TAKING DEVELOPMENT SERIOUSLY:

TOWARD A GENUINELY SYNTHETIC BIOLOGY

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Abstract

The Human Genome Project (HGP) is nearing completion, and shortly we will have access to the complete genetic sequence of an average human being. Hopes are high that the sequence will contribute profoundly to medicine in particular, but also to our understanding of our evolutionary past. Of course, detractors have long insisted that because the HGP represents a victory for formalism in biology, determining the *function* of DNA sequences will remain an outstanding problem for at least the next several decades. Moreover, it is not clear that having the complete sequence will be significantly useful to biologists seeking to understand gene function in the first place. What can we expect in the postgenomic era?

I reject the very idea that a complete, encapsulated sequence of a human genome is foundational to biological understanding. I set my investigation within the framework of the ancient debate between preformationists and epigenecists. I survey and conceptually analyze arguments on both sides, especially as they relate to the separation of genetics and embryology in the early part of the twentieth century. I identify modern variants of both preformationism and epigenesis, and note their reconciliation in the form of a Modern Consensus on development established after the neo-Darwinian Synthesis in biology in the 1940s.

Drawing on recent work in molecular and developmental biology, I challenge the seeming intuitiveness of the Modern Consensus and its subsumption of developmental concerns under the aegis of molecular genetics. I then propose and defend an alternative synthesis of preformationism and epigenesis, and of genetics and developmental biology, according to which development (epigenesis) does not reduce to mere gene activation. I underscore the practical benefit of my perspective through a lengthy discussion of the psychiatric genetics approach to schizophrenia.

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Evelyn Fox Keller sent me two of her forthcoming articles, both of which aided me in thinking through some of the problems addressed in this dissertation. Later, she acted as external examiner, and her comments were both challenging and very helpful. Two members of McMaster's Biology Department, Roger Jacobs and Steven Threlkeld, were provocative and appropriately skeptical at the examination. Susan Oyama read several parts of chapters in draft form, raising thoughtful objections and yet providing much encouragement.

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Chapter Four will appear (with some revisions) as "Schizophrenia Epigenesis?" in *Theoretical Medicine and Bioethics* 21.2, pp. 191-215; it is reprinted with kind permission from Kluwer Academic Publishers. In other chapters, I draw loosely on several of my recent publications: "The Metaphorical Unfolding of Biology"(*Research in Philosophy and Technology* 18 [1999]: 327-329); "Fastidious, Foundational Heresies" (*Biology and Philosophy* 15 [2000]: 133-145); and "Synthetic Biology" (forthcoming in *Studies in History and Philosophy of Biological and Biomedical Sciences* [2000]).

Lastly, I must thank my family and friends for their unconditional support especially during the past ten years as I have worked steadily toward the goal of a PhD in philosophy. I would not have made it without them, nor would I have wanted to.

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Introduction – Postgenomics, Indeed: But What About Development?

It is a little late to expend too much energy railing against the Human Genome Project (HGP). Thanks to enormous financial support in the United States, Japan, Great Britain, and elsewhere, as well as to crucial technological innovations such as the polymerase chain reaction and gene amplification, by at latest 2005 we will have the full consensus sequence of a hypothetical, abstract human genome, that of Hugo.[1] Less than a month ago, in fact, the first working draft of a complete human genome was announced in *Nature*.[2] Numerous vocal and persistent critics[3] have been unsuccessful in their attempts to depose biology's largest ever megaproject, and now, thanks largely to rhetoric and not results, the human genome looms larger than ever as our millennial panacea – what I like to call *security in letters*. But as we begin to enter the "postgenomic" era,[4] for humanists, social scientists, computer scientists, and, crucially, biologists, the real work has just begun.

The eminent philosopher of evolutionary biology Michael Ruse has written that the metaphysics of the Human Genome Project could be set out on the back of a postage stamp – with room to spare.[5] Maybe so. But surely that is not the case with postgenomic research programmes in biology, with the application of the information gained through the HGP. Despite the existence of what has come to be known as the "Interactionist Consensus", according to which no one any longer holds that either genes or

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[1] The name "Hugo" derives from that of one of the HGI's international overseers, the *HU*man *G*enome *O*rganization; Lippman (1992) reports that another, not so affectionate, name has been suggested in place of Hugo: *T*he *HU*man *G*enome, or THUG.

[2] Macilwain (2000).

[3] For instance, Lewontin (1992), (1991); Lippman (1992); Tauber and Sarkar (1993), (1992); Hubbard and Wald (1993); Keller (1995); Rose (1997); Robert (1998a).

[4] See Thieffry and Sarkar (1999).

[5] Ruse (1997), p. 591.

environment can by themselves be thought to generate or explain organismal traits, there are nonetheless clear metaphysical – as well as methodological, medical, and moral – impediments to Hugo's graceful coming out. Several of the problems are as follows:

Metaphysics: Concerns abound regarding the relationship of genotypes to phenotypes: how does Hugo's gerrymandered, pristine genome correspond to the vast organismic diversity observable in humans? How can a single genome be "representative" of the species? Is the genome the prime ingredient in human being, or are there other prime ingredients? (Is there even any such thing as a "prime" ingredient in an organism?) Is the genome itself sufficient to produce a human animal? If not, what else is required besides Hugo's DNA to yield the complex, specifically structured human? What are the steps and processes, twists and turns, leading from gametic through geriatric humanity? And, even more basically, are organisms appropriately understood as (complex) machines? In addition to these concerns, another, separate class of metaphysical issues pertains to the ideas of essential human nature, of determinism and free will, and of human subjectivity in a (post)genomic civilization.

Methodology: Additional troubles involve experimental approaches to complexity: how, if at all, can we model the ontogenesis of complex creatures like humans? What heuristics are most productive in studying human development? How can we build a modestly reductionistic research programme, a multileveled one which neither looks too low nor too high, to investigate the genesis and development of humans? How can molecular biology be shown – or made – to work in "the real world of the organism"?[6]

Medicine: Within the next five-or-so years, we will have sequenced the entire human genome, or, more sceptically, we will have constructed the sequence of a hypothetical normal human male. While some commentators are enthusiastic about the impact the sequence will have on human health, detractors insist that there are better – more effective and less costly – routes to human health than through the genome. Who is right? If the former, then how do we get from Hugo's normal genome to an

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[6] Cohen and Rice (1996), p. 251.

understanding of – and treatment prospects for – human diseases? If the latter, then will the sequence of Hugo's normal genome have any significant impact on human health?

Morality: If Hugo fails to deliver on the extravagant medical promises made on his behalf by free-spending genome-sequencing enthusiasts, then who if anyone will be held accountable? And if the promises are fulfilled, or at least some of them are, then how will we go about dealing with the presumably sensitive nature of genetic data, and delineating the appropriate scope of its applicability?

In what follows, my primary concerns will be metaphysical and methodological. My strategy will not be to address each of the above questions – or the many others I have yet to mention – individually and in turn. Rather, I will examine the theme that runs throughout them: how best to conceive an integrative approach to organismal biology, given the ascendancy of genetics.

This is primarily a work of conceptual analysis. In Chapter One, I sketch the history of the conceptual and professional divorce between genetics and embryology achieved in the early part of the twentieth century, and examine several attempts at reconciliation beginning in the 1930s. Chapter Two introduces an ancient debate between preformationism and epigenesis. In that chapter, I introduce what I take to be the Modern Consensus view on preformation and epigenesis. I then survey and assess various views on preformation from Hippocrates through James Watson, interrogating the move from "minuscule men" to genetic programs.

In Chapter Three I turn to the alternative of epigenesis, attending especially to its modern incarnation in the form of *epigenetics*. I provide a brief taxonomy of epigenetics, distinguishing my own view from several classes of distinct (and more popular) perspectives. Chapter Four is a case study of the epigenesis of schizophrenia, wherein I demonstrate some of the pitfalls of not taking development seriously enough in our construal of epigenesis; I further demonstrate the benefits of an alternative approach to investigating the schizophrenic phenotype.

Finally, in Chapter Five, I distinguish my own account of epigenesis – what I call *creative epigenesis* – from other extant accounts which, I contend, pay mere lip service to development: that is,

they fail to take development seriously. I then show how my approach may fruitfully direct research in the new biological discipline of evolutionary developmental biology in order to ensure a genuinely synthetic biology, as distinct from (yet another) instance of the subsumption of development by molecular genetics.

Chapter One – Development and the Modern Synthesis

> For many years, genetics and developmental biology were studied as separate disciplines but, with the advent of the powerful techniques of molecular biology, this is no longer the case. There is rapidly increasing information about genes involved in development, and also about striking homologies between such genes in different taxonomic groups. This has given rise to the widespread view that there are certain fundamental features of development that will soon be understood. Indeed, one can define the 'optimistic' school of thought which believes that the accumulation of more and more information will, by itself, reveal the whole mechanism of development from the fertilised egg to the adult. This optimistic viewpoint tends to regard epigenetics as an irrelevance. ... Another school of thought is not necessarily pessimistic, but believes that the molecular approach is, in effect, molecular description, or anatomy, at the DNA, RNA, and protein levels. This information alone will not solve the problem of development, however, because we do not yet have the necessary conceptual framework to put together all the components.
>
> – *Robin Holliday*[1]

1.1. The Great Divorce

One significant foe vanquished in the early days of "the rise of genetics"[2] – and only recently making a comeback – is the discipline of embryology. By the 1930s, only embryologists took embryology seriously, while most others were attuned to the elegance, austerity, and simple beauty of genetic models which reduced ontogeny to gene activity. As Gilbert, Opitz, and Raff have noted, thanks to its tremendously productive models genetics established a monopoly position in both evolutionary biology and embryology in the first half of the twentieth century: "just as evolution became redefined as the study

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[1]Holliday (1994), pp. 455-456.

[2]Morgan (1932). The literature is saturated with helpful histories of the early development of genetics and of related disciplines. Good starting points include Carlson (1966), Gilbert (1978), (1988), (1991), (1996); Allen (1986), Sapp (1987).

of changes in gene *frequency*, so embryology became redefined as the science studying changes in gene *expression*".[3] Embryologists were not corporately impressed with the theories of the geneticists, though, especially in the developmental realm.

"American geneticists repeatedly stated that one day they would be able to account for development in terms of the governmental control of chromosomal genes".[4] But as N.J. Berrill cheekily remarked, genes were no more than "statistically significant little devils collectively equivalent to one entelechy"![5] Nevertheless, embryologists feared the takeover of their discipline by "marauding intruders", as Berrill referred to the geneticists of the 1930s.[6] Hans Spemann remarked that the geneticists' "previous progress 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* [developmental mechanics]".[7] Ross Harrison, among others, warned against the geneticists' *Wanderlust*, their unwelcome intrusion into developmental realm; his concern was that the successes of genetics in the domain of transmission would lead to an overemphasis on the genes in the domain of development.[8] Harrison's counsel was, as we shall see, prophetic, and therefore unfortunately impotent.

Some geneticists had mixed feelings about embryology. Thomas Hunt Morgan was himself an

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[3]Gilbert, Opitz, and Raff (1996), p. 360; they cite Morgan (1934) in support of the claim.

[4]Sapp (1991), p. 237.

[5]Gilbert, Opitz, and Raff (1996), p. 361 (citing N.J. Berrill, "Spatial and Temporal Growth Patterns in Colonial Organisms", *Growth (Suppl.)* 5 (1941), pp. 89-111).

[6]Cited in Gilbert (1988), p. 317 (personal communication from Berrill to Gilbert, 1985).

[7]Cited in Sander (1986), p. 368 (translated by Sander from Hans Spemann, "Vererbung und Entwicklungsmechanik", *Z. Indukt. Abstammungs- und Vererbungslehre* 33 (1924), pp. 272-294, at p. 293).

[8]Cited by Gilbert (1988), p. 317 (from Ross G. Harrison, "Embryology and its Relations", *Science* 85 (1937), pp. 369-374, at p. 372).

embryologist, and one not easily won over to the geneticists' side.[9] Between the rediscovery of Mendel's paper (around the turn of the century) and 1910, Morgan was critical of Mendelian theories of heredity on the basis of their alleged adherence to some version of the ancient doctrine of preformationism.[10] Preformationism is, roughly (see below), the view that full, but tiny, organisms preexist in ova or sperm, and gradually grow (without significant transformation) into adult form. In other words, embryogenesis is the evolution (in its pre-Darwinian sense of unrolling) of an embryo's simultaneously preformed parts.[11] The doctrine has persisted in one incarnation or another ever since ancient Greece. Aristotle dismissed Hippocrates' preformationist idea that the bigger parts of an embryo appear earlier than the smaller parts not because they are formed earlier, but because their size makes them easier to see. Aristotle was able to demonstrate that the heart in the chick embryo appears sooner than the lungs, and yet the lungs are bigger (and thus should be visible sooner than the heart); therefore as it is visible earlier in development, the heart must have been formed prior to the lungs, and not contemporaneously with them.[12]

Of course, Hippocrates' version of preformationism does not exhaust the category, for there are many ways of being a preformationist. One may insist with Hippocrates that the embryo as such is a tiny, perfectly formed adult needing but fire and food to grow into an adult; views popular in the seventeenth and eighteenth centuries go a step further, from the embryo to the sex cell: many naturalists held that a future organism is coiled in the sex cell, and then merely evolves into its mature form – one was therefore an animalculist (spermist) or ovist depending on one's sex-cell orientation. The eighteenth-century ovist Charles Bonnet refined the latter position by dispensing with "minuscule men" in favour of the conviction

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[9]See Allen (1986) for an analysis of the changes in Morgan's views between 1900 and 1935.

[10]For an excellent and engaging history of preformationism, one unusually sympathetic toward this oft-berated position, see Pinto-Correia (1997). The debates between preformationists and epigenecists will be of interest in subsequent chapters; see below.

[11]Needham (1959), pp. 34-35.

[12]See, e.g., Moore (1987), p. 424; Aristotle's demonstration is in part II of *De Generatione Animalium*, 734a.

that the "germ" is a "loose sum of all the 'fundamental parts' of the future individual".[13] The version of preformationism to which Morgan objected was an updated variant of this germ doctrine, espoused by August Weismann, among others.

In his 1892 book *Das Keimplasm* (1893, *The Germ Plasm*), Weismann explained that he had earlier rejected the preformationist notion of the uncoiling of a tiny preformed organism; but now he had found that it was impossible to accept anything other than *some* kind of preformationism. He was therefore "forced into accepting" the position he once resisted.[14] For Weismann, though, there was "no simple growth of pre-existing form as earlier preformationists had held" – instead, "development involved the self-guided unfolding of pre-determined multiplicity of parts".[15] Weismann's position may be understood as an extension of the view of Bonnet, noted above, for what was preformed for Bonnet was neither the organism nor "the organs in miniature, but organic particles corresponding to *and determining the growth of* the organs".[16] Weismann identified these organic particles as the "idioplasm", by which he meant the chromatin granules in the nucleus. The idioplasm "exercises a direct formative influence upon the cell containing it, determining what sort of cell it will become. ... The idioplasm of the germ-cell – the hereditary or germinal substance proper [for Weismann] – is conceived to be of a complex and orderly architecture, built up of self-propagating units or determinants, each of which is destined to be the

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[13]Pinto-Correia (1997), p. 58. It is a main theme of Pinto-Correia's book – as well as of her 1999 – that preformationists never referred to these "minuscule men" as *homunculi*, a name "so easily subject to ridicule" (Pinto-Correia, 1999, p. 227) that it would have subverted the credibility of the preformationists had they used it. A majority of authors continue to ridicule the preformationists on this unsound basis (e.g., Schwartz, 1999, p. 167), leading to (1) a prejudicial, patronizing dismissal of an eventually very sophisticated theory, and often as well to (2) an uncritical acceptance of some fuzzy thesis of epigenesis as an alternative to the (putatively) obviously false notion of preformationism. As I will make clear in later chapters, there are far better grounds on which to dismiss (versions of) preformationism than the erroneous imputation of a silly thesis, and there is far stronger evidence for epigenesis than acclamation by default.

[14]Maienschein (1986), pp. 75-76.

[15]Maienschein (1986), pp. 77.

[16]Russell (1930), p. 31.

formative agent of some particular part of the organism or of some particular group of cells".[17] As is evident, for Weismann factors external to the nucleus are specifically irrelevant – they are simply the normal conditions for development – while internal factors alone determine ontogenesis. "A certain cell in a subsequent embryonic stage does not give rise to a nerve-, and muscle-, or an epithelial-cell because it happens to be so situated as to be influenced by certain other cells in one way or another, but because it contains [in its nucleus] special determinants for nerve-, muscle-, or epithelial-cells".[18]

These special determinants at first troubled Morgan. For a common feature of all these views of preformationism, from Hippocrates to Weismann, is that they disregard all developmental phenomena except growth (e.g., the phenomena of morphogenesis); they "ignore nature", according to Oscar Hertwig, a contemporary of Weismann, and his foremost German opponent.[19] For if we identify hereditary factors with characters, then we ignore every ontogenetic process between gene and phene – exactly those phenomena that have long since fascinated and baffled embryologists. In a passage reminiscent of both Bonnet and Weismann, the geneticist L.C. Dunn attempted to clarify this notion of genetic (pre)determination by claiming that the use of the word *determined* "does not mean that the character itself is present in the germ in any form, but rather that it is represented by substances or forces which not only *stand for* the character but in some way bring about its expression"[20] – as if there were some direct connection, some linear path between the factors and the characters. Morgan the embryologist, at least before 1910, could not ignore this ontogenetic lacuna in the theory, and therefore could accept neither Mendelism nor any chromosomal theory of heredity.

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[17]Russell (1930), p. 43.

[18]Cited by Woodger (1931), p. 190 (from August Weismann, *The Germ Plasm*, trans. W. Newton Parker and Harriet Rönnfeldt (New York: Charles Scribners, 1893), p. 134).

[19]Maienschein (1986), p. 78.

[20]Cited by Sapp (1986), p. 49 (from L.C. Dunn, "Nucleus and Cytoplasm as Vehicles of Heredity", *American Naturalist* 51 (1917): 286-300, p. 286).

Morgan the embryologist would not, could not, separate heredity from development.[21] "Learning about transmission of information between parents and offspring was of no value without also learning about the development of the trait into its ultimate adult form".[22] But for Morgan the geneticist, that is, Morgan after 1910, genetics properly dealt strictly with heredity (defined as transmission and no longer also as ontogeny), leaving for embryology the study of development. Thus, for the Morgan school, heredity did not refer to the development and reproduction of individual organisms, but only to the sexual transmission of their genes:[23] "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".[24] That the gene theory said nothing about ontogeny was no longer a problem for Morgan thanks to the new, restricted understanding of heredity, and thus he became a preformationist of sorts.[25]

Garland Allen has plausibly argued that Morgan bracketed the whole of ontogeny for pragmatic reasons. Embryonic development was knotty and messy; transmission was clear and straightforward, and experimental success with *Drosophila* in showing any number of genetic alterations was practically guaranteed. The distinction between genotype and phenotype, introduced in 1911 by Johannsen, facilitated this disciplinary and experimental wedge between genetics and embryology, and though

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[21]Gilbert (1978).

[22]Allen (1986), p. 120.

[23]Sapp (1987), p. 29.

[24]Cited by Russell (1930), pp. 69-70 (from Thomas Hunt Morgan, *The Theory of the Gene* (New Haven: Yale University Press, 1926), p. 26). Despite great strides in molecular biology, the situation is little different today; as Eva Neumann-Held (1999) has recently suggested, "so far, biology can describe organisms down to the molecular level of genes. However, the interactions of genes with other, non-genetic components to form an organism is far from being understood" (p. 107). See below.

[25]Morgan always left room for epigenesis, though, accepting a version of Wilson's (1925) putative synthesis of preformation and epigenesis: "in respect to a great number of characters *heredity is effected by the transmission of a nuclear preformation which in the course of development finds expression in a process of cytoplasmic epigenesis*" (p. 1112). I will return in later chapters to the merits and demerits of such a viewpoint.

Morgan remained interested in embryology, he felt a pressing need to push it aside in favour of transmission genetics.[26] Nevertheless, Morgan himself sometimes slipped, urging for instance in 1919 that "one could account for 'the organism as a whole' in terms of 'the collective interaction of genes'".[27]

In sum, though Morgan kept the disciplines of genetics and embryology officially separate, securing research funding for the former and helping to establish its monopoly position in American biology, he nevertheless occasionally insisted that development could, and should, be explained genetically – Morgan's 1926 sense that "the application of genetics was a most promising method of attack on the problems of development"[28] was widely held. And while he was at times "particularly anxious" to dismiss claims about the importance of extra-nucleic factors,[29] Morgan nonetheless proposed in 1934 a more expansive concept of the gene than was then commonplace, one that kept up his early (pre-1910) interest in the nongenetic elements of the organism. As Scott Gilbert has noted, on the last page of Morgan's 1934 book *Embryology and Genetics*, Morgan "suggests that the nuclear genes may not be the unchangeable entities that geneticists had (and until very recently still have) assumed". Morgan writes that it is "conceivable that the genes also are building up more and more, or are changing in some way, as development proceeds in response to that part of the protoplasm in which they come to lie, and that these changes have a reciprocal influence on the protoplasm".[30] In a sense then, Morgan was more generous in keeping embryology and genetics separate and retaining (at least some of the time) respect for both disciplines, than were those who, unlike Morgan, have since the 1930s attempted to reconcile genetic

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[26]Allen (1986), pp. 126-127, 138-139.

[27]Sapp (1991), p. 237 (citing Thomas Hunt Morgan, *The Physical Basis of Heredity* (Philadelphia: Lippincott, 1919), p. 241).

[28]Sapp (1987), p. 50, referring to Morgan's 1926 book *The Theory of the Gene*, pp. 491-496.

[29]Cited by Allen (1986), p. 131 (from a letter from Morgan to Jacques Loeb, 1919).

[30]Gilbert (1988), p. 315 (citing Thomas Hunt Morgan, *Embryology and Genetics* (New York: Columbia University Press, 1934), p. 234.

and embryological research programmes. I have in mind early proponents of such a synthesis, e.g., Richard Goldschmidt and Ernest Everett Just.

1.2. Early Efforts at Reconciliation

Just is one of very few biologists to have proposed a non-gene-centric reconciliation between genetics and embryology, for the vast majority of such proposals tend simply to subsume embryology under the aegis of genetics. Gilbert has summarized the main arguments of Just's 1939 book, *The Biology of the Cell Surface*, in which he "belittled the role of the genes, giving them minor roles to play in the essentially cytoplasmic process of development".[31] Allow me to quote Gilbert:

> The development of an organism is a history of its cellular interaction. Therefore, to Just, development was a property of the cytoplasm; for only the cytoplasm could respond. The most responsive part of the cytoplasm – as Just showed from fertilization studies [on the sea urchin] – is the cell cortex, the outermost cytoplasmic rim. It is this peripheral rim of material that Just championed as the prime mover of development, evolution and intelligence. Whereas the mainstream of cellular biologists believed and assumed that the cytoplasm took its instructions from the central nucleus, Just believed in the primacy of the cortex.[32]

Thus, as Gilbert notes, Just inverted the position of Weismann, holding instead that "all the hereditary potentials for development exist in the cytoplasm of the fertilized egg" rather than in the idioplasm.[33] For Just, "fertilization is essentially a process of the egg" – all the important work occurs at the surface of the egg cell, not at its nucleus.[34] On Just's account, then, "the nucleus did not give any orders to the cytoplasm"; rather, orders came "from the entire embryo". From such a perspective, Just redefined a mutation – that central concept of the geneticists – as "a defect in the cortical cytoplasm that

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[31]Gilbert (1988), p. 320 (referring to E.E. Just, *The Biology of the Cell Surface* (Philadelphia: P. Blakiston's Son & Co., 1939).

