Rethinking the Meaning of Genetic Determinism

EVELYN FOX KELLER

THE TANNER LECTURES ON HUMAN VALUES

Delivered at

The University of Utah
February 18, 1993

EVELYN Fox KELLER, who is currently a MacArthur Fellow, is Professor in the Program in Science, Technology, and Society at the Massachusetts Institute of Technology. She was educated at Brandeis University, Radcliffe College, and Harvard University, where she received her Ph.D. degree in physics in 1963. She has taught at Cornell, Northeastern, Northwestern, and New York universities, and at the University of Maryland and the University of California at Berkeley, among others, and was a member of Princeton's Institute for Advanced Study. In addition to her numerous published articles in the fields of mathematical biology, theoretical physics, and molecular biology, she has written widely on psychological, philosophical, historical, and feminist perspectives on the nature of scientific thought. Her books include *Secrets of Life, Secrets of Death* (1992), *Reflections on Gender and Science* (1985), and *A Feeling for the Organism* (1983), and she is the coeditor of *Keywords in Evolutionary Discourse* (in press), *Body/Politics: Women and the Discourses of Science* (1990), and *Conflicts in Feminism* (1990).

ABSTRACT: The term "genetic determinism" refers to a belief system that locates the cause of all biological development in an organism's genes: if we only knew enough about genes (about what they are and how they "act"), we could understand all of biology. Such beliefs — codified in what I call the "discourse of gene action" — have been of great importance to the history of genetics and, most recently, to the launching of the Human Genome Initiative. But what does it mean to attribute — or, for that matter, to deny — causal power to genes? Without question, this way of talking has been immensely productive to research in genetics, but it has also impeded the formulation of a conceptual framework adequate to the study of developmental phenomena. Today, with the dramatic resurgence of Developmental Biology as an independent discipline, the need for such a framework has become urgent.

Historians of biology routinely note that, for nineteenth-century biologists, the term "heredity" referred to both the "transmission of potentialities during reproduction *and* [the] development of these potentialities into specific adult traits." [1] The question that compelled their interests above all others was, as August Weismann put it in 1883, "How is a single germ cell capable of reproducing the entire body with all its details?" [2] However, a crucial change occurred in the early part of this century. With the rise of the new discipline of genetics, the two aspects of heredity (transmission and development) grew apart, and the term

[1] Gar Allen, "T. H. Morgan and the Split between Embryology and Genetics, 1910–1926," in T. J. Horder, I. A. Witkowski, and C. C. Wylie (eds.), *A History of Embryology,* p. 114.

[2] Quoted by Klaus Sander, "The Role of Genes in Ontogenesis — Evolving Concepts from 1883 to 1983 as Perceived by an Insect Embryologist," in Horder et al. (eds.), *History of Embryology,* p. 363.

"heredity" was redefined to refer exclusively to transmission. Henceforth, the study of transmission would become the province of genetics, while that of development remained the province of embryology.

These were two separate disciplines, with two different sets of concerns. In a passage from his 1926 book, *The Theory of the Gene,* T. H. Morgan described their relation as follows:

> Between the characters, that furnish the data for the theory and the postulated genes, to which the characters are referred, lies the whole field of embryonic development. The theory of the gene, as here formulated, states nothing with respect to the way in which the genes are connected with the end-product or character. The absence of information relating to this interval does not mean that the process of embryonic development is not of interest for genetics . . . but the fact remains that the sorting out of the characters in successive generations can be explained at present without reference to the way in which the gene affects the developmental process.[3]

Elsewhere the same year he cautioned that

> the confusion that is met with sometimes in the literature has resulted from a failure to keep apart the phenomenon of heredity, that deals with the transmission of the hereditary units, and the phenomena of embryonic development that take place almost exclusively by changes in the cytoplasm.[4]

Genetics provided a power methodology for tracking the transmission of differences among existing organisms, but it couldn't answer the question of how a single germ cell might produce an organism —that remained the province of embryology. Yet, even in the early days of genetics, when the gene was still merely an abstract concept, and the necessity of nuclear-cytoplasmic interactions clearly understood, geneticists took it for granted that these hypothetical particles, the genes, must somehow lie at the root of

[3] T. H. Morgan, *The Theory of the Gene,* p. 26.

[4] Ibid., p. 490.

development. If in some of his writings Morgan gave the impression of being ecumenical, granting to embryology a separate but equal disciplinary status, and a separate but equal object of study (the cytoplasm), at other times he was quite clear about the proper epistemological ordering of the two disciplines. Though he well recognized that geneticists could say nothing about what genes are, or how they were subsequently connected to the formulation of adult characters or traits, and little about how they interacted with the cytoplasm of the fertilized egg (the specifically maternal contribution), he nonetheless wrote in 1924, "it is clear that whatever the cytoplasm contributes to development is almost entirely under the influence of the genes carried by the chromosome, and therefore may in a sense be said to be indifferent. . . ." [5]

Others went even further. In an attempt to clarify Morgan's position, the geneticist R. A. Brink explained:

> The Mendelian theory postulates discrete, self-perpetuating, stable bodies —the genes —resident in the chromosomes, as the hereditary materials. *This means, of course, that the genes are the primary internal agents controlling development.* (my italics)

Brink described the great advantage of genetics over other approaches as follows:

> with the primary internal mechanism resolved into definite units which may be combined in various groups. . . . The hereditary complex need no longer serve merely as the passive object in physiological experimentation but may itself be varied in a precise fashion. . . . We are now in a favorable position to get at the dynamic properties of the hereditary mechanism by means of an analysis of the action of its separate elements. This, it seems to us, is the signal contribution which genetics makes to our outlook upon the problems of developmental physiology.[6]

[5] T. H. Morgan, "Mendelian Heredity in Relation to Cytology."

