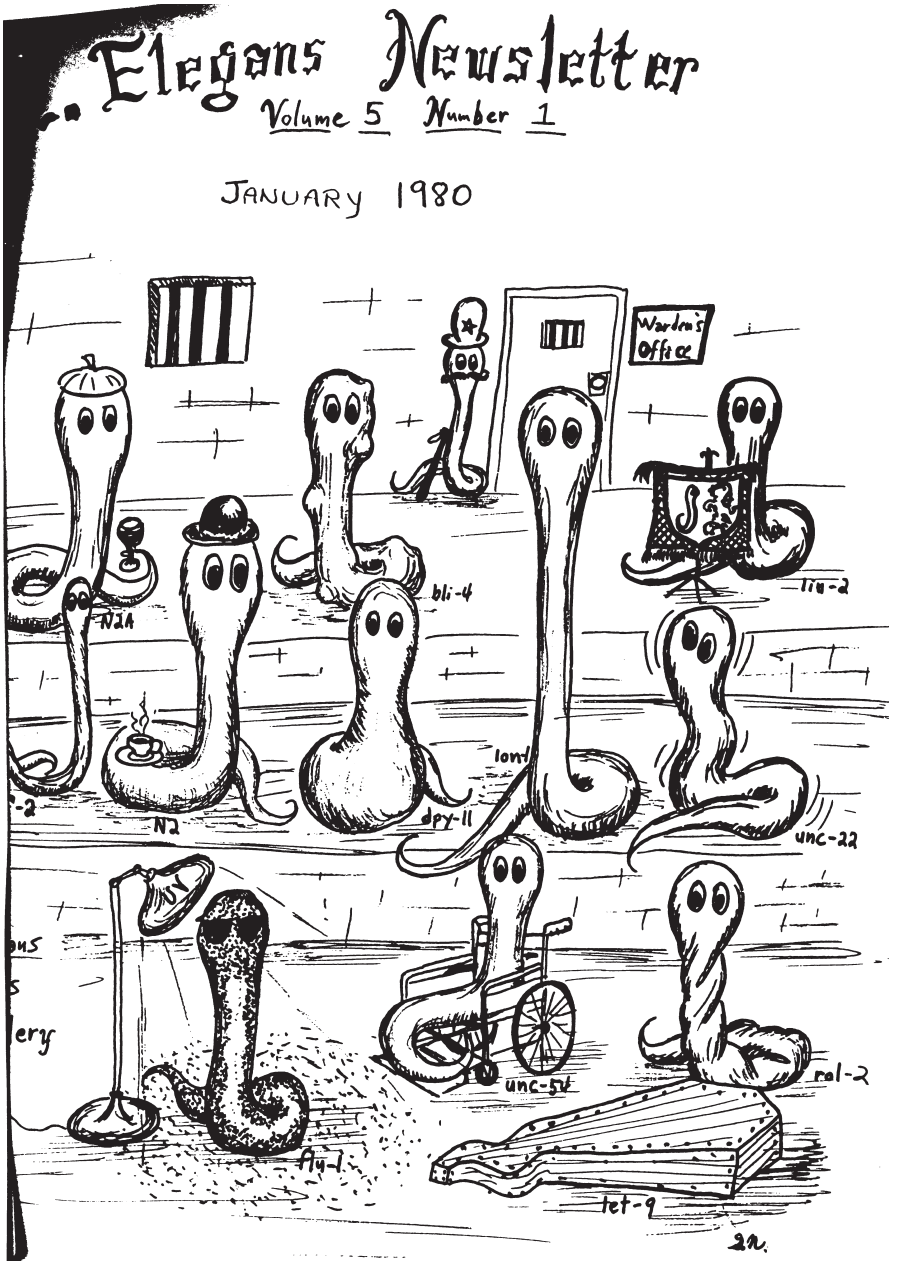


*Fig. 7. Cover of* C. elegans *Newsletter [usually called* Worm Breeder's Gazette*] featuring various mutants of the worm (Design by Greg Nelson. Courtesy Jonathan Hodgkin, Cambridge. Reprinted with permission).*

> There is better cooperation than in any field of biological research I am aware of. And there is a simple reason. The field is quite small, and it started with one person, Sydney Brenner. Many people who now head labs were friends 15 years ago in England. It is a community (Roberts, 1990, p. 1311).[40]