[32]Gilbert (1988), p. 334; he discusses the sea urchin fertilization studies on p. 329.

[33]Gilbert (1988), p. 331.

[34]Gilbert (1988), p. 329 (citing Just's *The Biology of the Cell Surface*, pp. 6-7).

directs development" rather than a defect in a gene.[35]

As a result, Just held that the relationship between genetics and embryology, between heredity and development, must be described in embryological terms. The gene plays a secondary role in development, and therefore the geneticists should play a role secondary to that of the embryologists. It may be inferred then that, in the mind of one such as Just, Morgan was mistaken to set aside embryology in the quest for results in genetics; "since heredity is expressed during the process of development",[36] the two domains are inextricably interrelated.[37]

Few biologists shared in Just's celebration of the cytoplasm, and few demoted the nucleus from the seat of development, still fewer from the seat of heredity. Just's 1939 book was relatively uninfluential, due in some small part at least to his to his use of ridicule in challenging the almost magical powers of the gene according to the gene theory. Throughout the twentieth century the nuclear gene has extended its monopoly position in the biological sciences, and an understanding of ontogeny vastly different from Just's has flourished throughout the biological realm.[38]

Embryology (now known as developmental biology) was left out of the Modern Synthesis, despite the efforts of Just or Goldschmidt, or Waddington or Schmalhausen.[39] While the synthesis of genetics and evolutionary biology made no room for the discipline of embryology, it did comprise an account, however incomplete, of embryogenesis. To be sure, whatever development meant after the Modern Synthesis, it

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[35]Gilbert (1988), pp. 333, 331.

[36]Gilbert (1988), p. 331 (citing Just's *The Biology of the Cell Surface*, p. 70).

[37]E.S. Russell was another biologist who refused the encroachment of the geneticists, and Russell, like Just, insisted that heredity is "primarily a feature of development" (Russell, 1930, p. 8) rather than some separable phenomenon.

[38]In this regard, Raphael Falk (1991) has remarked that "the fact that Morgan, a central figure in embryological research at the time, turned his back so absolutely on the problems of the phenotypic expression of the genotypic potentials, must have played a decisive role in the hegemony of the gene that has prevailed ever since in genetic research" (p. 470).

[39]On the latter two figures, see Gilbert (1994).

had nothing to do with embryology as an autonomous science; ontogeny, as I noted above, was redefined in genetic terms, leaving behind the heterogeneity of approaches to development that once characterized the discipline of embryology.

It is ironic that though Richard Goldschmidt's macroevolutionary thesis of "hopeful monsters" – at odds with the Neo-Darwinian hypothesis of gradual, microevolutionary change – was laughed out of the committee room, the integration of genetics and embryology that Goldschmidt espoused nonetheless became a central component of the Synthesis – even if Goldschmidt himself was not responsible for its inclusion. I add this qualification for two simple reasons: Goldschmidt had already burned bridges in the genetic mainstream, alienating himself from the Morgan school on a number of fronts in the previous quarter-century; and his 1938 synthesizing effort, *Physiological Genetics*, was deemed just as irrelevant as Just's *The Biology of the Cell Surface*.[40] It is nevertheless worth briefly rehearsing the main theme of *Physiological Genetics*, again for two reasons: its portrayal of the relation between genetics and development has persisted in one form or another throughout the twentieth century, and Goldschmidt has recently emerged as a hero in yet another effort at biological resynthesis, that of Jeffrey Schwartz.[41]

Goldschmidt's position is antithetical to that espoused by Just. For Goldschmidt, the discipline of genetics was primary, and embryogenesis was merely "the epiphenomenon of activities directed by nuclear genes".[42] This focus on the activities of genes is dissimilar from that of the Morgan school, which focused on their location along the chromosomes and their intergenerational transmission; furthermore, unlike the official line of mainstream genetics, Goldschmidt was interested less in the transmission of genes than in their expression. He admitted in *Physiological Genetics* that "we know next to nothing of

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[40]Gilbert (1988), pp. 320-321, 340.

[41]It is noteworthy, therefore, that Schwartz (1999a) makes no mention of Goldschmidt's *Physiological Genetics*, focusing instead almost exclusively on his 1940 *The Material Basis of Evolution*.

[42]Gilbert (1988), p. 320 (referring to Richard Goldschmidt's *Physiological Genetics* (New York: McGraw-Hill, 1938).

the action of the hereditary material in controlling development", but he shared the dream of many geneticists that a genetic account of ontogeny would be forthcoming; thus Goldschmidt's book was meant to exhibit all that was then known about gene expression in ontogeny.[43]

Goldschmidt's focus was in large part on the temporal basis of morphogenesis. One of the difficulties for the gene theory had been to explain just how it is that genes – identical in every cell in the body – could lead to the production of such diverse of body parts and structures as bones and kidneys, eyes and hearts. Goldschmidt's explanation was that the timing of gene activity was decisive, and in this regard he presented at length evidence of "homeotic mutations" which, as it were, transform body parts, e.g., antennae into legs, or halteres into wings. Goldschmidt showed that in mutant fruit flies changes in the timing of gene action could lead to an antenna instead of a leg, and thus, by extension, large-scale ontogenetic changes could be induced through small-scale changes in the (timing of the) activities of genes.[44] Development was a genetic affair – and so Morgan was wrong to separate the two.

Against Just and others, Goldschmidt held that it was the nuclear genes, and not the cytoplasm or anything else, that bore the weight of ontogeny; his position was based on the successes of nuclear transplantation experiments performed by Hämmerling – and ignored by Just. Hämmerling showed that in the unicellular protist *Acetabularia*, when the nucleus of one species is transplanted into the decapitated stem of another species, the recipient stalk would regenerate a cap not of its own species, but rather characteristic of that of the nuclear donor. On this basis, Goldschmidt inferred that nuclear genes directed ontogenesis, and that the cytoplasm merely responded to the genetic directives. The cytoplasm was strictly a substrate, an inert background for the crucial activity of the genes. "In Goldschmidt's model, the cytoplasm carries no potentials. It is impotent and subservient, a far cry from the potent, active

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[43]Gilbert (1988), p. 334 (citing Goldschmidt's *Physiological Genetics*, pp. v and 1).

[44]Gilbert (1988), p. 335.

cytoplasm proposed by Just".[45] Thus was Goldschmidt able to conclude that any developmental problem was in essence a genetic problem, and therefore embryology and genetics could be synthesized – under the banner of genetics.

Goldschmidt further held that small changes in the timing of gene activity could effect macromutational monsters, hopefully seeking a mate and a secure place in the biological world. This latter view was at odds with the microevolutionary bent of the Modern Synthesis, and Goldschmidt's proposed synthesis, bringing together genetic, ontogenetic, and phylogenetic considerations, was supplanted by the narrower version endorsed by the Modern Synthesizers. In this regard, Goldschmidt, according to Stephen Jay Gould, suffered the greatest ignominy of all: near-continuous neglect punctuated by ridicule.[46] Yet now Goldschmidt is having the last laugh, for work on homeotic mutations is at the forefront of developmental genetics, a new synthetic discipline seeking to explain ontogeny in genetic terms. Goldschmidt's monsters are still hopeful, though, for many developmental geneticists see no need to interpret their results as supporting any macroevolutionary doctrine, let alone Goldschmidt's particular version.[47]

Though Goldschmidt was a shadowy figure for much of the past six decades, having latched on to a macroevolutionary paradigm that remains somewhat marginal,[48] his view that development could be explained genetically was nonetheless commonplace in genetics circles throughout almost the whole of the twentieth century. Though there have been numerous, sometimes high-profile, detractors, such as C.H.

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[45]Gilbert (1988), p. 336, 337.

[46]Gilbert (1988), p. 321 (citing Stephen Jay Gould, "Introduction", in Richard B. Goldschmidt, *Material Basis of Evolution* (1940; reprint; New Haven: Yale University Press, 1980), pp. xiv-xv).

[47]E.g., Budd (1999).

[48]It is worth noting that Stephen Jay Gould and Niles Eldredge's theory of punctuated equilibrium need not, and should not, be interpreted as consilient with Goldschmidt's account of macromutation. Though some, e.g., Schwartz (1999a), seek in Gould a powerful ally in revitalizing Goldschmidt, homeotic mutations – and recent work on the homeobox genes – are not clearly evidence of macroevolution, and may also dramatically overrate the efficacy of genes in ontogeny.

Waddington, Brian Goodwin, Susan Oyama, and Steven Rose,[49] research agendas in biology over the past ninety years have tended to converge on a genetic account of ontogeny, one according to which the nucleus holds court over the rest of the cytoplasm; as Erwin Schrödinger pithily and presciently remarked, the genes are well-understood as "law-code and executive power – or, to use another simile, they are architect's plan and builder's craft – in one".[50] More than fifty years have passed since Schrödinger, a physicist, published *What Is Life?*, and it is remarkable that, ever since, this picture of the gene has become further deeply entrenched in biological research and ideology.[51]

1.3. Modern Developments

To be sure, geneticists to this day have virtually nothing to say in response to questions about the development of an organism from an egg – or, more remotely, from a genome. For instance, as Lewis Wolpert has noted:

> We have the feeling, perhaps an illusion, that we understand the basic principles controlling development. We can see how cascades of gene action and intracellular signalling can generate pattern. Even with the limb there are quite plausible models involving homeobox genes and growth factors (Wolpert and Tickle, 1993). Against that must be set our ignorance: there is not a single case in vertebrates where a signal molecule has been unequivocally identified; our understanding of cell structure with respect to the establishment of polarity is still primitive; so too is our understanding of morphogenesis at the molecular level. There are plausible models for gastrulation in flies, sea urchins and amphibians but the molecular basis and their genetic control is lacking. We are also particularly weak in our understanding of features like the regulation of

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[49]Waddington was convinced that a complete account of ontogeny would include reference to genes, but only in the context of the developing embryo; the account would therefore emanate from a genetically informed embryology, and not from genetics proper. For discussion, see, e.g., Gilbert (1991). Goodwin is a proponent of developmental structuralism, within which genes are largely irrelevant. Hull (1998) is an accessible review essay of Goodwin and Gerry Webster's *Form and Transformation* (Cambridge: Cambridge University Press, 1996). For a critique of developmental structuralism, see Mahner and Bunge (1997). Oyama (1985) is the *locus classicus* of developmental systems theory. Rose (1997) is a wholesale rejection of gene-centrism.

[50]Schrödinger (1944), p. 23.

[51]Murphy and O'Neill (1995) celebrates this half-centenary, complete with predictions for the next fifty years.

size and form.[52]

It is therefore surprising that four years earlier, Wolpert would unashamedly assert his conviction that "genes control development", that "DNA provides the programme which controls the development of the embryo and brings about epigenesis". In a passage reminiscent of Schrödinger, he extols the virtue of that "most golden of molecules":[53]

> *Ex ovo omnia* was on the frontispiece of William Harvey's book on embryology in 1651. *Ex DNA omnia* is more appropriate since development is dependent on DNA. The genes are made of DNA, which is both simple and complex, passive yet active, a truly magical molecule. It is the DNA, and the DNA alone, that carries the genetic information. But DNA is a rather passive molecule even though it rules our development. In contrast, it is the very active proteins that are the true wizards of the cell. The power of DNA lies in its containing both the instructions for making all the proteins in the cell, and the programme which controls their synthesis.[54]

According to Wolpert, then, (1) we know practically nothing about ontogeny, even though we imagine that we know something, and our knowledge is particularly limited at the molecular level; and (2) we know that DNA is (somehow) responsible for ontogeny, as both architect and master-crafter.

Evelyn Fox Keller has explained the basis of this seeming paradox: "molecular biologists could not say how an egg turns into an organism (in other words, they could say nothing 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".[55] Though we are hardly closer today than we were ninety years ago to bridging the gap between factor and character, gene and phene, or egg and

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[52]Wolpert (1995), p. 62 (the reference is to L. Wolpert and C. Tickle, "Pattern Formation and Limb Morphogenesis", in M. Bernfield (ed.), *Molecular Basis of Morphogenesis* (New York: Wiley-Liss, 1993), pp. 207-220).

[53]James D. Watson, cited in Bodmer and McKie (1994), p. 10.

[54]Wolpert (1991), pp. 1, 5, 77. For a commentary on claims about the putative magical powers of DNA, see, e.g., Nelkin and Lindee (1995).

[55]Keller (1995), p. 20.

organism, we have a vast technical vocabulary (borrowed largely from information theory) upon which to draw in making all sorts of claims about the genetic basis of all sorts of things – no longer just of bristle patterns in *Drosophila*, but also of risk-taking, schizophrenia, chess-playing ability, happiness, religiosity, dyslexia, divorce, suicide, and, of course, organismal development. We do not substantiate the rhetoric, and so speak of development only on the abstract level of genetic codes and programs; worse, we do not even recognize the need to do otherwise, thanks to our attendant conviction that "ultimate" explanations are genetic explanations, however fuzzy they may be.

A nice example of this fuzziness appears in Ernst Mayr's reflections on the discipline of biology. Mayr wants it both ways: genetic information is meaningful only in a complex cellular and organismal context (which is surely true), and genes alone dictate ontogeny (which is wishful, wrongful thinking). According to Mayr, research since the beginning of the twentieth century has shown that "the behavior of developing cells was attributable not just to genes but also to the cellular environment in which these cells found themselves at different stages in development". But, alas, Mayr further contends that "the genetic program is the underlying factor of everything organisms do. It plays a decisive role in laying down the structure of an organism, its development, its functions, and its activities. ... Whether we deal with physiology, development, genetics, neurobiology, or behavior, molecular processes are ultimately responsible for what happens".[56]

Another recent instance of this sort of thinking is Alex Rosenberg's assertion, following Lewis Wolpert, that from "the total DNA sequence and the location of all proteins and RNA" we could predict the development of an embryo or, alternatively, compute, or even construct, the embryo.[57] Of course, it must be emphasized that genetic research does not aim at the study of development as such, as Morgan

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[56]Mayr (1997), p. 152, 123.

[57]Rosenberg (1997). The quotation is from Wolpert (1994), p. 571. Keller (1999) is profoundly critical of Rosenberg's overenthusiastic and particularly fuzzy paper. I include "predict", "compute", and "construct", as Rosenberg and Wolpert both appear to slide casually from one to the next.

explained and Russell underscored, but rather strictly at the role that genes play against a constant background of enabling factors;[58] but Rosenberg takes the additional, unwarranted step of interpreting the genetic research as providing a full explanation of development. The reason he makes this move is clear: "just as cell-cell signaling is ultimately to be cashed in for a chain of molecular interactions that extend from one stretch of nucleic acids to another across several lipid bi-layers (the cell membranes), all other cellular structures implicated in the machinery of differentiation will eventually have to be disaggregated into their molecular constituents, if development is fully to be explained".[59] Yet it is not clear that such disaggregation constitutes an adequate explanation at all – Rosenberg merely assumes that it does. Martin Mahner and Mario Bunge have underscored that a microreduction is *prima facie* no more explanatory than a macroreduction.[60] And as Eva Neumann-Held has recently argued, scientific explanations are bipartite, having both differentiative and integrative components:

> A conceptual differentiation is indispensable to make the whole accessible to descriptions as structure or process. The crucial point is, however, that a conceptual fragmentation is not enough. To the contrary, the relationship of the conceptually differentiated entities between each other and to the system has to be worked out. This is the *integrative* part, in which the relations between the "pieces" and their variation in time become part of the description. In the description of organisms (more generally: of systems), biology still has to perform the integrative part. So far, biology can describe organisms down to the molecular level of genes. However, the interactions of genes with other, non-genetic components to form an organism is far from being understood. [61]

Recognition of this explanatory gulf is completely lacking in Rosenberg, and in all those who would posit that the development of an organism is merely a matter of genes in action, that the organism is simply an

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[58]E.g., van der Weele (1999), p. 24.

[59]Rosenberg (1997), p. 454.

[60]Mahner and Bunge (1997), pp. 116-117 and elsewhere.

[61]Neumann-Held (1999), pp. 106-107. Bob Perlman has pointed out (personal communication) that Neumann-Held does not quite follow her own counsel here. Her task is to provide an expansive concept of the gene adequate to developmental systems theory; but rather than offering an account which comprises the folded, functional DNA (analogous to the integrative component), she stops, short, at a linear polypeptide chain (analogous to the differentiative component).

epiphenomenon of the genome. Morgan, who is almost singlehandedly responsible for the early successes of genetics and the meteoric rise of the discipline, never made such a claim – and neither should we.

In a recent study, Soraya de Chadarevian has carefully reconstructed core elements of the history of Sydney Brenner's attempts to molecularize development by focusing on the nematode worm, *Caenorhabditis elegans*, beginning around 1963.[62] De Chadarevian points out that Brenner was influenced by the operon model of gene regulation proposed by Jacques Monod and François Jacob in 1961, but that he was critical of its usefulness for explaining development. As Brenner declared in 1974, in a passage equally applicable to Rosenberg and Wolpert, "it is not good enough to answer [questions regarding development] by saying it is simply a matter of turning some genes on and others off at the right times. It is true that molecular biology provides numerous detailed precedents for mechanisms by which this can, in principle, be done, but we demand something more than these absolutely true, absolutely vacuous statements" (Brenner, 1974, p. 786). Nevertheless, at that time Brenner left untouched the underlying notion that there was a logic of development, a genetic program controlling development that could be identified and elucidated.[63]

Gunther Stent, in a trenchant critique of the molecularization of development, particularly but not exclusively as undertaken by Brenner, scathingly declared that molecular biology has had a "noxious impact" on developmental biology, particularly because it endorses the belief that the genome houses a "genetic program for development, from zygote to adult".[64] For Stent, at best we have the illusion of a genetic or generative program. De Chadarevian notes that Brenner eventually came more or less to agree with his critic: "While celebrating the achievements of the worm project, Brenner, in an interview with

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[62]For an equally recent philosophical inquiry into behavioural genetics in *C. elegans*, see Schaffner (1998a), as well as the commentaries by Griffiths and Knight (1998), Gilbert and Jorgensen (1998), and Wimsatt (1998), and Schaffner's response (1998b).

[63]De Chadarevian (1998), p. 94 (citing Sidney Brenner, "New Directions in Molecular Biology", *Nature* 248 (1974), pp. 785-787, at p. 786).

[64]Stent (1985), p. 1.

Science, conceded that the original expectation that there would be a logic of development encoded in a genetic programme had had to be abandoned. The notion of a programme, Brenner now warned, must be handled with care, 'even when used metaphorically'".[65] Sadly, Brenner's hard-earned lesson has by and large not been heeded. Consider the case of the homeobox hustlers.

In 1984, the homeobox genes – a class of genes thought to be highly conserved even across remotely related phyla, and thought to play a role in the generation and evolution of organisms – were discovered, an event that developmental biologist Frank Ruddle heralds as "one of the major scientific breakthroughs of this century".[66] Ever since, often outlandish but always bold claims about homeobox genes have littered the science journals. Such claims have begun to excite philosophers as well. For instance, a recent paper by philosopher Alex Rosenberg, briefly discussed above, celebrates the homeobox hoopla with verve and vigor, and is not at all out of step with current hype in biology and anthropology. It is worth exploring briefly why this is a parade not worth joining.

The homeobox is a sequence of 180 nucleotides encoding 60 amino acids;[67] it was identified first in the fruit fly *Drosophila*, but has now been found in a wide variety of organisms. This sequence of nucleotides is highly conserved across homeotic genes; that is, homeotic genes all contain virtually this same sequence of nucleotides.[68] The amino acids specify a homeodomain, which is a DNA binding domain regulating interactions between DNA and the protein containing the homeodomain, thereby influencing DNA transcription. The proteins produced via homeoboxes play a variety of developmental roles, typically involving the regulation of cell fate and the activation of sometimes large numbers of other

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[65]De Chadarevian (1998), p. 96; citing Brenner from R. Lewin, "Why Is Development So Illogical?" *Science* 224 (1984), pp. 1327-1329.

[66]Ruddle (1998), p. ix.

[67]See Figure 3.5 in Gehring (1998:48) for a chart of these acids and their respective codons.

[68]For elaboration, see, e.g., Gehring (1998), Gilbert (1997), Hall (1998); Schlichting and Pigliucci (1998).

genes instrumental in the formation of basic body plans. One homeobox gene, *Ultrabithorax*, may be involved in regulating the activities of as many as 170 genes in *Drosophila*.[69] This is one of the reasons that homeobox genes are often referred to as "master genes": they are thought to be the first active genes in a developmental 'cascade' of regulatory genes, the genes that set in motion a complex of processes necessary for the formation of, e.g., a head or a limb. Of considerable interest to those of an evolutionary mindset is what we are to make of the growing consensus that although vertebrates and arthropods "have strikingly different body architectures, many of the regulatory genes they use to establish their body plan are conserved".[70] That is, the same homeobox genes are thought to regulate vastly different *Baupläne* in vastly different species.[71]

Now, what inferences are we entitled to draw from the claim that developmental cascades are apparently initiated by specific, phylogenetically widespread genes? In large part, that is an empirical question (though one not likely to be answered should recent trends in developmental genetics persist; see below). For now I will consider conceptually what is so far established, in an effort to guard against certain unsavory interpretations currently in vogue.

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[69]Mastick *et al.* (1995).

[70]Kmita-Cunisse *et al.* (1998), p. 3030.

[71]But what does it mean to say that mice and worms and fruit flies and humans and yeast have the "same" regulatory genes? Gilbert, Opitz, and Raff (1996, p. 364) discuss the general problem: "Vertebrate body segmentation and insect segmentation are thought to be independently evolved modifications. Insects don't have somites or bones. Vertebrates don't have germ bands or cuticles. It seemed that the molecular biologists had forgotten the distinction between homology and analogy. Then, something happened. First, it was shown that the homeotic genes of mice, humans, and other vertebrates are arranged in the same order on the chromosome as the homeotic gene complex in the fly. Second, it was shown that the anterior-posterior expression pattern of the individual genes was the same in the fly and in vertebrates. And last, it was shown that the enhancer region of a human homeotic gene, such as *deformed*, can function within *Drosophila* to activate gene expression in the same relative position as in the human embryo — in the head" (1996:363-364, references omitted). Sequence similarity, expression pattern similarity, and inductive similarity therefore are thought to amount to homology, if not of structure then at least of process.

