Environmental and Behavioral Influences on Gene Activity

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Abstract

The central dogma of molecular biology holds that "information" flows from the genes to the structure of the proteins that the genes bring about through the formula DNA → RNA → protein. In this view, a set of master genes activates the DNA necessary to produce the appropriate proteins that the organism needs during development. In contrast to this view, probabilistic epigenesis holds that necessarily there are signals from the internal and external environment that activate DNA to produce the appropriate proteins. To support this view, I review a substantial body of evidence showing that external environmental influences on gene activation are normally occurring events in a large variety of organisms, including humans. This demonstrates how genes and environments work together to produce functional organisms, thus extending the model of probabilistic epigenesis.

Keywords

central dogma; probabilistic epigenesis; predetermined epigenesis

A virtual revolution that has taken place in our knowledge of environmental and behavioral influences on gene expression has not yet seeped into the social sciences in general and the behavioral sciences in particular. Earlier, it was not recognized that environmental and behavioral influences play an important role in triggering gene activity. Paradoxically, in biology there is an explicit dogma, formulated as such, that does not permit environmental influences on gene activity: the central dogma of molecular biology, first enunciated by Crick in 1958.

Although the central dogma may seem quite remote from psychology, I think it lies behind some psychological and behavioral theories that emphasize the sheerly endogenous (internal) development of the nervous system and early behavior (e.g., Elman et al., 1996) and the "innate foundation of the psyche" (e.g., Tooby & Cosmides, 1990), independent of experience or functional considerations. Such theories follow from the essentially dichotomous view that genes and other endogenous factors construct part of the organism and environment determines other features of the organism. The present essay is an attempt to show how genes and environment necessarily cooperate in the construction of organisms, and specifically, to show how genes require environmental and behavioral inputs to function appropriately during the normal course of individual development.

THE CENTRAL DOGMA

The central dogma asserts that "information" flows in only one direction from the genes to the structure of the proteins that the genes bring about. The formula for this information flow is DNA → RNA → protein. (Messenger RNA, or mRNA, is the intermediary in the process of protein synthesis. In the lingo of molecular biology, the process by which RNA is formed from the DNA template is called transcription, and the process by which proteins are formed from the RNA template is called translation.) After retroviruses were discovered in the 1960s (in retroviruses, RNA reversely transcribes DNA instead of the other way around), Crick wrote a postscript to his 1958 article in which he congratulated himself for not claiming that reverse transcription was impossible: "In looking back I am struck not only by the brashness which allowed us to venture powerful statements of a very general nature, but also by the rather delicate discrimination used in selecting what statements to make" (Crick, 1970, p. 562). Any ambiguity about the controlling factors in gene expression in the central dogma was removed in a later article by Crick, in which he specifically said that the genes of higher organisms are turned on and off by other genes (Crick, 1982, p. 515). Figure 1 shows the central dogma of molecular biology in the form of a diagram.

THE GENOME ACCORDING TO CENTRAL DOGMA

The picture of the genome that emerges from the central dogma is one of (a) encapsulation, setting the genome off from influences above the genetic level (supragenetic influences), and (b) a largely feedforward (unidirectional) informational process in which the genes contain a blueprint or master plan for the construction and determination of the organism. In this

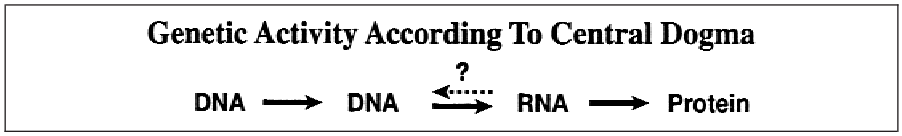

Fig. 1. The central dogma of molecular biology. The right-going arrows represent the central dogma. Retroviruses (represented by the left-going arrow from RNA to DNA) were not part of the dogma, but after their discovery, Crick (1970) said they were not prohibited in the original formulation of the dogma (Crick, 1958).

view, the genome is not seen as part of the holistic, bidirectional developmental-physiological system of the organism, responsive to signals from internal cellular sources such as the cytoplasm of the cell or to extracellular influences such as hormones, and the genome is seen as certainly not responsive to influences from outside the organism, such as stimuli or signals from the external environment.