[6] R. A. Brink, "Genetics and the Problems of Development," *American Naturalist* 61, no. 574 (1927), 280–83.

To Morgan's student, H. J. Muller, the most remarkable characteristic of the gene was that it possesses the property he called "specific autocatalysis" (by which he meant self-replication). "Still more remarkable," he wrote, "the gene can mutate without losing its specific autocatalytic power." Largely for this reason, he entitled his own 1926 paper "The Gene as the Basis of Life" (it is said that he refused to change his title to "The Gene as *a* Basis for Life"). There he concluded:

> the great bulk . . . of the protoplasm [is], after all, only a by-product of the action of the gene material; its "function" (its survival-value) lies only in its fostering the genes, and the primary secrets common to all life lie further back, in the gene material itself."[7]

I do not know when the term "genetic determinism" first came into use — it is not a term used by geneticists themselves — but the concept of genes as primary and self-sufficient cause, the notion that it is our genes that determine our biological fate, is clearly already evident here in these writings.

Today it is hard to see what might be controversial in such claims. The attribution of agency, autonomy, and causal primacy to genes has become so familiar as to seem obvious, even self-evident. What I want to do, however, is attempt to dislodge that familiarity — by citing these arguments in their historical context, using the now somewhat quaint language in which they were first posed, to enable you to see them as novel and thereby to see something of the process by which they acquired their familiarity and ring of truth.

In 1926 genetics was still a relatively new discipline, struggling to establish itself against the established hegemony of embryology and physiology. Earlier in the country the rediscovery of Mendel and the identification of chromosomes as the carrier of genetic

[7] H.J. Muller, "The Gene as the Basis of Life," *Proceedings of the International Congress of Plant Sciences* 1 (Ithaca, 1926), 897–921.

material had marked the start of this new discipline; and by the mid-1920s the taming of *Drosophila* and corn as model organisms for tracking the transmission of hereditary traits lent it a rigor and productivity that other disciplines could scarcely match. But the first generation of geneticists — Morgan and his school — did more than develop the techniques and practice of genetics as a rival of embryology; they also forged a way of talking about genes — about their role and meaning in reproduction, growth, and development. When Muller identified the gene as *the* basis of life, he was claiming for it both ontological and temporal priority. First the gene, then the remaining protoplasm (i.e., the cytoplasm), appearing as a "by-product" whose only function is that of facilitating environment, to "foster" the gene. First the gene, then life — or rather, with the gene comes life. The concept of gene invoked here is Janus-faced: it is part physicist's atom and part Platonic soul; at one and the same time, fundamental building block and animating force. Only the "action" of genes can initiate the complex manifold of processes constituting a living organism.

But what exactly is it that genes *do?* This of course Muller, Brink, and Morgan could not say. The notion of "gene action" may even have been facilitated by the very absence of knowledge of what a gene is (in the sense that not knowing what a gene is may have made it easier to attribute to it any, even miraculous, properties). But even though these early geneticists could tell us nothing about the nature of the presumed source of all subsequent growth and development, could give no scientific account of "gene action," they offered future generations of geneticists something equally valuable.

Scientists usually assume that only their data and theories matter for scientific progress, that how they talk about these data and theories is irrelevant to their actual work, but here, in introducing this particular way of talking, the first generation of American geneticists provided a conceptual framework that was of

critical importance for the future course of biological research. To capture both its rhetorical and conceptual force, I will call this way of talking the "discourse of gene action" —a discourse that was, for genetics, undeniably productive. It enabled geneticists to get on with their work without worrying about their lack of information about the nature of such "action" —to a considerable degree, it even obscured the need for such information. (Throughout the interwar period American geneticists routinely invoked the notion of "gene action" as if its meaning was self-evident.) At the same time, the attribution of agency, autonomy, and causal responsibility to genes lent primacy both to the object of geneticists' concern and to the discipline of genetics —in their own eyes and in the eyes of others. They were dealing with *the* basis of life. If, as Brink wrote, the hereditary complex is elevated from a "passive object" to a locus of primary activity, the student of that hereditary complex is, by the same move, also elevated to primary activity.

Indeed, I suggest that the discourse of gene action provides the specific hallmark (or trademark) of the American school of Morganian genetics, especially of its approach to development. If its first use was to bracket the question of development, later, in the mid-1930s, when a number of American geneticists did turn their attention to development, it helped define the approach they then took: it framed the questions that could or could not be meaningfully asked, the organisms they chose to study, the experiments that did or did not make sense to do, the explanations that were or were not acceptable. In this sense, it served cognitive as well as political functions. Ian Hacking has suggested that every scientific discipline has its own "style of reasoning," which constitutes the epistemological context of that science. In other words, it creates the very possibility for truth or falsehood and therefore determines what counts as objective.[8] My notion of "discourse" is close to Hacking's notion of "style."

[8] Ian Hacking, "Language, Truth, and Reason," in M. Hollis and S. Lukes (eds.), *Rationality and Relativism,* pp. 48–66.