One set of implications of homeobox gene activity involves individual development.[72] One of the discoverers of the homeobox genes, Walter Gehring, insists that there is "a precise developmental program which controls ontogeny", and that investigation of the homeobox has demonstrated "how much of the developmental program is written into our genes"; in fact, Gehring's position is the bolder one that "the genetic program" of the homeobox genes actually "controls development and evolution".[73] *Antennapedia* (*Antp*) is Gehring's homeobox gene of choice; it is involved in the same homeotic mutation as that studied by Goldschmidt: the replacement of legs with antennae or antennae with legs (hence the name "Antennapedia"). *Antp* is involved in selecting between two alternative developmental pathways, and because Gehring holds to the notion of a genetic program controlling development, Gehring interprets *Antp* as a "master control gene" – rather than as a (less baggage-laden) "switch" or "selector" gene. The latter locutions are preferred by many developmental biologists, specifically because the notion of a genetic program is so problematic.[74]

Gehring, though, insists on the genetic program trope, and because the *Antp* is thought to be the first active gene in the developmental 'cascade' leading to one or the other outcome, it is the master-controller of leg formation. It is worth noting briefly (though I will flesh the point out in later chapters) that gene activation is crucially context-dependent, and a large number of interacting agents and processes must be in place for *Antennapedia* to be activated at all. *Antennapedia* does not arise from nowhere and operate in a precursorless void. For "apart from the developmental system there is no informational flow

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[72]For heuristic reasons, I will set aside consideration of the other prime area of concern, namely the evolutionary implications of homeobox genes, for another occasion. Let me say simply that there are two main sets of considerations in this regard: whether homeobox gene activity could be a mechanism of macroevolution, and what evolutionary lessons are to be drawn from claims about the wide phylogenetic distribution of similar (homologous?) developmental mechanisms. For a start on these questions, see, e.g., Budd (1999), and Schwartz (1999a,b) on macroevolution, and Akam *et al.* (1994); Akam (1995); Hall (1998); Shubin *et al.* (1997); and Valentine *et al.* (1999) on the evolution of development.

[73]Gehring (1985), p. 3; Gehring (1998), pp. xi, xiii.

[74]Burian (1997), p. 257. See also L. Moss (1992), and the discussion in chapters two and three of the present dissertation.

starting from the DNA".[75] Moreover, the whole idea of a developmental 'cascade' – a linear sequence of events – is rapidly being undermined by work in molecular biology on dynamically interacting complex systems.[76] Though we may find a gene whose product is necessary for a given developmental event to occur, it is a mistake to think either that the causal pathway is linear, or even that the causal pathway ends (or begins) with that gene. "The causal pathway is endless and involves not only genetic, but manifold structural, chemical, and physicochemical events, a defect in any of which can derail the normal process".[77] Thus putative master control genes are themselves "controlled" – and the genetic program of development is nowhere to be found.[78]

Nevertheless, this idea of master control genes encoding developmental programs has numerous adherents, including paleoanthropologist Jeffrey Schwartz, mentioned above as a champion as well of Goldschmidt. Schwartz holds the usual positions on gene action in ontogeny: that genes "encod[e] for the characteristics that make up an entire, functioning individual", that "genes produce features" including both morphological and behavioural features, that genes are "at the base of morphology", and that "a change in a gene produce[s] a change in morphology".[79] To these commonplaces (however misguided), Schwartz contributes an even more far-fetched claim about the ontogenetic role of homeobox genes: "It is mind-boggling to realize that, *for all intents and purposes*, many differences between a fruit fly and a human may lie pretty much where and when certain homeobox genes are activated. To be sure, there are some other differences between a fruit fly and a human at the molecular level. But, *fundamentally*, the main difference between organisms lies in alterations in development that result from differences in the

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[75]Neumann-Held (1999), p. 126.

[76]Keller (1999), p. 326.

[77]Nijhout (1990), p. 442; see also Wolf (1995).

[78]For elaborate critiques of the notion of a genetic program beyond the scope of this presentation, see Oyama (1985); Nijhout (1990); Moss (1992); Mahner and Bunge (1997).

[79]Schwartz (1999a), pp. 211, 38, 357. Each of these statements is either problematic or mistaken.

timing of homeobox gene activity".[80] Schwartz then goes even further, contending that "when particular genes are turned on for certain lengths of time and in certain regions, a worm may emerge. If the same or other genes are expressed for different lengths of time and in different regions, a more complex organism may develop".[81] Such a suggestion is plainly false – worms do not produce frogs, no matter how many experimental manipulations of homeobox genes one performs. Worms produce worms: while we may induce species-*X*-specific structures in an organism of species *Y*, this is a long way from *X*s birthing *Y*s thanks to small changes in the timing of gene expression! For there is far more to development than the expression of homeobox genes – all the minutiae of organismal reproduction, for instance.

Yet it is exactly those details – the modular, spatiotemporally specific networks of gene-protein-organism-environment interaction – that are left out of too many accounts of development circulating under the banner of developmental genetics, in favour of claims about the necessary and sufficient (given an amenable background) role of preformed "instructions" in the genes. Nevertheless, Philip Kitcher has recently argued that biology today – operating in the shadows of the Human Genome Initiative and the homeobox hype – is sufficiently rich to resist "the hegemony of molecular biology". Kitcher identifies molecular hegemony as the (unacceptable) position that "real (rigorous, complete) explanations of the properties of living things trace those properties to interactions among molecules"[82] – exactly the position proudly held by Dunn, Spiegelman, Mayr, Rosenberg, and Gehring, for instance. Kitcher believes that we can couple biological work that does not appeal to molecular biology – mathematical modeling of the diversity of mammalian coat patterns, for instance – with its necessary "molecular base", and thereby achieve a multi-leveled theoretical approach to development.[83] It is a nice idea, a romantic vision of how

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[80]Schwartz (1999a), p. 13, emphasis added.

[81]Schwartz (1999a), p. 352.

[82]Kitcher (1999), p. 196.

[83]Kitcher (1999), p. 196.

biology might have been, had we somehow managed to avoid the last seventy years. But as Gilbert has maintained, during the 1930s battles between geneticists and embryologists, "the geneticists claimed that development could be approached as an epiphenomenon of genetic control and therefore that genetics could best obtain the answers to developmental questions. In fact, all biology was seen as epiphenomenal of the genetic processes, so it was natural for them to assert that genetics should be primary". Meanwhile, embryologists were more pluralistic in their outlook, recognizing and celebrating the heterogeneity of approaches – including, for some, genetic approaches – necessary to elucidate developmental phenomena. The geneticists, though, were (and are) methodological monists;[84] they won out over the embryologists, and the geneticists' dream of the molecularization of development (and evolution, and, "for that matter, everything else under the biological sun"[85]) has come to fruition.

Perhaps Kitcher is right to be optimistic, though. After all, recent work in molecular biology is itself pointing up the limitations of molecular biology.[86] But his insistence that development necessarily has a molecular basis is disarming, not least because the same sentiment has driven the geneticization – and now the molecularization – of biology ever since Morgan. To be sure, Kitcher holds that molecular work in comparative genomics, for instance, cannot "proceed by ignoring macro-level studies of development and physiology", and thus we ought to resist hegemonic claims that "molecular biology is all the new biology we need".[87] But he nevertheless insists that his multi-leveled approach to development needs its molecular base – which is far too often a recipe for ideological, epistemological, ontological, and methodological overemphasis on genes.

I want, deeply, to share in Kitcher's optimism. But important work remains to be done. In the

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[84]Gilbert (1988), pp. 316-317.

[85]Pinto-Correia (1997), p. 309.

[86]See, e.g., Keller (1999).

[87]Kitcher (1999), pp. 208, 200.

chapters that follow, I will describe and critically assess various perspectives on the role of genes in ontogeny, several of which would surely undermine Kitcher's confidence, and only one of which bolsters my own. Joseph Needham remarked that the contrast between preformationism and epigenesis is "an antithesis which Aristotle was the first to perceive, and the subsequent history of which is almost synonymous with the history of embryology".[88] I shall set my investigations within this illustrious framework.

Conventional wisdom has it that neither preformation nor epigenesis alone is sufficient, but that some compromise between them will suffice as a starting point in the explanation of development. Seems simple enough. Yet there is a vast variety of competing definitions of these concepts, and just as many different attempts at reconciliation. I will attempt a taxonomy of modern perspectives on preformation-epigenesis combinations; my account will be representative rather than comprehensive. Then I will propose an alternative synthesis and elaborate on its metaphysical and methodological strengths.

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[88]Needham (1959), p. 40.

Chapter Two – The Persistence of Preformationism

> Epigenesis may be an extremely sensible position to take,
> but preformation just will not go away.
> – *Clara Pinto-Correia*[1]

2.1. The Modern Consensus

Public discourse about genetics is saturated with technical words and concepts tossed about, almost willy-nilly; ordinary speakers do not really have much if any idea what they are speaking of when they use these words – such as, for instance, "gene" or "genetic predisposition".[2] But they nonetheless continue to use these poorly understood words, and the words have powerful connotations for their efforts to grasp what happens to them when they go to the doctor, are asked to take a test, decide thanks to the advice of a genetic counselor to chart their genetic inheritance, read about an important new medical "breakthrough", and so on. Rather than becoming bogged down in this public morass of "fascinating genetalk",[3] I will instead attend to a word that ordinary people have never heard, let alone used in casual conversation at the water cooler: that word is *epigenesis*. My contention is that our understanding of biological activity, and the very nature of living things, hinges crucially on our understanding of epigenesis as the basic process of organismal development. In fact, our very sense of the possibilities of gene action is constrained by our conception, whether implicit or explicit, of epigenesis. The idea of epigenesis has a rich history dating back to Aristotle, and is typically understood as the antipode of

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[1]Pinto-Correia (1997), p. 308.

[2]For discussion, see, e.g., Robert (1998a). It is worth underscoring that neither do biologists corporately agree on the definition of 'gene', a concept that has distinct incarnations in population genetics, oncology, psychiatry, and cell biology, for instance. For recent discussions of the meaning of 'gene', see, e.g., Falk (in press) and Neumann-Held (1999).

[3]The phrase is Kitcher's (1996).

"preformation"; thus both epigenesis and preformationism will occupy me in the following chapters, beginning here with preformationism.

Throughout the twentieth century, commentators have claimed to have reconciled the two positions – positions described by Thomas Hunt Morgan as Scylla and Charybdis[4] – such that development is now standardly construed as the epigenesis of something preformed. Thus we are all presumably both epigenecists and preformationists – though there is a broad range of opinion as to exactly what "epigenesis" and "preformation" are supposed to mean. Care must be taken in specifying the meanings of these terms, else we risk merely pretending to have achieved consensus on the explanation of development.

The concept of preformation is supremely plastic, hurled as an epithet by one camp, updated for the modern world by another. It is generally agreed that *something preformed* develops (epigenetically) into a mature organism; as Løvtrup suggests, "that something is 'preformed' at the outset of each individual case of ontogenesis is so evident that it seems incredible that it has sometimes been thought necessary to supply experimental evidence in support of this point".[5] Yet what exactly that preformed something is, and how it is preformed, is a matter of dispute – Løvtrup's incredulity notwithstanding. Let us then begin with several representative modern statements of the distinction between preformation and epigenesis, before proceeding to a critical interrogation of their bases in this and the next chapter.[6]

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[4]Maienschein (1991a), p. 257 (citing Thomas Hunt Morgan, "Sex-Determining Factors in Animals", *Science* 25 (1907): 382-384 at p. 384). The invocation of this dyad is common in the history of biology in the nineteenth and twentieth centuries; for instance, each of E.S. Russell (1933), Wilhelm Roux (1894), and Timothy Lenoir (1982, discussing Blumenbach) employs the metaphor in characterizing the materialism-vitalism disputes.

[5]Løvtrup (1974), p. 8.

[6]Needham (1959), p. 40, remarks that the antithesis between epigenesis and preformation is coextensive with the history of embryology. For the pre-twentieth-century history of the "antithesis" see, e.g., Needham's seminal work (1959), and also Pinto-Correia's brilliant and entertaining analysis from the perspective of the vanquished – that is, of the preformationists (1997). Actually, as we shall see, the preformationists have arisen anew in modern garb, and with a host of new problems in addition to some of the old ones.

The eminent biologist and philosopher Ernst Mayr has recently proposed a problematic (because ambiguous and somewhat inaccurate) formulation of the dispute – demonstrating the propriety of Woodger's remark that "in biology our fundamental notions are for the most part so vague and lacking in precise definition that it is impossible to work out their logical consequence".[7] Mayr provides quite unhelpful (circular, circumscribed, contrived) glossary entries of the terms that concern me: "preformation" refers to the theory "that an embryo develops from material in which the essential form of the adult is 'preformed', that is, already exists in its essential structures", while "epigenesis" is the theory "that new structures originate during ontogeny from undifferentiated material with the help of a vital force [*vis essentialis*]". So construed, Mayr is correct to refer to both positions as "now-discredited".[8] But he also claims that the positions are "partly right and partly wrong", requiring the advances of twentieth-century genetics and molecular biology to resolve the problem of development once and for all.

> The first step came from the field of genetics, which distinguished between a genotype (the genetic constitution of an individual) and a phenotype (the totality of the observable characteristics of an individual) and showed that during development the genotype, by containing the genes for becoming a chick, could control the production of a chick phenotype. By thus providing the information for development, the genotype is the preformed element. But by directing the epigenetic development of the seemingly formless mass of the egg, it also played the role of the *vis essentialis* of the epigenesis.
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> Finally, molecular biology removed the last unknown by showing that the genetic DNA program of the zygote was this *vis essentialis*. The introduction of the concept of a genetic program terminated the old controversy. The answer was thus, in a way, a synthesis of epigenesis and preformation. The process of development, the unfolding phenotype, is epigenetic. However, development is also preformationist because the zygote contains an inherited genetic program that largely determines the phenotype.[9]

This passage is an excellent starting point for my analysis, containing as it does central elements

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[7]Woodger (1930), p. 5. Mayr's book is his (1997).

[8]Mayr (1997), pp. 310, 307.

[9]Mayr (1997), pp. 156, 157-158. A pre-DNA-era perspective is that of E.B. Wilson, writing in 1925: "In respect to a great number of characters, *heredity is effected by the transmission of a nuclear preformation which in the course of development finds expression in a process of cytoplasmic epigenesis*" (Wilson 1925, p. 1112; emphasis in the original). Note, however, that Mayr would appear to be making a still stronger point, namely that epigenesis is *directed by* the "nuclear preformation".

of what might be construed as the Modern Consensus on epigenesis and preformation.[10] These are the overlapping and mutually reinforcing theses of Genetic Informationism (that genes contain preformed, species-specific developmental information); Genetic Vitalism (that a genetic program in the zygotic DNA controls [directly or indirectly] the development of an organism); and Genetic Primacy (that DNA is the prime ontogenetic mover and that the phenotype is the secondary unfolding of what is largely or wholly determined by the genes). Thus are preformation and epigenesis reconciled – the (preformed) genetic program in the zygotic DNA contains specific ontogenetic information and determines the (epigenetic) development of an organism. There is no need for the previous centuries' preformationists' "strange tales of small men" in reproduction,[11] nor for the epigenecists' vital force acting from without – the very idea of the genetic program solves this seminal problem of embryology.

But there are several difficulties with this picture: for instance, there is no such thing as a genetic program; genes do not already contain developmental information, nor do they initiate or direct ontogeny; and there is no straightforward unfolding relation from genotype to phenotype.[12] The putative Modern Consensus is a failure on all counts – yet it persists in the writings and research programmes of a wide range of biologists.

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[10]For a sample of the "Premodern Consensus", as it were – apparent in the writings of C.O. Whitman, for instance – see Whitman (1894); for discussion, see Maienschein (1986), but beware of sometimes prejudicial anachronisms in her characterization of his views. One example: Whitman asks "how far is post-formation to be explained as the result of preformation, and how far as the result of external influences?" (Whitman 1894, p. 221) – which Maienschein renders as "How much depends on the developmental response to external conditions rather than on *programmed* internal unfolding?" (Maienschein 1986, p. 91; my emphasis). It must surely be recognized that Whitman in his lecture during the summer of 1894 had no concept of an ontogenetic *program*, for the use of computer language in biology is of much more recent origin. In placing words in Whitman's mouth, Maienschein evidences the propriety of Evelyn Fox Keller's argument that with the rise of processor-mediated language, computer-age concepts dominate our biological imagination (Keller 1995, p. 118) – even facilitating the misrepresentation of historical positions. Since part of my thesis is that there are lessons to be learned from those biologists (particularly embryologists) who resisted the hegemony of genetics in the early part of the twentieth century, I should strive for greater accuracy in the portrayal of their positions.

[11]The phrase belongs to Pinto-Correia (1999).

[12]See, e.g., Moss (1992), Neumann-Held (1999), Wolf (1995), and Strohman (1993), respectively.

Mayr's version of the Modern Consensus is by no means idiosyncratic. For instance, in 1970 Alex Fraser conjectured that "the preformed basis of an individual has its identity in the constant informational content of the genes (the homunculus has a nucleic acid morphology). The epigenetic translation of the genetic information involves complex sets of genes acting in a variable milieu of genetic and environmental effects, such that constant progression and fixed end points eventuate".[13] And Jane Maienschein cites the position of the Medawars as "fairly typical": "the genetic instructions according to which development proceeds are indeed preformed, but their realization is *epigenetic*, i.e. turns upon influences acting upon the embryonic cell from the outside".[14] Similarly, J.A. Mazzeo, in his introduction to the 1977 edition of Oscar Hertwig's classic 1896 book *The Biological Problem of To-Day: Preformation or Epigenesis?*, writes:

> In our own time, the progress of molecular biology has finally elucidated that structure of the gene, a one-dimensional segment of DNA, which can both duplicate itself and serve as a "template" for intermediary substances, messenger RNA and transfer RNA, which build the three-dimensional structure of the protein, and the organism is understood as the "translation" of the information contained in the gene. The gene is, thus, a "message," and the truth of preformation is that what is "preformed" is the information for making an organism.[15]

Mahner and Bunge therefore remark that in modern incarnations of preformationism, "encapsulated miniature adults or preformed morphological parts have been replaced by 'coded instructions'".[16]

Two final instances of the Modern Consensus, construing the reconciliation of preformation and epigenesis as the epigenetic triggering of preformed genetic information, are those of Stephen Jay Gould

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[13]Fraser (1970), p. 57. On the impropriety of invoking the homunculus in discussing preformation, see Pinto-Correia (1999) and (1997).

[14] Maienschein (1986), pp. 101-102, citing P.S. and J.S. Medawar, *The Life Science* (New York: Harper and Row, 1977).

[15]Pinto-Correia (1997), p. 308; citing Joseph Anthony Mazzeo, "Introduction", in *The Biological Problem of To-day: Preformation or Epigenesis? The Basis of a Theory of Organic Development*, authorized trans. by P. Chalmers Mitchell (Oceanside, NJ: Dabor Science Publications, 1977). Of course, DNA, as an inert molecule, cannot replicate itself but must rather be replicated in the process of ontogeny.

[16]Mahner and Bunge (1997), p. 280.

and A.L. Peck. Gould remarks that

> The solution to great arguments is usually close to the golden mean, and this debate is no exception. Modern genetics is about as midway as it could be between the extreme formulations of the eighteenth century. The preformationists were right in asserting that some preexistence is the only refuge from mysticism. But they were mistaken in postulating preformed structure, for we have discovered coded instructions. (It is scarcely surprising that a world knowing nothing of the player piano – not to mention the computer program – should have neglected the storage of coded instructions.) The epigeneticists, on the other hand, were correct in insisting that the visual appearance of development is no mere illusion.[17]
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> With this rapprochement, one might think that the two original views would be equally respected in the historical paragraphs of modern textbooks in embryology. Yet these paragraphs almost invariably read like the script of a western movie, with epigeneticists as "good guys," preformationists as "bad guys," and the supposed triumph of epigenesis as the foundation of modern embryology. In so doing, preformationism is rendered as an absurd caricature of itself.[18]

Peck, meanwhile, is somewhat less charitable toward preformationism: in a footnote in his translation of Aristotle's *De Generatione Animalium* – the *locus classicus* of epigenesis – Peck describes the triumph of epigenesis over preformationism as an overdue vindication of Aristotle. Nevertheless, he notes that preformationism is not and was not entirely barren: "like many erroneous theories, preformationism contained some truth, for we know to-day that the course of the embryo's development is predetermined by its genetic constitution".[19]

But do we in fact know this? Is it really the case that "the course of the embryo's development" is in any way "predetermined by its genetic constitution"? Surely that is Mayr's position, and Gehring's, too, as I suggested in Chapter One. Irving Gottesman, a leading schizophrenia researcher whose work I discuss below in Chapter Four, in describing his perspective on the complexity of gene-environment interaction, sums up the diathesis-stressor (predisposition-trigger) approach in the slogan "Nature proposes and Nurture disposes" – an idea rendered pithily by the Medawars as "genetics proposes,

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[17]This comment about the visual appearance of novelty points all the way back to Aristotle, as described briefly in Chapter One.

[18]Gould (1977), pp. 18-19; see also his (1997), p. xv. Pinto-Correia's (1997) is meant to correct for this imbalance of attributed respect.

[19]Peck in Aristotle (1953), p. 145 note *a*.

epigenetics disposes".[20] Such a perspective also clearly underwrites the effort to map and sequence all the genes in the human genome. Once we have the sequence of an abstract human, we can use it as a template to understand the complex activations and interactions which constitute the developmental unfolding of the genotype. Bodmer and McKie offer just such an explanation of the value of the Human Genome Project: "by learning about how our genes affect our bodies and minds, we can subtract that influence from our equations and learn more about the others".[21] Similarly, Zinder, Grisolia, and others imagine uncovering "the recipe to construct human beings" or "the instructions for building human organisms", while Alan Wolffe claims that "when the Human Genome Project reaches its goal, there will be a complete parts list for a human being".[22] By mapping and sequencing the genes of a hypothetical normal human, we solve for nature, and then can hold nature constant while solving for nurture (which reduces, in the main, to environmental triggering of genetic potentiality).[23]

Clearly such gene-centric claims about the HGP are reductionistic, in the sense of attributing to genes foundational, determinative powers unleashed by environmental interactions. Marga Vicedo attempts to defend the Project by suggesting that we are mistaken to assume that such pronouncements on the HGP – which are clearly of the gene-as-catholicon variety – are valid depictions:

> The pejorative characterizations of the HGP as reductionistic suggest that the simplistic and misleading claims made about the project by some of its participants will promote a simplistic conception of human biology. ... It is possible that these assertions are only made to attract social interest and the attention of agencies to fund the project. They are, nevertheless, unsupported by our current knowledge of biology. This point concerns not the epistemological claims about a discipline, but the ethical position of scientists as experts when addressing the public. While this latter issue is important, it should not be confused with the epistemological problem of

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[20]Gottesman (1991), p. 91; Schlichting and Pigliucci (1998), p. 230, citing P.B. Medawar and J.S. Medawar, *Aristotle to Zoos: A Philosophical Dictionary of Biology* (Cambridge: Harvard University Press, 1983). For a discussion of "epigenetics" and its relation to "epigenesis", see below, Chapter Three.

[21]Bodmer and McKie (1994), p. viii.

[22]See Zinder (1990); Grisolia (1991); Smith and Hood (1987); Wolffe (1995).

[23]Of course, there is more to nature than genes, though the formula genes=nature is rampant in the literature on the HGP.

reductionism.[24]

Here Vicedo makes one good and two less good points. The claim that "our current biological knowledge" disavows the kind of remarks just cited (those of Wolffe and the others) is not wholly satisfactory. As I shall show, there is a strong sense in which "our current biological knowledge" is pretty well divided over the question of the relative value of genes in the constitution of the organism. If "our current biological knowledge" were of a piece, there would be no problem, and Vicedo's warning not to mistake rhetoric for science would be well taken. But we cannot be so optimistic as that. There are plenty of gene-centrists within the biological establishment; thus we need to be more suspicious than Vicedo implies – even though it is also true that a number of biologists explicitly disown gene-centrism.

