Genes, Behavior, and Developmental Emergentism: One Process, Indivisible?*

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The question of the influence of genes on behavior raises difficult philosophical and social issues. In this paper I delineate what I call the Developmentalist Challenge (DC) to assertions of genetic influence on behavior, and then examine the DC through an in-depth analysis of the behavioral genetics of the nematode, *C. elegans,* with some briefer references to work on *Drosophila.* I argue that eight "rules" relating genes and behavior through environmentally-influenced and tangled neural nets capture the results of developmental and behavioral studies on the nematode. Some elements of the DC are found to be sound and others are criticized. The essay concludes by examining the relations of this study to Kitcher's antireductionist arguments and Bechtel and Richardson's decomposition and localization heuristics. Some implications for human behavioral genetics are also briefly considered.

*Received September 1996; revised February 1997.

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‡Based in part on papers presented at Boston University, the International Society for History, Philosophy, and Social Studies of Biology Meeting in Leuven, July, 1995, Notre Dame University, and the University of Maryland. The research leading to this article has been partially supported by the National Science Foundation's Studies in Science, Technology, and Society Program and by a National Institutes of Health Grant R13 HG00703 to the University of Maryland. I would like to thank Drs. Cori Bargmann, Martin Chalfie, and Shawn Lockery for providing me with information about their research, and to them and to Joshua Lederberg for very helpful comments on an earlier draft of the *C. elegans* parts of this paper. I am indebted to Rachel Ankeny, Robert Cook-Deegan, Paul Griffiths, Eric Turkheimer, the Editor-in-Chief, and two anonymous referees for comments on this paper. I am also grateful to Robert C. Olby for discussions and pointers to the history and philosophy of neuroscience literature, and to Robin Bhaerman-Dillner for research and proofing assistance.

Philosophy of Science, 65 (June 1998) pp. 209–252. 0031-8248/98/6502-0002$2.00

1. Introduction. Explanations that involve genetics, and in particular those that also encompass behavior, can raise three sorts of philosophical problems. First, they evoke whatever current controversies are circulating that echo the century-old "nature-nurture" debate. That debate has been declared closed in recent years, but as we shall see further below, the *terms* of the closure are still the subject of contentious arguments.[1] Second, explanations that appeal to genetics quickly find themselves in the center of an at least partially political imbroglio, fueled by such books as *The Bell Curve*, and attacked from both the right and the left.[2] Third, explanations that involve genetics are played out against a backdrop that has led, with only a few exceptions, to an ironic antireductionist consensus among philosophers. I use the term "ironic" because this consensus has firmed up as the molecular biologists are accomplishing what the biologists view as major progress toward a reduction of classical biology, including genetics, to molecular biology (Alberts et al. 1994, 41; Lewin 1994, Ch.1; Waters 1990).

The purpose of this essay is to tackle the first and third of these problems at their nexus, and to attempt to characterize the nature of explanations in molecular behavioral genetics. The second, more political, set of issues will be addressed briefly toward the conclusion of this paper, but will not be given the extensive treatment it deserves, though some references to recent literature will be provided. It is important to stress at the outset that *philosophical* issues arise in the following essay in two somewhat different contexts, though both relate to organism development. More classical philosophical issues that are concerned with the themes of reduction and emergence are discussed toward the end of the paper. However, another set of philosophical issues that arises in the context of debates between orthodox developmental studies and those I term the "developmentalists" poses a series of newer philosophical problems, that reflect positions at least partially orthogonal to reductionist-antireductionist views. Some philosophers of biology, including Kitcher and Rosenberg, are antireductionists, yet defend more orthodox developmental views (Kitcher in press, Rosenberg 1997).

1. For example, Johnston (1987, 1988) asserts closure on interactionist grounds and Turkheimer, Goldsmith, and Gottesman (1995) on quite different pervasive genetic influence grounds.

2. The right, for example, and in particular the religious right, argues against genetic influence on sexual orientation (Interactive Bible 1996), and the left (and some in the center) see behavioral genetics as likely leading to discrimination and labeling (King 1992), if not as tantamount to eugenics (Duster 1990, Horgan 1993).

2. The Developmentalist Challenge. I will begin by briefly describing what might be termed the "developmentalist" challenge to a standard view of molecular genetics, and also to behavioral genetics. Though the popular media reinforces an oversimplified single-gene, preformationist, and deterministic picture of behavioral genetics through stories on the fat gene (Zhang et al. 1994), happiness genes (Goleman 1996), and genes for sexual orientation (Hamer et al. 1993, Hu et al. 1995), behavioral geneticists are more sophisticated.[3] They tend to subscribe to theses about the action of many genes having small joint effects on behavior, and are highly sensitive to the roles of environment and learning. But this received sophisticated view of behavioral geneticists, ably summarized by Plomin, McClearn, and McGuffin 1994, has been criticized by a number of writers who collectively represent what I term the "Developmentalist Challenge."

The Developmentalist Challenge affects a far broader area than behavioral genetics—it has relevance for *any* claims about the disentangleable effects of genes and environment on *any* traits[4]—but it has its greatest force and has been applied most vigorously to behavioral traits (Lewontin 1993, 1995). There, it attacks the traditional "nature-nurture" distinction, and also directs some powerful criticisms against the "innate-learned behavior" dichotomy. The term "developmentalist" may not be the best to describe this loosely knit set of criticisms of genetic determinism and DNA primacy. Some who fall into this group prefer the term "interactionist" (e.g., Johnston 1988) or "constructionist" to describe their approach (e.g., Gray 1992 and, I believe, Lewontin 1993), but that latter term carries somewhat misleading connotations of "social constructionism" with which the developmentalist view should not be conflated. Thus I shall use the term 'developmentalist'.[5]

Developmentalists hold to views of differing strength that are critical of the received distinctions mentioned, but I think it fair to say that virtually all (strong) developmentalists appear to accept the following 11 theses. These are listed in a rough order from very general theses affecting all organism traits to more specific theses critical of genetic explanations of behavioral traits. Several of these theses also indicate how organisms' behavior can be appropriately studied. The 11 theses are:

3. See Nelkin and Lindee 1995 for an in-depth account of this oversimplified use of genetics in the media.

4. Authors such as Gottlieb (1992), Gray (1992), and Griffiths and Gray (1994) stress the *evolutionary* implications of their developmentalist/interactionist position. In this paper these implications are not explicitly considered.

5. That these terms are heavily freighted with complex metaphors is a thesis that van der Weele explores in depth in her 1995.

(1) The nature-nurture distinction is outmoded and needs to be replaced by a seamless unification approach in which genes and environment are "interacting and inseparable shapers of development." (Lewontin 1995, 72).
(2) The relation between genes and organisms is "many-many" and the existence of significant "developmental noise" (chance events during development) precludes both gene-to-organism trait predictability (including behavioral traits) and organism trait-to-gene inferences (Lewontin 1995, Stent 1981). Thus the outcome is emergent (Gottlieb 1995, 135; Lewontin 1995, 27).
(3) Genes do not "contain" the "information" that is a blueprint for traits, rather information discernible in maturing organisms *develops*—the information is the *product* of an ontogeny (Oyama 1985).
(4) DNA sequences have no fixed meaning, but are informational only in context (Lewontin 1993, Oyama 1985).
(5) Characterizing genes as causes of traits reflects outmoded preformationist thinking (Johnston 1987). Genes do not even make neural structures in any direct way, they produce proteins that affect cell differentiation to yield neurons that become specific types of neurons in specific places with particular connections with other neurons (Gottlieb 1995, 132; Stent 1981).
(6) Developmental causation is not just "bottom up," but is also "top down." Genes are not the principal actors that produce traits (including behavioral traits), but are part of a complex system, in which the cytoplasm can influence the genes, extracellular hormones can influence the nucleus, external sensory stimulation can influence the genes, and the hormones can be influenced by the external environment (see Bateson 1983; Gottleib 1995, 138; Gray 1992, 180 for references).
(7) The most accurate way to describe trait development is to use the "norm of reaction" approach which "is a list or graph of the correspondence between different possible environments and the phenotypes that would result" (Lewontin 1995, 21), but this does not yield deterministic predictions (Gottlieb 1995). Even norms of reactions have to have a temporal developmental dimension added to them (Gray 1992, Gottesman 1996).
(8) The classical ethology approach of Lorenz 1965 that distinguished between "learned" and "innate" behavior has to be replaced by an "interactionist," "epigenetic," "ecological," or

"life cycle" approach. (See Lehrman 1970, Johnston 1987, Bronfenbrenner and Ceci 1994, Griffith and Gray 1994).

(9) Classical behavioral genetics is also committed to a false nature-nurture dichotomy that mistakenly believes it can distinguish between the contributions of heredity and environment to behavior (Johnston 1987).

(10) An analysis of variance is not the same thing as an analysis of causes (Lewontin 1974, Gottlieb 1995). Because classical behavioral genetics is a population-based discipline with its main method being analysis of variance, it can say nothing about the causes of individual development (Gottlieb 1995). Classical behavioral genetics thus can only address the question "how much of the variance" is "attributable to heredity and how much to environment," but not "*how*" hereditary and environment actually produce their effects (Bronfenbrenner and Ceci 1994).

(11) The concept of 'heritability' found at the core of classical behavioral genetics is generally useless and misleading (Lewontin 1995, 71–72); the nonadditivity of genetic effects will not permit its applicability except in highly specialized artificial circumstances (Layzer 1974, Wahlsten 1990).

In contrast to models of development in which (a) genes, or (b) environments are determinative, Lewontin (1995, 27–28) provides what he characterizes as (c) the "correct model of development" that incorporates interactions as well as random "developmental noise." Figure 1 (a,b, and c) represents these three alternatives diagrammatically.

The upshot of the developmentalist criticism is to seriously call into question both the methods and the results of the discipline known as behavioral genetics. This certainly seems to be the implication of the strongest form of this criticism, as we find in Gottlieb 1992, 1995, Gray 1992, and Lewontin 1993, 1995. Others such as Bronfenbrenner and Ceci (1994) accept many of the above points, but see ways to employ many of the results and methods of classical behavioral genetics within an expanded approach that these authors term a "bioecological model." Some behavioral geneticists see value in these criticisms, but maintain that they are seriously overdone (Turkheimer, Goldsmith, and Gottesman 1995), and still others are dismissive of the criticisms (Scarr 1995).

The approach in this paper will initially be bottom-up, in the sense that it will proceed from an account of how a number of contemporary scientists are developing explanations of behavior in simple living systems, frequently called "model organisms." I start from the simplest

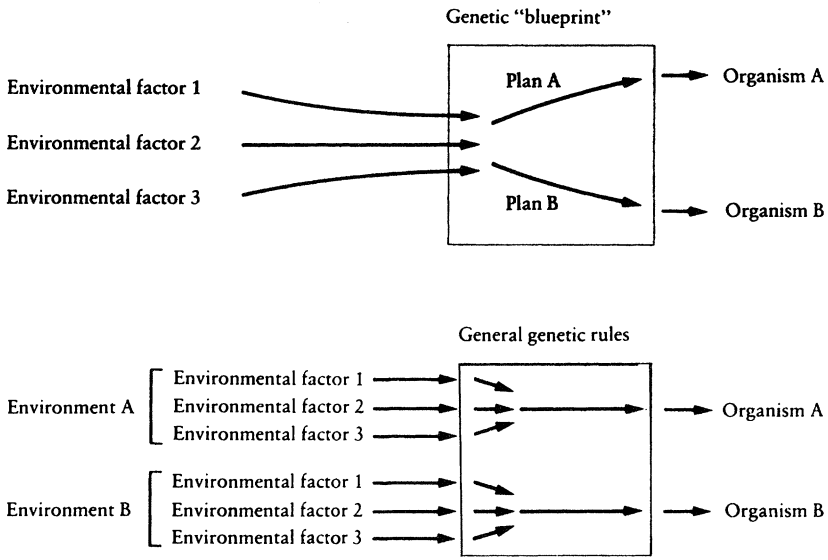

Figure 1 (a and b). From Lewontin 1995, depicting Genetic Determinism in (a) [at top] and Environmental Determinism in (b) [lower figure].