Needless to say, this way of talking about the relation between genes and development —a way that recasts the dynamics of development as a consequence of "gene action" —was markedly less congenial to most embryologists. It offered the student of development not a separate domain of inquiry (as Morgan's remarks implied), but rather a promissory note for inclusion or, more accurately, for incorporation. As early as 1924 the German embryologist Hans Spemann, Morgan's most important counterpart, wrote:

> The previous progress [of genetics] has been amazing, and it is not from a feeling of futile labours but rather from being aware of their paramount powers of appropriation that geneticists now are on the look-out for new connexions. They have cast their eye on us, on *Entwicklungsmechanik* . . .[9]

And a decade later, in his presidential address to the AAAS, Ross Harrison sounded a similar warning:

> Now that . . . the "Wanderlust" of geneticists is beginning to urge them in our direction, it may not be inappropriate to point out a danger in this threatened invasion.
>
> The prestige of success enjoyed by the gene theory might easily become a hindrance to the understanding of development by directing our attention solely to the genome. . . . Already we have theories that refer the processes of development to genic action and regard the whole performance as no more than the realization of the potencies of the genes. Such theories are altogether too one-sided . . .[10]

Embryologists had good grounds for concern. Not only was the status of their discipline under threat; so too was the status of their question: How *does* a germ cell develop into a multicellular organism? If the genetic content of all cells in an organism is the same, then how is one to make sense of the emergence of the mani-

[9] Hans Spemann, "Vererbung und Entwicklungsmechanik," *Z. Indukt. Abstammungs- und Vererbungslehre* 33 (1924), 293.

[10] Ross Harrison, "Embryology and Its Relations," *Science* 85 (1937), 369–74.

fest differences among all the cells that make up a complex organism? To them, it seemed self-evident that this problem of differentiation, so deeply at the heart of their own concerns, was simply incompatible with the notion that the gene was the exclusive locus of action.[11] As Morgan himself subsequently admitted (speaking now as an embryologist) :

> The implication in most genetic interpretation is that all the genes are acting all the time in the same way. This would leave unexplained why some cells of the embryo develop in one way, some in another, if the genes are the only agents in the results.[12]

Few if any geneticists heeded Morgan's warning. (Even Morgan did not heed his own warning.) Instead, those interested in the relation between genes and development found another route: they changed the subject —or, more precisely, they transformed the embryologist's question into a different one. Alfred H. Sturtevant spelled out how to do this. Sturtevant opened his paper on "the developmental effects of genes" at the 1932 International Congress of Genetics by observing:

> One of the central problems of biology is that of differentiation —how does an egg develop into a complex many-celled organism? That is, of course, the traditional major problem of embryology; but it also appears in genetics in the form of the question, "How do genes produce their effects?"

Between "the direct activity of a gene and the end product," he argued, "is a chain of reaction." And the task of the geneticist is to analyze these "chains of reaction into their individual links." [13]

[11] Geneticists, after all, could only study variations in already existing organisms; the question of how organisms come to be formed in the first place was thus beyond their ken.

[12] T. H. Morgan, *Embryiology and Genetics,* p. 9.

[13] Alfred H. Sturtevant, "The Use of Mosaics in the Study of the Developmental Effects of Genes," *Proceedings of the Sixth International Congress of Genetics* (1932), 304.

What does this rephrasing accomplish? Actually, quite a lot. Once the problem of development is translated into the question of "how genes produce their effects," the task is immediately—and almost miraculously—simplified. No longer need one get bogged down in the complex dynamics of eggs and multicellular organisms; it ought to suffice to study single-celled organisms, where one should have a better chance of analyzing "chains of reaction." George Beadle and Edward Tatum chose *Neurospora,* a single-celled organism that can be cultured *in vitro,* and their choice paid off handsomely. In 1940 they proposed their famous "one gene–one enzyme" hypothesis as an explanation of how genes produce their effects. At last, the mysterious notion of "gene action" seemed to have real content. Beadle and Tatum provided a particular kind of answer to the question of how a gene produces its effects, namely, "It makes an enzyme." Accordingly, developmental genetics could henceforth be understood as the biochemistry of gene action.

Together, the turn to *Neurospora* and the "one gene–one enzyme" hypothesis proved to be of decisive importance to the future development of genetics. It provided critical encouragement for the development of bacterial genetics and, eventually, of molecular biology. The rest of the story you all know. In 1953, with the definitive identification of DNA as the genetic material, Watson and Crick struck gold. Simple hydrogen bonding turned out to provide the secret of how genes reproduce themselves, and nucleic acid sequences, of how they make enzymes. As they discreetly wrote, "In a long molecule, many different permutations are possible, and it therefore seems likely that the precise sequence of the bases is the code which carries the genetical information." [14] All one needed to know was the code, and soon that was forthcoming as well.

[14] J. D. Watson and F. Crick, "Genetical Implications of the Structure of DNA," *Nature* 171 (1953), 964–67.

There it is: what *must* be the answer! DNA carries the genetical information (or program), and genes "produce their effects" by providing the "instructions" for protein synthesis. DNA makes RNA, RNA makes proteins, and proteins make us — without doubt, one of the greatest milestones in the history of science. But in what sense is it the answer? What in fact do "information," "program," "instruction," or even the verb "makes," actually mean?