In addition to the common period of training in Brenner's lab, through which researchers came to share a culture, the worm community was held together by the services of the Caenorhabditis Genetics Center at the University of Missouri; it maintained and dispensed mutant strains and, twice a year, issued the *Worm Breeder's Gazette* (Fig. 7). *C. elegans* meetings were held biannually.[41]

Similar 'exchange networks' (Kohler, 1994, pp. 133–170) existed also among drosophilists and the phage group.[42] What was new in the worm project, however, was the combined effort to arrive at a 'total description' (Hodgkin, 1991, p. 951) of *C. elegans*. This plan was not there from the beginning, but 'gradually it became clear that it was both feasible and desirable' to achieve this aim (Hodgkin, 1989, p. 2).

In the early 1960s molecular biologists were starting to think big. This is clear from the plans for a European Molecular Biology Laboratory (EMBL) to be modelled on CERN. Discussions for such an enterprise started on an informal level straight after the Nobel ceremony for Watson, Crick, Wilkins, Kendrew and Perutz in 1962, even if the plan took one and a half decades to materialize. Among the research schemes discussed for the laboratory was 'Project K: The Complete Solution of *E. coli*' proposed by Crick and based on discussions with Brenner (Crick, 1973).[43] The main reason given for the aim of arriving at a full description of the bacterial cell was 'intellectual satisfaction'. The project as envisioned by Crick involved a huge work load and pooling results from many laboratories. A central laboratory could assist and coordinate this work by developing advanced technologies, by producing and circulating mutants, chemical components of cells and results, and thus reducing waste and avoiding overlaps.

Crick's Project K was never embraced as such, but much of its vision was realized in the worm project, especially in the genome mapping and sequencing project.

[40]The interaction of the worm workers is also attributed to the worm itself which, in many instances, resisted subdivision, or at least encouraged collaboration; see Hodgkin (1991) and interview with J. Hodgkin, Cambridge, 28 June 1994.

[41]Both the *Gazette* and the stock collection of *C. elegans* were started in an informal way in the 1970s before a grant from the National Institute of Health allowed them to be built up on a bigger scale. A uniform genetic nomenclature, modeled after the one introduced by Brenner in the early 1970s, was agreed upon at the first *C. elegans* meeting at Woods Hole in 1977; see Horvitz (1977). Cells, nerves and their connections were also uniformly named.

[42]Significantly, Robert Edgar, who started the worm newsletter, was part of the phage group before joining the worm project. On the 'phage influence' on work on the worm see Hodgkin (1989, p. 2). For a long time, the worm researchers, like other organism groups, formed a fairly separate community. This means that there was more interaction among people working on separate aspects of the same organism than, say, researchers working on the development of the nervous system in *C. elegans* and in the mouse. I believe this throws important light on the question of model organisms. More recently, however, the growing importance of comparative sequence data is drawing the different communities nearer together.

[43]Crick acknowledged Brenner for having invented this project title (Crick, 1973, p. 67, footnote).

It marked a shift in the way molecular biology was practised and knowledge produced.

The history of the worm project contradicts many of the standard accounts of the history of molecular biology which have been constructed along with it. Despite Brenner's important role in starting the worm project, what has been achieved did not rely on the bright ideas and ingenious breakthroughs of a few individuals, but rather on 'backbreaking' and painstaking work on a standardized organism by a large group of researchers who were all trained in the same laboratory. Prestige, funding, institutional expansion and technological innovations were imaginatively and aggressively used to build a project which would attract researchers in an increasingly competitive field.

*Acknowledgements*—I learned much about the worm project from my discussions with Sydney Brenner and Jonathan Hodgkin, who also gave me access to some papers in their private collections, among them some early issues of the *Worm Breeder's Gazette*. I gratefully acknowledge their collaboration. I am also grateful to Silvia Frenk, Jean-Paul Gaudillière and Michel Morange for making unpublished papers and pertinent material available to me. A first version of this paper was presented at the Rathenau Summer Academy 'Communicating Nature: die Semiotisierung der Natur im 19. und 20. Jahrhundert', Berlin, July 1994. I thank the participants of the summer school and especially the commentator, Anke te Heesen, for stimulating discussions. My thanks also go to Rachel Ankeny for fruitful exchanges on the worm, to Nick Hopwood who provided extensive and insightful comments on a revised draft of the paper and to an anonymous referee. This paper is part of a larger project on the history of molecular biology in postwar Britain. Research was supported by a grant from the Wellcome Trust.