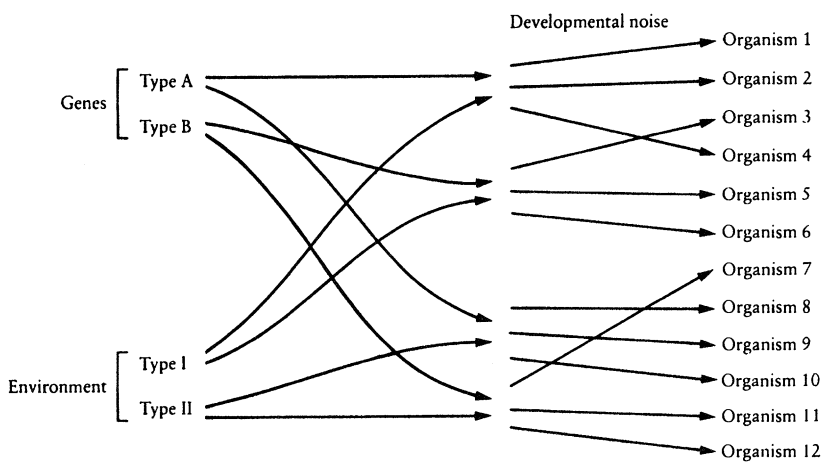

Figure 1c. From Lewontin 1995, depicting what he characterizes as the "correct model" of development.

model organism that possesses a working nervous system, the round worm *Caenorhabditis elegans* (*C. elegans* for short), and then proceed to a much briefer discussion of that favorite of geneticists since T. H. Morgan's work began in 1910, the fruit fly, *Drosophila melanogaster.* This approach represents a philosophical analogue of what is termed the "simple systems" approach, widely adopted in learning and memory studies in "psychology, physiology, biochemistry, genetics, neurobiology, and molecular biology" (Gannon and Rankin 1995, 205). It is one of the theses of this paper that only by examining quite recent work at the interface of *molecular* genetics, neuroscience, and behavior can some of the controversies raised by the Developmentalist Challenge be clarified, and at least partially settled.[6] The conclusions of an account of behavioral explanation in simple systems will then be reassessed in connection with more complex organisms, including what these conclusions may tell us about humans.

3. *C. elegans* as a Model Organism. The nematode *Caenorhabditis elegans* is one of the "model organisms" targeted by the Human Genome Project as a source of potential insight into the working of human genes.[7] Though the organism has been closely studied by biologists since the 1870s (see von Ehrenstein and Schierenberg 1980 for references), it was the vision of Sydney Brenner that has made *C. elegans* the model organism that it is today. In 1963 Brenner had come to believe, as had some other molecular biologists including Gunther Stent (1969), that "nearly all of the 'classical' problems of molecular biology" had been solved or soon would be solved, and that it was time to move on to study the more interesting topics of development and the nervous system.[8] Brenner argued that the nematode had a num-

6. I emphasize *molecular* genetics here (though the neuroscience can also be molecular, but may also be cellular and/or a cellular network) because of the limitations of classical behavioral genetics to populations, and because the classical techniques do not tell us anything about which genes influence behavior or how they do so. Compare the quotation from Greenspan et al. 1995 on this point on p. 215.

7. *C. elegans* sequencing is being conducted as a joint project at Washington University, St. Louis, and the Sanger Centre (U.K.). Details of the sequence are available in ACeDB (A Caenorhabditis elegans Data Base); for an overview see Eeckman and Durbin 1995.

8. Brenner published his letter to Max Perutz of June 5, 1963, in which he develops this belief in his (1988) Foreword to Wood's 1988 reference volume on the nematode. In that same Foreword, Brenner also includes portions of his October 1963 Proposal to the Medical Research Council laying out the reasons why the nematode (though at this point it was *C. elegans'* cousin, *C. briggsiae*, that was mentioned) would be a model organism for these studies. Brenner has indicated that, though several people have told him they planned to write a history of *C. elegans* and its community of researchers, none to his knowledge has yet been done so (S. Brenner, personal communication,

ber of valuable properties, such as a short life cycle, small size, relatively few cells, and suitability for genetic analysis, that could make the nematode the *E. coli* of multicellular organisms. By 1967 Brenner had isolated the first behavioral mutants of *C. elegans*, and in 1970 John White began detailed reconstruction of its nervous system (Thomas 1994, 1698). In his 1974, Brenner published the first major study of the genetics of this organism. In the past 20 years, *C. elegans* has been intensively studied, and a landmark collection of essays summarizing the field appeared in 1988 (Wood 1988). That volume, and especially the appendices containing lists of parts, neurons, etc., illustrates the power of the "brute force" of the approach taken to this organism.[9] The *C. elegans* community is an international one, numbering about 1,000 researchers, and displays extraordinary cooperativity. A current snapshot of its extensive resources is available on the World Wide Web at Leon Avery's homepage (http://eatworms.swmed.edu).

In his pioneering article of 1974, Brenner laid out the rationale and general methodology for studying *C. elegans*. Of related interest to the "simple systems" approach is his comment within this general methodological framework citing the utility of a similar methodology for the study of *Drosophila*. Brenner wrote:

> In principle, it should be possible to dissect the genetic specification of a nervous system in much the same way as was done for biosynthetic pathways in bacteria or for bacteriophage assembly. However one surmises that genetical analysis alone would have provided only a very general picture of the organization of those processes. Only when genetics was coupled with methods of analyzing other properties of the mutants, by assays of enzymes or *in vitro* assembly, did the full power of this approach develop. In the same way, the isolation and genetical characterization of mutants with behavioral alterations must be supported by analysis at a level intermediate between the gene and behavior. Behavior is the result of a complex and ill-understood set of computations performed by nervous systems and it seems essential to decompose the problem into two: one concerned with the question of the genetic specification of nervous systems and the other with the way nervous systems work to produce behavior. Both require that we must have some way of analyzing a nervous system.

March 1995). This oversight may soon be remedied, since Dr. Rachel Ankeny recently completed her Ph.D. dissertation at the University of Pittsburgh on "The Conqueror Worm: An Historical and Philosophical Examination of the Use of the Nematode *C. elegans* as a Model Organism," and is planning a series of publications on this history.

9.The term "brute force" as used here is Horace Judson's (personal communication).

> Much the same philosophy underlies the work initiated by Benzer on behavioral mutants of *Drosophila* (for review, see Benzer, 1971). There can be no doubt that *Drosophila* is a very good model for this work, particularly because of the great wealth of genetical information that already exists for this organism. There is also the elegant method of mosaic analysis which can be powerfully applied to find the anatomical sites of genetic abnormalities of the nervous system . . . .
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> Some eight years ago, when I embarked on this problem, I decided that what was needed was an experimental organism which was suitable for genetical study and in which one could determine the complete structure of the nervous system. *Drosophila*, with about 10^5 neurons, is much too large, and, looking for a simpler organism, my choice eventually settled on the small nematode, *Caenorhabditis elegans* . . . . (Brenner, 1974, 72)

C. elegans is a tiny worm, about 1 mm long, that can be found in soil in many parts of the world. It feeds on bacteria and has two sexes: hermaphroditic (self-fertilizing) and male. Figure 2 shows a simple diagram of the worm (from Chalfie et al. 1985; ignore for the present the depiction of the internal structural cells [then called microtubule cells]). Its life cycle to the reproductive stage is three days with a typical life span of 17 days (Wood 1988). The organism has been studied to the point where there is an enormous amount of detail known about its genes, cells, organs, and behavior. The developmental lineage of all cells in the nematode have been traced from the single-celled zygote. The adult hermaphrodite has 959 somatic nuclei and the male 1,031

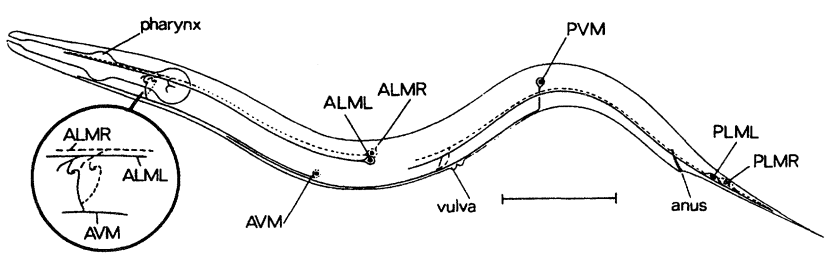

Figure 2. From Chalfie et al. 1985. Original legend reads: "Diagram of the microtubule cells in an adult *C. elegans* hermaphrodite. Cells consist of a microtubule-containing process that runs longitudinally (the receptor process) and a radial branch (the synaptic branch). The anterior microtubule cells *(ALMR. ALML* and *AVM)* are joined by gap junctions at the ends of their synaptic branches (area shown in the *inset*). These cells are the touch receptors for touch-induced movement in the head. The posterior microtubule cells (*PLMR* and *PLML*) are required for the touch response in the head; they are not joined by gap junctions. Bar, 100 μm (Used by permission of Elsevier Publications, Cambridge)."

nuclei; there are about 2,000 germ cell nuclei (Hodgkin et al. 1995). The haploid genome contains 8×10^7 nucleotide pairs, organized into five autosomal and one sex chromosome (hermaphrodites are XX, males XO), comprising about 13,000 genes. The organism can move itself forward and backward by undulatory movements, and responds to touch and a number of chemical stimuli, of both attractive and repulsive forms. More complex behaviors include egg laying and mating between hermaphrodites and males (Wood 1988, 14). The nervous system is the largest organ, comprising, in the hermaphrodite, 302 neurons, subdividable into 118 subclasses, along with 56 glial and associated support cells; there are 95 muscle cells on which the neurons can synapse. The neurons have been fully described in terms of their location and synaptic connections. The neurons are essentially identical from one individual in a strain to another (Sulston et al. 1983, White et al. 1986), and form approximately 5,000 synapses, 600 gap junctions, and 2,000 neuromuscular junctions (White et al. 1986). The synapses are typically "highly reproducible" from one animal to another, but are not identical.[10]

In 1988, Wood, echoing Brenner's earlier vision, wrote that:

> The simplicity of the *C. elegans* nervous system and the detail with which it has been described offer the opportunity to address fundamental questions of both function and development. With regard to function, it may be possible to correlate the entire behavioral repertoire with the known neuroanatomy. (1988, 14)

Seemingly, *C. elegans* is indeed what Robert Cook-Deegan (1994, 53) called "the reductionist's delight."