Watson and Crick have gotten a lot of credit for their work, and deservedly so, but one contribution has, I fear, been overlooked: the introduction of the "information" metaphor into the repertoire of biological discourse was a stroke of genius. The story of this metaphor —its uses and implications —is an immensely rich one, but perhaps a few brief comments might nonetheless be in order. Just a few years earlier the mathematician Claude Shannon had proposed a precise quantitative measure of the complexity of linear codes. He called this measure "information" —by design independent of meaning or function —and by the early fifties "information theory" had become a very hot subject in the world of communications systems. It seemed to hold enormous promise for the analysis of all sorts of complex systems, even of biological systems. And the fact that DNA seemed to function as a linear code made the use of this notion of information for genetics appear natural. But as early as 1952 it was recognized that the technical definition of information simply could not serve for biological information. (It would, for example, assign the same amount of "information" to the DNA of a functioning organism as to a mutant form, however disabling that mutation was.) The notion of "genetical information" that Watson and Crick invoked was thus not literal, but metaphoric. But it was an extremely powerful metaphor. Even though it permitted no quantitative measure, it authorized the expectation, anticipated in the notion of "gene action," that biological information does not increase in the course of development: it is already fully contained

in the genome. By this move, and even more, by the subsequent collapse of "information" with "program" and "instruction," the concept of gene action was vastly fortified. Just as Erwin Schrödinger had anticipated, the "chromosome structures are law-code and executive power —or, to use another simile, they are architect's plan and builder's craft —in one." [15]

Classical embryologists would surely not have been happy with this turn of events —their questions, their organisms (even the lowly *Drosophila* had come to be seen as too complex, too messy), and they themselves had been left behind —but a new generation of biologists had little cause to look back. The first generation of molecular biologists could not answer the question of how an egg turns into an organism (could say nothing, e.g., about how a gene comes to make the particular enzymes that are needed for the development of a many-celled organism, in the right amounts, at the right time and in the right place), but they had a powerful new rhetorical resource for managing such questions. They could talk instead about "development" in the abstract, and the genetic programs or instructions that are needed to guide it. In his presidential address to the BAAS in 1965, Sir Peter Medawar offered something of a retrospective eulogy to embryology:

> Wise after the event, we can now see that embryology simply did not have, and could not have created, the background of genetical reasoning which would have made it possible to formulate a theory of development. . . . Embryonic development . . . (must) be an unfolding of pre-existing capabilities, an acting-out of genetically encoded instructions.[16]

The progression from Watson and Crick to the Human Genome Initiative, as Watson himself has so often reminded us, appears straightforward and logical. If all development is merely an un-

[15] Erwin Schrödinger, *What Is Life?,* p. 23.

[16] Sir Peter Medawar, "A Biological Retrospect," *Nature* 207, no. 5004 (1965), 1328–29.

folding of preexisting instructions encoded in the nucleotide sequences of DNA —if our genes make us what we are —then it makes perfect sense to set the identification of these sequences as the primary, and indeed ultimate, goal of biology.

What, then, do I mean when I say that the discourse of gene action —now augmented with metaphors of information and instruction —exerted a critical force on the course of biological research? Can words have force in and of themselves? Of course not. They acquire force only through their influence on human actors. Through their influence on scientists, administrators, and funding agencies, they provide powerful rationales and incentives for the mobilization of resources, for the identification of particular research agendas, for focusing our scientific energies and attention in particular directions. The discourse of gene action has worked in just these ways. And it would be foolhardy to pretend it has not worked well. The history of twentieth-century biology is a history of extraordinary success; genetics —first classical, then molecular —has yielded some of the greatest triumphs of modern science. Indeed, this way of talking has proven so powerful that now, after all these years, it seems to be finally on the verge of making good the promissory note that Morgan and his school extended in the early part of the century —and not just rhetorically, but in actual scientific practice. Over the last few years molecular biology has made extraordinary progress in elucidating just how it is that (as they say) "genes control development."

But a funny thing happened on the way to the holy grail. That extraordinary progress has become less and less describable within the discourse that enabled it. The dogmatic focus on gene action called forth a dazzling armamentarium of new techniques for analyzing the behavior of distinct gene segments; and the information yielded by those techniques is now radically subverting the doctrine of the gene as sole (or even primary) agent. It has also become conspicuously evident that there were all along serious

problems with the discourse of gene action — besides its productive blindness to questions of development and cell differentiation. As Richard Lewontin reminds us:

> DNA is a dead molecule, among the most nonreactive, chemically inert molecules in the world. . . . [It] has no power to reproduce itself. Rather it is produced out of elementary materials by a complex cellular machinery of proteins. While it is often said that DNA produces proteins, in fact proteins (enzymes) produce DNA. The newly manufactured DNA is certainly a copy of the old, . . . but we do not describe the Eastman Kodak factory as a place of self-reproduction [of photographs] . . .

He continues:

> Not only is DNA incapable of making copies of itself, . . . but it is incapable of "making" anything else. The linear sequence of nucleotides in DNA is used by the machinery of the cell to determine what sequences of amino acids is to be built into a protein, and to determine when and where the protein is to be made. But the proteins of the cell are made by other proteins, and without that protein-forming machinery *nothing* can be made. There is an appearance here of infinite regress . . . , but this appearance is an artifact of another error of vulgar biology, that it is only the genes that are passed from parent to offspring. In fact, an egg, before fertilization, contains a complete apparatus of production deposited there in the course of its cellular development. We inherit not only genes made of DNA but an intricate structure of cellular machinery made up of proteins.[17]

Of course, you may say. We knew this all along. Well, yes and no. Yes in the sense that, apart from the reference to DNA, it is the sort of observation embryologists used to make all the time. But no in the sense that, except for an occasional aside (like

[17] Richard Lewontin, "The Dream of the Human Genome," *N.Y. Review of Books,* May 28, 1992, p. 33.