The second of Vicedo's problematic claims is related to the good point she makes. While she refreshingly recognises that an ethical responsibility attaching to claims to know is sometimes abused by HGP proponents in efforts to secure public and financial support (the good point),[25] she nonetheless holds that there is a valid demarcation between science and scientistic propaganda (or rhetoric). Though she does not elaborate, it is clear from the passage just cited that she distinguishes between actual biological knowledge and "simplistic and misleading" claims about such knowledge made for the express purpose of generating attention and financial support. Philip Kitcher has made related claims about misguided critics of the HGP who pay too much attention to popular accounts and not enough to the actual work carried out under the auspices of the Project.[26] But I am not convinced that we can so easily separate the two. Scientists have long since benefitted from this ideological contrast between science and popularization; all manner of careless assertions by experts are excused as mere popularization, while the real science in all its complexity, warts and all, is left in the lab, far from the prying eyes of the laity.

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[24]Vicedo (1992), p. 273.

[25]For elaboration, see, e.g., Allen (1998) and Robert (1998b).

[26]Kitcher (1999), p. 207.

Nevertheless, the careless assertions are the ones that contribute to public policy-making and funding decisions, and we ought not to downplay the deeply entrenched contribution of the science media to the continuing education of scientists in terms of both the exchange of research results and also the accessibility (thanks to the simplicity) of their accounts to scientists who are not specialists in some particular field.[27]

Nor ought we not to ignore the very real changes in laboratory practice engendered by traffic in popular though misguided metaphors: when research programmes with no gene-sequencing component are altered to include such a component in order to receive funding, the very nature of the work in that lab is changed; some components of the programme may be discontinued, and solutions will be sought through new (but perhaps inappropriate) experiments. We ought not, then, to downplay the role of often oversimplified and popular representations in the definition and orientation of scientific research strategies. Imagining organisms as machines or DNA as coded developmental information has a profound impact on the direction of research, for as Richard Lewontin has recently suggested, "science cannot be conducted without metaphors".[28] That includes the metaphorical notion that DNA encodes information foundational to – and, when triggered in the appropriate environment, sufficient for – the generation of traits and whole organisms. On this view, once we have the DNA sequence of a hypothetical human, we will be able to identify the individual genes (construed as stretches of DNA) involved in particular ontogenetic processes, and to elucidate the (genetic and nongenetic) mechanisms for

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[27]For some brief, helpful remarks on the role of the science media, see Glen (1994), pp. 85-88; see also Robert (1998a), pp. 233-236.

[28]Lewontin (1996), p. 1. Lewontin continues: "Yet, at the same time, these metaphors hold science in an iron grip and prevent us from taking directions and solving problems that lie outside their scope". See also Rose (1997, p. 120): "it is hard to know which had more impact on the future directions of biology – the determination of the role of DNA in protein synthesis, or the organizing power of the metaphor within which it was framed" – namely, the *master-molecule* trope. For detailed analyses of the role of metaphor in the progress of science, see Keller (1995), (1994); Doyle (1997); Dreger (1997); for an overview, see Robert (1999).

their activation.[29] It is at least not obvious, then, that we can draw a viable distinction between actual and popular science, for popular accounts (or their analogues) contribute to the development of actual science, just as actual scientists are often themselves responsible for the ostensibly rhetorically inflated popular accounts.[30]

2.2. Historical Precedents, Contemporary Counterparts

But of more moment for my purposes in the present chapter are the particular construals of Genetic Information and Genetic Vitalism identified above in the Modern Consensus on the reconciliation of epigenesis and preformation. I will address these in some detail, as well as such notions as ontological emergence, reductionism, and systemism, in the present chapter. The Modern Consensus remains close to an 18th-century position put forth by Kant and J.F. Blumenbach, updated thanks to input from Watson and Crick, and re-presented in the impressive-sounding but highly ambiguous terms so characteristic of biology in the second half of the twentieth century. Kant helped to systematize a consensus which had been forming among biologists during the latter half of the eighteenth century. Blumenbach had set out his primary ideas in a 1781 treatise, *Über den Bildungstrieb und das Zeugungsgeschäfte*, which Kant discussed in his 1790 *Critique of Judgement*. Lenoir notes that Blumenbach's work is usually celebrated for what Lenoir (incorrectly, it would seem) terms a "relatively modest achievement", namely the

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[29]Or, on Rosenberg's interpretation of the homeobox genes (the discovery of which is not dependent on the HGP), once we have identified the "master control gene" (certainly a metaphor!) at the "top" of the developmental "cascade" (another metaphor) for the eye, for instance, then "identifying the other genes in the cascade that produces the entire eye should in principle be a piece of normal science" (Rosenberg 1997, p. 454). For a critical interrogation of Rosenberg, see Keller (1999). The reason I place the word "top" in scare quotes is to foreshadow my critique of the Genetic Primacy thesis, to be addressed in the next chapter.

[30]In Chapter Four, below, I discuss the nature of work in a gene-obsessed modern psychiatry, and distinguish it from the sort of work to be encouraged within a psychiatry not subject to the hegemony of the gene.

overthrow of classical preformationism in favour of an epigenetic account.[31] But it is better to characterize Blumenbach's achievement (with the help of Kant) as an early reconciliation of preformationist and epigenecist points of view.[32]

Blumenbach accounted for organic structure by invoking a new, pseudo-Newtonian, specifically biological force – the "development drive" or *Bildungstrieb*. According to Blumenbach, the *Bildungstrieb* could not be reduced to chemical particles, and he portrayed it in plainly teleological terms. But it was not an *ante res* force acting from without, or somehow imposed on matter. In this regard, Blumenbach was not a standard-issue vitalist: rather, for Blumenbach the *Bildungstrieb* had no existence apart from its material constituents. But it was emergent from these constituents and was not reducible to them.[33] Pinto-Correia notes that the *Bildungstrieb* was thought by Blumenbach to be inherited through the germ cell, and she characterizes the position as a model according to which "development could proceed epigenetically through a predetermined force inherent in the matter of the embryo — the primordia of modern developmental biology".[34]

Martin Mahner and Mario Bunge provide an account of emergence which would appear to dovetail nicely with Blumenbach's idea (though perhaps not with the minutiae of his account, especially regarding teleology). The idea of emergence is presently experiencing a renaissance, as numerous authors attempt to wrest it from its vitalist roots and place it firmly in modern biology.[35] Mahner and Bunge

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[31]Lenoir (1982), pp. 2, 18.

[32]Pinto-Correia (1997), pp. 4-5, 304-305.

[33]Pinto-Correia (1997), p. 4; Lenoir (1982), pp. 20, 21.

[34]Pinto-Correia (1997), p. 5.

[35]See, for instance, the very different accounts given by Spencer-Smith (1994-1995); Humphreys (1996); Emmeche *et al.* (1997); Schaffner (1998).

reconcile emergence with (some version of) reductionism, and of materialism.[36] They begin by noting that despite being broadly misunderstood, the emergence of qualitative novelty is central to evolutionary biology, as well as to other branches of science. They contrast *emergent* properties with *resultant* ones: if some whole x has a property p possessed as well by at least one of the components of x, then p is said to be resultant; but if x has some property q not found among the components of x, then q is said to be an emergent property of x. Emergence is thus an ontological, not an epistemological, notion; an emergent property is not epiphenomenal – it will not disappear once we understand the relevant processes more completely – but is rather an inescapable feature of the real world.[37] (Nevertheless, emergence may represent a problem for epistemology as well, for emergent properties cannot (always) be explained and predicted from our knowledge of lower-level systems.)

Crucial to the elucidation of Mahner and Bunge's account of emergence is their analytical approach to systems. Their basic model of material systems focuses on the composition-environment-structure triple; hence the *CES analysis of systems*. By *composition (C)*, they refer to the collection of the component parts of a system. Its complement is the system's immediate or proximate *environment (E)*, referring to those things related to but not part of the system.[38] The final element, *structure (S)*, comprises

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[36]Wimsatt (in press [a]) suggests, against the usual story, that reductionism and emergence are not actually in opposition; instead, "claims involving emergent properties in discussions of non-linear dynamics, connectionist modelling, chaos, artificial life, and elsewhere give no support for traditional anti-reductionism or wooly headed anti-scientism". See also Wimsatt (1997) and (1986a).

[37]Mahner and Bunge (1997), pp. 29-31 (the quotations are from p. 29). Mahner and Bunge's materialist orientation, their commitment to the slogan that "matter matters", is the reason they prefer the baggage-laden notion of emergence over the more biophilosophically mainstream – but stuff-free – notion of *supervenience* (pp. 32-33, 150).

[38]Note that the environment, so construed, is a set only, and not itself a system; consequently, an environment is to be defined relative to a given system, at a given time (Mahner and Bunge 1997, pp. 25-26). Mahner and Bunge cite Lewontin (1983) as offering a comparable analysis. It is worth noting that it may sometimes be difficult to separate the composition of a system from its environment. Mahner and Bunge want to avoid the perils of anti-analytic holism, but must also avoid erring too far on the side of atomism: not only are environments relative to systems, but so too are systems relative to environments; the components of one shape the components of the other, and the reverse, as well.

both internal and external features of a system – its endostructure and exostructure. Since Mahner and Bunge's concern is with biological systems, they call their position *biosystemism*, and they conceive the *bios* as "an emergent level rooted to the chemical one".[39]

Mahner and Bunge insist that to ignore any of the three factors they distinguish is to misconstrue the system, and many researchers are guilty on this count: atomists attend to composition at the expense of environment and structure; holists attend to environment or supersystem, ignoring composition and structure; and others endorse structuralism and neglect composition and environment. A biosystematist, however, holds that no system reduces to just one or two of these coordinates, but rather is emergent from all three of them:

> If the emergentist-materialist ontology underlying biology (and, as a matter of fact, all the factual sciences) is correct, the *bios* [life] constitutes a distinct ontic level the entities in which are characterized by emergent properties. The properties of biotic systems are then not (ontologically) reducible to the properties of their components, although we may be able to partially explain and predict them from the properties of their components. ... The belief that one has reduced a system by exhibiting [for instance] its composition, which is indeed nothing but physical and chemical, is insufficient: physics and chemistry do not account for the structure, in particular the organization, of biosystems and their emergent properties.[40]

The ontological categories of atomism and holism thus have epistemological counterparts, namely microreductionism and macroreductionism (or anti-reductionism), respectively. Mahner and Bunge are, not surprisingly, critical of these epistemological categories, too. The former approach holds that science is ultimately reducible to physics, while the latter, at its most extreme, precludes the possibility of science altogether. "The microreductionist thesis is that we know a thing if we know what it is 'made' of [its composition], while the macroreductionist thesis is that we know it if we figure out its place in 'the scheme of things' [its environment]". But the whole point of systemism is the coalescence of knowledge of both the compositional and environmental elements, along with the endo- and exostructures of the system – charting a new course, as it were, for the unity of science: through integration, not

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[39]Mahner and Bunge (1997), pp. 24, 25-27, 140.

[40]Mahner and Bunge (1997), pp. 28, 197.

reduction.[41] Mahner and Bunge's "modest reductionism" – comparable to Wimsatt's "articulatory reductionism"[42] – as a research programme therefore involves the following two heuristics: expect (and account for) material emergence; and reduce where possible, either in full or in part, but never greedily and always according to the *CES* analysis of systems.

Several of these ideas were presaged in Kant's elucidation of Blumenbach's problematic notion of the *Bildungstrieb*. As Lenoir explains:

> it was difficult to see how in Blumenbach's view the formative force could be completely rooted in the constitutive materials of the generative substance, to the extent that altering the organization of these constituents would result in the production of different organisms, and still somehow be incapable of reduction pure and simple via chemical and physical laws to the constitutive material itself; how it could be both dependent on and independent of the materials constitutive of the generative substance.[43]

According to Lenoir, Blumenbach sidestepped this question; but Kant treated it directly in an effort to explain exactly how the proposal could appeal to both teleology (akin to vitalism) and mechanism (akin to reductionism) without plunging into inconsistency. For Kant, the problem is that a strictly mechanical mode of explanation is inadequate to the organic realm. As John MacFarland explains:

> Anything which is an organized system [i.e., an organism] and not an aggregate of parts which might have been thrown together at random, is entirely contingent as far as the question of mechanical laws [cause and effect] is concerned ... He [Kant] does not claim that we will never be able to explain organisms mechanically because they are too complicated ... Kant believes that it is impossible in principle. For Kant, as for many of his contemporaries, the distinctive characteristic of organisms is simply their non-mechanical nature.[44]

Hence Kant's definition of organism, which he also calls "natural purpose": the parts enjoy the very possibility of their existence through their relationship to the whole (the unified whole is prior to both the form and being of the parts), and the parts of the unified whole are mutually cause and effect of each

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[41]Mahner and Bunge (1997), pp. 111, 116.

[42]I am unsure as to where (if anywhere) Wimsatt uses this phrase in print, though he does use it in conversation; for the basic idea, see Wimsatt (in press [a]), (1997), (1994), (1986a).

[43]Lenoir (1982), p. 24.

[44]McFarland (1970), pp. 136-137.

other.[45]

According to Lenoir, Kant infers the existence of such natural purposes "as an objective fact of experience", on the basis of two sets of evidence. First, organisms cannot be produced by mechanical means – which continues to be true, despite the best efforts of adherents to the strong Artificial Life programme, for instance.[46] Artificial Life (AL) comes in two variants, one strong and one weak. According to the weak programme, we can (and should) attempt to understand living systems by means of mechanical and computer modeling; but proponents of the strong programme go much further in trying actually to synthesize living systems. But, as Mahner and Bunge have persuasively shown, AL rests on an ontological mistake. AL proponents insist that the composition of a system is irrelevant, for the properties of the whole (the living system) do not rely in any significant way on the properties of its component parts. But Mahner and Bunge argue that "matter matters": any emergent property of a system (such as 'being alive') depends on the properties of its component parts. "Mimicking one or the other emergent property of a biosystem does not suffice to create a biosystem proper".[47]

Kant's second type of evidence for the existence of natural purposes is based on organic reproduction. "The evidence of generation, even in the cases of misbirths, indicates that something analogous to 'purpose' or final causation operates in the organic realm, for the goal of constructing a functional organism is always visible in the products of organic nature, including its unsuccessful attempts".[48] Kant concludes that the biological organism is, accordingly, both cause and effect of itself.

In sum, then, the Blumenbach-Kant position reconciles a version of preformationism with a

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[45]Lenoir (1982), p. 25, who cites Kant (1951), p. 219.

[46]Lenoir (1982), p. 25, who cites Kant (1951), pp. 217-218.

[47]Mahner and Bunge (1997), pp. 149-153; the quotation is from p. 150.

[48]Evelyn Fox Keller would appear to be referring to the same phenomenon without the explicit teleological commitments, when she discusses the "robustness" of the zygote – which may have some affinity with the spirit (if not the letter) of Wolpert's notion of "triumph of the embryo". See Keller (in press); Wolpert (1991). I take up this idea of robustness in some detail in Chapter Five.

version of epigenesis; what is preformed is a material development drive which emerges from and yet also guides the epigenetic development of the individual organism. The organism is thus both cause and effect of itself – the embryo embodying and fulfilling "the law of its own being".[49] The position avoids the usual charges against vitalism by insisting that the vital organizing force is not an independent entity, but rather an emergent property materially and lawfully dependent on the composition, order, and arrangement of the parts of the ontologically prior whole organism.

In commenting on the position of Kant and Blumenbach, as well as on the fate of preformationism in the 18th century, Pinto-Correia notes that "we have to admit that Kant's and Blumenbach's last conciliatory concept ..., in which epigenesis is directed by a set of preprogrammed instructions, is not, in its essence, all that far removed from our current views in developmental biology".[50] Which is exactly my point regarding Mayr's statement of the Modern Consensus. Of course, Kant and Blumenbach had no sense of the "preprogrammed instructions" Pinto-Correia projects onto them – Mayr, too, updates their reconciliation by invoking DNA as what is preformed, and by describing the whole ontogenetic process in terms borrowed largely from cybernetics. But, as I hinted above, this revision of the 18th-century position is impoverished; I shall now indicate my reasons for this assessment.

2.3. Genetic Informationism

Mayr, too, is an emergentist in epistemology and methodology: "in a structured system, new properties emerge at higher levels of integration which could not have been predicted from a knowledge of the lower-level components. ... Analysis should be continued downward only to the lowest level at which this approach yields relevant new information and insights". But Mayr also contends that the organicist

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[49]Russell (1930), p. 7. This passage in Russell is not about Kant and Blumenbach, though his understanding of preformation and epigenesis is, I think, largely compatible with theirs. For discussion, see below (this chapter and Chapter Three).

[50]Pinto-Correia (1997), p. 305.

emergentism position requires a further concession: that "it is the genetic program which controls the development and activities of the organic integrons that emerge at each successively higher level of integration".[51] In fact, writes Mayr, "the genetic program is the underlying factor of everything organisms do. It plays a decisive role in laying down the structure of an organism, its development, its functions, and its activities". For Mayr, then, the "genetic program" – "the information coded in an organism's DNA" – generates the emergent organism.[52] Thus does Mayr's account of ontogenesis combine the three theses of Genetic Informationism, Genetic Vitalism, and Genetic Primacy identified above. But what is genetic information? What – and where – is the genetic program? And whence does the ontogenetic primacy of genes issue? I will address the latter question in the next chapter, and attend now to genetic informationism and vitalism.

Mahner and Bunge (following the work of Bunge and Ardila) identify six different meanings of "information" in circulation in modern molecular biology, and argue that not a single one is defensible.[53] The six meanings, with critical remarks in square brackets, are as follows:

Information$_1$ = meaning *qua* semantic information [but meaning is a semantic not a biochemical concept – regardless of the wizardry of biochemists, they cannot get meaning from reactions in a beaker].

Information$_2$ = signal and Information$_3$ = message carried by a pulse-coded signal [these interpretations stem from classical information theory, and thus "presuppose a genuine information system, which is composed of a coder, a transmitter, a

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[51]Mayr (1997), pp. 19, 20. The concept of the "integron" is borrowed from François Jacob: "At each level, units of relatively well-defined size and almost identical structure associate to form a unit of the level above. Each of these units formed by the integration of sub-units may be given the general name 'integron'. An integron is formed by assembling integrons of the level below it; it takes part in the construction of the level above" (Jacob 1973, as cited by Mayr 1997, p. 19).

[52]Mayr (1997), pp. 123, 307.

[53]Mahner and Bunge (1997), pp. 280-284; see also Bunge and Ardila (1997).

receiver, a decoder, and an information channel in between. No such components are apparent in a chemical system. ... Many assertions to the contrary notwithstanding, the expression 'genetic information' is unrelated to the concept of information as it is rigorously defined in the statistical theory of information"[54]].

Information$_4$ = quantity of order (negentropy) of a system [efforts to quantify information – e.g., by listing all of the instructions by which biosystems could be assembled from their component parts – all depend on the components on which we choose to focus; if we focus on atoms, we will arrive at an estimate vastly different from our estimate if we focus instead on cells; consequently, such efforts measure not the quantity of order in the system (ontological), but rather our knowledge of the composition and organization of the system (epistemic)].

Information$_5$ = knowledge or instruction [as for knowledge, note that there is no knowledge beyond the brains of knowers, and thus there is no knowledge in the genes; as for instructions, the very notion of an instruction – or of a rule or an order – presupposes a being able to respond to that instruction (or rule or order). For Mahner and Bunge, there is no such being, and so genetic information-as-instruction fails, as well].

Information$_6$ is a medley of two other interpretations of information = the communication of Information$_5$ (construed as knowledge) by social behavior (such as speech), involving Information$_2$ (a signal) – and so fares no better than either of them taken separately.

As Mahner and Bunge show, most biologists do not mean to invoke Information$_4$ when using the

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[54]Mahner and Bunge (1997), p. 281; they refer to Apter and Wolpert (1965) at the end of the second sentence. For similar remarks, see Oyama (1985), pp. 64-67.

phrase "genetic information" – the Information$_4$ content of two genes may be 1000 bits each; that is, the two genes have identical Information$_4$ contents; but, presumably, the genes have nonidentical functions, which would suggest that the genes do not in fact have the same informational content. Hence Mahner and Bunge suggest that what biologists really mean by "genetic information" is rather either Information$_1$ or Information$_5$.

Given these various senses of "information", it is plausible to suggest that "information" is what linguist Uwe Poerksen calls a *plastic word*, an amorphous but scientifically saturated word stretched so far beyond its appropriate field of applicability that it loses coherent meaning.[55] Mahner and Bunge suggest that "information", which is at best a metaphor if not a misnomer, has by now become an "all-purpose term" in biology. "It sounds very scientific, and seemingly indicates some deep insight, but it is often nothing but a disguise of ignorance, inviting people to proceed according to the rule 'If you don't know what it is, call it *information*'". Mahner and Bunge do contend that there is exactly one legitimate, non-metaphorical, biological use for the phrase "genetic information" – namely, to "refer only to the specific composition and structure of the genetic material" – but because of the slipperiness of the notion they urge that we cease and desist from information talk altogether in both molecular and developmental biology.[56]

Another critic of genetic informationism is Evelyn Fox Keller, whose masterful book, *Refiguring Life*, addresses the play of metaphor in the development of biology. Keller notes that biologists have only lately begun to rediscover the critical importance of extra-nucleic factors in ontogenesis, transmuting the reductionistic "discourse of gene action" into the discourse of gene *activation*; thus biologists would appear to have begun to understand the organism as more complex and corporeal than a mere translation of the genetic sequence. Yet Keller urges that the body which now re-enters biological discourse is vastly different from "the organism that the old embryologists sought to understand", and so she sets out to

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[55]See Poerksen (1995); for some elaboration, see also Robert (1996).

[56]Mahner and Bunge (1997), pp. 281, 284.

understand the subtle and overt transformations in the organism that biology has ostensibly re-discovered.[57]

As Keller makes clear, a major contributor to these somatic transformations is the simplest of computer-age metaphors, the body as information system. Keller traces the history of the information metaphor, and of the "communication" of "information", through the past century, emphasizing quite different instantiations in various disciplines. Her concern throughout is to establish the bodily impact of the metaphorical traffic in information, to note both the mechanizing of organisms and the vitalizing of machines. She concludes that thanks to the rise of processor-mediated language, the computer "dominates our imagination", producing "the body of a new machine", and introducing "dramatically new ways of experiencing and interacting with that body".[58]

A particularly clear instance of this conceptual transformation – replete with a completely uncritical acceptance of its propriety – is a recent paper by Werner Müller. Tracing an ostensible history from Aristotle to modern molecular genetics, Müller is specifically concerned to characterize the moderns' fortunate "recognition" of genetic information as "an essential principle governing living beings":

> To understand the dawning of an imminent, silent revolution in science we should be aware that "information" and related terms, which are now among the most often used terms in Biology, were introduced in science only in the second half of our century. Today's biologists can hardly imagine a *Biology without (genetic) "information", without (genetic) "code", without "transcription" and "translation", without "messenger molecules", "signals", "receptors", "signal transmission and transduction", without antibodies that are able to "recognize" antigens, without "control", "regulation" and "data processing".*[59]

It is helpful to draw out the similarities between Müller's and Mayr's perspectives on Aristotle, vitalism, and DNA.