In this essay, my goal is to show that the normally occurring influences on genetic activity include influences from the external environment, that is, to demonstrate that the genome is not encapsulated and is in fact a part of the organism's general developmental-physiological adaptation to environmental stresses and signals: Genes express themselves appropriately only in responding to internally and externally generated stimulation. Further, in this holistic view, although genes participate in the making of protein, protein is also subject to other influences, and protein must be further stimulated and elaborated to become part of the nervous system (or other systems) of the organism. Thus, genes operate at the lowest level of organismic organization, and they do not, in and of themselves, produce finished traits or features of the organism. The organism is a product of epigenetic development, that is, a process that involves not only the genes but also many other supragenetic influences. Because this latter point has been the subject of numerous publications (reviewed in Gottlieb, 1992), I do not deal with it further here, but, rather, restrict this essay to documenting that the activity of genes is regulated in just the same way as the rest of the organism, being called forth by signals from the normally occurring external environment, as well as the internal environment. Although this fact is not well known in the social and behavioral sciences, it is surprising to find that it is also not widely appreciated in biology proper (Strohman, 1997). In biology, the external environment is seen as the agent of natural selection in promoting evolution, not as a crucial feature of individual development. Many biologists subscribe to the notion that "the genes are safely sequestered inside the nucleus of the cell and out of reach of ordinary environmental effects" (Wills, 1989, p. 19).

FROM CENTRAL DOGMA OF MOLECULAR BIOLOGY TO PROBABILISTIC EPIGENESIS

As can be seen in Table 1, a number of different naturally occurring environmental signals can stimulate gene expression in a large variety of organisms from nematodes to humans. To understand the findings summarized in Table 1, the nongeneticist needs to know that there are three levels of evidence of genetic activity in the right-hand column of Table 1: protein expression or synthesis, mRNA activity, and genetic activity itself. As the middle column of the table shows, there are important environmental and behavioral signals affecting genetic activity, even though the activity of the genes is quite remote from these stimuli. After proteins are made, many factors must intervene before neurons or behaviors are realized; the route from protein to neuron or behavior is not direct. The fact that normally occurring environmental events stimulate gene activity during the usual course of development in a variety of organisms means that genes and genetic activity are part of the developmental-physiological system and do not stand outside of that system.

The main purpose of this essay is to place genes and genetic activity firmly within a holistic developmental-physiological framework, one in which genes not only affect each other and mRNA but are affected by activities at other levels of the system, up to and including the external environment. This holistic developmental system of bidirectional, coacting influences is captured schematically in Figure 2. In contrast to the unidirectional and encapsulated genetic predeterminism of the central dogma, a probabilistic view of epigenesis holds that the sequence and outcomes of development are probabilistically determined by the critical operation of various stimulative events that occur both within and outside the organism.

The probabilistic-epigenetic framework presented in Figure 2 not only is based on what we now know about mechanisms of individual development at all levels of analysis, but also derives from our understanding of evolution and natural selection. Natural selection serves as a filter and preserves reproductively successful phenotypes (outcomes of development). These successful phenotypes are a product of individual development, and thus are a consequence of the adaptability of the organism to its developmental conditions.

Table 1. *Normally occurring environmental and behavioral influences on gene activity*