Morgan's), geneticists did not; Lewontin, interestingly, is a geneticist, not an embryologist. The simple fact is that for many years geneticists had little reason to refer to eggs and their cytoplasmic structure, and even less reason to talk about events prior to fertilization. The discourse of gene action had established a spatial map that lent the cytoplasm scientific invisibility to geneticists ("indifferent" was how Morgan described the cytoplasm) and a temporal map that defined the moment of fertilization as origin, with no meaningful time before fertilization. In this schema, there was neither time nor place in which to conceive of the egg's cytoplasm exerting *its* effects.

With the emergence of molecular biology in the 1950s and 1960s, and its powerful metaphors of information and programs, the significance of the cytoplasm eroded even further. And once the bacterium *E. coli* came to serve as the model organism (recall Jacques Monod's famous remark, "What's true for *E. coli* is true for the elephant"), questions about eggs and fertilization ceased to be applicable. What is new is that Lewontin's commonplace observations can now not only be articulated, but actually heard. They have once again come to make sound biological sense, even in genetics. Current research —drawing on the phenomenal technical successes of molecular biology, and even on the sequence information emerging from the Human Genome Initiative —invites (ever more insistently) a shift in locution in which the cytoplasm is just as likely as the genome to be cast as the locus of control. What has happened?

Part of the precondition of this transformation has been the return of higher organisms to center stage. With that return, the study of embryogenesis has become fashionable, indeed a site of intense activity for geneticists. And *that,* it turns out, has made an important difference.

As recently as 1984 David Baltimore was still invoking the more familiar language of molecular biology to explain the dis-

tinction between modern genetics and classical physiology (or embryology) :

> The approach of genetics . . . is to ask about blueprints, not machines; about decisions, not mechanics; about information and history. In the factory analogy, genetics leaves the greasy machines and goes to the executive suite, where it analyzes the planners, the decision makers, the computers, the historic records. . . . Biologists needed to find the cell's brain."

But today he writes of the extent to which differentiation is governed by "active control" mechanisms, in which "the expression state of each gene [is] determined by the dynamic interaction of regulatory proteins present in the cell at any given time."[19]

Indeed, even as Baltimore spoke of the need to find the cell's brain in "the executive suite" (i.e., the DNA), the "cell's brain" was already in the process of moving out of the executive suite and into the factory. In 1984 Sidney Brenner, himself one of the major architects of molecular biology, confessed:

> At the beginning it was said that the answer to the understanding of development was going to come from a knowledge of molecular mechanisms of gene control, . . . I don't know if anyone believes that anymore. The molecular mechanisms look boringly simple, and they don't tell us what we want to know. We have to try to discover the principles of organization, how lots of things are put together in the same place. I don't think these principles will be embodied in a simple chemical device, as it is for the genetic code.[20]

Today the really "smart genes" are seen as those that have the capacity to respond to a complex of signals encoded in cytoplasmic proteins. Genes may be "smart," but the "brain of the smart gene"

[18] David Baltimore, "The Brain of a Cell," *Science* 84 (November 1984), 150.

[19] Helen M. Blau and David Baltimore, "Differentiation Requires Continuous Regulation," *Journal of Cell Biology* 112, no. 5 (1991), 781–83.

[20] Quoted in Roger Lewin, "Why Is Development So Illogical?" *Science* 224 (1984), 1327–29.

is not to be found in the genes themselves: as Eric Davidson puts it, it is a "complicated assemblage of proteins known as a transcription complex."[21] The point is that, as we learn more about how genes actually work in complex organisms, talk about "gene action" subtly transmutes into talk about gene "activation," with the locus of control shifting from genes themselves to the complex biochemical dynamics (protein-protein and protein-nucleic acid interactions) of cells in constant communication with each other. *Scientific American* glosses this shift as the "news" that "organisms control most of their genes."

New metaphors abound. Marking the long-overlooked distinction between program and data, Henri Atlan and Moshe Koppel suggest "an alternative metaphor of DNA as data to a parallel computing network embedded in the global geometrical and biochemical structure of the cell."[22] A yet more radical inversion is proposed by H. F. Nijhout. In lieu of the metaphors of "control" and "programs" that have so pervaded modern thinking in molecular, developmental, and evolutionary biology and that, he says, "have shaped priorities in research," Nijhout suggests that "a more balanced, and useful, view of the role of genes in development is that they act as suppliers of the material needs of development and . . . as context-dependent catalysts of cellular changes . . ."[23] "Genes," he concludes,

> are passive sources of materials upon which a cell can draw, and are part of an evolved mechanism that allows organisms, their tissues and their cells to be independent of their environment by providing the means of synthesizing, importing, or structuring the substances (not just gene products, but all substances) required for metabolism, growth and differentiation.

[21] Quoted in Tim Beardsley, "Smart Genes," *Scientific American* (August 1991), *87.*

[22] Henri Atlan and Moshe Koppel, "The Cellular Computer DNA: Program or Data," *Bulletin of Mathematical Biology* 53, no. 3 (1990) 335–48.