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[57]Keller (1995), pp. 28, 24-25, 42.

[58]Keller (1995), pp. 97, 118, xvii.

[59]Müller (1996), pp. 21, 22 (italics, inexplicably, in the original).

Mayr suggests that though Aristotle was an impressive thinker, his primitive "scientific" work lacked the methodological rigor of modern science. He laments the "backward state of biological explanation" available to Aristotle (and everyone else prior to the twentieth century). Aristotle was preoccupied with explaining the specificity of development, why it is that frogs give birth to frogs and not kittens.[60] As we have already seen, Kant held the specificity of development to be indicative of natural purpose; so did Aristotle, who posited a kind of "final cause" in the zygote. Aristotle, according to Joseph Needham, "put forward a conception of the unfertilised egg as a complicated machine, the wheels of which would move and perform their appointed function in due course when once the master-lever had been released" by the sperm.[61] What ensures that the wheels go round, churning out real structures from potential ones? Aristotle gives a teleological response, according to which "'that for the sake of which' a series of events takes place is the intrinsic endpoint in which, if nothing fatally interferes, that series normally culminates".[62]

Marjorie Greene argues that it is a mistake to interpret this Aristotelian notion of "that for the sake of which" -- of *telos* -- in terms of purpose or plan. "What usually happens to a fertilized robin's egg, for instance? A baby robin hatches out of it; that is its *telos*. There is absolutely no question of any kind of 'purpose' here, either man's or God's. To suppose otherwise is to introduce a Judeao-Christian confusion of which Aristotle must be entirely acquitted". "In general the 'soul' of any living thing is its style of operating on and in its environment, no more, but also no less". Thus when Aristotle posits an *entelechy* to account for the embryonic actualization of potential structures in the sex cells, he is not attributing purpose or intention to the embryo, but rather "an orderly development toward a normal

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[60]Mayr (1997), pp. 107, 12, 154.

[61]Needham (1959), p. 55.

[62]Greene (1972), pp. 397-398.

end".[63] On this account, the end itself does not temper the means; the end is simply the result of the process of development, and not somehow involved (as intention or purpose) in directing the means to that end.

Yet for Mayr, the specificity of development indicates that the egg contains "information" to "guide it toward its intended goal". Thus does he conclude that "only in our time was it realized that Aristotle's *eidos*, the seemingly metaphysical agent, is nothing else but what we now refer to as the genetic program, hence strictly explicable by physicochemical factors. The development of a fertilized egg is guided by a genetic program" – by which Mayr means information encoded in DNA. Similarly, Mayr contends that any vitalist tendencies in the history of biology – from Aristotle to Driesch – can be corrected merely by substituting "genetic program" for the antediluvian "entelechy" or "eidos".[64]

Müller, too, sets out to update "soul" and "entelechy" through the (in his view) more satisfactory notion of genetic information. In short, Müller replaces the soul with the gene.[65] Several comments are in order. First, Müller's account of Aristotle, like Mayr's, suffers from the misinterpretation that Greene cautions against: imbuing it with purposiveness rather than order.[66] Secondly, though Müller has several complaints about Drieschian "entelechy" and Aristotelian "soul", his account of genetic information is almost coextensive with them. For instance, he complains of Driesch's "entelechy" that it is immaterial; yet despite unresolved disputes about whether information itself is "material", Müller insists, without argument, that "whatever the outcome, it is simply a fact that genetic information is carried by macromolecules". Likewise, he bemoans that "Driesch's entelechy grew to a universal entity just like the

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[63]Greene (1972), pp. 398, 414, 399.

[64]Mayr (1997), pp. 154, 307 – Mayr's glossary entry for "genetic program" is "the information coded in an organism's DNA".

[65]This theme is explored in great detail in Nelkin and Lindee (1995).

[66]Barry Allen has reminded me that David Hume argued this point in *Dialogues Concerning Natural Religion*: we cannot assume that wherever there is order, there is purpose.

soul of Aristotle. It governs life in all its qualities ... [and has become] a source of universal information capable of governing all that could not be explained in the terms of contemporary science". But it is unclear why Müller should complain of the universal ontological and epistemic invocation of entelechy in almost the same breath as he lauds "the recognition of internal *(genetic) information* as an essential principle governing living beings".[67] It would appear that Müller objects to those who would stretch the capacities of entelechy too thin, but Müller (and many others) may be guilty of the same charge regarding genetic information.

Despite his claim that genetic information is "an" rather than "the" essential governing principle, Müller equivocates between these two positions. On the one hand, he suggests that Drieschian vitalism is easily overcome by reference to genetic information. In order to assess this claim, allow me briefly to give the background to the experiments of Driesch, and hence of Wilhelm Roux (1850-1924), as well. Roux – along with August Weismann (1834-1914), working independently – was a proponent of so-called mosaic development, according to which nuclear materials hive off qualitatively into different daughter cells during cell division: each resulting piece of the organism contains a different bit of nuclear material, though each individual, semi-independent piece is also an integral part of the whole (of the larger picture, as it were).[68] In one of the first experiments on an embryo, in 1888, Roux attempted to test his hypothesis of mosaic development.

Roux hypothesized that an embryo at the two-cell stage will have the determinants of the left side of the organism in one blastomere, and those of the right side in the other blastomere. Thus, if one were to kill one of the two cells at this stage, the embryo would retain only half of the determinants of the organism, and should develop into only a half-embryo. Roux therefore killed one of the two cells of a

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[67]Müller (1996), pp. 23, 24, 21 (italics in the original).

[68]Maienschein (1991b), p. 48. As Maienschein has shown, the work of Wilhelm His (1834-1901) on germinal localization was an important backdrop for the Roux-Weismann hypothesis; see her (1991b), as well as Moore (1993).

two-celled frog embryo using a hot needle. The other cell continued the usual cleavage process apparently independently of the dead cell, and a half-blastula resulted, which then experienced an abnormal gastrulation, producing in the end what Roux interpreted as a half-embryo. Hence Roux believed he had experimentally vindicated his hypothesis that the embryo is a mosaic of cells, each able to produce only a specific part of the developed organism.[69] Roux continued to experiment on embryos, and became convinced of mosaic development; and when he achieved results that contradicted his hypothesis, as Jane Maienschein reports, he elaborated adjunct hypotheses to protect his core belief.[70]

In a series of experiments on sea urchin embryos performed several years later, Hans Driesch (1867-1941) expected to confirm Roux's results, though Roux's methodology in 1888 may have been flawed in that he did not remove the dead cell; the behaviour of the other cell may have been influenced by the presence of the dead cell, rather than manifesting mosaic development.[71] It is noteworthy, therefore, that Roux had been unable to separate the blastomeres, though Oscar and Richard Hertwig had shown in 1887 that vigorous shaking in water would suffice. Thus did Driesch separate his sea urchin blastomeres in order to confirm Roux's results on mosaic development. The next day, he found – much to his surprise – that the separate blastomeres had each developed into "typical, actively swimming blastulae of half size".[72] The blastomeres therefore remained *totipotent*, able to respond to (intraorganismal)

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[69]Moore (1972), pp. 262-263.

[70]Maienschein (1991b), p. 51: "For example, in the few cases in frogs in which a whole embryo did result from the one blastomere, he suggested that there exists a reserve idioplasm (or set of nuclear materials). This reserve comes into action in the special cases when regeneration or postgeneration (following injury) occurs".

[71]Maienschein (1991b), p. 50. In 1910, J.F. McClendon was able to repeat Roux's experiments but to obtain Driesch's results – having separated the blastomeres. See J.F. McClendon, "The Development of Isolated Blastomeres of the Frog's Egg", *American Journal of Anatomy* 10 (1910): 425-430; see also Gilbert (1991), p. 289.

[72]Maienschein (1991b), p. 51, citing Hans Driesch, "Entwicklungsmechanische Studien I. Der Werth der beiden ersten Furchungszellen in der Echinodermentwicklung. Experimentelle Erzeugen von Theil — und Doppelbildung", *Zeitschrift für wissenschaftliche zoologie* 53 (1891), pp. 160-178, translated and abridged in B. Willier and J.M. Oppenheimer (eds.), *Foundations of Experimental*

environmental conditions and to transform themselves accordingly. Each cell retained the ability to regenerate whatever material went missing in the separation-by-shaking of the two blastomeres.[73] Rather than becoming a differentiated future part of the organism, each blastomere is able to regulate its development in order to produce a whole (not a half) organism. Hence the epithet "regulative development".

Driesch allowed for both mosaic and regulative development, and did not emphasized the differences between his results and those of Roux. Had Roux been able to separate the frog blastomeres, rather than permitting the dead one (which Driesch thought may in fact not have been dead after all, but rather merely maimed) to remain in contact with the live one, perhaps the embryo would have developed normally after all, as was the case with Driesch's sea urchins.[74] Later, though, Driesch would contend that there was a vast difference between his and Roux's results, at which point he renounced the study of embryology and set out to produce an antipredeterminist, antimosaic, vitalistic philosophy of development.

Müller claims that Driesch's misguided metaphysical speculations are easily sidestepped by invoking the notion of genetic information: "in teaching students, recent lecturers instantly have at hand a seemingly simple explanation of why isolated daughter cells or pieces of a Hydra are capable of doing the same as the fertilized egg: A complete development out of parts is possible because each cell is endowed

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Embryology (New York: Hafner Press, 1974), pp. 38-50, at p. 46 of the translation. The full passage, evincing Driesch's astonishment, is as follows: "I must confess that the idea of a free-swimming hemisphere or a half gastrula with its archenteron open lengthwise seemed rather extraordinary. I thought the formations would probably die. Instead, the next morning I found in their respective dishes typical, actively swimming blastulae of half size".

[73]Maienschein (1991b), pp. 51, 52. For a brief discussion of Driesch's 1893 experiment, as well as of what were eventually shown to be the limitations of Driesch's experiments, see Gilbert (1991), pp. 287*ff.*

[74]Maienschein (1991b), p. 52, citing the translation of Driesch's 1891 paper, at p. 48.

with the whole genetic information".[75] But that is no explanation at all! In fact it begs the very question at issue: if every cell has the same genetic endowment, then why should some cells become brain cells and others form the sphincter? For Roux, cell fate is predetermined in mosaic fashion; for Driesch, it is emergent depending on (initial and ongoing) conditions. But how exactly is the dispute decided by invoking a metaphor about predetermined but presumably nonmosaic genetic materials? More basically, how exactly is the debate over alternative accounts of development resolved by merely ignoring development?

Notwithstanding Müller's assertion that Driesch's "severely mistaken" enterprise can be avoided altogether by talking about "genetic information", he attempts to clarify his position: we must distinguish between varieties of information and not allow ourselves to be overwhelmed by universal umbrella terms such as "entelechy". But surely "genetic information" itself is just such a term, as when Müller says that each cell in the Hydra, or each blastomere in the sea urchin, "is endowed with the whole genetic information", as if that suffices to explain the differential details of development! Yet despite his occasional carelessness, Müller in the end commends the work of those biologists throughout the twentieth century who have, within the universal category "information" (to which Müller subscribes as the ontological basis of ontogenesis), distinguished between "genetic information" (encoded in mitochondrial and nuclear DNA), "epigenetic information" (such as Wolpert's notion of positional information), and "maternal information" (cytoplasmic maternal determinants). Though Müller is oddly silent on this matter, it would appear that these latter two categories of information make the vast ontogenetic difference between billions of cells endowed with identical genetic information.[76]

Nevertheless, Müller is again somewhat uncautious. He is concerned to avoid the error of, as it

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[75]Müller (1996), pp. 21-22.

[76]I should note that I adhere to a position thematically closer to Driesch's than to Roux's, epitomized by a version of the notion of a morphogenetic field as revived and elucidated by Gilbert *et al.* (1996); see the discussion in chapters 3 and 5, below.

were, the 'causal universalism' of Driesch. But Müller insists that cytoplasmic maternal determinants derive specifically from maternal genetic information (rather than any other maternal developmental resource), and his example of "epigenetic information" – in particular, positional information – has been reduced by one of its proponents, Lewis Wolpert (to whom Müller refers glowingly), to genetic information, as discussed in Chapter One. (Of course, Wolpert himself is remarkably un-careful, at times insisting that development is specified in the genes, at other times insisting that it is specified in the cells, and at still other times insisting that it is not specified at all but rather emergent from nuclear-cytoplasmic interaction.[77]) Despite occasional protestations to the contrary, genetic information is no less explanatorily universal for Müller than entelechy was for Driesch and Aristotle.

Another critic of genetic informationism is Susan Oyama, an originator of developmental systems theory (DST), a position to which I will attend in more detail in later chapters. She writes:

> The discovery of DNA and its confirmation of a gene theory that had long been in search of its material agent offered an enormously attractive apparent solution to the puzzle of the origin and perpetuation of living form. A material object housed in every organism, the gene seemed to bridge the gap between inert matter and design; in fact, genetic *information*, by virtue of the meanings of *in-formation* as "shaping" and "animating", promised to supply just the cognitive and causal functions needs to make a heap of chemicals into a being.[78]

But as Oyama makes abundantly clear, the promise has not been fulfilled. She is particularly critical of the Information$_2$ and Information$_3$ interpretations of genetic information, as well as the Information$_5$ interpretation, especially when invoked in concert with the thesis of Genetic Vitalism (to which I turn in the next section). In fact, it is helpful to distinguish yet another notion of "information", one of which Oyama is also critical (as would Mahner and Bunge be):

Information$_7$ = causal control.[79]

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[77]For an instance of each, respectively, see Wolpert (1991), pp. 77, 148, and 87.

[78]Oyama (1985), p. 12.

[79]Oyama (1985), pp. 67-70. François Jacob, for instance, characterizes information as "the power to direct what is done" (Oyama 1985, p. 67, citing Jacob 1973, p. 251).

This idea of genetic information captures all three theses of the Modern Consensus: genes encode preformed information, which is causally efficacious in controlling the development of the organism, itself nothing but the unfolding of what is genetically (informationally) preordained. For this reason, I will examine Information$_7$ in the context of the second thesis of the Modern Consensus.

2.4. Genetic Vitalism

Recall Mayr's twin claims that a genetic program is the information encoded in an organism's DNA, and that the genetic program controls the development and activities of the whole organism.[80] Mahner and Bunge, who as I noted are critical of the metaphor of genetic information, are equally critical of the notion of a program (which is, at least for Mayr, a series of instructions – genetic Information$_5$). They note that drawing an analogy with computer programs is unhelpful in specifying the nature of putative genetic programs, for a computer program is such only on account of its relation to the intentional programmer.[81] Susan Oyama makes a similar criticism, despite the fact that the use of "genetic program" has become so routine that it now constitutes a dead metaphor.[82] Oyama worries about the teleological perspective driving the invocation of genetic programs, the idea that a genetic program encodes information to direct ontogenesis toward a particular, species-specific goal:

> As we contemplate the nature in and around us, the argument from design is ever present. When we remember that our cognitive metaphors are motivated by it, as is the case when we say that an embryo develops as though it had a full set of instructions, all is well. When we forget, we entrap ourselves in the worst kind of pseudoexplanation. What is "worst" about such explanation is not that it explains nothing, but that it seems to explain everything.[83]

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[80]Recall as well my remarks in Chapter 1 about Wolpert, Gehring, Brenner, and genetic programs for development.

[81]Mahner and Bunge (1997), pp. 282-283.

[82]"Having entered the intellectual public domain, it seldom functions to point out a similarity between two phenomena, but instead is taken as a statement of fact" (Oyama 1985, p. 61).

[83]Compare my diagnosis of Müller, above.

But it is worth asking, nonetheless, what the concept of a genetic program is supposed to explain. I am not convinced that it is in any way explanatorily helpful, nor am I convinced that it is philosophically well-motivated. Of particular critical moment to proponents of DST – such as Oyama, Paul Griffiths, Russell Gray, and Neumann-Held – is the notion that information *qua* ontogenetic-controller-of-developmental-instruction is supposed to be present *in the genes*. But as Gray has argued, "developmental information is not *in* the genes, nor is it *in* the environment, but rather it develops in the fluid, contingent *relation* between the two".[84] That genes and environments interact in the production of organisms is not in question; Mayr and Wolpert, for instance, would have it no other way. But exactly what such interaction entails is a matter of dispute. My thesis is that proponents of the Modern Consensus – and of gene-centrism more generally – pay lip service to interactionism and then proceed as if genes were the primary generating and determining factor. The task of justifying this assessment will preoccupy me throughout the rest of this chapter and the next, and the point will surface again in my consideration in Chapter Four of an extended example from psychiatry.

Some uncontroversial facts about DNA point up the dubiousness of the "genetic program" trope. DNA is a relatively inert molecule, requiring activation from without. Further, in eukaryotes (cells with nuclei), DNA is covered in histone proteins and therefore not immediately accessible without cellular triage. The cellular environment which exploits the DNA is complex: even the simplest eukaryotic cells have a ribosomal 'machinery' comprising "a giant assemblage of sub-units together containing more than 80 different proteins, and RNA sequences containing more than 6,700 nucleotide bases. Without it, without the complex biochemical environment the cell provides, 'genes' ... simply can't function". Moreover, gene activation is irreducibly spatiotemporal, depending on the developmental history of the particular cell in which it is located – particularly, the cell's location in the developing embryo and the number of times the cell line that leads to it has divided. Thus, it is evident that genes are not passive

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[84]Gray (1992), p. 177.

providers of encoded instructions that retain their structure across generations, but are "reactive complexes that are in constant and dynamic interaction with their carriers". In short, in the production of an organism segments of DNA interact with proteins, metabolites, nutrients, and other segments of DNA according to a specifically structured schedule within a specifically structured environment which enables such interactions, and which is necessary for their occurrence.[85]

Despite the fact that certain of these complex processes can be made to appear to function in a programmatic way, that is not evidence of a genetic program. At most, "program in this context is an a posteriori description of a structure, and not an a priori instruction for generating a structure".[86] The ostensibly preformed informational "instructions" are not "just there" to begin with, but rather emerge progressively during ontogenesis. Thus, Eva Neumann-Held argues that "independently of context and system, the DNA has neither structure, nor function, nor program, nor information. Rather, the constancy of the transcriptional processes [e.g.] has to be attributed to the constancy of the patterns of interaction of the participating components. ... The basic DNA sequence and the developmental context determine in reciprocal contingency the structure (and function) of all regulatory sequences of transcription or translation; they *co-define* and *co-construct*".[87] Thus there is no underlying genetic program, but at most

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[85]Mahner and Bunge (1997), pp. 284-286; Rose (1997), pp. 127-128, 110; Plotkin (1994), p. 39; Nijhout (1990); Wolf (1995).

[86]Wolf (1995), p. 143; see also Oyama (1985), p. 54.

[87]Hence the euphemism "developmental contructionism", another name for DST. Compare also Burian (1997), pp. 259-260: "It is clear that many incredibly intricate multi-level domains, mechanisms, processes, structures, and so on enter into development. Furthermore, many of these are formed (pardon the pun) "on the fly" – that is, they are not laid out in advance but arise in interactions between genes and proteins that come to form a rapidly-shifting tartan of boundaries between domains and define something like morphological fields in the midst of ongoing processes of cell-type specification, tissue formation, organogenesis, etc. At any stage of development some of the relevant modules that enter into normal development preexist, others are formed in the course of events, and others will or will not be formed according to the status and condition of interacting units and modules at key moments in the processes in question".

the illusion of a such a program in the ontogenesis of an organism.[88]

Lenny Moss has subjected Mayr's claims about genetic programs (from his earlier book, *The Growth of Biological Thought*,[89] but reiterated in *This Is Biology*) to critical scrutiny. Moss attempts, in vain as it turns out, to localize the genetic program, reified or treated as a substantial entity by those committed to Genetic Vitalism. According to Moss, part of the reason that Genetic Vitalists adopt the genetic program trope is that they draw unjustified inferences from their primary investigative tool: viruses as model organisms.[90] The attribution of agency to genes is facilitated by the dramatic evidence of the formidable effects that the introduction of a virus can have on an organism. The penetration of viral DNA (or RNA) can have a drastic impact on the behavior of an infected cell, and the observation of this impact may have led investigators to overestimate the agentic role of DNA in ontogenesis. But as Moss points out,

> what becomes easy to overlook in the midst of such apparent power and efficacy is that viruses are molecular parasites whose ability to act entirely presupposes a living system, in relation to which the virus is a kind of trigger or perturbant. Shooting DNA constructs into a cell and shouting 'Now dance!' does not constitute an explanation of the mechanisms by which 'the genetic program informs and instructs ontogeny' or 'supervise[s] its own precise replication and that of other living systems such as organelles, cells, and whole organisms' (even if the cell dances).[91]

Despite historical and contemporary overstatements of the agency of the genes, Moss is open to the possibility that the notion of a genetic program may perform actual explanatory work in cell and molecular biology, yet he finds no evidence to this effect. With regard to transcription, for instance, he

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[88]Neumann-Held (1999), p. 119; cf. Nijhout (1990), p. 443. The notion of a genetic blueprint fares no better; see Mahner and Bunge (1997), p. 283, and particularly Oyama (1985) and Neumann-Held (1999).

[89]Ernst Mayr, *The Growth of Biological Thought* (Cambridge: Harvard University Press, 1982).

[90]For recent discussion of model organisms in biological research, see, e.g., Burian (1992); Bolker (1995); Gilbert and Jorgensen (1998); Schaffner (1998); and Wimsatt (1998). [The latter three papers focus on a particular model organism: the nematode worm, *Caenorhabditis elegans*.]

[91]Moss (1992), pp. 340-341; the quotations are from Mayr's *The Growth of Biological Thought*.

concludes that the harder one looks for the proximal cause of the transcriptional activation of a particular gene, the quicker one is thrust into a complex array of antecedent conditions – a point made as well by Nijhout:

> When we trace the causal pathway of a developmental event, we may often (but not necessarily always) encounter a gene whose product is required for that event, and without which that event would not take place. But the causal pathway does not end there. The expression of the gene or the activity of its product must itself be controlled by a specific stimulus, perhaps an ionic or organic inducing molecule, or through the product of a regulatory gene. Regulatory genes, in turn, owe their timely activity to stimuli external to themselves, and so forth. The causal pathway is endless and involves not only genetic, but manifold structural, chemical, and physiochemical events, a defect in any of which can derail the normal process.[92]

Reflecting upon cellular self-replication, Moss notes that the three-dimensional structure of a cell is required for DNA to be able to function as a template for the amino acid sequence of proteins; meanwhile, it is not DNA but rather the organelles, variously found in the plasma of a cell, that serve as their own template for replication. As I mentioned above, without the highly structured cellular environment, which is itself not constructed by the DNA, DNA is inert, relatively unstructured, nonfunctional, and so ontogenetically meaningless. Moss thus plausibly judges that any quest for causal origins (or ontological primacy) culminates in the intricacies of the cell/organism *as a whole* as the causal basis of "gene action". Accordingly, he concludes that the "genetic program" upon which Mayr relies so deeply is in fact "nowhere to be found".[93]

Mayr's version of the Modern Consensus, despite being an updated version of a position originally urged by Kant and Blumenbach, actually deviates from their perspective at just the wrong place, blunting its significance. The sticking point is the organism-as-a-whole – and its ontological, epistemological, and methodological sequelae. Mayr claims to hold an organicist (as well as emergentist) position. He tries to integrate the Kant-Blumenbach idea that the organism is both cause and effect of itself, noting that "development, behavior, and all other activities of living organisms are in part

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[92]Nijhout (1990), p. 442.