## References

Aldhous, P. (1993) 'Europe's Genomes Come Home to Roost', *Science* **260,** 1741.

Benzer, S. (1971) 'From the Gene to Behavior', *Journal of the American Medical Association* **218,** 1015–1022.

Blow, D. M. (1962) 'The Molecular Approach to Biology', *Contemporary Physics* **3,** 177–193.

Brenner, S. (1973) 'The Genetics of Behaviour', *British Medical Bulletin* **29,** 269–271.

Brenner, S. (1974a) 'New Directions in Molecular Biology', *Nature* **248,** 785–787.

Brenner, S. (1974b) 'The Genetics of *Caenorhabditis elegans*', *Genetics* **77,** 71–94.

Brenner, S. (1984) 'Nematode Research', *Trends in Biochemical Sciences* **9,** 172.

Clarke, A. E., and J. H. Fujimura (eds) (1992) *The Right Tools for the Job: At Work in 20th-Century Life Science* (Princeton: Princeton University Press).

Cook-Deegan, R. (1994) *The Gene Wars: Science, Politics, and the Human Genome* (New York and London: Norton and Co.).

Crick, F.H.C. (1973) 'Project K: "The Complete Solution of E. Coli" ', *Perspectives in Biology and Medicine* **17,** 67–70.

de Chadarevian, S. (1998) 'Following Molecules: Hemoglobin Between the Clinic and the Laboratory', in de Chadarevian and H. Kamminga (eds), pp. 171–201 *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s–1970s* (London: Harwood Academic Publishers).

Doyle, R. (1994) 'Dislocating Knowledge, Thinking Out of Joint: Rhizomatics, Caenorhabditis elegans, and the Importance of Being Multiple', *Configurations* **2,** 47–58.

Fox Keller, E. (1995) 'The Body of a New Machine: Situating the Organism Between Telegraphs and Computers', in *idem, Reconfiguring Life: Metaphors of Twentieth-Century Biology* (New York: Columbia University Press), pp. 79–118.

Frenk, S. E. (1993) *Embryology in Its Relation to Genetics and Evolution. Experimental Analysis and Historical Perspectives* (Ph.D. Thesis, University of Cambridge).

Fujimura, J. H. and Fortun, M. (1996) 'Constructing Knowledge Across Social Worlds: The Case of DNA Sequence Database in Molecular Biology', in L. Nader (ed.), *Naked Science. Anthropological Inquiry into Boundaries, Power and Knowledge* (New York and London: Routledge), pp. 160–173.

Gaudillière, J.-P. (1991) *Biologie moléculaire et biologistes dans les années soixante: la naissance d'une discipline. Le cas français*. (Thèse du doctorat, Université Paris VII).

Gaudillière, J.-P. (1994a) 'La nouvelle biologie du développement: Aspects historiques et épistémologiques', paper presented at a conference in Lille, 13 May 1994.

Gaudillière, J.-P. (1994b) 'Regulation of Information: the Rhetoric and Practice of Molecular Biology In and Out of the Pasteur Institute', paper presented at the Rathenau Summer Academy 'Communicating Nature: Die Semiotisierung der Natur im 19. und 20. Jahrhundert', Berlin.

Gilbert, S. E. (1991) 'Induction and the Origins of Developmental Genetics', in *idem* (ed.), *A Conceptual History of Modern Embryology* (Baltimore: The Johns Hopkins University Press), pp. 181–206.

Greenspan, R. J. (1990) 'The Emergence of Neurogenetics', *Seminars in the Neurosciences* **2,** 145–157.

Hodgkin, J. (1989) 'Early Worms', *Genetics* **121,** 1–3.

Hodgkin, J. (1991) 'The Interactive Worm', *The New Biologist* **3,** 951–954.

Horvitz, H. R. (1997) 'A Uniform Genetic Nomenclature for the Nematode *Caenorhabditis elegans*' *The Worm Breeder's Gazette* **2**, No. 3, Part B, 1–14.

Jacob, F. (1989) *The Logic of Life: A History of Heredity* and *The Possible and the Actual* (London: Penguin) [French: *La Logique du vivant: Une histoire de l'hérédité* (Paris: Gallimard, 1970)].

Kay, L. (1995) 'Who Wrote the Book of Life? Information and the Transformation of Molecular Biology, 1945–1955', *Science in Context* **8,** 609–634.