[23] H. F. Nijhout, "Metaphors and the Role of Genes in Development," *Bioessays* 12, no. 9 (1990), 441.

> The function of regulatory genes is ultimately no different from that of structural genes, in that they simply provide efficient ways of ensuring that the required materials are supplied at the right time and place.[24]

Nijhout's proposal may be extreme. But there is no question that a new way of talking is in the air, in keeping with the emergence of a new biology: molecular biologists have discovered the organism. The new developmental biology brings with it a resurgence of interest in many of the problems of "organization" and morphogenesis that had occupied an earlier generation of embryologists, and even a resurrection of a number of the same experimental protocols. The findings that result point neither to cytoplasmic nor to nuclear determination, but rather to a complex but highly coordinated system of regulatory dynamics that operates simultaneously at all levels: at the level of transcription activation, of translation, of protein activation, and of intercellular communication —in the nucleus, in the cytoplasm, indeed, in the organism as a whole.

So what is it that I, and I hope by now you too, find so interesting about this story? For a scientist (even a semilapsed scientist), what compels the greatest interest must surely be the specific content of the conceptual revolution now under way. The shift in discourse we are now seeing in the literature marks a conceptual shift of startling magnitude; it will require us to learn how to think in radically new ways. Sixty years ago men like Joseph Needham, C. H. Waddington, and J. H. Woodger sought a language for the complex dynamics relating nuclear and cytoplasmic elements in the process philosophy of Alfred North Whitehead. Today Whitehead's language is too foreign to us to be of use. But we have other resources to compensate —especially in mathematics and computers. For some time now a number of workers — Stuart Kauffman and René Thomas, among others —have been

[24] Ibid., 444.

developing models for genetic networks that represent a great advance over more simplistic notions of gene action. These models illustrate how networks of genes in interaction can give rise to stable, self-perpetuating patterns of biochemical dynamics of a kind radically different from anything autonomously acting genes could ever yield. In so doing, they give substance to Waddington's earlier notions of epigenetic pathways and, at the same time, automatically and irrevocably undermine traditional divisions between genetic and epigenetic. But as interesting as they are, such models are only a beginning. In keeping with the new talk of cytoplasmic control, it would also be useful to develop models of somatic networks of interacting proteins, in which genes would be the covert intermediaries of protein interaction, rather than proteins being the intermediaries of gene interaction (as they are in gene network models), Ultimately, of course, one needs full-scale models of genes and proteins in interaction —of a kind that large-scale computers are now making possible. In the end, I think that the most important function of all these models will be to stimulate the growth of just those intuitions about interactive and emergent phenomena that past discourses have so helped to stymie. I have no doubt that the effect will be a transformation in the way we think about biological systems that will make the changes we have already begun to witness look like mere harbingers.

For an observer of scientific change, however, this story provokes other questions. Put simply, they are twofold. First, what lent the discourse of gene action such persuasiveness for so many years? Second, why is it now giving way? (Or relatedly we might ask, why did embryology languish for so many years, and what has permitted its return today?) These are different versions of the same questions just because of the extent to which the fate of embryology has been so intimately linked historically to talk of gene action. Posed either way, they are far more difficult to answer than naive empiricism might suggest. The simplistic answers might go like this: embryology languished because it was bad and un-

productive science; we talked about gene action because we didn't know better; indeed, developmental phenomena are so difficult to study that real progress was impossible until the advent of the techniques of recombinant DNA that molecular biology has brought. All of these claims might be true — and still only part of the story. What they leave out is the entire issue of motivation.

Relatedly, they also ignore the awkward fact that the first experimental studies to spark the interest of molecular biologists in the early development of higher organisms relied solely on classical techniques that were labor intensive to be sure, but that had long been available. I think especially of the studies of "maternal (or cytoplasmic) effect" mutants and of cytoplasmic rescue in *Drosophila* first undertaken by Alan Garen and others in the early 1970s and carried to such dramatic fruition a few years later by Christianne Nusslein-Volhard and her colleagues. What these studies did was to establish the critical role played by the cytoplasmic structure of the egg *prior to fertilization, before* time zero. The most conspicuous question is, why were these efforts undertaken in the 1970s, and not before? I do not have time to go into the details of these studies, but they reveal, as Garen and others confirm, that no technical impasse prevented their being done years, if not decades, earlier. Maternal effect mutants — even in *Drosophila* — had been accumulating since the early part of the century; and the most crucial technical instrument, the micromanipulator, had been developed and used in the 1930s. Of course, it is well known that *Drosophila* was an exceedingly difficult organism to study embryologically, but even this ostensible impasse had been largely overcome by the early 1950s — again, by the application of long-available techniques. What was missing — both for the study of *Drosophila* embryology and for the more specific examination of maternal effects — was the motivation to invest the necessary effort. The very term geneticists invoked for "maternal effects" worked to discourage interest — since 1930 they had argued for the term "delayed inheritance" as a more accurate

description of these mutants. More generally, the belief —prevalent among geneticists at least since the mid-1920s —that the genetic message of the zygote "produces" the organism, that the cytoplasm is merely a passive substrate, could not but sap the motivation needed to undertake such undeniably difficult experiments. The question therefore becomes, what overcame that assumption?