4. Difficulties and Complexities with *C. elegans*' Behavioral Genetics. Unfortunately there are some limitations that have made this optimistic vision difficult to bring to closure easily. In this section, I will first discuss the progress that has been made in characterizing the relation between neurophysiology and behavior in the worm, and then consider the extent to which *developmental* influences involving genes and environmental factors are addressed in current research on *C. elegans*.

10. Bargmann quotes figures from Durbin 1987: "For any synapse between two neurons in any one animal, there was a 75% chance that a similar synapse would be found in the second animal . . . [and] if two neurons were connected by more than two synapses, the chances they would be interconnected in the other animal increased greatly (92% identity)" (Bargmann 1993, 49).

4.1 Neurophysiology and Behavior: Function.

4.1.1 Methodology and "Rules" Relating Genes to Behavior. Chalfie and White had noted in 1988 that "because of the small size of the animal, it is at present impossible to study the electrophysiological or biochemical properties of individual neurons" (1988, 338), but they added that the much larger neurons in another closely related nematode, *Ascaris suum,* permits some analogical inferences about *C. elegans'* neurons. Only very recently have patch clamping and intracellular recordings from *C. elegans* neurons begun to be feasible and some of this recent work will be discussed later (see Raizen and Avery 1994; Avery, Raizen, and Lockery; 1995; Lockery 1996). It is the case, however, that information obtained from *Ascaris* continues to play an essential role in modeling neuronal interactions (see below, p. 226).

In her 1993 review article, Bargmann writes that "heroic efforts" have resulted in the construction of a wiring diagram for *C. elegans* that has "aided in the interpretation of almost all *C. elegans* neurobiological experiments." But Bargmann goes on to say that:

> However, neuronal functions cannot yet be predicted purely from the neuroanatomy. The electron micrographs do not indicate whether a synapse is excitatory, inhibitory, or modulatory. Nor do the morphologically defined synapses necessarily represent the complete set of physiologically relevant neuronal connections in this highly compact nervous system. (Bargmann 1993, 49–50)

She adds that the neuroanatomy needs to be integrated with other information to determine "how neurons act together to generate coherent behaviors," studies that utilize laser ablations (of individual neurons), genetic analysis, pharmacology, and behavioral analysis (Bargmann 1993, 50).

In this paper, I will not have the space to present the details of the many and varied painstakingly careful studies that have been done comparing behavioral mutants' behaviors with neuronal ablation effects, in attempting to identify genetic and learning components of *C. elegans'* behaviors. These include the specifics of Brenner's pioneering work already cited, as well as Avery and Horvitz's work on pharyngeal swallowing and muscle control (see Avery and Horvitz 1989 for references). Rather I will focus on two laboratories' work, and say something briefer about two more, that provide us with representative studies of the worm's behavior. I will begin with Bargmann and her associates who have examined the nematode's complex response to volatile odorants (Bargmann et al. 1993, Sengupta et al. 1994, Thomas 1994) and then briefly discuss Chalfie and his colleagues' work on the worm's touch response. After that I turn to the electrophysiological

investigations of Avery's, Lockery's, and Rankin's laboratories. After covering the issue of *function* of the genes and neuronal circuits, I then look, in a section on *development*, in more detail at Chalfie's developmental investigations of the touch response.

One of the ongoing research projects in Bargmann's laboratory investigates the nematode's sensory response to various compounds (by taste and smell) and its response behavior. *C. elegans* is able to distinguish among at least seven classes of compounds and react by movement toward (or away from) the odorant-emitting compounds—a behavior known as chemotaxis. These seven classes of odorants are distinguished using only two pairs of sensory neurons, named AWA and AWC. Laser ablation studies of these neurons and the identification of mutations in about 20 genes affecting very similar behaviors, indicate that these genes are required for AWA and AWC sensory neuronal function.

Bargmann and her associates describe about half a dozen *odr* (odorant response) mutations that affect the AWA and AWC neurons (Bargmann et al. 1993, Sengupta et al. 1994), and in the latter study have focused on the *odr-7* mutation, which has an exceptionally specific effect on the two AWA neurons. The general rules regarding the relation of genes to behavior are stated by Avery, Bargmann, and Horvitz who write that:

> One way to identify genes that act in the nervous system is by isolating mutants with defective behavior. However the intrinsic complexity of the nervous system can make the analysis of behavioral mutants difficult. For example, since behaviors are generated by groups of neurons that act in concert, a single genetic defect can affect multiple neurons, a single neuron can affect multiple behaviors and multiple neurons can affect the same behavior. In practice these complexities mean that understanding the effects of a behavioral mutation depends on understanding the neurons that generate and regulate the behavior. (1993, 455)

Let us consider these and other general principles, which I shall call "rules," governing the relation between genes and behavior that are discernible in the investigations of this extraordinarily well-worked-out simple organism. (I use the term "rules" for these principles, and not laws, because in some cases they admit of exceptions, but hold generally, and I think are default assumptions for all organisms.[11])

11. The claim that these should be default assumptions partly follows from the simplicity of the organism investigated. The rules delineated below suggest that even in *C. elegans* the relations between genes and behavior are quite complex. A preliminary analysis of *Drosophila* supports these rules as well. It is therefore very unlikely that still

It is probably almost a truism to point out that a single neuron is the product of many genes, but it is a starting point and might be termed the rule of *many genes—one neuron.* In the quote from Avery et al. immediately above, we encounter several other similar rules. If (1) is the *many genes-one neuron* rule, then we may term as (2) a *many neurons-one behavior* rule. Further, it is a generally recognized fact that frequently genes are not specialized to affect just one cell type, but affect many different features and different cell types (Bargmann 1993, 66), a phenomenon termed "pleiotropy." This could be called (3) a *one gene-many neurons* rule. Moreover, in addition to *genetic* pleiotropy, there is the additional fact that any given nerve cell (neuron) may play roles in *several different behaviors* (Churchland and Sejnowski call these "multifunctional neurons"; 1992, 349), thus complicating, but not making impossible, an analysis of how behaviors are caused by the neurons. Bargmann cites some minor neurons involved in the chemotaxic response that are also required to regulate the developmental decision between dauer and nondauer development (Bargmann 1993, 61).[12] Chalfie et al. (1985) in their investigation of touch circuit neurons (to be discussed later) points out that one sensory neuron (or one type of sensory neuron) can serve a variety of functions (movement, egg-laying, pharyngeal pumping, and possibly the control of other sensory neurons). Similar multifunctional neurons have been identified in the leech and modeled using connectionistic neural nets by Lockery and Sejnowski (1993). This rule might be termed (4) a *one neuron-many behaviors* rule.[13] There is another consideration raised by Durbin's (1987) observations that apparently strain-identical animals will have somewhat different synaptic connections in their nervous systems. It is not yet clear exactly what is the cause (or causes) of this variation. This may be due to presently hidden genetic differences, an adaptive response to subtly different internal environments in development, or it may possibly be due to partially stochastic processes in development—

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more complex organisms such as mice and humans will *generally* conform to simple relations such as one gene type-one behavior type. I discuss some exceptions to the complex rules further below.

12. The dauer stage of development refers to an alternative developmental pathway brought on by a limited food supply available to larvae. In such a state, *C. elegans* can survive up to three months without food (Wood 1988, 14–15). Also see pp. 228–230 below.

13. These one-many, many-one, and ultimately, many-many relations, are akin to a thesis advanced independently by David Hull 1974 and Jerry Fodor 1974, developed by Rosenberg in his 1985 and 1994. These authors, whose views I have extensively critiqued in my 1993, esp. Ch. 9, infer biological unpredictability and antireductionist themes from such relations, whereas I infer a manageable complexity (see below).

what Waddington (1957), Stent (1981), and Lewontin (1995) term "developmental noise." For pragmatic reasons, we could aggregate these three processes under the heading of a currently apparent stochastic element, and add this as an additional "rule" that later investigations may further circumscribe.[14] This might best be termed (5) a *stochastic development-different neural connections* rule. In addition to these five rules, a plasticity or learning/adaptation dimension needs to be considered. Short term sensory adaptation has been observed to occur in *C. elegans*. Sengupta et al. (1993) note that after 2 hours exposure to an odorant such as benzaldehyde, the organism loses its ability to be attracted by that substance, though it still is attracted to other odorants. These authors point out that "a more extensive form of behavioral plasticity occurs when animals are starved or crowded. Water soluble chemicals that are strong attractants to naive animals are ignored by crowded, starved animals," and add that "these changes induced by crowding and starvation persist for hours after the worms are separated and fed" (Sengupta et al. 1993, 243; also see Colbert and Bargmann 1995 for additional details). Thus, to the five rules already noted, there is (6) a sixth rule of *different environments/histories-different behaviors,* that further complicates the predictability of behavior, and indicates the impossibility of accounting for behavior from purely genetic information. These six rules are generalizations involving principles of genetic pleiotropy, neuronal multifunctionality, and plasticity. When we turn more explicitly to developmental considerations below, we will have occasion to add to these, to represent genetic interactions, but these six will suffice for now. But like virtually any generalization or set of generalizations in biology, they are likely to have exceptions, or near-exceptions. I consider one type of exception involving an almost "one gene-one behavior type" association in the following section, since it is illustrative of a search for "simplicity" of a sort in behavioral genetics.

4.1.2 A Successful Reductionistic Exception in C. elegans*' Behavioral Genetics.* Though the analysis of the *unc-31* (uncoordinated behavior) gene reported in the article from which the Avery et al. quotation is taken illustrates the complexity of effects summarized in the six rules introduced in the previous section, a recent study of the *odr-7* gene in

14. One of the anonymous referees for this journal suggests there may even be additional reasons for neuronal connectivity variation, speculating that "rewiring based on stimulus" might occur "at crucial development stages." Something like this possibility is being pursued by Peckol and Bargmann (cf. note 20), but the inquiry is in the early stages. Also see Ferris's 1996 discussion of vulnerable periods of development in the hamster and the effects of different stimuli during these periods on subsequent behavior.

C. elegans published in *Cell* in December 1994 appears to be considerably more specific, and almost supports a "one gene-one type of behavior" analysis. As Sengupta et al. (1994) show, a null mutation in the *odr*-7 gene causes *C. elegans* to fail to respond to all odorants detected by the AWA neuron pair. A missense mutation in this gene results in a specific defect in one odorant response (1994, 971).

Sengupta et al. also were able to map *odr*-7 to the X chromosome, and further localize the gene by restriction fragment length polymorphism (RFLP) mapping as well as by "germline rescue of the *odr*-7 diacetyl chemotaxic defect with cosmids from a defined interval"[15] (Sengupta et al. 1994, 973). These investigators were then able to clone the gene, sequence it, and to determine its transcript, one that encoded a "predicted protein product" 457 amino acids in length. The *odr*-7 gene sequence was also compared with other sequences in available databases, a comparison that indicated that the gene is a member of "the [super]family of nuclear hormone receptors" (1994, 974).

Sengupta et al. have speculated on the manner in which odr-7 functions, writing:

> Three general classes of models could account for the phenotype of *odr-7* mutants. First, Odr-7 could be involved in the cell type-specific expression of receptor or signal transduction molecules in the AWA olfactory neurons. Second, Odr-7 could determine the cell fate or development of the AWA neurons. Third, Odr-7 could interact directly with odorants in an unusual signal transduction cascade. Our results favor the first possibility. (1994, 977).