Species	Environmental signal or stimulus	Resulting alteration
Nematodes	Absence or presence of food	Diminished or enhanced neuronal *daf-7* gene mRNA expression, inhibiting or provoking larval development
Fruit flies	Transient elevated heat stress during larval development	Presence of proteins produced by heat shock and thermotolerance (enhanced thermal regulation)
Fruit flies	Light-dark cycle	Presence of PER and TIM protein expression and circadian rhythms
Various reptiles	Incubation temperature	Sex determination
Songbirds (canaries, zebra finches)	Conspecific song	Increased forebrain mRNA
Hamsters	Light-dark cycle	Increased pituitary hormone mRNA and reproductive behavior
Mice	Acoustic stimulation	Enhanced c-*fos* expression, neuronal activity, and organization of the auditory system
Mice	Light-dark cycle	c-*fos*-induced mRNA expression in hypothalamus, circadian locomotor activity
Rats	Tactile stimulation	Enhanced c-*fos* expression and increased number of somatosensory (sense of touch) cortical neurons[a]
Rats	Learning task involving vestibular (balance) system	Change in nuclear RNA base ratios in vestibular nerve cells
Rats	Visual stimulation	Increased RNA and protein synthesis in visual cortex[a]
Rats	Environmental complexity	Increased brain RNA diversity
Rats	Prenatal nutrition	Increase in cerebral DNA (increased number of brain cells)
Rats	Infantile handling, separation from mother	Increased hypothalamic mRNAs for corticotropin-releasing hormone throughout life
Cats	Visual stimulation	Increased visual cortex[a] RNA complexity (diversity)
Humans	Academic examinations taken by medical students (psychological stress)	Reduced mRNA activity in interleukin 2 receptor (immune system response)

Note. mRNA = messenger RNA; PER and TIM are proteins arising from activity of *per* (*period*) and *tim* (*timeless*) genes; activity of c-*fos* genes leads to production of c-FOS protein. References documenting the findings listed can be found in Gottlieb (1998, Table 2).
[a]Cortex is the outer covering of the brain, or gray matter.

Therefore, natural selection has preserved (favored) organisms that are adaptably responsive to their developmental conditions, both behaviorally and physiologically. Organisms with the same genes can develop very different phenotypes under different developmental conditions, as witness the identical twins shown in Figure 3. These men were raised in different homes and developed striking physical, behavioral, and psychological differences, despite their identical genomes.

Because the probabilistic-epigenetic view presented in Figure 2 does not portray enough detail at the level of genetic activity, it is useful to flesh that out, to show how it differs from the previously described central dogma of molecular biology. As shown in Figure 4, the original central dogma explicitly posited one-way traffic—DNA → RNA → protein—and was silent about any other flows of information (Crick, 1958). The bottom of Figure 4 illustrates probabilistic epigenesis, which is inherently bidirectional in the horizontal and vertical levels (Fig. 2). Thus, this diagram has information flowing not only from RNA to DNA, but from protein to protein and from DNA to DNA. The only relationship that is not yet supported is protein → RNA, in the sense of protein altering the structure of RNA, but there are other influences of protein on RNA activity (not its structure) that would support such a directional flow. For example, a process known as *phosphorylation* can modify proteins so that they activate (or inactivate) other proteins (protein → protein), which, when activated, trigger rapid production of mRNA (protein → RNA activity). When mRNAs are transcribed by DNA, they do not nec-

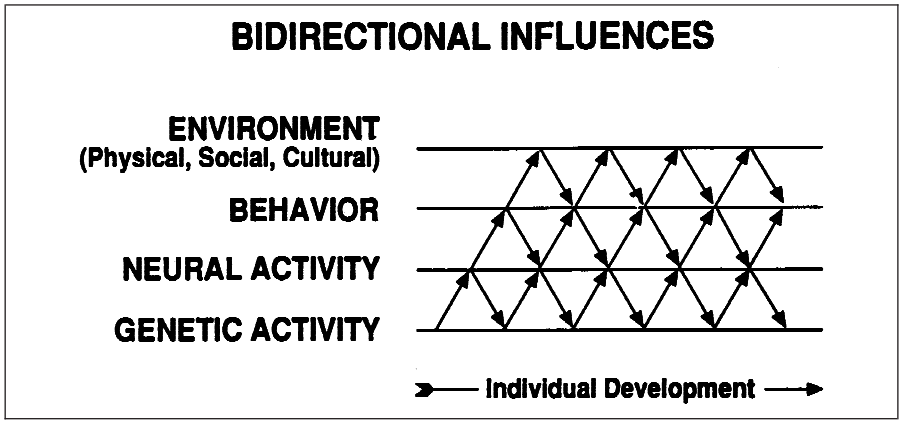

Fig. 2. The probabilistic-epigenetic framework. The diagram depicts the completely bidirectional and coactive nature of genetic, neural, behavioral, and environmental influences over the course of individual development. From *Individual Development and Evolution: The Genesis of Novel Behavior* (p. 152), by G. Gottlieb, 1992, New York: Oxford University Press. Copyright 1992 by Oxford University Press, Inc. Reprinted with permission.