Kay, L. (1998) *Who Wrote the Book of Life? A History of the Genetic Code* (Stanford: Stanford University Press). In press.

Kohler, R. E. (1994) *Lords of the Fly. Drosophila Genetics and the Experimental Life* (Chicago: Chicago University Press).

Lederman, M. and Burian, R. M. (1993) 'Introduction', *Journal of the History of Biology* **26,** 235–237.

Lewin, R. (1984) 'Why Is Development So Illogical?', *Science* **224,** 1327–1329.

Morange, M. (1995) 'De la régulation bactérienne au contrôle du développement', *Bulletin d'histoire et d'épistémologie des sciences de la vie* **2,** 205–220.

Morange, M. (1996) 'Construction of the Developmental Gene Concept: The Crucial Years: 1960–1980', *Biologisches Zentralblatt* **115,** 132–138.

Moscona, A. A., and A. Monroy (eds) (1966) *Current Topics in Developmental Biology* (New York and London: Academic Press).

Pickvance, S. (1976) ' "Life" in a Biology Lab', *Radical Science Journal* **4,** 11–28.

Rheinberger, H.-J. (1992) 'Experiment, Difference, and Writing: I. Tracing Protein Synthesis', *Studies in History and Philosophy of Science* **23,** 305–331.

Rheinberger, H.-J. (1994) 'Experimental Systems: Historiality, Narration, and Deconstruction', *Science in Context* **7,** 65–81.

Roberts, L. (1990) 'The Worm Project', *Science* **248,** 1310–1313.

Stent, G. S. (1968) 'That Was the Molecular Biology that Was', *Science* **160,** 390–395.

Stent, G. S. (1980) 'The Genetic Approach to Developmental Neurobiology', *Trends in Neurosciences* **3,** 51.

Stent, G. S. (1981) 'Strength and Weakness of the Genetical Approach to the Development of the Nervous System', *Annual Review of Neuroscience* **41,** 163–194.

Stent, G. S. (1985a) 'Thinking in One Dimension: The Impact of Molecular Biology on Development', *Cell* **40,** 1–2.

Stent, G. S. (1985b) 'Hermeneutics and the Analysis of Complex Biological Systems', in D. J. Depew and B. H. Weber (eds), *Evolution at a Crossroad: The New Biology and the New Philosophy of Science* (Cambridge, MA: MIT Press), pp. 209–225.

Stent, G. S. and Weisblat, D. A. (1982) 'The Development of a Simple Nervous System', *Scientific American* **246,** 100–110.

Sulston, J. E., Schierenberg, E., White, J. G. and Thomson, J. N. (1983) 'The Embryonic Cell Lineage of the Nematode *Caenorhabditis elegans*', *Developmental Biology* **100,** 64–119.

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

Sulston, J. (1992) 'The *C. elegans* Genome Sequencing Project: A Beginning', *Nature* **356,** 37–41.

Waddington, C. H. (1968) 'Theoretical Biology and Molecular Biology', in *idem* (ed.), *Towards a Theoretical Biology: Vol. I: Prologomena* (Edinburgh: Edinburgh University Press), pp. 103–108.

White, J. G. (1974) *Computer Aided Reconstructions of the Nervous System of* Caenorhabditis elegans. (Ph.D. Dissertation, University of Cambridge, England).

White, J. G., Southgate, E., Thomson, J. N. and Brenner, S. (1986) 'The Structure of the Nervous System of the Nematode *Caenorhabditis elegans*', *Philosophical Transactions of the Royal Society London B* **314,** 1–340.

Wood, W. B. and the Community of *C. elegans* Researchers (eds) (1988) *The Nematode* Caenorhabditis elegans (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory).

Yoxen, E. (1982) 'Giving Life a New Meaning: The Rise of the Molecular Biology Establishment', in N. Elias, H. Martins and R. Whitley (eds), *Scientific Establishments and Hierarchies*, Sociology of the Sciences Yearbook VI (Dordrecht: Reidel Publishing Company), pp. 123–143.

Yoxen, E. (1986) 'Form and Strategy in Biology: Reflections on the Career of C. H. Waddington', in T. J. Horder, J. A. Witkowski and C. C. Wylie (eds), *A History of Embryology: The Eighth Symposium of the British Society for Developmental Biology* (Cambridge: Cambridge University Press), pp. 309–329.