Additionally, the authors discuss more detailed speculations as to how this first possibility may be realized discussed by the authors, but they need not concern us here (see Sengupta et al. 1994, 977).

The *odr*-7 gene is clearly more specific in its effects than typical behavior-influencing genes. In work by Bargmann and her associates not yet published, this specificity has been further confirmed by results using antisera against the endogenous gene product that shows that *odr*-7 is only expressed in a single cell type (Bargmann, personal communication). Though *odr*-7 appears in the account described above to be monofunctional, more recent unpublished work suggests that *odr*-7 mutations have at least two effects. In addition to its chemotactic function, *odr*-7 also helps integrate olfactory information over time, prob-

15. This is a powerful result, though the terms in which it is necessarily described, "RFLP mapping" and "germline rescue . . . with cosmids from a defined interval," are highly technical. For lucid definitions and a discussion involving these terms see Alberts et al. 1994, 304–305, 315, and 328.

ably through the function of the AWA neurons (Bargmann, personal communication). The results thus far then suggest that ord-7 is exceptional in its specificity, though not monofunctional, thus preserving in attenuated form the general principles of genetic pleiotropy, multifunctionality, and plasticity described above.

4.1.3 Circuits, Connectionist Themes, and the Need for Neural Network Modeling in C. Elegans. Identification of genes that are "necessary for" specific behaviors, as described in the previous sections, represents one way to indicate the causal role that genes play in generating behaviors. As stressed in Section 4.1.1, however, genes work in concert and through combinations of neurons synapsing on other neurons and muscle cells to produce those behaviors. To achieve a more *sufficient* explanation of behavior, one that would provide a fuller description of the functional aspect of a nervous system, it is not a "*gene(s) for*" account of behavior that is required, rather it is a "*neural circuit for*" analysis that needs to be provided.[16] *C. elegans* researchers have identified a number of such circuits and are in the process of determining additional ones. The chemotaxis circuit, in which Bargmann's laboratory's work will be situated, is one that should shortly be completed (Bargmann, personal communication). A fairly detailed neural network for *C. elegans' thermo*taxis behavior was published in 1995 (Mori and Ohshima 1995). Chalfie's and others' work sketched the circuit for touch sensitivity in the worm a dozen years ago (Chalfie et al. 1985), and additional features of that circuit have since been identified (see Section 4.2). A closely related (in fact, overlapping) circuit for a tap withdrawal reflex has been characterized in Rankin's laboratory (Wicks and Rankin 1995, Wicks et al. 1996). If this view of the importance of circuits is right, then this suggests we will need a slight modification of our second rule introduced earlier, the one that indicated that *many neurons → one behavior*. The modification is to reflect that the neurons productive of behavior act in an integrated way as part of a well-defined circuit. Thus our rule (2) becomes (2′): *many neurons (acting as) one neural circuit → one type of behavior.*

This article cannot present the details of each of these various circuits. Suffice it to show Chalfie et al.'s touch sensitivity circuit in its simplified form (see Figure 3) as an illustration of the connectivity of

16. Necessary condition forms of explanation once received considerable attention from philosophers of science, and especially from philosophers of biology, since they seemed biologically distinctive. As I argue in my 1993, Ch. 7, however, in part following Beckner 1959, these types of "explanation" are not distinctive and are essentially just empirically weak types of explanation.

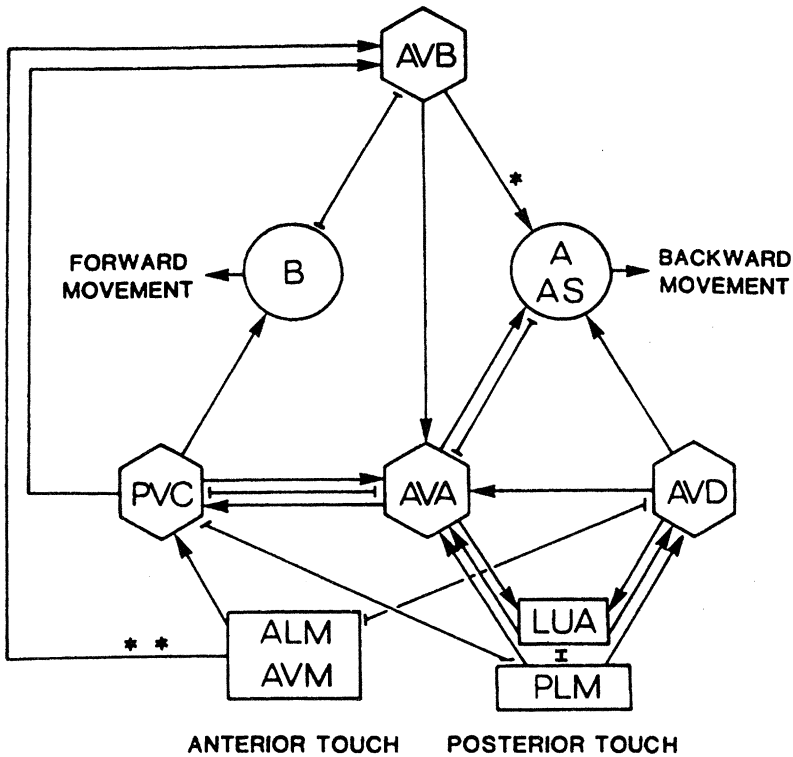

Figure 3. From Chalfie et al. 1985. Original legend reads: "Neural circuitry for touch-induced movement. The touch cells and the touch cell connector, LUA, are designated by *rectangles,* the interneurons are designated *by hexagons,* and the motor neurons are designated by *circles.* Both chemical synapses (→) and gap junctions (⊣) are indicated. The diagram represents a composite of data and does not indicate the changes that occur in the circuitry during development e.g., the connections from *AVM* to *AVB* are formed late in larval development. Missing from the diagram are the gap junctions between identical motor neurons and interneurons and the gap junctions joining *AVM* and *ALM. AVB* forms chemical synapses only with the *AS* cells, not the *A* cells (*); only *AVM* of the anterior touch cells chemically synapses onto *AVB* (**). The connections made by the interneurons are taken from White et al., (1976; J. G. White, E. Southgate, J. N. Thomson, and S. Brenner, unpublished data)."

neurons in the worm. This involves a reflex circuit that generates a movement away from a fine touch stimulus—typically the stroking of the animal with a thin hair. This circuit has input from five touch receptor neurons (ALML, ALMR, PLML, PLMR, and AVM), then acts through five pairs of interneurons and motorneurons on muscle cells to generate forward and backward movements. It is also necessary to point out that all of these circuits are at present strongly underde-

termined by any *direct* evidence regarding their polarities and modes of action. As indicated earlier, only in the past year or so has the electrophysiology of the worm begun to be examined. A complete connectivity map at the ganglion-level for the worm's nervous system has been constructed and encoded in a computerized database (Achacoso and Yamamoto 1992, Cherniak 1994). A study done by Raizen and Avery (1994) employed a newly developed method for recording currents, producing what they term "electropharyngeograms," to infer specific neuronal effects. Shawn Lockery's laboratory at the University of Oregon has begun a research project to obtain detailed electrophysiological data in *C. elegans*. In the early 1990s, Lockery worked with Terry Sejnowski to develop a sophisticated connectionist model of the bending reflex in the leech (see Churchland and Sejnowski 1992, 339–353 for a general "philosophically-oriented" introduction to this work; also Lockery and Sejnowski 1993 for an update). Lockery and Sejnowski also constructed what they termed two "preliminary models" to represent chemotaxis in *C. elegans* (see Lockery, Nowlan, and Sejnowski 1993). In the past year Lockery has developed some special techniques for recording from single neurons in *C. elegans*, and has embarked on a research program to develop and test connectionist models for *C. elegans.*

In spite of these recent advances, however, current investigations still need to rely on analogical inferences from the neuronal properties of *C. elegans'* cousin *Ascaris* (see Ferrere et al. 1996, Wicks et al. 1996). The latter paper is from Rankin's laboratory, and introduces an intriguing novel methodology for inferring neuronal activity in the tap withdrawal circuit (Wicks et al. 1996) involving a dynamic network simulation.[17] Lockery's laboratory has both been able to make recordings from individual neurons in *C. elegans* (Lockery and Goodman, unpublished), and is also in the process of modeling those results by utilizing connectionist optimization strategies (specifically a simulated annealing algorithm) that yields predictions in rough agreement with the worm's chemotaxis behavior (Ferrere et al. 1996). Furthermore, the approaches of Rankin's and Lockery's groups both employ general equations for neuronal signal propagation that, though complex, are neuroscientifically well-established and introduce powerful physicochemical constraints on the inferred neural networks. Further modeling

17. Wicks and Rankin point out in their 1995 that "hypotheses about what polarity configurations might best account for behavioral observations . . . are difficult given the complexity of the [tap withdrawal] circuit. However these hypotheses can be aided by the formulation of an appropriate computational model of the circuitry." Such a model has been published in Wicks et al. 1996.

of *C. elegans* is likely to be done by various investigators involving still higher fidelity models of neuron compartments and molecular signaling mechanisms. Two promising modeling tools that could be used in such an endeavor are the neural simulation programs NEURON (Martin 1995) and GENESIS (Bower and Beeman 1995).[18]

4.2 Neurophysiology and Behavior: Development.

4.2.1 Generation and Specification: The Light-Touch Reflex Circuit Redux. Thus far, I have primarily been characterizing the "functional" aspect of *C. elegans'* behavioral genetics, and have related that to a neural net modeling approach. I now turn to more explicitly developmental considerations, in order to complete the picture, and thus follow Brenner's methodological suggestion that any analysis of behavior also must consider not only the *functioning* of the nervous system, but *also* "the question of the genetic specification of nervous systems." This will also better prepare us to reconsider the Developmentalist Challenge discussed earlier. Here we look more closely at the light touch reflex response, a circuit for which was introduced in the previous section.[19] The major recent work on this component of the worm's behavioral repertoire has been done in Martin Chalfie's lab at Columbia University. Currently over 450 touch mutants have been identified involving defects in 17 genes, with the mutations being classified into four groups primarily affecting "generation, specification, maintenance, and function" (Chalfie 1995, 179).

The genes in the groups affecting generation and specification are those centrally involved in the development of the nervous system in *C. elegans*. Two known genes that affect generation of the touch receptors are *lin-32* and *unc-86*. Mutations in these genes result in the cell lineages that normally give rise to the receptors never making the touch receptor cells (Chalfie and Au 1989). Chalfie summarizes evidence that the protein (UNC-86) that *unc-86* encodes acts as a direct *trans*-activator of touch cell differentiation by targeting the *mec-3* gene required for touch cell *specification* and also *maintenance* (Chalfie 1995, 180). But the process is probably not a simple linear series of transcription factors successively being activated. Chalfie reports that the downstream *mec-4* and *mec-7* genes—two of the 14 genes that are required for *function*—are under an "accumulative" form of control in which UNC-86 and MEC-3 (the protein that *mec-3* encodes) act in "combinatorial fashion" to activate these downstream genes.

18. I thank David Touretzky for referring me to these two programs.

19. The early embryology of *C. elegans* is becoming better understood, but is still not as well characterized as is *Drosophila*'s (Roush 1996).