[93]Moss (1992), pp. 344, 335.

controlled by genetic (and somatic) programs that are the result of the genetic information accumulated throughout the history of life"; yet he urges that "it is the genetic program which controls the development and activities" of the organism. He insists that twentieth-century biologists have finally understood that "the behavior of developing cells [is] attributable not just to genes but also to the cellular environment in which these cells found themselves at different stages in development"; yet he claims that "the genetic program is the underlying factor of everything organisms do. It plays a decisive role in laying down the structure of an organism, its development, its functions, and its activities".[94]

2.5. A Note on Reductionism

Well, which is it? Is ontogenesis "partly controlled" or "wholly controlled" by a genetic program? Is the genetic program "decisive", or is "decisionmaking" rather a function of the cellular environment? Mayr seems to see two ways to establish the autonomy of biology, one of his longstanding concerns: by distinguishing between life and non-life on the basis of genetic programs, and by underscoring the unique role of emergence in biology. These two ideas are conjoined in Mayr's pseudo-antireductionistic account of organicism, but, as I shall suggest, the position is inconsistent.

I refer to pseudo-antireductionism for several reasons: first, Mayr is not an antireductionist in the antianalytical sense sometimes implied, for he encourages reduction where appropriate; secondly, Mayr's position on reductionism is somewhat ambiguous, as he fails to draw the usual distinction between different varieties of reductionism: methodological, epistemological (or theoretical), and ontological (or philosophical) reductionism. I will briefly rehearse these distinctions and their place in biology, drawing on the work of Michael Ruse and Steven Rose, before reaching my final appraisal of Mayr's position.

Methodological reductionism holds that the best strategy for understanding wholes is to understand their smallest parts. There are those who think that "small is beautiful" and those who think

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[94]Mayr (1997), pp. 21, 20, 152, 123.

that small is skimpy. Surely, sometimes small *is* beautiful; but Rose and Ruse (and Mayr) insist that we cannot let our admiration for simple elegance degenerate into praise for the simplistic. Ruse cites the geneticist Francisco Ayala: "The complete nucleotide sequence of the human genome might be helpful to biologists and health scientists as a data base for experiments. But I do not believe that it would contribute any more toward solving major biological or health problems than a computer printout of all the roads in the United States and of all the cars traveling over them in a particular year would help to ascertain the significant causes of highway accidents".[95] Thus there is a worry that methodological reductionism in biology may lend undue credibility to genetic determinism.

Nevertheless, Rose lauds the explanatory power of a reductionist methodology, attributing many of the successes of modern science, including biology, to its microreductionist method; but we must be wary here, he warns, for the simplifications required by a reductionist methodology are often inappropriate to the complexity of living systems. Thus, the method is valuable to a point but has its limits. Ruse concurs: methodological reductionism as a research strategy "can answer questions only of a certain kind ... [but] there are other important questions which need addressing".[96] Hence the need for a complementary methodology, one which corrects for the oversimplifications characteristic of biological reductionism.

There is significant interplay between epistemological (or theoretical) reduction and ontological (or philosophical) reduction. Epistemological reduction is the reduction of one theory to another presumably more basic theory, or of one discipline to another presumably more basic discipline; hence the putative reduction of Mendelian genetics to molecular genetics, or of embryology to genetics. Rose is unhappy with epistemological reductionism, and worries that if interpreted strictly it tips over into what

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[95]Ruse (1994), pp. 38, 39. Ayala was writing before his HGP-inspired transformation into a full-blown methodological reductionist – the reference is to Francisco J. Ayala, "Two Frontiers of Human Biology: What the Sequence Won't Tell Us", *Issues in Science and Technology* 111 (1987): 51-56.

[96]Rose (1997), p. 79; Ruse (1994), p. 41.

he takes to be an objectionable philosophical reductionism. Ruse meanwhile holds that ontological reduction is a good and necessary part of molecular biology, while reserving judgement on epistemological reductionism.

On the question of ontological reduction – the basic sticking point between Ruse, Mayr, and Rose – Ruse argues that "genetics generally is clearly committed to ontological reductionism. The claim is not that every organism is made up of genes and nothing but genes. We know that that is false. Rather, the claim is that the overall physical body – animal, plant, or microorganism – is no more than the parts, of which the genes are a subset". For Ruse, the only alternative to such an ontology is vitalism. But both Rose and Mayr are materialists too, and posit no mystical extra-material force. Note the polemical character of the debates between reductionists and holists. Both Ruse and Rose are hostile toward New-Age holism, and Mayr, too, worries about the metaphysical commitments of certain holists. While Ruse dismisses alternatives to ontological reductionism as mere paeans to vitalism, Rose notes that to some, "reductionism" is

> an unqualified boo-word, representing a way of emptying life of its manifold rich meanings, of turning individual personal experience into chemistry and physics, mere mechanisms. This search for other meanings lies at the heart of New Age philosophy's rejection of reductionism – a rejection abetted by a few ex-biologists, well-exemplified by Rupert Sheldrake and his theories of 'morphic resonance' – indeed, I can think of no one who better fits Dawkins' epithet 'holistier than thou'.

But while Ruse cannot imagine a materialist alternative to ontological reductionism, Rose's main task in *Lifelines* – and one of my tasks in this dissertation – is to attempt to flesh one out.[97]

What kind of reductionist is Mayr? With regard to methodological reductionism, there is some slipperiness in his discussion. On the one hand, as I noted above, he advises against greedy (methodological) reductionism, insisting that "analysis should be continued downward only to the lowest level at which this approach yields relevant new information and insights". On the other hand, Mayr falls prey to a certain genetic determinism in his endorsement of an ontogenetically primary and decisive

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[97]Ruse (1994), p. 37; Rose (1997), pp. xi, 73.

genetic program.[98] Mayr contends that the recognition of emergence tempers the apparent reductionism and determinism of a focus on genetic programs; but I harbor doubts.

As for the other two forms of reductionism, Mayr appears to support neither epistemological reduction (hence his effort to establish the autonomy of biology, and to refuse the reduction of biology to physics and chemistry) nor ontological reduction. In order to assess Mayr's proposal on this count, it is helpful at this point to return to the work of Mahner and Bunge introduced above. They distinguish between ontological microreductionism (atomism), ontological macroreductionism (holism), ontological structuralism, and ontological systemism, analyzing systems into the composition-environment-structure (*CES*) triple. Atomists argue that the organism is the sum of its parts (composition); holists argue that the organism is the product of its context (environment); structuralists argue that the organism is distinguished by its organization (structure). Accordingly, Ruse is an atomist; Sheldrake is an holist (or as close to one as I can find in the literature); and Mayr is a structuralist.

The basic features of Mayr's distinction between animate and inanimate matter are the genetic program (*qua* depository of developmental information and director of ontogenesis), and the presence in animate matter of properties emerging from the particular organization (structure) of animate matter. Only living beings have and are generated by genetic programs – hence the (ontological) autonomy of the biological subject-matter. And given the emergent properties of living beings, which implies the unpredictability of higher-level properties from knowledge of lower-level properties, biology must be an (epistemologically) autonomous science. That, in a nutshell, is Mayr's organicist-structuralist position on the autonomy of biology.

Mahner and Bunge also offer an epistemologically antireductionist account of biology, but one which is neither structuralist nor premised on the twin theses of Genetic Informationism and Genetic Vitalism; it is, consequently, substantially more adequate than Mayr's. As systemists, they argue that an

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[98]Mayr (1997), p. 20.

organism is an emergent outcome of composition, environment, and structure, whereas Mayr ignores environment altogether and denies the importance of composition: "the unique characteristics of living organisms are not due to their composition but rather to their organization". Yet as is plainly evident, Mayr also holds that the key compositional feature of an organism is its informational genetic program, which is responsible for the generation of "integrons" at all higher levels of organization throughout development.[99] How can he reconcile these views?

In brief, he can't. Mayr also neglects to clarify the ontological status of what he argues is the basic compositional element of organisms, their genetic program. A genetic program is, apparently, not immaterial, for Mayr claims that vitalism is superfluous; but whether it is strictly physical is also unclear, for Mayr rejects physicalism, as well. He makes no effort to clarify which (if any) of $\text{Information}_{1\text{-}7}$ he endorses in claiming that a genetic program just is the "information" encoded in an organism's DNA.[100] Nor does Mayr adequately justify the epistemological component of his account of emergence: if a genetic program encodes and directs the organization of the organism, and the higher-level properties are "emergent" from the genetically preprogrammed organization of lower-level parts, then it is unclear why the higher-level properties should be unpredictable for Mayr.

I suggest that the way Mayr or someone attracted to his position might avoid all of these problems is to insist on genuine (ontological) emergence; to exchange structural organicism for systemism; to drop the very notion of a genetic program; and to insist (with developmental

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[99]Mayr (1997), pp. 16, 19-20, 14, 8, 307.

[100]Mahner and Bunge would note an additional difficulty, namely that Mayr, as a structuralist, does not hold an emergentist position, but a supervenience thesis. They claim that accounts of emergence which do not focus on its material nature are actually notions of supervenience. Supervenience refers to the idea that the "emergent" properties of the whole are independent of the properties of its component parts – in other words, the idea that all that matters is organization – whereas emergence proper implies that the emergent properties of a whole "depend lawfully on the properties of its components" (Mahner and Bunge 1997, p. 150). Since in Mayr's account of emergence, he emphasizes the epistemological element (unpredictability) without illuminating the ontological element, his structuralism therefore leads him to supervenience, a position which Mahner and Bunge find to be inadequate to the nature of organisms.

constructionists[101]) that whatever seeming unpredictability exists is an artifact of too quick and exclusive a focus on genetic information as generating the prediction in the first place.

Before proceeding with my own constructive proposal, I will now turn to the nature of epigenesis.

[101]In particular, I have in mind Griffiths and Knight (1998) and Keller (1999).

Chapter Three – The Enigma of Epigenesis

> The preformation idea has always led to immediate, if temporary successes; while the epigenetic conception, although laborious, and uncertain, has, I believe, one great advantage, it keeps open the door for further examination and re-examination. Scientific advance has most often taken place in this way.
> – *Thomas Hunt Morgan*[1]

3.1. Exploring Epigenesis

Recall the Medawars' slogan: "genetics proposes, epigenetics disposes".[2] My claim is that this tidy phrase represents a poor first approximation. This seemingly benign compromise in the dispute between preformation and epigenesis locates (all) the preformed elements of ontogeny in the DNA, and attributes to epigenesis the secondary role of unpacking the primary preformed potential. In Chapter Two I showed that the claim that preformed DNA alone is transmitted between generations is obscure: that DNA is preformed at all is unclear, and the identity of the event to which anything is *pre*-formed is similarly unsettled. The same claim is also wrong: considerably more than DNA is inherited, and if anything at all is preformed, it is surely other (or at least more) than DNA.

In various versions of the Modern Consensus, differential states of activity are attributed to "preformed" and "epigenetic" elements. For the Medawars, genes encode developmental instructions that are triggered from outside the cell, suggesting relatively passive (preformed) genes in a relatively active (epigenetic) environment; for Mayr, though, encoded instructions in genes simply *are* in themselves a genetic program for development (that is, in fact, his definition of a "genetic program") – suggesting a rather active role for the preformed component. I shall urge a perspective somewhat closer to the

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[1]Morgan (1909), p. 366.

[2]Schlichting and Pigliucci (1998), p. 230, citing P.B. Medawar and J.S. Medawar, *Aristotle to Zoos: A Philosophical Dictionary of Biology* (Cambridge: Harvard University Press, 1983).

Medawars than to Mayr, but one which also recognizes a deep problem with the Medawars' approach. I have already suggested (and will continue to do so) that genes are both much less active than Mayr presumes, and also that genes, *qua* passive suppliers of (some of) the materials of ontogeny, 'propose' by no means all but rather only part of those materials to be 'disposed of' epigenetically. In what follows, I will endorse an account of epigenesis distinct from and not reducible to the differential expression of (preformed) genes. That is, as against some commentators, I will distinguish between epigenesis proper and the relatively recent notion of "epigenetics", and I will also distinguish several different understandings of the latter concept, of which I will urge only one is acceptable.

Epigenesis as a concept remains remarkably elastic, such that even those with drastically different perspectives on the role of genes in ontogeny will describe their position as "epigenetic"; some investigators have even changed the name of their model from "genetic" to "epigenetic" without changing the model at all;[3] still other investigators propose an account of epigenesis but refuse to call it "epigenesis" because of the historical conceptual baggage attaching to that term.[4] It is worthwhile, therefore, to begin by surveying various perspectives on the meanings of "epigenesis" and "epigenetics".

As I indicated in previous chapters, the concept of "epigenesis" – if not the word itself – dates back to Aristotle.[5] Insofar as organismal development is a perennial problem in biology, it is therefore

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[3]For instance, Irving Gottesman co-authored a book on schizophrenia in 1982 entitled *Schizophrenia: The Epigenetic Puzzle*; his 1991 book is entitled *Schizophrenia Genesis*; and then a paper of his that appeared in 1994 is entitled "Schizophrenia Epigenesis" – but the aetiological, epistemological, methodological, and ontological considerations remain virtually unchanged throughout all three works. For some discussion of Gottesman's rhetorical slide, see Robert (in press [a]), as well as Chapter Four of the present dissertation.

[4]Oyama (1985) consciously prefers the word "ontogeny" over "epigenesis" for what is, in my mind, clearly an epigenetic process.

[5]Some writers are careless in this regard: some have suggested that Aristotle invented the word "epigenesis" rather than merely the (proto)concept (Schwartz 1999); others have suggested, apparently in ignorance of Aristotle and of William Harvey (who did, in fact, coin the word "epigenesis" in 1601), that both the word and the concept emerged sometime in the nineteenth century (e.g., Coleman 1971, p. 35). Similar ambiguity surrounds the word "epigenetics" – Schlichting and Pigliucci (1998, p. 257), for instance, draw no distinction between "epigenesis" and "epigenetics", and therefore attribute the coining

entirely appropriate that Moore should contend that "all of biology is a footnote to Aristotle".[6] While, as Clara Pinto-Correia has engagingly and convincingly shown,[7] more sophisticated variants of preformationism were advanced and defended, Aristotle's basic insight about epigenesis – that the appearance over time of structures in the developing organism ought to be interpreted as evidence not merely of growth but rather also of change (development) – remained stable and important for over two millennia, though in a variety of guises.

Thus William Harvey's perspective on epigenesis, according to which the unformed (un*pre*formed) organismal substance takes up a form that is in it potentially, but not actually, has much in common with the various theses of Aristotle. So too does the more preformationistic perspective of Leeuwenhoek, whereby an organism takes up a (preformed) form that was there only potentially, not actually, requiring as it did a stimulus for its expression.[8]

But as I hinted in Chapter Two, Aristotle's notion of an entelechy, however misinterpreted, led to his guilt by association with those who posited vitalistic accounts of epigenesis. In order to explain development from the relatively homogeneous, unstructured gametes through the increasingly complex organism, early epigenecists (without having recourse to the easy – though mistaken – answer provided by their preformationist opponents) had to invoke some teleological force from without – some *vis essentialis*

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of "epigenesis" to C.H. Waddington who, truth be told, rather coined the word "epigenetics"! While J.H. Woodger was mistaken to suggest that formalization is all that is required for biological progress, surely cleaning up our collective linguistic act is a good starting point!

[6]Moore (1993), p. 33.

[7]In suggesting that there was considerable alteration in the concepts of epigenesis and preformation in the seventeenth and eighteenth centuries, Pinto-Correia (1997, p. 4) is bucking a tradition defended, e.g., by Moore (1993, p. 123), according to which not much of interest happened between Aristotle and the middle of the nineteenth century. I suspect that Pinto-Correia, and Steven Jay Gould for that matter, would hold that the basis for Moore's assessment is an unfortunate undervaluing of the import of preformationist theories in the development of the life sciences. For the general argument, see Pinto-Correia (1997) and Gould (1977; 1997).

[8]Pinto-Correia (1997), pp. 3, 85.

or *élan vital*, for instance. Epigenecism and vitalism have therefore been almost constant companions. Given the demise of vitalism, more recent epigenecists have sought form and structure elsewhere, usually within the organism itself. But the best of the lot typically settle, sadly, on the nevertheless *vitalistic* (and otherwise problematic) idea of a genetic program.[9]

There are few pure epigenecists in the world today, those who would hold to some thesis about a complex organism emerging as it were magically from a primitive homogeneous mass. This is the force of Løvtrup's assertion, cited in Chapter Two, that epigenetic processes *by necessity* act on some preformed material substrate. But are these the only options: either *ex nihilo* epigenesis or some variant of the Modern Consensus on a preformationist-epigenecist hybrid? I do not believe that these categories exhaust the alternatives.

For example, let us presume, despite occasional slips in the literature to the contrary, that no one today holds that epigenesis is just the (actual and not merely visual) naturally unaided appearance of novelty in the unfolding of the 'informationally preformed' organism. But, as is evident from even a cursory review of papers on gene activation and regulation, a genome does not run the developmental show – despite the protestations of Human Genome Project enthusiasts and gene-centric science popularizers, and despite the fact that the position is nonetheless compatible with certain popular accounts of genetic programs. Such incisive thinkers as even Jacques Monod are prone to error on this count. Monod, himself discussing the debates between preformationists and epigenecists, argues that

> no preformed and complete structure preexisted anywhere; but the architectural plan for it was present in its very constituents. It can therefore come into being spontaneously and autonomously, without outside help and without the injection of additional information. The necessary information was present, but unexpressed, in the constituents. The epigenetic building of a structure is not a *creation*; it is a *revelation*.[10]

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[9]Consider Mayr's updated version of Aristotelian epigenesis, whereby Aristotle's "metaphysical agent" is replaced by a genetic program for development (Mayr 1997, p. 157).

[10]Oyama (1985), p. 28, citing Jacques Monod, *Chance and Necessity*, trans. A. Wainhouse (New York: Knopf, 1971), p. 7. This position may be rendered more or less palatable by specifying what are to count as constituents; but my concern in what follows depends less on the content and more on the form of

For Monod, then, the instruction set is primary, is contained *in toto* in the genes, and manifests itself by self-activation in organismal development.

Monod is somewhat careless here, though, for surely the co-author (with François Jacob) of the *lac* operon model of gene *activation* understands the necessity of "outside help" in the actualization of genomic potential! Yet the deep dispute is not over outside activation, which is granted, though not taken seriously enough, by everyone concerned; but rather over the remainder of the conjunction, regarding the "injection of additional information". In other words, it is not in dispute that insofar as genomic potential is in fact actualized, the 'activation' – as it were – of the genome is context-dependent, triggered – as it were – by some extragenomic developmental component.

In fact, the thesis of development-as-unfolding ("evolution") may be better construed as a relatively sophisticated, though presently unpopular, kind of preformationism – one capable of integrating an explanation of the observable changes in an organism during ontogenesis – rather than as genuine epigenesis. For quite some time, only epigenecists could explain this observation, while preformationists were stuck with a theory about growth and no more. But preformationists could now offer an equally plausible account by suggesting that the adult structures are not physically present (fully formed but very tiny) in the embryo, but rather only the (preformed) genetic potential for those structures is present. It is this latter kind of preformationism that underwrites careless talk about genetic determinism, which helps to substantiate the recent charge that gene centrists are merely preformationists in modern garb.[11] Of course, there are no self-avowed preformationists among the ranks of geneticists and philosophers of biology. They rather see themselves as offering a preformationist-epigenecist hybrid (the Modern Consensus), and thus think of themselves as having more in common with Mayr or Monod than with, say, Malebranche. But there are still problems here.

Monod's claim.

[11]See, e.g., Oyama (1985); Mahner and Bunge (1997).

There are, for instance, two distinct perspectives on the idea of the external triggering of genomic potential: one compatible and another (Monod's) incompatible with the ontogenetic requirement of specific environmental information – that is, information beyond the bare instruction 'switch on the preformed genetic program for development now' and its ilk. My sense is that most theorists hold to the former, not the latter, position, though in moments of weakness some theorists blur the distinction. But I want to suggest in this chapter that even the former perspective is misguided in many of its numerous instantiations; all the while, I will presume that the latter perspective is surely mistaken, as well.

Allow me to reiterate the distinctions I have been drawing. (1) *Epigenesis-as-unaided-evolution* (or epigenesis-as-unaided-unfolding) is rather a sort of pseudoepigenesis, one not currently well-represented in the biological or biophilosophical literature. Next, I will retain the euphemism of 'triggering' for two distinct positions: (2a) *epigenesis-as-initial-triggering* is the account of epigenesis whereby the whole of the developmental potential resides in the genome, requiring mere activation from without for the production of an organism; and (2b) *epigenesis-as-contextual-triggering* is the more sophisticated position that, while developmental potential resides exclusively in the genome, its actualization occurs over time as the result of many external and internal activations or regulations (or both). The core idea of both (2a) and (2b) is represented in the following passage:

> One can surmise that there must exist a machine to interpret the content of a DNA sequence. This machine is a preexisting living cell, made of a large but finite number of individual components organized in a highly ordered way. Given such a machine, a fragment of DNA, provided it contains a well-formed sequence, is necessary and sufficient to produce a specific behavior representing part or all of the structure and dynamics of an organism.[12]

In other words, "at fertilization the diploid genome contains all the information necessary to regulate (or 'cause') individual ontogenesis, requiring only an appropriately permissive and supportive environment for full genomic expression to occur".[13] In (2a), the cellular 'machine' triggers the production of the

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[12]Danchin (1996), pp. 107-108.

[13]M. Moss (1981), p. 366. Moss, I should note, is critical of such a perspective.

'behavior' pre-specified in the DNA fragment; in (2b), the cellular 'machine', in reactive interplay with the DNA fragment, regulates the expression of the preformed genetic information in the production of the 'specific behavior'. The latter position is, as I take it, the standard account of ontogenesis, and can be made to fit all three dogmas of the Modern Consensus on epigenesis and preformation. It is also, as I will contend, mistaken.

Contrast this perspective with that of Schlichting and Pigliucci:

> It seems clear that, no matter how strong our belief in the power of reductionism as an explanatory scheme, the nature of the phenotype of any organism cannot be mechanistically deduced, even if we possess a complete DNA sequence of its genome. The elucidation of the utterly fascinating (and mind-numbing) gymnastics that comprise transcription and translation *has definitively crushed that hope*. Thus "emergence" arises somewhere between DNA and the phenotype. This black box, often referred to as epigenetics, is now only being perforated with numerous small holes, shedding some dim light on portions of its contents.[14]

(As will become evident in later chapters, I would expand consideration beyond the space between DNA and the phenotype, focusing instead on that between the fertilized egg and the mature organism.)