essarily become immediately active but require a further signal to do so. The consequences of phosphorylation could provide that signal (protein → protein → mRNA activity → protein). A process like this appears to be involved in the expression of "fragile X mental retardation protein." This protein is produced as described under normal conditions but is missing in the brain of fragile X mental retardates; thus, fragile X mental retardation represents a failure of gene (or mRNA) expression rather than a positive genetic contribution.[2]

CONCLUSIONS

The central dogma lies behind the persistent trend in biology and psychology to view genes and environment as making identifiably separate contributions to the phenotypic outcomes of development. Quantitative behavior genetics (the study of the heritability of behavior when one does not know how many or which genes are correlated with a given trait) is based on this erroneous assumption. Although genes no doubt play a constraining role in development, the actual limits of these constraints are quite wide and, most important, cannot be specified in advance of experimental manipulation or accidents of nature. There is no doubt that development is constrained at all levels of the system (Fig. 2), not only by genes and environments.

Finally, I do hope that the emphasis here on normally occurring environmental influences on gene activity does not raise the specter of a new, subtle form of "environmentalism." I do not think I would be labeled an environmentalist if I were to say organisms are often adaptably responsive to their environments. So, by calling attention to genes being adaptably responsive to their internal and external environments, I am not being an environmentalist but merely including genetic activity within the probabilistic-epigenetic framework that characterizes the organism and all of its constituent parts.

In view of the findings reviewed here, in the future it would be most important to eschew both genetic determinism and environmental determinism, as we now should understand that it is truly correct

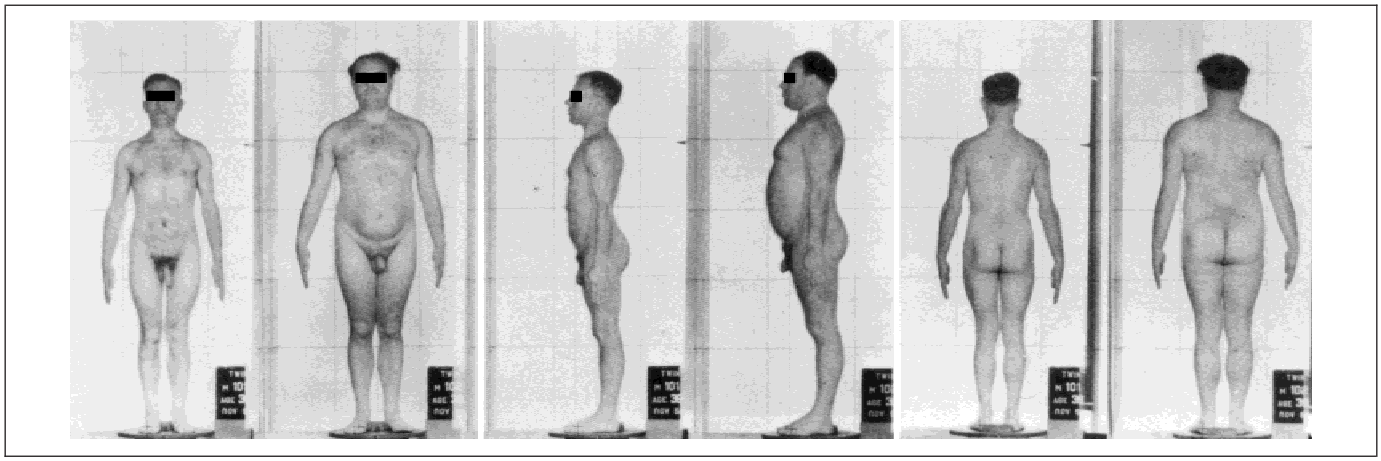

Fig. 3. Remarkable illustration of the enormous phenotypic variation that can result when monozygotic (single-egg) identical twins are reared apart in very different family environments from birth. From *Fetus Into Man* (p. 120), by J.M. Tanner, 1978, Cambridge, MA: Harvard University Press. Copyright 1978 by Harvard University Press, renewed 1989 by J.M. Tanner. Adapted with permission.