Differentiation of the touch cells involves some further complications as well. *unc-86* and *mec-3* are expressed in cells that do not become touch receptors, and in seeking to find other regulators, Chalfie and his colleagues have identified seven other genes needed to constrain the number of touch cells to the normal six. These seven include programmed cell death genes *ced-3* and *ced-4* that delete four cells that could become touch receptors. Chalfie writes that "together positively and negatively acting genes as well as genes needed for programmed cell death are needed to produce the correct number of touch receptors within the animals (Chalfie 1995, 180). Chalfie has summarized these genetic interactions in the development of the touch receptor neurons in a model that is reproduced as Figure 4.

As mentioned, 14 additional genes appear to affect touch cell *function*, in that mutations in these genes do not affect the number or the anatomy of the touch cells, but do result in nonfunctioning touch cells. One of these (*mec-7*) encodes for a protein found in microtubules specific to the touch cells. Two others have an effect on the extracellular matrix, perhaps securing a touch receptor to the body wall. Still other genes seem to be involved in mechanosensory transduction, perhaps affecting parts of sodium conductance channels (Chalfie 1995, 181). Recently, Chalfie and his colleagues have proposed a model for mechanosensory transduction in the touch receptor neurons that shows how the gene products may interact structurally (Gu et al. 1996, esp. Figs 2 and 3), but some parts of the interactions are still speculative. Thus, though considerable progress has been made in identifying the actions of function genes, much more research will need to be done to clone all the genes, fully identify the gene products and modes of action, and bring this project to completion.

The developmental features of the worm considered in this section suggest a seventh addition to our six rules discussed in Section 4.1.1 (with the addition of the circuit rule modification added above on p. 224). This rule notes the frequent effects of genes on other genes, ranging from possibly simple sequences of activation to the nonlinear combination noted by Chalfie. Thus we add (7) *one gene → another gene . . . → behavior (gene interactions, including epistasis and combinatorial effects)*.

4.2.2 Environmental Influences: Temperature Sensitivity, Maternal Influence, and the Dauer State. Earlier, the short-term effects of the history and environmental influences on *C. elegans* were briefly mentioned in connection with the worm's behavioral plasticity (learning). Here I consider some of the significant long-term effects of the environment on *C. elegans* that investigators have discovered. I confine my

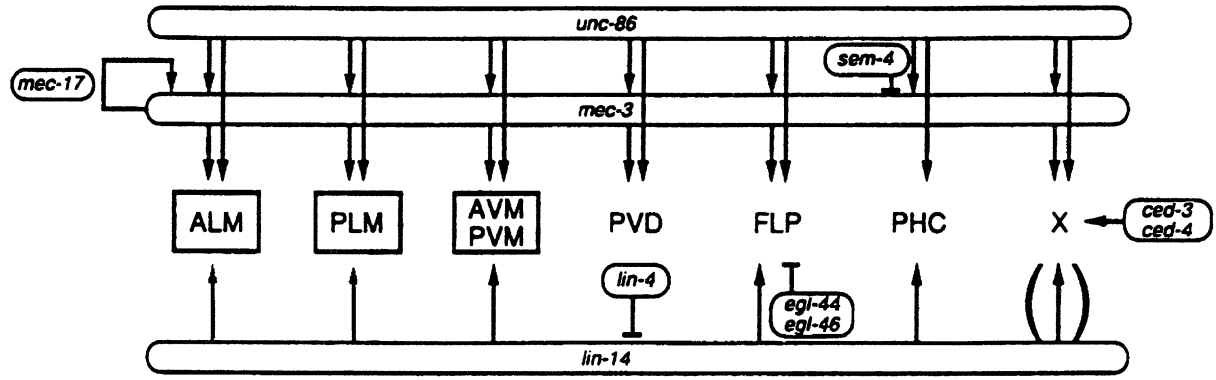

Figure 4. Chalfie's development model. From Mitani et al. 1993. Original legend reads: "Genetic interactions in the regulation of touch receptor characteristics. Wild-type animals contain a pair of each of the indicated cell types and four relevant dying cells (X). Only the boxed cells expressed touch receptor characteristics in wildtype animals. →, positive regulatory effects; ⊣, negative regulatory effects. The *lin-32* gene (not indicated on the figure) is presumed to act before *unc-86*. The double arrow from *unc-86* denotes that this gene may act both in regulating *mec-3* and, subsequently, with *mec-3,* on target genes such as *mec-7 and mec-4* (A. Duggan and M. Chalfie, unpublished data). The arrow from *mec-3* onto itself signifies the role of this gene in maintaining its own expression, maintenance of touch receptor differentiation (but perhaps not of other cells) also requires the *mec-17 gene* (Way and Chalfie, 1989). The arrows from *lin-14* to the ALM and PLM cells are shaded [in the original diagram] to indicate that its function with regard to these cells is not known. The effect of *lin-14* on the expression of the cells that do not die in *ced-3* and *ced-4* animals is hypothesized; it has not been tested."

attention to the detection of temperature-sensitive mutants, some seen in maternal effects, the production of the dauer state.[20]

Temperature-sensitive mutants are encountered in many species. Briefly, a temperature-sensitive (*ts*) mutant is "an organism or cell carrying an genetically altered protein (or RNA molecule) that performs normally at one temperature but is abnormal at another (usually higher) temperature" (Alberts et al. 1994, G-22). In *C. elegans*, some of the phenotypes are stronger at 25°C. than at 15°C. A number of *ts* mutants have been investigated in the worm and can be found in Appendix 4B in Wood 1988. Some of the most interesting are associated with anomalies in sexual differentiation (Hodgkin 1988).

One especially interesting set of temperature sensitive mutants involve those that show a maternal effect. Herman offers the following account of the transforming mutation *tra-3*:

> Homozygous mutants self-progeny of a heterozygous parent are fertile hemaphrodites, but their self-progeny are transformed by *tra-3* to psueudomales (Hodgkin and Brenner, 1977). Homozygous *tra-3* hemaphrodites, generated from *tra-3*/+ mothers, will produce hemaphrodite progeny, however, when mated with wild-type males; this indicates that zygotic expression of *tra-3* (+) is sufficient to prevent sexual transformation. (Herman 1988, 27)

Maternal effects in other species, in which the environment apparently has an effect on maternal gene expression in egg production, have been discussed recently (see Pennisi 1996 for references).[21] Similar egg-affecting mutations (but without a demonstrated maternal environmental component) have been investigate in *C. elegans* (see Wood 1988, 256).

A perhaps even more dramatic an effect of the environment on *C. elegans* is the consequence of crowding and a diminished food supply on worm development. An "enduring" or dauer form of the larval stage of *C. elegans* arises under the influence of a worm-secreted pher-

20. There is an additional most interesting prospect of identifying effects of sensory stimulation on the development of neuronal pathways, but this investigation (Bargmann, personal communication) is still in its preliminary stages (see "Does Sensory Neuron Activity Affect the Development of Sensory Neurons?" by Peckol and Bargmann, which was presented at the Early 1996 West Coast Worm meeting; see Avery 1996 for access to this Abstract).

21. It is of interest to note that for many years maternal effects were disregarded and interpreted as "random noise that tended to obscure the genetic variation we were interested in"—Pennisi quoting T. Mosseau in Pennsini 1996, 1334. This suggests that one should be *very* cautious in accepting any hypothesis appealing to an irreducible "developmental noise."

omone, food supply, and temperature (Riddle 1988, 398). In the dauer form, these nonaging worms can survive for four to eight times the three week life span of non-dauer forms (Riddle 1988, 393). A genetic pathway showing the interactions of environmental cues, sensory processing, and morphogenesis has been worked out for the worm (Riddle 1988, 405).

This information about *C. elegans* temperature sensitivity and its dauer state suggest a final "rule" relating genes and behavior. This is *(8) Environment → gene expression → behavior.* It is of interest to note that *C. elegans* investigators do not use the "norm of reaction" (or "reaction norm") terminology (Bargmann and Chalfie, personal communications), although the *Drosophila* community does so. Nevertheless, the worm community does clearly acknowledge the importance of environmental influences on both genes and developmental processes.

A summary of our now eight "rules" is presented in Table 1.[22] In my view, these rules, based on empirical investigations in the simplest model organism possessing a nervous system that has been studied in the most detail, should serve as the default assumptions for further studies of the relations of genes and behavior in more complex organisms.[23] These eight rules are generalizations involving principles of ge-

TABLE 1: Some Rules Relating Genes (Through Neurons) to Behavior in *C. elegans*

1.	many genes → one neuron
2′.	many neurons (acting as a circuit) → one type of behavior (also there may be overlapping circuits)
3.	one gene → many neurons (pleiotropy)
4.	one neuron → many behaviors (multifunctional neurons)
5.	stochastic [embryogenetic] development → different neural connections*
6.	different environments/histories → different behaviors* (learning/plasticity) (Short-term environmental influence.)
7.	one gene → another gene . . . → behavior (gene interactions, including epistasis and combinatorial effects)
8.	Environment → gene expression → behavior (Long-term environmental influence.)

*in prima facie genetically identical (mature) organisms
The → can be read as "affect(s), cause(s), or lead(s) to."

22. Johnston and Hyatt (unpublished) have developed an interactionist model for development that would most likely result in even more "rules" than discerned in *C. elegans* research.

23. Why these are default assumptions is defended in note 11. An anonymous referee for this journal posed a point that takes a rather different tack, suggesting that these eight rules at the level of the generalizations as presented in Table 1 below are simply "common sense," generally accepted by "sophisticated geneticists and philosophers of biology long before any particular examination of the work on *C. elegans*." The same referee urges that "the rich detail behind" these rules should find its way into a "sharper instrument" to use in addressing the philosophical problems of this paper. I agree that it would be useful to formulate what I would see not necessarily as a "sharper," but as

netic pleiotropy, genetic interaction, neuronal multifunctionality, plasticity, and environmental effects, and like virtually any generalization in biology, they are likely to have exceptions, or near-exceptions, but I think these will be rare.

4.3. Other Simple Systems: Drosophila. The lessons gleaned above from *C. elegans*, and embodied in the eight "rules" proposed above, also seem to apply to other biological organisms, including *Drosophila.* Earlier I cited Brenner's comparison of *C. elegans* and *Drosophila*, in which Brenner referred to Benzer's early investigation of this organism. In the years since Brenner's comment of 1974, Benzer's student, Jeffery C. Hall, and then Hall's own student in turn, Ralph Greenspan, among others, have probed deeply into the cellular and genetic aspects of the behavior of *Drosophila.* Many of these studies have focused on *Drosophila*'s courtship behavior, and have resulted in the identification of a number of behavioral mutants, including several types of male mutants termed *fruitless (fru)*, that court other males as actively as they do females. Hall's investigations into this and other courtship mutants are reviewed in depth in a recent article in *Science* (Hall 1994), and very recently Hall collaborated with several other groups in identifying *fru* as "the first gene in a branch of the sex determination hierarchy functioning specifically in the central nervous system (CNS)" (Ryner et al. 1996, 1079). Greenspan's group's work has extended the technique of mosaic creation, (Ferveur et al. 1995), and has been summarized by Greenspan (1995) in another recent and accessible article. The conclusion of this work, as Greenspan puts it, is that "behaviors arise from the interactions of vast networks of genes, most of which take part in many different aspects of an organism's biology" (1995, 78). To this theme of networks involving multifunctional neurons, Greenspan also adds that evidence from *Drosophila's* courtship behavior indicates that both male and female fruit flies "have the ability to modulate their activity in response to one another's reactions," adding:

> In other words, they can learn. Just as the ability to carry out courtship is directed by genes, so too is the ability to learn during the experience. Studies of this phenomena lend further support to

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a more robust, "model," intermediate between the rich details discussed in the text and the eight generalizations, but I believe this must wait on further comparative examination of other organisms, such as *Drosophila* and *Mus*. The eight rules and their implications are in point of fact used in addressing the Developmentalist Challenge in the following section where they appear sufficiently "sharp" to perform this function. Moreover, many sophisticated geneticists will probably find them too strong; compare Bargmann's comment in note 35.