I will need to invoke yet another euphemism to account for (i) the idea that specific ontogenetic information is dispersed throughout the developing system and environment and therefore not localized (exclusively) in the genome; and (ii) the further idea that 'activation' does not quite capture the nature of developmental phenomena or the interrelationships between genes and other elements of the developmental system. In this regard, recall Monod's final admonition, in the passage cited above, that "the epigenetic building of a structure is not a *creation*; it is a *revelation*" – in particular, a revelation of what is genomically preformed. I will urge the opposite view in this and subsequent chapters; hence, (3) *creative epigenesis*.[15] My account of (3), to be offered in Chapter Five, should be taken as a rejection of

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[14] Schlichting and Pigliucci (1998), p. 27; emphasis added. In this passage, I have deleted references to Levins and Lewontin (1985) and Nijhout (1990) at the end of the first sentence, and to Lewin (1997) after the word "translation" in the second sentence.

[15] Another possible epithet is *constructive epigenesis*, but the word "constructive", even when intended literally – and not in the sense implied by social constructionists (whatever that may be: see, e.g., Hacking 1999) – nonetheless raises hackles. Of course, so too does "creative epigenesis", especially in the light of Bergson's "creative evolution" – but I am more comfortable with the latter association than with

all three theses comprising the Modern Consensus: Genetic Informationism, Genetic Vitalism, and Genetic Primacy. Having addressed the first two of these in Chapter Two, it is to the latter thesis (that DNA is the prime ontogenetic mover and primary supplier and organizer of material resources for development) that I now turn.

3.2. Epigenesis and "Epigenetics"

The standard models of epigenesis – patterned after (2b) and, to a lesser extent, (2a) – hold that while genes may not be the whole story, they are nonetheless *prime causes* of development. Witness Lewis Wolpert's pithy recasting of "*ex ova omnia*", the famous dictum of the seventeenth-century epigenecist, William Harvey. According to Wolpert's version, "*ex* DNA *omnia*". Thus, for adherents to the Modern Consensus, the organismal body is merely epiphenomenal, the extranucleic parts of the cell merely supportive, and all developmental information and causal power rest in the genes. Yet thanks to what we have learned, especially since the early 1960s, about complicated networks of gene regulation, it has become evident that "there is no unidirectional regulation or control of development from gene to phene" – and thus 'the body' (both cellular and, more broadly, organismal) has a far more substantial role in ontogenesis than is typically conceded.[16] I will return to this question of the body in Chapter Five. Some discussion of what we now know about gene regulation will serve to introduce my approach to epigenetics.

Conrad Hal Waddington first coined the word "epigenetics" in 1940. René Thom explains that Waddington sought to marry the classical notion of epigenesis (that ontogenesis, whatever else it may be,

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the former. In Chapter Five, I discuss the work of Gilbert Gottlieb on what he calls "probabilistic epigenesis", which bears some affinity with my own view; Bidell and Fischer (1997) rename Gottlieb's position "constructive epigenesis" – a further reason to offer a distinct euphemism for my distinct view. As I will urge that epigenetics is a subspecies of epigenesis, I will urge below an account of epigenetics that I call "constitutive epigenetics", before turning to creative epigenesis in Chapter Five.

[16]Mahner and Bunge (1997), p. 286; see also Gottlieb (1998) and Keller (1995) and (in press).

is not merely the growth of preformed miniatures or potential structures) to the discipline of 'genetics'. Thom notes that "epigenetics" has managed well as a concept, not least because of experimenters and theorists who resist the by-now common sense that the development of organisms is somehow coded in the genes. Such critics were "inclined to emphasise the importance of local morphogenetic factors such as mechanical strains on tissues (following the *Entwicklungsmechanik* of Roux), the contact with nearby tissues, local environmental influences like external gradients, etc.; hence the need for a new word subsuming all these local events".[17] But what is the nature of this marriage between "epigenesis" and "genetics"? Is it a kind of 'reconciliation' between genetics and embryology, whereby embryonic (and, more broadly, organismal) development may be understood as the cellular triggering of genomic potential? If so, as Thom would appear to suggest,[18] then Waddington's new word applies to an old notion, and is not particularly true to what I will argue ought to be the core of epigenesis. But what if Waddington meant something more by "epigenetics" than this – or, given much contemporary usage, what if Waddington *should have* meant something more than this?

Waddington introduced the explicitly metaphorical notion of an "epigenetic landscape". An epigenetic landscape is an undulating terrain roughly in the shape of a cone (small-end-up), comprising both valleys (or "chreodes") and peaks. The chreodes are not independent but rather occasionally intersect; further, they begin as shallow indentations and gradually deepen as one moves from the top to

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[17]Thom (1989), pp. 2, 3.

[18]On the heels of the passage just cited, Thom proceeds to render the meaning of both 'genetic' and 'epigenetic' so broad as to be vacuous. "If you were to follow Aristotle's theory of causality (four types of causes: material, efficient, formal, final) you would say that from the point of view of material causality in embryology, everything is genetic – as any protein is synthesised from reading a genomic molecular pattern. From the point of view of efficient causality, everything is also 'epigenetic', as even the local triggering of a gene's activity requires – in general – an extra-genomal factor" (p. 3). For an argument against material causation, see Mahner and Bunge (1997). More importantly, though, note the restriction of 'epigenetics' in this context to mere triggering of genomic potential – which both (1) fails to capture a wide variety of phenomena typically deemed 'epigenetic' (such as methylation, to be discussed below), and (2) restricts the space of epigenetic activity to the distance between gene and phene, which is not quite broad enough.

the bottom of the diagram (or as one proceeds through the ontogenetic cycle). A ball at the "mouth" of the cone represents a system (e.g., a totipotent or pluripotent cell), and its development is represented by the movement of the ball from the top to the bottom of the diagram through the valleys (developmental pathways). Multiple pathways may lead to the same outcome, but of course not all pathways converge. A (by necessity small) lateral change anywhere along the course will often (but not always) lead to some change in outcome. Further, the likelihood of a larger change in outcome (from left to right or right to left) being produced by a small lateral change is greatly increased if the change is early, and greatly diminished if the change is late.[19] Moreover, any lateral change brings with it consequences about future developmental opportunities, such that the possibility of achieving a particular outcome may be increased or decreased, guaranteed or precluded, depending on the developmental history of the cell.

Development begins with the ball/cell proceeding downward, pushed by some factor or other into an initial chreode until reaching a bifurcation point (an intersection with another chreode). Again, the ball takes one or the other course and proceeds downward until the next bifurcation point -- and so on. Melvin Moss underscores that the 'decision-making' at each bifurcation point is not predetermined genomically, but rather that the "instantaneous epigenetic state" regulates the decision; in other words, it is determined contextually by the state of the system as a whole.[20]

What, then, is 'epigenetics'? Consider the following three distinct responses to this question. Writing in 1975 with this model in mind, Waddington offered a straightforward definition: Epigenetics$_1$ denotes the "causal interactions between genes and their products which bring the phenotype into being". This first perspective offers, to be sure, a narrow definition of epigenetic phenomena, in that the causal interactions are nuclear, occurring between only genes and gene products, without consideration of

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[19]In this regard, the idea behind epigenetic landscapes is compatible with von Baer's law, especially as captured by Wimsatt's notion of generative entrenchment; see Wimsatt (1986b).

[20]M. Moss (1981), p. 373. Diagrams of epigenetic landscapes are reproduced in, e.g., M. Moss (1981); Gilbert (1991b); and Schlichting and Pigliucci (1998). For a teleological interpretation of such diagrams, see Sheldrake (1981), pp. 304-305.

nongenic (e.g., cytoplasmic, hormonal, or positional) factors. It thus takes for granted a certain genetic preformationism, and bears an affinity with either version of (2) identified above.[21]

Wolf's definition of 'epigenetics', Epigenetics$_2$ is somewhat broader, referring to "the interactions between genes and their products, *and the various other conditions composing the milieu required for developmental processes to take place*. Epigenetic changes are the result of these interactions, and may contribute significantly to the phenotype".[22] On this second account, genes interact not only with their products but also with other (presumably nongenic) developmental factors. Though genes are crucial ontogenetically, they simply are not decisive. There is no hierarchical relationship between genotype and phenotype: it would be arbitrary, Wolf argues, to assign genes a privileged

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[21]Schlichting and Pigliucci (1998), p. 231, citing C.H. Waddington, *The Evolution of an Evolutionist* (Ithaca: Cornell University Press, 1975), p. 218. Cor van der Weele (1999, p. 31) has noted that "the effect of Waddington's work is ambiguous". Waddington drew attention to the fact that the course of development is not determined exclusively by the genome, but rather and importantly also by the developmental environment (including, particularly, the developmental history of individual cells). Nevertheless, within Waddington's work there is an undeniable emphasis as well on genetic control, even in the context of putatively environmental switches. (Compare recent interest in "the genetics of epigenetics" [Gasser *et al.* (1998)]; see also Goldsmith *et al.*'s [1997, p. 383] discussion of so-called non-Mendelizing genetic effects [such as genomic imprinting], wherein they remark that the identification of such effects will lead to the revelation of "unsuspected sources of genetic influence" – rather than to analytical refocusing beyond the gene!) At the same time, and to make matters somewhat murkier, Waddington always retained a focal interest in the embryo/organism-as-a-whole, irreducible to some underlying genomic constitution.

For present purposes, it is sufficient to recognize the ambiguity van der Weele has identified, especially given the quite different interpretations of epigenetic landscapes, and of epigenetics as such, available in the literature. For further discussion of epigenetic landscapes, see, e.g., Sheldrake (1981); Gilbert (1991a, 1991b); Zelditch *et al.* (1993); Schlichting and Pigliucci (1998); and van der Weele (1999, esp. pp. 26*ff.*). On epigenetics in its various formulations, see the collection edited by Russo *et al.* (1996) on epigenetic mechanisms of gene regulation, including the overview by Riggs and Porter (1996); see also Holliday's (1994) introduction to a special issue of *Developmental Genetics* (volume 15) devoted to epigenetics; Henikoff and Matzke (1997)'s introduction to a special issue of *Trends in Genetics* (volume 13, number 8) devoted to epigenetic effects; and Lewin's (1998) introduction to a special issue of *Cell* (volume 93) devoted to dispelling the "mystique" of epigenetics. See also Jablonka and Lamb's controversial book (Jablonka and Lamb 1995) on epigenetic inheritance, and especially the twin reviews by Griesemer (1998) and Keller (1998) in *Biology and Philosophy*, as well as the many reviews of their target article (Jablonka and Lamb 1998) in the *Journal of Evolutionary Biology* for 1998 (volume 11); both sets of commentaries include a response by the authors. I review some of the material on epigenetics in the remainder of this section.

[22]Wolf (1995), p. 128 (emphasis added).

ontogenetic place over and above gene products, positional information, or cytoplasmic factors. Wolf suggests that "the phenotype is, thus, the product of ontogenetic development rather than the mere consequence of the genetic constitution of the zygote", and that "the phenotype is not deducible from the genotype".[23]

Much of what Wolf says here is beyond reproach. But note that a third definition goes further than either Waddington or Wolf. Despite the narrowness of Waddington's 1975 statement, there is in the very notion of the epigenetic landscape room for a broader account of epigenetics, one capable of integrating genetic interactions with nongenic ontogenetic factors, *and also (non-genetic) interactions between these nongenic ontogenetic factors themselves.* This is the sort of definition offered by Schlichting and Pigliucci, for instance, and I will call it Epigenetics$_3$: "Epigenesis[24] is an ensemble of processes that propagate phenotypic characteristics throughout development. These processes derive from either indirect effects of gene action (emergent properties) or from non-genetic phenomena (e.g., cell-cell or hormone-target communications)".[25] Such an account permits 'epigenetics' to refer to more than gene expression as such, and so begins to construct the ontogenetic edifice on a foundation broader, deeper, and wider than the mere building blocks of DNA. But though Schlichting and Pigliucci's definition is on the right track, it is still not quite adequate. For its broadness, Schlichting and Pigliucci's definition of 'epigenetics' is preferable to either Waddington's or Wolf's. But for its depth and specificity, something like Wolf's is preferable. I shall strive to combine elements of both in what follows.

Note at the outset that the distinction between the second and third of these definitions is a difficult one to draw, and it is made even more so by Schlichting and Pigliucci's careless substitution of 'epigenetics' for 'epigenesis' and *vice versa*. It is imperative to keep the words and concepts distinct for,

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[23]Wolf (1995), pp. 128 (emphasis added), 144, 127, 144.

[24]As I will indicate below, Schlichting and Pigliucci are to be faulted for treating 'epigenetics' and 'epigenesis' as interchangeable.

[25]Schlichting and Pigliucci (1998), p. 232 (repeated verbatim at p. 258).

as I will argue, 'epigenetics' is but a subspecies of 'epigenesis' – and confusion ensues when one is mistaken for or collapsed into the other.

Part of the difficulty is that the root of the adjective 'epigenetic' could derive from either 'epigenetics' or 'epigenesis', and the very meaning of the prefix 'epi-' is sufficiently vague as to permit a variety of incommensurable interpretations. In a recent review, for instance, Griesemer notes that because "'epi' means 'placed or resting upon'", we must conclude that 'epigenetic' implies logical or physical reliance/supervenience/dependence "upon the genes".[26] But there are two problems with this move: (1) 'epi-' has more meanings than 'placed or resting upon'; and (2) there is no reason to automatically prefer '-genetics' over '-genesis' in interpreting the root of the adjective 'epigenetic'. Regarding (1), note that other *OED* definitions of 'epi-' include: 'upon, at, or close upon (a point of space or time), on the ground or occasion of, in addition'. Consequently, the relation of logical or physical reliance/supervenience/dependence does not exhaust the possible relations between the prefix 'epi-' and the word it modifies. Moreover, with regard to (2), it is crucial to recognize that whatever is 'epigenetic' may in fact rest or follow upon (or whatever) *genesis* – generation, origination, production, reproduction, creation, construction, development – *in lieu* of *genetics* as such. Put differently, there is more to genesis than genetics, and so more to epigenesis than epigenetics. Epigenesis captures both genetic and epigenetic phenomena, construing both in creative, constitutive terms.

3.3. Exploring Epigenetics

Before elucidating my own account of epigenetics, let us return briefly to the marriage between genetics and development that Waddington sought to sanction. In the present section, I shall survey some

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[26]Griesemer (1998), p. 110. To be sure, Griesemer recognizes an immediate problem with the 'resting upon genetics' interpretation of 'epigenetic': "This literal sense holds true for the chromatin marking systems, whose elements are literally sitting on the nucleotides. It is less appropriate for steady-state and structural inheritance systems, which not only may operate autonomously from DNA replication, but may have even evolved before there was a genetic inheritance system for them to 'rest upon'". For this reason and others, I find it crucial to be especially careful here.

recent reviews of epigenetic phenomena in order to ascertain the nature and status of epigenetics in current biology.

Løvtrup adopts an enormously broad definition of 'epigenetics' – Epigenetics$_4$: "the study of the mechanisms responsible for the effectuation of ontogenetic development". He adds that "this definition is, I believe, in close agreement with the intentions of Waddington when he originally coined the expression".[27] Holliday, and Henikoff and Matzke, hold to a somewhat different perspective as to both Waddington's intentions and the appropriate present-day meaning of the word he invented:

> The term 'epigenetics' was introduced by Conrad Waddington to describe changes in gene expression during development. Nowadays, epigenetics in the Waddington sense refers to alterations in gene expression without a change in nucleotide sequence. However, this definition is so broad that an issue in *Trends in Genetics* devoted to epigenetics would read more like a modern biology textbook than a series of critical reviews. A more focused description of epigenetics refers to *modifications in gene expression that are brought about by heritable, but potentially reversible, changes in chromatin structure and/or DNA methylation.*[28]

Note four aspects of this depiction (which has some elements in common with both Waddington and Wolf): Epigenetics$_5$ refers to the regulation of gene expression; the regulatory mechanisms are inherited; the regulatory mechanisms are relatively independent of the DNA sequence; and the regulatory effects may be modulated or even reversed. The basic idea is that genes are not ready *tout court* to be expressed; whatever message they contain must be accessed through the efforts of various heritable, nongenetic regulatory mechanisms.

In their recent book on epigenetic inheritance systems, Jablonka and Lamb propose the phrase "the phenotype of the gene" to account for the context-dependency of DNA transcription.[29] Heritable

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[27]Løvtrup (1988), p. 189. Mahner and Bunge (1997) do not distinguish between 'epigenetics' and 'epigenesis'; nevertheless, they presume that 'epigenesis' = 'ontogenesis' = 'development', which results in a position similar to Løvtrup's, according to which the whole of development amounts to epigenetic processes – which is both true and vapid.

[28]Henikoff and Matzke (1997), p. 293 (emphasis added). At the end of the first sentence quoted, they refer to R. Holliday, "The Inheritance of Epigenetic Defects", *Science* 238 (1987): 163-170.

[29]Jablonka and Lamb (1995); for discussion, see Griesemer (1998); Hall (1998), pp. 117*ff.*; Keller (1998).

phenotypic features of genes – e.g., methylation patterns, chromatin structure, genetic imprinting – comprise the epigenetic response to the question 'how do disparate cells containing the same complement of DNA, and the same cell at a different spatiotemporal location, express differentially in time and space in the developing organism?'[30] I will address each of these epigenetic phenomena briefly in turn.

Much controversy has attended to the function of DNA methylation since its discovery in the mid-1970s.[31] Methylation involves "the addition of a methyl group to some of the cytosine residues of DNA to form 5-methylcytosine", thereby influencing the transcription of the DNA, "highly methylated DNA being less transcriptionally active than less methylated or unmethylated DNA".[32] Given our current state of biological knowledge, it is plausible to suggest that methylation helps to determine the segregation of parts of the genome into inactive and active compartments. Appropriate compartmentalization is absolutely crucial to gene expression, for the DNA sequence itself is ontogenetically relatively uninformative.[33]

Another aspect of the phenotype of the gene is generated by the structural conformation of the chromatin. Chromatin structure has a "dynamic nature" that may be modified by genetic restructuring during gametogenesis, for instance, or by genomic imprinting:

> Chromatin is a dynamic complex of DNA, RNA, histone, and non-histone proteins embedded within the eukaryotic nucleus and nuclear matrix. The nuclear matrix is thought to provide the spatial arrangement and the structural framework needed for DNA replication, transcription, recombination, and nuclear transport. During mitosis, chromatin and the supporting nuclear matrix are efficiently disassembled, partitioned, and subsequently reassembled into daughter nuclei.[34]

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[30]Wolffe (1998), p. 1.

[31]Henikoff and Matzke (1997), p. 294.

[32]Hall (1998), p. 118

[33]Wolffe (1998), pp. 3, 2.

[34]Riggs and Porter (1996), p. 39.

One leading suggestion is that the structure of the chromatin plays a role in rendering most of the DNA in a cell off-limits to the transcriptional machinery, such that only the requisite segment of DNA is transcribed at a given time and place.[35] "Alteration or modification of chromatin-related structural proteins may provide a dominant means of controlling the transcriptional activity of individual genes, domains, and entire chromosomes".[36]

A third epigenetic influence during development is the imprinting of the genome at the level of single genes.[37] "In genomic imprinting, two copies of a gene (either maternal versus paternal, or one allele) do not function equivalently during development".[38] More specifically, in the case of the differential functioning of alleles depending on parental origin, whether a heterozygote for a particular mutation manifests the phenotype in question is contingent upon which parent transmitted the mutant allele. Thus, in the case of Prader-Willi syndrome, the responsible allele must have been transmitted by the father, while in the case of the Angelman syndrome, the mutant must be maternal. In other words, only one of the parents transmits the allele involved in the phenotype – in apparent violation of Mendelian rules of inheritance.[39] This is the take-home lesson of Jablonka and Lamb's study of epigenetic inheritance systems: "many evolutionary and developmental phenomena, which appear puzzling or anomalous on the received view that the origin of all variation traces ultimately to changes in nucleotide sequences, can be understood as having an epigenetic, rather than a genetic, basis".[40]

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[35]Wolffe (1998), p. 2. Wolffe attributes this thesis to S.-Y. Lin and A.D. Riggs, "The General Affinity of *lac* Repressor for *E. coli* DNA: Implication for Gene Regulation in Procaryotes and Eucaryotes", *Cell* 4 (1975): 107-111. Thus does Wolffe conclude that "chromatin, chromosomes and nuclear structure itself are now known to be compartmentalized with respect to function" (p. 2).

[36]Riggs and Porter (1996), p. 40.

[37]For a review, see Peterson and Sapienza (1993).

[38]Hall (1998), p. 118.

[39]Wolf (1995), p. 130.

[40]Griesemer (1998), p. 107, summarizing the conclusions of Jablonka and Lamb (1995).

These three sources of epigenetic influence during development do not operate in isolation. Genomic imprinting may affect the structural conformation of the chromatin, while DNA methylation may be involved in genomic imprinting or in gene inactivation.[41] The deep context-dependency of gene expression generated by such epigenetic effects prompts Wolffe to suggest a kind of genetic systemism: "for the propagation of a state of gene activity it is necessary to replicate not only the DNA sequence, but also to duplicate the chromosome and to recruit a gene to the appropriate nuclear compartment". In other words, "the epigenetic mark on gene expression [results in] the difficulty of recapitulating the correct control of gene expression without the appropriate developmental history or chromosomal context".[42]

Immediately, then, one recognizes an important constraint on the image of epigenesis and epigenetics promulgated by the Modern Consensus: *not just* any *'supportive environment' will do for the proper transcription of genes.* A very particular environment, one laden with details of spatiotemporal developmental context and cellular memory,[43] is prerequired for genes to make phenotypic sense. We should go still further: "the nature of the phenotype of any organism cannot be mechanistically deduced, even if we possess a complete DNA sequence of its genome".[44] Hence no *Jurassic Park.* In order to understand the relationship between genotype and phenotype, we must transcend the dichotomy between them in two ways: we must grasp the phenotype of the gene, and we must recognize that the relevant developmental space does not begin nor does it end with the genome-in-context. It begins, instead, with the genetically *co*-defined primary *morphogenetic field* – the cell, the embryo, the organism; and it ends with the developed adult organism, which itself continues developing. *Contra* Monod, then, development does indeed require *specific information beyond the genome – viz.* epigenetic information.

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[41]Hall (1998), pp. 118-119.

[42]Wolffe (1998), pp. 3, 1.

[43]"Cellular memory" refers to "the faithful transmission of determined states to progeny cells" (Riggs and Porter 1996, p. 29).

[44]Schlichting and Pigliucci (1998), p. 27.