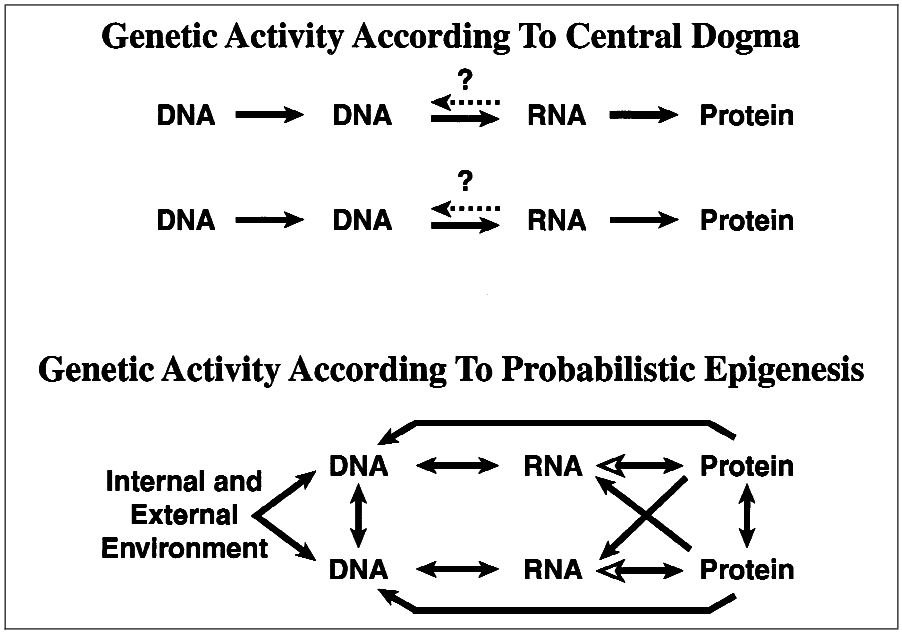

Fig. 4. Influences on genetic activity according to the central dogma (top) and probabilistic epigenesis (bottom). The filled arrows indicate documented sources of influence, and the open arrow from protein back to RNA indicates what remains a theoretical possibility in probabilistic epigenesis but is prohibited in the central dogma (as are protein ←→ protein influences). Protein → protein influences occur (a) when prions (abnormally conformed proteins) transfer their abnormal conformation to other proteins and (b) when, during normal development, proteins activate or inactivate other proteins (as in the case of phosphorylation, described in the text). The filled arrows from protein to RNA represent the activation of mRNA by protein (e.g., as a consequence of phosphorylation). DNA ←→ DNA influences are termed epistatic, referring to the modification of the expression of genes depending on the genetic background in which they are located. In the central dogma, genetic activity is dictated solely by genes (DNA → DNA), whereas in probabilistic epigenesis, internal and external environmental events activate genetic expression through proteins (protein → DNA), hormones, and other influences. To keep the diagram manageable, the fact that behavior and the external environment exert their effects on DNA through internal mediators (proteins, hormones, etc.) is not shown; nor is it shown that the protein products of some genes regulate the expression of other genes. (See the text for further discussion of this figure.)

(not merely a verbalism) to say that environments and genes necessarily cooperate in bringing about any outcome of individual development.

Recommended Reading

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Notes

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2. "Genetic" disorders, both mental and physical, often represent biochemical deficiencies of one sort or another due to the lack of expression of the genes and mRNAs needed to produce the appropriate proteins necessary for normal development. Thus, the search for "candidate genes" in psychiatric or other disorders is most often a search for genes that are not being expressed, not for genes that are being expressed and causing the disorders. So-called cystic fibrosis genes and manic-depression genes, among others, are in this category. The instances that I know of in which the presence of genes causes a problem are Edward's syndrome and trisomy 21 (Down syndrome), wherein the presence of an extra, otherwise normal, chromosome (18 and 21, respectively) causes problems. In some cases, it is of course possible that the expression of mutated genes can be involved in a disorder, but, in my opinion, it is often the lack of expression of normal genes that is the culprit.

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