> the likelihood that behavior is regulated by a myriad of interacting genes, each of which handles diverse responsibilities in the body. (Greenspan 1995, 75–76)

If this "network" type of genetic explanation holds for most behaviors, including even more complex organisms than worms and fruit flies, such as mice and humans, it raises barriers both to any simplistic type of genetic explanation, as well as for the prospects of easily achievable medical and psychiatric pharmacological interventions into behaviors. In addition, the eight "rules" that capture this network perspective may be some of the reasons why it has been so difficult to find single gene explanations in the area of human behavior. These complexities and the extent they relate to the Developmentalist Challenge are the topic of the remaining sections of this paper.

5. Which Developmentalist Themes Do Simple Systems Support? I have now surveyed a number of aspects of the relations between genes, development, and behavior in simple systems, with a primary focus on *C. elegans.* I now turn to a consideration of the various theses of the Developmentalist Challenge in the light of this empirical research. For the purposes of this section and the next, it will be useful to distinguish between (1) a set of *five core concepts* found in the Developmentalist Challenge that apply both to molecular biology and to classical behavioral genetics, and (2) those criticisms more directed at classical behavioral genetics. This section deals with the five core concepts.

All of the five core concepts apply to genes, and the last two of these to the relation of genes and environment, in connection with traits or phenotypes. The concepts are those of *parity, nonpreformationism, contextualism, indivisibility,* and *unpredictability.* Basically, *parity* means genes are not special—not "master molecules." *Nonpreformationism* implies that we do not find "traitunculi"—little copies of the traits the genes determine—in the genes. *Contextualism* indicates that genes have little meaning (as "informational molecules") per se, only in context with other genes, and in an environment that is cellular, extracellular, and extraorganismic. *Indivisibility* refers to the thesis that genes and environment cannot be identified by their effects on traits in any separable sense: the effects are a seamless unification, an amalgam. *Unpredictability* means that from total information about genes and environment, we cannot predict an organism's traits: they are, accordingly, emergent. These five concepts seem to capture the core of the 11 or so theses described in Section 2. What do successful research programs in the *C. elegans*' area tell us about the soundness and applicability of these concepts?

Parity. It would seem that genes *do* have a special set of roles to play in *C. elegans* research (and in biology more generally). Genes are the common bridge between successive generations of organisms, are similar between closely related strains, and display important homolog relations among distantly related species in strongly conserved sequences of DNA. DNA is a *linear* molecule, and as such is "one-dimensional and conceptually simple" in contrast to "most other processes in cells [that] result solely from information in the complex three-dimensional surfaces of protein molecules. Perhaps that is why we understand more about genetic mechanisms than about most other biological processes" (Alberts et al. 1994, 223).[24] In addition, there is a consensus in biology that a simple form of the "central dogma of protein synthesis" is correct. This form of the "central dogma" holds that information flow is *from* DNA (or RNA) *to* protein, and thus that DNA (or RNA) has a special *informational* priority. (I also view this form of the central dogma as a material implementation of the denial of the inheritance of acquired characteristics.) Both Oyama (1985) and Lewontin (1993, 1995) would disagree with this informational interpretation, though I hasten to add that neither Oyama nor Lewontin, in disputing an informational priority for DNA, would subscribe to a thesis of the inheritance of acquired characteristics. Genes are also seen as special, because methods have been developed to screen for mutants, map "genes for" traits (as a first approximation), localize those genes, clone them, and test their role as "necessary" elements for a trait using sophisticated molecular deletion and rescue techniques.

No *C. elegans* investigator ever thinks genes act alone—they all recognize the need for the cellular and extracellular supporting environments, and also look for environmental effects on the organism (*rule 6*) and on the genes (*rule 8*). Naked DNA (or RNA) is not sufficient to produce interesting biological traits, in spite of the significant cell-free systems, and origin of life, experiments that can be accomplished with polynucleotides. Thus, *causally,* genes have parity with other molecules as severally necessary and jointly sufficient conditions (to produce traits), but *epistemically* and *heuristically,* genes do seem to have a *primus intra pares* status.[25,26]

24. I first heard this point about the significance of DNA's "linearity" as a basis for the importance of genetic (DNA) considerations in biology from Allan Tobin, though here the citation is to Alberts et al.'s (1995) influential text on the molecular biology *of the cell.* Tobin also suggested another, more sociological reason, for the importance of DNA in contemporary biology, namely that many biologists believed that "really smart people" work(ed) on DNA (personal communication, October 1996).

25. Paul Griffiths has suggested to me that the reason why genes (and DNA) have a special heuristic value is "*because* they have been so thoroughly investigated" (personal

I think the best discussion of the special role that genetics plays in behavior appears in Stent's (1981) analysis, and in his distinction between what he terms the "ideological" and the "instrumental" views of genetics in neuroscience. The *ideological* view represents a complete genetic determinism: sufficient information is in the genes to determine a neural circuit that determines behavior. (Stent cites articles by Benzer, Hall, and Greenspan that hold this position.) Stent argues against this approach in favor of an *instrumental* analysis, in which "the genetic approach appears as the study of the *differences* in neurological phenotype between animals of various genotypes, without any particular interest (other than *methodologic*) in the concept of genetic specification" (1981, 162; my emphasis). Stent quotes from statements by several authors supporting the instrumentalist approach. Genetic mutations are "an exciting and unique way of lesioning the system at the level of cell interactions," and genetic mutations are "models for inherited disease" both in mice and in humans (Mullen and Herrup 1979). The mutant approach may in addition "provide convenient experimental preparations to which other techniques can be applied" (Pak and Pinto 1976). Though some *C. elegans* investigators *may* hold the stronger "ideological" thesis, the weaker "instrumental" approach clearly is supported by the accounts of work in *C. elegans* described in the present article and summarized in *rules (1)–(8)*. It should be stressed, however, that this sense of 'instrumental' is not to be identified

communication, December 1996). This is a nice (partly sociological?) parry to Alberts et al.'s view, quoted above, that we do "understand more about genetic mechanisms than about most other biological processes," perhaps because the molecule is one-dimensional.

26. One of the anonymous referees has suggested that the account developed here is compatible with (some) genes being "master molecules," citing Gehring's group's work on the *eyeless (ey)* gene in in *Drosophila* (Halder, Callaerts, and Gehring 1995). This group does use language referring to *ey* as a "master control gene," but, in my view this is not entirely on point regarding the causal parity issue. Gehring's' master control gene, like the recently discovered properties of the *fru* gene in Drosophila (see p. 232 above), is a gene that acts first in a linear branch of development, and seems to code for a transcription factor that regulates genes that are distal in the pathway. Sometimes there are simple linear cascades with a "master control gene" at "the top" but more frequently there are not. In *C. elegans* there are very few such "master control genes," at least recognized at present (Chalfie, personal communication). The genetic programs are apparently typically regulated by a more complex accumulative and combinatoric logic, as in Chalfie's touch circuit described earlier, though there is a "sex determination hierarchy" that has been identified in *C. elegans* (see Ryner and Swain 1995 for an overview). Even the *ey* gene acts *in concert with* protein synthesis machinery, which reaffirms the point about causal parity. For additional discussion of the "master molecule" concept, and some of the colorful metaphors that are associated with that notion, see van der Weele 1995, esp. 15–16.

with the philosophical sense of denying realism (see Rosenberg 1994); rather it sees genetics and mutational analysis as powerful heuristics that could point the way toward, but are not equivalent to, a complete realism-based explanation of behavior.[27]

Nonpreformationism. No *C. elegans* investigator known to this author seems to think of a DNA sequence as representing a behavioral "trait": the nature of a sequence of DNA nucleotides, that sequence's relation to other sequences or genes (*rule 7*), and its relation to protein synthesis machinery, as well as developing heuristics for ascertaining the functional role certain types of protein sequences may play in cells, is part of the training of competent researchers in this domain.

Contextualism. The previous paragraph would seem to indicate that contextualism is accepted by the *C. elegans* community; see again *rule 7*, as well as *rules 6* and *8*.

Indivisibility. C. elegans researchers do distinguish the causal effects of DNA sequences, operating through protein synthesis and protein folding and assembly, from the effects of other molecules (e.g., pheromones) and conditions (e.g., heat/temperature). The causal schema is a complex web, but not an indivisible one from the point of view of analysis. Again, no *C. elegans* investigator ever thinks genes act alone—they all recognize the need for the cellular and extracellular supporting environments. It will also be useful here to recall Brenner's perspicacious methodological comment (the full quote is on pp. 216–217 above) that "Behavior is the result of a complex and ill-understood set of computations performed by nervous systems and it seems essential to decompose the problem into two: one concerned with the question of the genetic specification of nervous systems and the other with the way nervous systems work to produce behavior" (Brenner 1974). Investigators such as Bargmann's, Lockery's, and Rankin's groups pursue primarily functional investigations: examining the adult neural circuits and components of them to ascertain what the parts are that are necessary components of behaviors, as well as how the parts are connected. Chalie's group has investigated both functional and developmental issues in connection with touch circuit neurons. Thus these two aspects of a simple organism's behavior can be conceptually teased apart and investigated.

27. Rosenberg would surely disagree, and see Stent's point as supporting philosophical instrumentalism, but I do not believe that Stent would draw such an inference.

Unpredictability. *C. elegans* investigators deny a strong unpredictability thesis, but seem to accept the likelihood of some stochasticity, both in development and in analysis of function (*rule 5*). They also accept the many-many thesis (see Lewontin and thesis 2 above, p. 212) that follows from *rules 1–4* above. The stochasticity is apparently filterable out using populations and averaging, and occasionally employing standard statistical methods (for an example, and additional references, see Bargmann et al. 1993 525–526). *C. elegans* researchers also deny any strong emergentist claim, but that is an issue that deserves its own treatment, and it is to that that I turn in the following section.

Thus the assessment of the Developmentalist Challenge's core concepts is a mixed one. Two of the developmentalists' core concepts, contextualism and nonpreformationism, are accepted as warranted, and are utilized. Three are denied: parity (but only heuristically and epistemically), indivisibility, and unpredictability (and, a fortiori, emergence).

6. Genes, Simplification, and Reduction. In the previous section, I considered the implications of the analysis of a simple biological system for five core concepts of the Developmentalist Challenge. Here I broaden the approach to examine more philosophical themes concerning what the analysis thus far indicates about the nature of *explanation* of behavioral traits. Any explanations of general aggregative properties, such as behavioral traits, raise the question of emergence and, correlatively, the issue of reduction.

The discussion in this section ties the philosophical results of the analysis of the Developmentalist Challenge back into more traditional debates about reduction and emergence. The views delineated here are, by necessity, presented quite tersely, but I think correctly, and without bias. More nuanced analysis will have to wait on later essays. Suffice it to say that the following compressed discussion leads through an account of *why* the antireductionist consensus is at least partially correct, to ways in which computational complexity encountered in *C. elegans*, and represented in the eight rules of Table 1 above, may still yield some useful determinations of the effects of genes on behavior.