If, as I have been arguing, the ways in which we talk about scientific objects are not simply determined by empirical evidence, but, rather, actively influence the kind of evidence we seek (and hence are more likely to find), then other factors must be considered if we are to understand the strength and persistence of the discourse of gene action. Let me, in my remaining minutes, very schematically indicate what some of these other factors were, at least as they operated between the two world wars.

In the 1930s the Swiss embryologist Oscar Schotté liked to illustrate the relations between embryology and genetics with a sketch of two views of the cell: as perceived by the embryologist, the nucleus is very small; but as perceived by the geneticist, it virtually fills the entire cell.[25] In this sketch, the nucleus and cytoplasm are employed as tropes for the two disciplines —both lend to their object of study a size in direct proportion to their perceived self-importance. In like fashion, the two disciplines lent to each object, nucleus and cytoplasm, their own self-attributes of agency, autonomy, and power. As L. C. Dunn put it, "Genetics had to be a bit pushy in order to get itself established."[26] In addition, however, the nucleus and cytoplasm also came to stand as tropes for national importance, agency, and power, with the former, as the domain in which American genetics had come to stake its unique strengths, associated with American interests (and prowess) and the latter, with European, and especially German, interests and prowess. German biologists were often explicit about what

[25] Sander, "The Role of Genes."

[26] L. C. Dunn, Oral History Transcript, Columbia University Oral History Project (1959), p. 319.

they saw as the attempt by American geneticists to appropriate the entire field. In 1927, for example, V. Haecker described the field between genetics and development as the "no-man's land" of somatogenesis —"a border field which by us has been tilled for quite some time. . . . The Americans have taken no notice of this." [27] This tension persisted throughout the interwar years and was resolved only with the resounding defeat of Germany (and the destruction of German biology) in World War II.

But the most conspicuous metaphoric reference of nucleus and cytoplasm is surely to be sought in sexual reproduction. By tradition as well as by biological experience, at least until World War II, nucleus and cytoplasm are also tropes for male and female. Until the emergence of bacterial genetics in the mid-1940s, all research in genetics and embryology, in both Europe and the United States, focused on organisms that pass through embryonic stages of development; and for these organisms, a persistent asymmetry is evident in male and female contributions to fertilization: the female gamete, the egg, is vastly larger than the male gamete, the sperm. The difference is the cytoplasm, deriving from the maternal parent (a no-man's land indeed) ; by contrast, the sperm cell is almost pure nucleus. It is thus hardly surprising to find that, in the conventional discourse about nucleus and cytoplasm, cytoplasm is routinely taken to be synonymous with egg. Furthermore —by an all too familiar twist of logic —the nucleus was

[27] V. Haecker, "Phänogenetisch gerichtete Bestrebungen in Amerika," *Z. indukt. Abstammungs- und Vererbungslehre* 41 (1926), 232–38. Richard Goldschmidt, the leading figure in Germany in physiological genetics, registered a similar complaint, attributing American indifference to "the rise of a school of geneticists to whom biological knowledge apart from Mendelism did not seem necessary, whereby they were entirely content with knowing the work of the schools most closely akin to their own approach" (trans. by Sander, "The Role of Genes," p. 389). And elsewhere he commented, "It is really too bad that Morgan and his students . . . have got stuck in such a narrow interpretation of genetic phenomena and oppose at all costs any new idea, especially a physiological one. . . . I have discussed this at length with my dear frieind Morgan, but he insists that a thing [phenotype] has been explained once one has mapped a corresponding Mendelian factor" (quoted in Jonathan Harwood, *Styles of Scientific Thought: The German Genetics Community, 1900–1933,* p. 50).

often taken as a stand-in for sperm. Theodore Boveri, for example, argued for the need to recognize at least some function for the cytoplasm on the grounds of "the absurdity of the idea that it would be possible to bring a sperm to develop by means of an artificial culture medium" (published posthumously in 1918 and translated in Fritz Baltzer, *Theodor Boveri,* pp. 83–84).[28]

Many of the debates about the relative importance of nucleus and cytoplasm in inheritance thus inevitably reflect older debates about the relative importance (or activity) of maternal and paternal contributions to reproduction, where the overwhelming historical tendency has been to attribute activity and motive force to the male contribution, while relegating the female contribution to the role of passive, facilitating environment. In Platonic terms, the egg represented the body, and the nucleus, the activating soul. (In a related vein, E. B. Wilson's remarks about Morgan's early passion for embryology may also be worth noting: "It is an open secret that even now he sometimes escapes from the austere heights where Drosophila has its home in order to indulge in the illicit pleasures of the egg and its development.")[29] In these associations surely lies part of the background for both the force of the assumption of gene action and for its gradual fading away from the status of self-evident truth.

Change, of course, did not come overnight. While embryology was no longer a thriving research enterprise after the war, the memory of that disciplinary struggle took time to abate. It also took time — roughly two decades — for German biology to rebuild. Lastly, it took the women's movement to change our ideas about gender, and perhaps the hiatus of bacterial genetics (where no one had to think about male and female contributions) for these changes to creep into biology. By the time that the study of higher organisms began to reemerge in the 1970s, the entire

[28] See also E. E. Wilson, *The Cell in Development and Heredity,* p. 262.