6.1 Explanation, Reduction, and Explanatory Extensions. If there is a single pervasive theme that ties together the 8 rules summarized at the end of Section 4, it is that there is no *simple* explanatory model for behavior even in simple organisms. What *C. elegans* presents us with is a tangled network of influences at genetic, biochemical, intracellular, neuronal, muscle cell, and environmental levels. The analyses are, however, not simply descriptive accounts of the worm's behavioral repertoire: the *C. elegans* researchers cited are attempting to provide *expla-*

nations of those behaviors. Here I will not attempt to even sketch the enormous literature on scientific explanation that has occupied the attention of philosophers of science for the past fifty years; for that see Kitcher and Salmon 1989 and for my own views my 1993. At this point I will mainly focus on some of the proposals made by Kitcher about reduction and on his notion of an "explanatory extension" to introduce the issue of simplifications. I will argue that the issue of simplifications, the conditions that warrant them, and the heuristics that scientists may use to detect them, are critically important considerations in behavioral genetics.

It might do well to briefly background the discussion of Kitcher on reduction by noting that an antireductionist consensus of sorts has developed over the past twenty years among philosophers of biology (Waters 1990; Rosenberg 1994, 1997) that is critical of earlier work on reduction (see Nagel 1961, Schaffner 1967). In my view, some aspects of that consensus are warranted and other are not well-supported by either biology or sound philosophical argument. In this paper I will not review those complex arguments (but see Waters 1990, Rosenberg 1994, and my 1993, esp. Ch. 9), but do want to stress that the general approach to theory structure and explanation I favor in biology, that stems from my 1980 essay, emphasizes the importance of interlevel causation that is consistent with many of the themes on the Developmentalist Challenge. My (1993, esp. 487–500) extends this interlevel and causal approach to issues involving reduction, indicates the limits it places on classical theory reduction, and also emphasizes the importance of the concept of partial and fragmentary reduction.

Interestingly, one of the more developmentalist-oriented treatments of explanation and reduction can be found in several of Kitcher's articles, in spite of the fact that Sterelny and Kitcher's "Return of the Gene" article (1988) has been strongly criticized by Gray (1992) writing as a developmentalist. In his 1984 essay that is widely recognized as a forceful statement of an "antireductionist" position (e.g., see Rosenberg 1994, 40–54), Kitcher does suggest that there is a *weaker surrogate* of sorts for the reductionist's global relation between theories, though it only holds "between special fragments of these theories" of classical and molecular genetics.[28] This weaker surrogate is the concept of an 'explanatory extension'. In two later publications, Kitcher (1989) and Culp and Kitcher (1989) have elaborated further on this notion. An explanatory extension was characterized as follows: "a theory T′ pro-

28. In this section I do not discuss the very complex arguments regarding reduction and theory construction in biology developed in Kitcher's articles, but see my 1993, Ch. 6 and 9.

vides an *explanatory extension* of a theory T just in case there is some problem-solving pattern of T one of whose schematic premises can be generated as the conclusion of a problem-solving pattern of T′ " (1984, 365). In his 1989, Kitcher again affirms this recommendation, stating that "the outmoded concept of reduction, which is tied to an inadequate account of scientific theories, should be replaced with the notion of an explanatory extension, and disputes about the virtues of reductionism reformulated accordingly" (1989, 448). Similarly, Culp and Kitcher write "the intertheoretic relationships that philosophers have often tried to describe in terms of reduction are best reconceived in terms of the embedding of the problem-solving schemata of one field of science in those of another" (1989, 479).

Especially relevant to our concerns in this paper is *why* the notion of an explanatory extension is weaker than a relation of global reductionism. I believe Kitcher's answer to the question points the way toward the most appropriate interpretation of how genes function in the explanation of behavior. Kitcher notes in his 1984 that when we compare classical and molecular explanations of phenotypes, we can sometimes, as in the molecular explanation of sickle cell anemia by a point mutation, discern what appears to be a reduction—an apparently complete explanation of the tendency of a red blood cell containing a mutant hemoglobin (with an amino acid substitution of *glu* → *val* at the β6 position) to "sickle" under conditions of low oxygen tension. But this, Kitcher adds, is misleading, because "in effect, one concentrates on the *differences* among the phenotypes, takes for granted that in all cases development will proceed normally to the extent of manufacturing erythrocytes—which are, to all intents and purposes, simply sacks for containing hemoglobin molecules—and compares the difference in chemical effect of the cases in which the erythrocytes contain different molecules. *The details of the process of development can be ignored.* However it is rare for the effect of a mutation to be so simple." Generally, Kitcher adds in considering the limits of an explanatory extension, that even by confining our attention to molecular explanations of classical genetics "it would be folly to suggest that the extension is provided by molecular genetics alone" (1984; in Sober 1994, 395).

Thus Kitcher raises a view *akin* to the developmentalist position, that an account citing genes per se will not suffice for an explanation (of much of anything). I believe there are, however, important differences between Kitcher's view and the Developmentalist Challenge, reflecting at least implicit denials of their theses of indivisibility, unpredictability, and emergence (for Kitcher's specific views on Lewontin's version of the Developmentalist Challenge, see Kitcher in press). In point of fact, Culp and Kitcher (1989) provide an outline of a simple

hierarchy of molecular biological questions, as well as an *expanded* hierarchy, in which (parts of) developmental biology are explicitly cited (1989, 467, Figure 2). It is through such an expanded hierarchy that a complete explanation of biological traits becomes possible, at least in principle. But to reemphasize my main point, the issue that Kitcher raises for us, and which I believe will continue to concern behavioral geneticists generally, is whether the kinds of *simplifications* found in the sickle cell anemia example are to be found in the behavioral area.

6.2 Explanation and Simplifications. We have seen in the account given above of *C. elegans*' behaviors, that there will only be rare instances in which a single gene type is closely tied to a single type of behavior. The *odr-7* gene was introduced as representative of that kind of example, and can serve as the exemplar of what kinds of "gene for" explanations molecular behavioral genetics can warrant. Recall that even though this example was taken to the molecular level regarding the type of protein and its receptor function, *no circuit for chemotaxis* is yet available, in the context of which the role of the product of the *odr-7* gene would become a *more* sufficient type of explanation of a behavior. This example suggests that the kind of explanations molecular behavioral genetics will provide for behavior in the foreseeable future are *causal-sketch explanations*. By this term I mean that the criteria for a necessary condition explanation have been met, in the sense that appropriate controls have been identified and gene localization and expression confirmed, but no complete causal chain with identified intermediates has yet been delineated. Thus the pathway from gene to behavior is "gappy." In a sense, this feature was what I believe Stent was getting at with his term "instrumental" discussed above. Furthermore, the criteria for a claim that warrants terming a single gene "a necessary condition" requires the identification of a simplified isolated and localized pattern of causal influence within an otherwise complex system. Such simplifications are possible, and when found are likely to be highly prized. How such simplifications may be identified is the final question to which I turn in this paper.

6.3 Heuristics for Obtaining Simplifications Leading to Behavioral Genetic Explanations.

6.3.1 Common Pathways. It seems to me that even within a complex system of the genetically influenced neural networks described for *C. elegans* and *Drosophila*, there are two or three ways in which causal simplification may occur that may result in something close to a single-gene or only a few genes ("oligogenetic") explanation of a type of behavior. One simplification, that can also perhaps provide points of

potential intervention, occurs when a "common pathway" emerges. This is usually referred to as a "*final* common pathway" in medical and physiological etiology, in which many different parallel-acting weak causal factors (often termed "risk factors") can coalesce in a funneling toward a common set of outcomes. An example from infectious medicine is the pathogenetic mechanism by which the tuberculosis bacterium acts in a susceptible host after parallel risk factors predispose the host to infection (Fletcher, Fletcher, and Wagner 1982, 190). However, investigators probably need to be attentive to the possibility of common pathways emerging at *any* stage (early, intermediate, and final) in the temporal evolution of a reticulate network involving multiple causes and complex "crosstalk."[29] Determining the effects of factors in complex networks is methodologically difficult and typically requires complicated research designs with special attention to controls.[30] The existence of a common pathway, perhaps a specific neural circuit with a specific set of metabolites, might permit intervention by manipulation of the metabolites in such a common pathway.[31]

6.3.2 Dominating Pathways. Another type of simplification that can emerge in a complex network of interactions is the appearance at any given stage of a *dominating* factor. Such a dominating factor exerts major effects downstream from it, even though the effects still may be weakly conditioned by other interacting factors.[32] I suspect that different neurotransmitters at different points in a complex system may be dominating factors. Manipulation of such a dominating factor may thus have major effects on the future course of the complex system, though such effects can be quite specific and affect only a small number of event types. Such factors are major leverage points that can permit interventions, as well as simpler explanations, which focus on such factors. The distinction between common pathways and dominant pathways is not always sharp: in a parallel system, the limiting case of a dominant pathway will be a common pathway.

29.The term "crosstalk" for complex regulatory interactions is used by Egan and Weinberg in their description of the *ras* signaling network (1993, 783).

30.See my 1993, esp. 142–152 for a discussion of this type of problem.

31.It might be that focus *only* on common pathways could lead to an overly simplistic, reactive, and reductionistic approach to health care, and to a downgrading of more complex "risk factor" types of influences. For cautionary comments along these lines, see Rose 1995.

32.It is possible that some of the work on temperament might reflect such a dominating factor/gene, or it may be that this is such a broad "phenotype" that generalizations in this area reflect many different factors. (See Kagan 1994 for an account of this research area.)

Whether such dominating factors exist, as well as whether any common pathways exist, is an empirical question to be solved by laboratory investigation of specific systems. This is, in point of fact, where the power of model organisms is likely to become most evident.[33] Carrying out an investigation in an organism several orders more complex than *C. elegans* becomes considerably more difficult. One might hazard a guess that the difficulty may increase exponentially with the numbers of genes and neurons. The prospects of recognizing highly specific single gene and single neuron effects in complex organisms is likely to be accomplished only if highly homologous and strongly conserved genes can be identified in much simpler model organisms. Such identifications can give us powerfully directive hints where to look for such genes in more complex organisms, and may help begin to characterize dominating factors or common pathways.[34] As in connection with the behaviors of even simple organisms such as *C. elegans* and *Drosophila*, however, the answer thus far appears to be that dominating factors and common pathways will be rare.[35]

6.3.3 Bechtel and Richardson on Decomposition and Localization. Isolating and localizing causal pathways in complex systems—possibly including what I have called common and dominating pathways—is a goal that Bechtel and Richardson set themselves in their recent (1993) book on *Discovering Complexity*. In their 1993 monograph, Bechtel and Richardson state that one of their aims is to understand how to arrive at mechanistic explanations in the context of "complex systems in biology" (1993, 17). Their main strategy is to examine how far what they refer to as two heuristics (or guiding principles) can take them in formulating "mechanistic" explanations. These two heuristics are what they call "decomposition" and "localization." Roughly, decomposition means that an investigator can divide up the system of interest into separate subprocesses. In their words, decomposition "assumes that one activity of a system is the product of a set of subordinate functions performed in the system . . . , that there a small number of such functions, . . . and that they are minimally interactive" (1993, 23).