[29] E. B. Wilson, "Opening Address," *Proceedings of the Sixth International Congress of Genetics* (1932), 82.

world had changed, and so had the ways that seemed natural to talk. Embryology was no longer a rival, Germany had become a friend, and gender equity was all the rage. There were of course also other changes, which I have not talked about —most notably, perhaps, the emergence of a discourse of feedback and of bodies as cyborgs, both associated with the extraordinary developments in systems analysis and computer science. And last but hardly least were the equally extraordinary developments internal to molecular biology, especially the techniques of recombinant DNA. Concurrent with the changes in the way we talked, and thought, these developments soon effected dramatic changes in what could be done in the lab. Over the last decade the world of technical feasibility has changed beyond recognition. These very different kinds of changes —in how we talk and in what can be done in the lab —have worked in concert and in mutual reinforcement, the one creating the opportunity and the other the need to radically rethink the meaning of genetic determinism.

Acting in synch (as it always does), the social, cognitive, and technical history of twentieth-century biology has once agaiii brought us to a dramatic and critical juncture. Now all that is needed is for scientists to take advantage of the opportunity that has been created and respond to the need that has been uncovered. But if there is a moral to this story, it is this: lest we be too quick to congratulate ourselves for our newfound enlightenment, we should remember that our predilections —grounded though they must be in our particular social and political realities —are all we have to guide us. Thus there is no guarantee that the opportunity now before us will not be seized by new doctrinaires; indeed, there is every reason to expect that it will. After all, how else can science proceed? Still, I retain the hope that, as scientists, we may become more aware of the weight and force of the language that we have no choice but to borrow from the larger culture of which we, inescapably, are part.

BIBLIOGRAPHY

Allen, Gar. "T. H. Morgan and the Split between Embryology and Genetics, 1910–1926." In T. J. Horder, I. A. Witkowski, and C. C. Wylie (eds.), *A History of Embryology,* pp. 113–46. Cambridge: Cambridge University Press, 1986.

Atlan, Henri, and Moshe Koppel. "The Cellular Computer DNA: Program or Data." *Bulletin of Mathematical Biology* 52, no. 3 (1990), 335–48.

Baltimore, David. "The Brain of a Cell." *Science* 84 (November 1984)) 150.

Baltzer, Fritz. *Theodor Boveri.* Translated by Dorthea Rudnick. Berkeley: University of California Press, 1967.

Beardsley, Tim. "Smart Genes." *Scientific American* (August 1991), 87–95.

Blau, Helen M., and David Baltimore, "Differentiation Requires Continuous Regulation," *Journal of Cell Biology* 112, no. 5 (1991)) 781–83.

Brink, R. A. "Genetics and the Problems of Development." *American Naturalist* 61, no. 574 (1927)) 280–83.

Hacking, Ian. "Language, Truth, and Reason." In M. Hollis and S. Lukes (eds.), *Rationality and Relativism,* pp. 48–66. Cambridge, Mass.: MIT Press, 1986.

Haecker, V. (1926) "Phänogenetisch gerichtete Bestrebungen in Amerika." *Z. indukt. Abstammungs- und Vererbungslehre* 41 (1926), 232–38.

Harrison, Ross, "Embryology and Its Relations." *Science* 85 (1937)) 369–74.

Harwood, Jonathan, *Styles of Scientific Thought: The German Genetics Community, 1900–1933.* Chicago: University of Chicago Press, 1993.

Horder, T. J., J. A. Witkowsky, and C. C. Wylie (eds.). *A History of Embryology.* Cambridge: Cambridge University Press, 1986.

Lewin, Roger. "Why Is Development So Illogical?" *Science* 224 (1984)) 1327–29.

Lewontin, Richard. "The Dream of the Human Genome." *N. Y. Review of Books,* May 28, 1992.

Medawar, Sir Peter. "A Biological Retrospect." *Nature* 207, no. 5004 (1965), 1327–30.

Morgan, T. H. "Mendelian Heredity in Relation to Cytology." In E. V. Cowdry, *General Cytology,* pp. 691–734. Chicago: University of Chicago Press, 1924.

———. "Genetics and the Physiology of Development." *American Naturalist 60,* no. 671 (1926)489–515.

———. *The Theory of the Gene.* New Haven: Yale University Press, 1926.

———. *Embryology and Genetics.* New York: Columbia University Press, 1934.

Muller, H. J. "The Gene as the Basis of Life." *Proceedings of the International Congress of Plant Sciences* 1 (Ithaca, 1926), *897–921.*

Nijhout, H. F. "Metaphors and the Role of Genes in Development." *Bioessays 12,* no. 9 (1990) 441–46.

Sander, Klaus. "The Role of Genes in Ontogenesis —Evolving Concepts from 1883 to *1983* as Perceived by an Insect Embryologist." In Horder et al. (eds.), *History of Embryology,* pp. 363–95.

Sapp, Jan. *Beyond the Gene.* Oxford: Oxford University Press, 1987.

Schrödinger, Erwin. *What Is Life?* Cambridge: Cambridge University Press, *1944.*

Spemann, Hans. "Vererbung und Entwicklungsmechanik." *Z. Indukt. Abstammungs- und Vererbungslehre* 33 (1924),272–94.

Sturtevant, Alfred H. "The Use of Mosaics in the Study of the Developmental Effects of Genes." *Proceedings of the Sixth International Congress of Genetics* (1932))304.

Watson, J. D., and F. Crick. "Genetical Implications of the Structure of DNA." *Nature* 171 (1953), 964–67.

Wilson, E. B. *The Cell in Development and Heredity.* New York: Macmillan, 1896.

———. "Opening Address." *Proceedings of the Sixth International Congress of Genetics* (1932), 82.