33.I thank Sally Moody for the suggestion that this point needs emphasis here.

34.A good example of the utility of model organisms is the discovery of the DNA repair gene in humans, termed hMSH2, that is strikingly similar to the MutS gene in *E. coli* and to the MSH2 gene in the eukaryotic yeast *S. cerevesiae* (see Schaffner and Wachbroit 1994 for a discussion).

35.Bargmann takes a more optimistic view and believes not only that dominating factors will become evident as research proceeds, but that "dominant genes will be quite common in behavior once we succeed in breaking behavior down into small precisely defined components" (personal communication, August 1995).

Localization means that the investigator can point to the component parts (in the cell or in the brain, for example) where these subprocesses occur. That is, localization "is the identification of the different activities proposed in the task decomposition with the behavior or capacities of specific components" (1993, 24). These guiding principles of decomposition and localization work well in some contexts, and Bechtel and Richardson (1993, 72–92) provide examples of Wieland's localization of cell respiration in dehydrogenase enzymes, and Warburg's competing localization of respiration in membrane iron. But as Bechtel and Richardson proceed through a number of rich examples of increasing complexity, they eventually come to systems where decomposition and localization "fail" (172, 199–201, 228). Of special interest to us is Bechtel and Richardson's claim that decomposition and localization fail when they are applied to "'emergent' phenomena in interconnected networks," represented, for example, by connectionistic neural nets (and also by genetic regulatory networks of the type investigated by Kauffman 1993).

6.3.4 Neural Networks Redux. Now a claim of the failure of the decomposition heuristic would *seem* to support the *indivisibility* theme we encountered earlier in the Developmentalist Challenge, but Bechtel and Richardson are more subtle than some thinkers of the developmentalist persuasion. They argue that though decomposability (and near decomposability) would be "hopeless, or even misguided" as applied to interconnected networks (202), nonetheless "there is a clear sense in which . . . [network models] are mechanistic . . . [: t]he behavior of the system is a product of the activities occurring within it" (228). Such networks validate the concept of "emergent" properties, but "without waxing mysterious" (229). They add, underscoring the innocuous character of *this* notion of emergence that "in calling the systemic properties of network systems emergent, we mark a departure from the behavior of simpler systems and indicate that traditional mechanistic strategies for understanding neural network systems may simply fail. But the behavior of the systems is not unintelligible or magical: it follows from the nature of the connections between the components within the system" (229).

Using a neural network approach, then, according to Bechtel and Richardson, is not obviously a *simplification* strategy, which is how I tend to view their heuristics of decomposition and localization. And, perhaps it needs to be emphasized that the networks discussed by Bechtel and Richardson are actually far simpler than the neural networks found in *C. elegans*—not in terms of numbers of network connections, but in terms of the inner complexities of the neurons, the effects of gene

products on the neurons, the types of synapses, and the effects of short- and long-term environmental influences. In spite of this complexity of the real biological system, for *C. elegans* researchers a kind of near decomposability also seems to hold, in that various neural circuits are isolable (though they overlap) *within C. elegans,* and they are analyzable using standard neuroscience tools. Thus behavior is explicable in terms of the interacting parts, and these neural networks offer one of the most promising keys to explaining behavior.

There is a sense, however, in which Bechtel and Richardson do acknowledge that even a network approach, as powerful as it may be in explaining complex behaviors, may fail to yield any type of mechanistic explanation and become "mysterious." They write that "We may not be able to follow the processes through the multitude of connections in a more complex system, or to see how they give rise to the behavior of the system. We may fail in the attempt to understand such systems in an intuitive way" (229). It is at this point that Bechtel and Richardson's position appears to merge with Rosenberg's (1985, 1994) anti-reductionist view: as a *pragmatic* failure of human intellect. Whether *C. elegans* researchers will encounter this problem, or if they do not, whether it will be met in *Drosophila*, or in mice, or in humans, is only food for important speculation at present. It is possible, however, as even Rosenberg (1985) seems to admit, that increasingly powerful computers and software will enable scientists to manage and deal with this complexity, should behavioral neuroscience begin to enter this "mysterious" realm.

7. Summary and Conclusion; Implications for Human Behavioral Genetics. In this article I have examined a simple organism, *C. elegans*, for the light that it can throw on the contentious area of behavioral genetics. Some of the debate about the roles that genes play in phenotypic trait production centered on what I characterized as the Developmentalist Challenge. In examining that simple system that we know the most about concerning the relations between genes and behavior, it became evident, I believe, that there is no simple type of genetic explanation for behavior: a tangled network with all of the complexities summarized in the eight "rules" given in Table 1 is the default vision, even in this simplest of model organisms. But several of the claims of the Developmentalist Challenge were questioned, among them the *indivisibility* and *unpredictability* theses. In addition, a thesis of *emergence*—at least in any strong and "mysterious" sense—was also viewed as not supported. The *parity* thesis was given a somewhat complex reading: genes are special, but are at best "necessary condition explainers," and genes, through the analysis of mutations, offer pow-

erful tools for investigating behavior. The article closed with a brief examination of philosophical investigations of explanations and reductions that employ genes as explanatory factors, and considered some of the ways that simplifications of the tangled network might be detected that would provide simple "gene-behavior" explanations.

It would be well to recall at this point that much of the debate about behavioral genetics takes place against a complex social policy backdrop, such as we have witnessed recently in the debate about *The Bell Curve.* Currently, a series of debates is underway as to how best to utilize the burgeoning amount of genetic information regarding humans.[36] Many thoughtful scholars have argued that *genetic* information is a *very special kind* of information, and must have carefully crafted safeguards put in place so as not to violate individuals' privacy, discriminate against them, or reinforce ethnic and racial stereotypes.[37] Behavioral traits are especially suspect in this connection, in no small way because of the horrific history of eugenics, including sterilization practices in the U.S., and the Holocaust under the Nazis, where various behavioral traits including so-called "feeble-mindedness" and sexual orientation were targeted by these programs. Several writers have warned about a new form of eugenics that may be developing based on the advances of the Human Genome Project.[38]

Critics of the more classical forms of behavioral genetics, including Lewontin 1993, 1995 and Wahlsten 1990, among many others, address this social context explicitly—frequently in considerable depth. Wahlsten, for example, wrote at the conclusion of his generally technical article questioning the applicability of the heritability concept in both animal and human genetics that "many of the founders of human behavioral genetics were committed to a program of eugenics. The only practical application of a heritability coefficient is to predict the results of a program of selective breeding" (1990, 119). Other behavioral ge-

36. These debates have already generated a rapidly growing literature. For excellent examples, see the anthologies edited by Kevles and Hood 1992, Annas and Elias 1992, Murphy and Lappé 1994, and Kitcher 1996a. Much of this work is supported by the U.S. National Institutes of Health's National Center for Human Genome Research, through its Ethical, Legal, and Social Implications of genetics program (ELSI), and also through the Department of Energy's counterpart ELSI program.

37. Arguments for the special character of genetic information, as distinct from other biomedical information, are made by, among others, Annas, Glantz, and Roche 1996 and by Wikler (in press). To some extent, these arguments parallel the discussion about parity of genetic (and DNA) explanations above.

38. See Duster 1990, King 1992, and Paul 1994. Kitcher's initially somewhat optimistic 1996a position now seems less plausible to him, as indicated in his recent review (1996b) of LeVay's 1996.

neticists disagree with this view (Plomin et al. 1994), but it would take me well beyond the scope of this paper to consider the pros and cons of these arguments (see Sarkar forthcoming, esp. Ch. 5, and Falconer and Mackay 1996, Chs. 8–10). In the full account I presented of the Developmentalist Challenge in Section 2, the critics of behavioral genetics, including Gottlieb and Lewontin, formulate their objections as powerful methodological objections that are synergistic with their more general criticisms of the special character of genetic explanations.

An important new dimension of the debate about human behavioral traits arises because we are now being barraged by a number of claims about molecularly-identified "genes for" these traits. Classical behavioral genetics is population based, i.e. , based on twin and adoption studies. This represents a weakness, in the sense that though such studies are valuable they "do not tell us anything about how many or which genes are important, let alone how genes affect behavior" (Greenspan et al. 1995, 557). However that weakness is also a social safeguard against being able to identify individuals (but perhaps, unfortunately, not necessarily groups[39]) as possessing a specific genetic endowment. But we are now moving to a new molecular phase in which *individuals* can be tested for *specific genes* that, it is claimed, can account for at least some of their behavior.

At present, there are only a few candidates for *molecularly* characterized human behavioral genes, among them are the novelty seeking gene reported in two articles in early 1996 in *Nature Genetics* (Ebstein et al. 1996; Benjamin et al. 1996), and the MAOA mental retardation/impulsivity gene based on two studies by Brunner et al. (1993a, b) (but see also the valuable critique of the generalizable implications of this work by Brunner 1996). In addition, there is the homosexuality genetic work that has largely been based on Hamer's studies (Hamer et al. 1993, Hu et al. 1995). More recently, an allele that influences anxiety-related traits (neuroticism) has been reported (Lesch et al. 1996). Whether these results will continue to hold up in replication studies, and whether a notion of genetic influence on human behavior can be defended against complex, and perhaps overriding, psychosociocultural conflators, is a topic for another essay at another time.[40] Suffice

39. Imputing a trait to a group can not only lead to discrimination that can affect individual members of that group; it can also easily be based on a conflation of genetic and environmental causes. For an example that is as amusing as it is a warning, compare Lander and Shork's cautionary account (1994, 2041) of the association of the allele HLA-A1 with the ability to use chopsticks (in an Asian population in San Francisco).

40. More recent attempts to replicate the novelty-seeking gene association have in fact failed to confirm it. See Pogue-Geile et al. 1998 for one such example and additional references.

it to say that nothing in the account developed for simple systems above implies the *impossibility* of finding one or a few genes in more complex organisms, including *Homo sapiens*, that may have a strong effect on behavior. I suspect, however, that these strong effects will be more evident in the cases of *general derangements*—perhaps including schizophrenia and bipolar disorder. This would be similar to the types of physical behavioral changes we encounter in neurotransmitter-based disorders such as Parkinson's disease. Normal personality genetic research may also discover some *diffuse* effects on behavior, much as Prozac and other neurotransmitter-affecting substances influence behaviors, including personality (in some cases). I do not believe, however, that such effects will have sufficient specificity to guide any social programs that might seek to ameliorate social ills involving such complex behaviors as criminal activity.

This is because the complexities involving tangled neural systems, and the roles of environmental influences on both development and function, generally make the likelihood of single genetic or oligogenetic effects quite small, if not undetectable. There are, thus, some important morals that follow from the account presented above of *C. elegans*—the simplest multicellular organism that exhibits rudimentary forms of behavior, possesses a nervous system, and in which we can trace the relations between genes and behavior. The principal take-home lesson here is that genes act in a complex interactive concert and *through* nervous systems, systems that are significantly influenced by development, and exhibit short- and long-term learning that modifies behavior. The environment plays critical roles in development and also in which genes are expressed and when. Characterizing simple "genes for" behaviors is, accordingly, a drastic oversimplification of the connection between genes and behavior, *even when we have the (virtually) complete molecular story.* The melody of behavior represents no solo performance – it is outcome of an extraordinarily complex orchestra—and one with no conductor.

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