In a recent statement of the Modern Consensus, Brian Hall insists that "the genetic basis for development lies preformed in the DNA of the egg and subsequently in the zygote", though he also permits some room for epigenetic events to direct developmental processes.[45] As should be evident, I worry, in contrast, that we ascribe too much of ontogenesis to genetics, without sufficient attention to epigenetic processes. Hall would scold me here: for Hall, "it is a mistake to speak of epigenetics as nongenetic or of genetic versus epigenetic factors as if one is always in the ascendancy or acting to the exclusion of the other. ... Epigenetic control is control of gene expression. ... The genotype is the starting point and the phenotype is the endpoint of epigenetic control". Yet Hall also describes "the phenotype as more than the physical expression of the genotype".[46] I suggest that in order to make good on this latter claim, Hall should adopt an alternative interpretation of epigenetics, in particular the version I call *constitutive epigenetics.*

3.4. Whole Organisms

Let me now take up from where I left off in Chapter Two. Despite Mayr's gesture toward a focus on the organism-as-a-whole, he conspicuously neglects this selfsame whole organism, and, despite his claims to organicism, it is evident that he misses a central defining feature of the position in subscribing to a thesis of Genetic Vitalism. Russell makes the point nicely with regard to Aristotle, in a statement equally applicable to the Kant-Blumenbach position described in Chapter Two: "The passage in which Aristotle points out that 'there is no such thing as face or flesh without life or soul in it'[*De Generatione Animalium*, 734b] is cardinal to an understanding of his view. It is important to realize that this view was not 'vitalistic' in the modern sense of implying a dualism of matter and 'entelechy'; for Aristotle 'soul' in this connexion was an expression for the total functional activity of the organic unit or part considered –

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[45]Hall (1998), p. 113.

[46]Hall (1998), pp. 114, 399.

its activity *as a whole*". It is to this topic that I finally turn, with my own proposal for a new synthetic approach to ontogenesis.[47]

In a recent paper, Keller underscores a crucial distinction between genetic program and developmental program. Both concepts, borrowed directly from computer science, came into circulation in the 1960s. Keller notes that the idea of a developmental program was elucidated by, e.g., Michael Apter in 1966, but then faded into obscurity, overtaken by Monod's and Jacob's (and Mayr's) alternative account of a genetic program.[48] While Keller urges the importance of the former (the notion of a program dispersed throughout the zygote), she is highly critical of the latter (the notion of a program located in the genome). Thus, while she agrees with Lenny Moss that a genetic program is nowhere to be found, she extends his account by suggesting that a developmental program is, by contrast, "everywhere to be found"![49]

For Keller, the very idea of a genetic program rests on the conflation of two independent distinctions: between program and data, and between genetic and "epigenetic".[50] The result is the association of genes with programmatic agency, and the association of everything-else-ontogenetic with relative passivity. The idea that a genetic program "explains" development can be understood in part as a product of its time: development begins with the fertilization of the (inactive) egg by the (active) sperm;

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[47]Russell (1930), p. 20.

[48]Keller (in press); she cites Michael J. Apter, *Cybernetics and Development* (Oxford: Pergamon Press, 1966), and François Jacob and Jacques Monod, "Genetic Regulatory Mechanisms in the Synthesis of Proteins", *Journal of Molecular Biology* 3 (1961), pp. 318-356. It is noteworthy that Apter co-authored a 1965 paper with Lewis Wolpert, in which they argued that developmental instructions are not localized at particular sites within the organism, but rather that the system develops as a dynamic, integrated whole. Clearly this was written sometime before Wolpert was converted to the "genetic program" paradigm (which had occurred, according to Keller, by 1975)! The paper is Apter and Wolpert (1965). As will become obvious below, I am much more sympathetic toward this early view than toward Wolpert's later fuzziness (as in his 1995; 1994; and 1991).

[49]Keller (in press).

[50]"Epigenetic" here should be understood as "nongenetic ontogenetic resource/process".

the cytoplasm was then thought of as inactive, implying that the active component of development must be the almost wholly nuclear sperm; so the genetic information in the nucleus must contain the program for the sequential activity of genes in development.

But there is a difficulty with, for instance, Jacob's 1976 assertion that a genetic program equates the genetic material with a computer's magnetic tape. The metaphor is quite optional, even gratuitous. As Keller notes, genetic material "might just as well be thought of as encoding 'data' to be processed by a cellular 'program'. Or by a program residing in the machinery of transcription and translation complexes. Or by extra-nucleic chromatin structures in the nucleus". Though it may be historically understandable why some thinkers were tempted to talk this way, attributing agency to genes is ontologically and ontogenetically misguided. Thus, Keller prefers the alternative image of a developmental program dispersed throughout the cell-organism, according to which the genome is not programmatic but rather provides (some of the) data for the developmental program.

There is a very short conceptual distance between preformed miniatures, predetermined germplasm, and preprogrammed macromolecules, requiring for its negotiation only the appearance of transmission genetics, the adoption of the computer metaphor, and in some cases (but not all) the exchange of actuality for potentiality. That this distance is indeed short is evidenced by the affinity between the preformationist-informationist element of the Modern Consensus and the preformationist (and pre-informationist) position of August Weismann, according to which development was the self-guided unfolding of multiple pre-determined parts.[51] But this preformationist route is not our only option.

As Jan Sapp and others have noted, and as I indicated in Chapter One, embryologists in the early part of the twentieth century – such as the early Morgan, Yves Delage, and E.G. Conklin – resisted the conception of preformed particulate elements. "The notion that the whole organism subsisted only by means of reciprocal action of the single elementary parts was for them inadequate to explain the

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[51]Maienschein (1986), p. 79.

harmonious whole manifested by the organism. The fact that each of the parts of the egg was capable of developing into a complete organism, and yet did not do so when left in its natural position, proved that the developing germ, the embryo, was an integrated unit".[52] For whole-organism biologists, such as E.S. Russell and those whose works he discusses, this is a fundamental fact of biology. Partly because Russell's writings on development have by and large been ignored by biologists and philosophers of biology,[53] and partly because Russell's views clearly foreshadow those of Keller,[54] I will outline Russell's position as elucidated in his 1930 gem, *The Interpretation of Development and Heredity*, as well as in a 1933 paper, "The Limitations of Analysis in Biology".[55]

Russell's credo is that "the organism develops essentially as a whole, as a unitary individual, persisting in time". Russell identifies the germ-plasm of the gene-theorists as a problematic "material entelechy":[56]

> The germ-plasm is, as it were, a material entelechy. The attempt to find an internal formative mechanism as the cause alike of heredity and development, which is characteristic of nearly all modern theories, results necessarily in [the] separation of agent and material, just as the attempt of the vitalists to reintroduce life into the mechanistic abstraction that stands for organism results in a dualism or opposition between the immaterial agent and the material mechanism which it in some way controls. In either case one arrives at a *Deus in machina*. The nuclear organization, the germ-plasm, or the gene-complex of modern theories, is accordingly invested with semi-magical powers of control.

Thus, Russell seeks to distinguish himself, both metaphysically and methodologically, from the progenitors of the "genetic program" trope (and from certain older vitalists, such as Driesch, whose ideas

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[52]Sapp (1987), p. 7.

[53]See, e.g., Lauder (1982), p. xiii. It is rare to find mention of Russell in the biological or biophilosophical literature outside of discussions of morphology, where his *Form and Function* (Russell 1916) is justifiably regarded as a classic. But I am aware of only two modern treatments of Russell's (1930) in particular: Nagel (1961) and Roll-Hansen (1984) – both of which are very critical appraisals.

[54]As espoused in Keller (in press); see below for details.

[55]Russell (1930) and (1933).

[56]Herein, Russell presages the problem with Mayr and Müller, as discussed in Chapter Two.

persist – in spirit if not always in name – in the Genetic Vitalists). With regard to methodology, Russell believes that the (ontological) unity of the organism is "not decomposable without loss":

> To regard any process or structure by itself without relating it to the general activity of the organism is to deal with something which is in large measure abstract and unreal. To re-invest it with some degree of concrete reality it is necessary to re-integrate it into the whole. Its isolation by analysis should be provisional only, and after analysis there should always follow re-integration. We know that the reconstitution of the original unity will be incomplete, but we must make it as complete as possible.

Yet, Russell contends, too many biologists fail to recognize the limitations of analysis, and fail to follow any sort of reintegrative strategy.[57]

Eva Neumann-Held, for one, as I noted in the previous chapter, has recently spoken to the persistence of such a failure, distinguishing between the "differentiative" and "integrative" aspects of scientific descriptions and explanations. Differentiation is crucial in order to access biological structures or processes, but analysis is not enough; by itself, it degenerates into mere fragmentation, offering no comprehension of the interactive and inter-reactive relationships among elements of the system of which they are an integral part.[58] Working out these relationships is the focus of the integrative element of science. Neumann-Held concludes that "in the description of organisms (more generally: of systems), biology still has to perform the integrative part. So far, biology can describe organisms down to the molecular level of genes. However, the interactions of genes with other, non-genetic components to form an organism is far from being understood".[59]

In order to address this integrative task, Russell proposes two "cardinal principles" of biological method: (1) "*The activity of the whole cannot be fully explained in terms of the activities of the parts*

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[57]Russell (1930), pp. 6, 154 (for an extended critique of the ghost in the machine, see Oyama 1985); Russell (1930), p. 147; Russell (1933), pp. 111, 155.

[58]Alfred North Whitehead might have labeled this problem 'misplaced concreteness'; and William James, following Henri Bergson, might have seen it as the 'intellectualism of modern biology'. For discussion of James and Bergson on 'intellectualism', with some comments on the nature of organisms, see Robert (in press [b]).

[59]Neumann-Held (1999), pp. 106-107; the quotation is from p. 107.

isolated by analysis, and it can be the less explained the more abstract are the parts distinguished"; and (2) "*No part of any living unity and no single process of any complex organic activity can be fully understood in isolation from the structure and activities of the organism as a whole*".[60] These two precepts capture the epistemological and methodological elements of Mahner and Bunge's "systemism", without pitching us into the analytical void of holism (or vitalism).

As for his ontological commitments, Russell argues that

> There is a unity of the whole organism – it develops as a whole, and acts as a whole – and this unity is not a secondary or composite thing, but primary and original. To distinguish cells as independent unities, having their own modes of action independent of the action of the whole, is to regard them abstractly, and to introduce an artificial simplification. ... The ovum and the embryo are from the very beginning unitary organisms ... [T]he unity of the organism is not something which comes to be during the course of development, but is there *ab initio*.

Hence D'Arcy Thompson's depiction of the biological organism as "a most complex integral". Thus, as Neumann-Held contends, though methodological integration is (or ought to be) of concern to biologists, ontological integration is, as Russell says, "not a problem for biology":

> If we reject, as I think we must, any vitalistic interpretation in terms of an entelechy or other organizing agent, we have no alternative but to accept the observed facts of development and make the best of them. It follows that the unity of the organism, which is there at the beginning, must be accepted as fundamental; unity or integration is not a problem for biology, but an axiom, a master-fact to which we must relate all other facts about the organism.

That this relation between the unified whole and its parts is not merely methodological or epistemological (having to do with ease of investigation or parsimony of explanation) is evident in Russell's further insistence that "integrative or 'whole' action means that the activities of the parts are subordinated to the activity of the whole".[61] To elucidate this latter point, he invokes the idea of the *autonomy* of the developing organism, "its relative independence of environment, its self-containedness, its steady persistence towards the goal of the finished form":

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[60]Russell (1930), pp. 146-147; italics in the original.

[61]Russell (1930), pp. 234-235, 148 (citing D'Arcy Wentworth Thompson, *On Growth and Form* [Cambridge: Cambridge University Press, 1917], p. 712); Russell (1933), p. 155; Russell (1930), p. 232.

> The developing organism acts *as if* it were fulfilling an end or purpose – that of arriving at the typical form and modes of activity of the species; it tends towards this goal in spite of difficulties, and the end is more constant than the way of attaining it. The environment supplies the conditions for development, provides the means, and also acts as a limiting factor, but the developing organism reaches its definitive form as it were in spite of environment, utilizing environment where it can, and seeking other conditions when the environment becomes unfavourable to its development. ... Alteration of environmental conditions [excepting the absence of essential environmental factors] will not produce an essentially different embryo.

In this passage, we see Russell's signature emphasis on the organism's remarkable ability to self-regulate (the observation of which sent Driesch beyond regulative development toward his eventual preoccupation with metaphysical vitalism). For Russell (as for Kant, incidentally), "if the conditions do not permit of a straightforward normal development, if for instance the developing organism suffers deformation or loss of parts, it has to a considerable degree the power of so modifying the course of its development as to cope with the unusual situation, replacing, for example, the missing parts". In other words, it is characteristic of life, or of an organism (in contrast to a machine) to find some other way to achieve its species-typical form of organization.

Russell notes additionally that "this typical form is an amazingly exact replica of the form of its parent or parents", and he calls this "the fact of *heredity*" itself. As such, "repetition of type must be regarded as one of the main characteristics of development", leading Russell finally to "treat of heredity as being primarily a feature of development" – without any need for genetic programs.[62]

Two crucial implications of Russell's position relate directly to my concerns. First, though he is by no means a supporter of the (nuclear) gene theory of development, neither does his position support any preformationist cytoplasmic developmental theory. His insistence on the original unity of the zygote (the fertilized egg comprising both nucleus and cytoplasm) leads him to recognize "obviously complex, intimate, and ever-changing" relations between cytoplasm and nucleus:

> There cannot be any absolute separation between the functions of the nucleus on the one hand and the functions of the cytoplasm on the other. Their relations are reciprocal, each affecting each in constant succession. Nor can either be understood save in relation to the other, and to the

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[62]Russell (1930), pp. 6-7, 109, 7-8.

> activity of the cell as a whole, for neither is capable of long-continued existence apart from the rest of the cell. To establish then a rigid distinction between the nucleus and the cytoplasm, to allot to each element clearly defined and separate functions, is to deal with unreal abstractions. To regard one as controlling the other is quite illegitimate and introduces that dualism of agent and thing acted upon which runs through and vitiates all theories of nuclear dominance.

Similarly, after citing a passage from E.G. Conklin urging the view that the preformed cytoplasm directs the egg and sperm nuclei, Russell underscores that "it is the entire cell, both nucleus and cytoplasm, that is concerned in heredity and differentiation".[63] "We do not consider for example, like Conklin and Loeb, that the 'embryo in the rough' is determined by the cytoplasm only, any more than we agree that the chromosomes are solely responsible for the finer characteristics which appear later in development. ... For us, nucleus and cytoplasm are indissolubly wedded in their action upon development".[64] As a result, Russell's is not a particulate account of development or of heredity; it is, rather, systemic – and therefore stands in contradistinction to the Modern Consensus regarding both nuclear vitalism and nuclear primacy (the precursors of Genetic Vitalism and Genetic Primacy).

Secondly, recall from Chapter One that the later Morgan most often (but not always) segregated (the study of) transmission and development; similarly, E.B. Wilson's 1925 putative reconciliation of epigenesis and preformation – cytoplasmic epigenesis overlaying nuclear preformation – was actually a claim to the effect that cytoplasmic and nuclear effects are separable and ought to be addressed separately (by embryologists and geneticists, respectively). Thus does Hall remark that, "for Wilson, the preformation-epigenesis dichotomy was a nuclear-cytoplasmic dichotomy".[65] But, for Russell, there was no such dichotomy, and thus there should be no division of labour between geneticists (and evolutionists)

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[63]Russell (1930), pp. 157, 87; Conklin's remarks (summarized here) are from E.G. Conklin, *Heredity and Environment in the Development of Men*, 2nd ed. (Princeton, 1916), p. 184; for more on Conklin see, e.g., Maienschein (1986), especially pp. 96-98. Incidentally, Sapp (1991, p. 238) defines cytoplasmic preformation as postulating "a primordial, physicochemical structure in the cytoplasm of the egg which provided a guide for genes and sufficed to determine the first steps in the differentiation of the organism".

[64]Russell (1930), p. 284.

[65]Maienschein (1986), p. 95 (referring to Wilson [1925], p. 1112); Hall (1998), p. 113.

and embryologists. Russell's insistence that heredity is a feature of development therefore prescribes an alternative to the Modern Synthesis of transmission genetics (population genetics) and evolutionary biology.

The Modern Synthesizers' indifference to development or developmental biology is evident from a brief consideration of the basic framework of population genetics.[66] (1) Start with a population; (2) select a breeding population; (3) generate an offspring population; (4) apply a selective filter; (5) the result is a new, post-selection population, and we are (1) ready to begin again. Between (2) and (3) we have the whole of (transmission) genetics; between (4) and (5) we have selection pressures, and hence evolutionary biology. What is missing from this model is *development* (between (3) and (4)) – within (3), we get from zygotes to adults instantaneously! As Wimsatt notes, "in a world in which genes are king, the phenotype is a black box which acts only as a scalar multiplier for gene frequencies". The Modern Synthesis in biology is therefore insensitive to anything like actual developing organisms in their ecological and evolutionary complexity.[67]

On Russell's approach to whole-organism biology it is impossible to ignore development, for heredity itself is a feature of the development of the whole organism.[68] As I mentioned, for Russell, the remarkably true repetition of species-specific type is the fact of heredity; but it is also the "goal" (or natural purpose) of the organism: "the unique character of the living individual as the fundamental unit of biology stands out unmistakably, for the individual is essentially a functional unity, whose activities are co-ordinated and directed towards the development, maintenance, and reproduction of the form and

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[66]For the schema, I am grateful to Bill Wimsatt (pers. comm., 24 May 1999); see also Wimsatt (1999, pp. 288-289) and Griesemer (1998, p. 104*ff.*) for germane remarks.

[67]Wimsatt (1999), p. 288 – also missing from the traditional population genetics model are (at least) physiology, ethology, ecology, biogeography, and geophysics, leading Wimsatt to a sense of amazement that the usual model has been as productive (in terms of generating both research and results) as it has; see Wimsatt (in press [b]); (1999); and (1986b).

[68]See also Lerner (1993).

modes of action typical of the species to which it belongs". Despite his characterization of reproduction as "one of the master-functions of the organism, in a sense the crown and completion of individual development", Russell laments the way in which "reproduction has ceased to be taken seriously as a primary biological problem, ever since the general acceptance of the germ-plasm theory" – a trend that persists to this day.[69] Reproduction is a whole-organism activity, requiring all the diverse resources of a whole organism for initiation and maintenance, and resulting in the production of a whole organism – but biology is currently ill-equipped to deal with whole organisms, trading as it does only in genotypes and phenotypes.

This latter claim helps to explain the (sociological, if not logical, ontological, or epistemological) success of the notion of a genetic program, as against the relative insignificance of a developmental program. But given the difficulties with the former notion, it is imperative to marshal a case in favour of something like the developmental program alternative, as I will in Chapter Five.

3.5. Embodiment: Constitutive Epigenetics

Developing an appropriate conceptual, ontological, and methodological framework for evolutionary, developmental, and molecular biology is a daunting task. Keller takes, in my estimation, a crucial first step in this direction with her "beyond the gene but beneath the skin" approach to biology, which I will explicate and elaborate in Chapter Five as part of a synthetic theory of creative epigenesis. But first I must elucidate my account of constitutive epigenetics which I characterize as a subspecies of creative epigenesis.

It is noteworthy that a set of orchestral metaphors has recently been employed in order to move away from earlier notions of genetic control, and of genes as programs, blueprints, or instructions. For instance, Ernst Mayr has remarked that, "by necessity, the analysis of genes and gene-controlled

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[69]Russell (1930), pp. 166, 9.

biochemical processes had to be reductionist at the beginning, but it was soon realized that the genes interact with one another and with the cellular environment, much like musicians in an orchestra. The study of this well-orchestrated interaction of genes and cells during the making of an individual is currently the frontier of developmental biology". Steven Rose has suggested further that, "far from being isolated in the cell nucleus, magisterially issuing orders by which the rest of the cell is commanded, genes, of which the phenotypic expression lies in lengths of DNA distributed along chromosomes, are in constant dynamic exchange with their cellular environment. The gene as a unit determinant of a character remains a convenient Mendelian abstraction, suitable for armchair theorists and computer modellers with digital mind-sets. The gene as an active participant in the cellular orchestra in any individual's lifeline is a very different proposition".[70]

Eva Jablonka and Marion Lamb offer a version of this musical metaphor somewhere between Mayr and Rose, which is then extended and elaborated by Keller:

> If the score represents hereditary information in DNA, the phenotype is a specific interpretation of this score at a certain time by certain artists. The interpretation does not affect the score. However if there is another transmission system – recordings – through which a particular interpretation can be transmitted from generation to generation along with the written score, the situation is rather different. There can then be evolution of interpretations of the score, based on the influence that one interpretation has on subsequent interpretations, and that these have on still later ones, and so on. Both the phenotype (the present interpretation) and the genotype (the written score) influence subsequent interpretations.

For Jablonka and Lamb, the phenotype of the gene – instantiating epigenetic processes such as chromatin marking and genomic imprinting – is this alternative transmission system. But, as Keller notes, "to do justice to their full argument, their analogy should have been taken further".

> Not only does the phenotype (the present interpretation) influence subsequent determinations through epigenetic inheritance, but it can also participate in the modification of the genotype (the written score) itself – as if, e.g., marks were inserted in the score in response to current interpretations. For Jablonka and Lamb, the real (and most radical) conceptual payoff comes not so much from the existence of multiple inheritance systems as from the interaction with actual

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[70]Mayr (1997), pp. 152-153; Rose (1997), pp. 125-126. For Rose, a "lifeline" is an organism's "unique trajectory through time and space" (1997, p. 98).

nucleotide sequences.[71]

What I take Keller to be emphasizing here is that the epigenetic inheritance systems of which Jablonka and Lamb write are not best thought of as "in addition to" genetic inheritance systems, but rather the two systems are in a nonadditive relationship of interaction. I would go still further: there is neither score nor recording except in performance; the orchestra and conductor together create the score anew with each performance. In other words, epigenetics is neither additive nor transitive, but constitutive.

According to a constitutive account of epigenetics, epigenetics does not reduce to gene regulation, for genes themselves do not preexist developmental processes. The starting point of epigenetic control cannot be the genome, for the genome does not precede the cell-organism, nor is the latter ever coextensive with or delimited by the former. In other words, constitutive epigenetics is not a genes-plus account of epigenetics; epigenetic relations are not additive so much as formative.

In contradistinction to $\text{Epigenetics}_{1\text{-}5}$ identified above, my definition of constitutive epigenetics, Epigenetics_{6}, is as follows: epigenetic events are developmental cointeractions within the whole cell-organism in its developmental context, between any and all of such factors as cytoplasmic structures, DNA sequences, mRNA, histone- and non-histone proteins, enzymes, hormones, positional information, parental effects, temperature cues, and metabolites. Many epigenetic structures are not stable and do not preexist the cointeraction, but rather emerge from these cointeractions in ontogenetic space and time.[72] These cointeractions *generate genes*, which are not sequences of DNA encoding amino acid sequences;[73]

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[71]Keller (1999), p. 114, citing Jablonka and Lamb (1995).

[72]Burian (1997):259-260.

[73]In this, I am following Neumann-Held (1999, p. 125): "The analysis of the molecular mechanisms of polypeptide expression shows quite clearly that there is no fundamental way by which the classical-molecular gene concept could be applied to DNA segments. One focuses at the same bit of DNA, and different structures and functions appear. One focuses on different levels of the expression process (DNA, primary mRNA, mature mRNA, edited mRNA, polypeptide), and again different structures and functions appear. Introns can become exons, which can become promoters, and so on. Regarding the aspect of function, there is no general rule that a particular sequence codes for only one polypeptide. Also, in principle, no discrete material unit segment on the DNA can be identified as coding

on my account, a gene is rather the *process* producing a functional, folded, three-dimensional structure, which results from the connected structure of cointeractively produced coding regions and regulatory sequences (which lead only intermediately to a polypeptide chain).[74] In turn, genes-so-produced help to regulate ontogenetic processes in the developing organism as participants in nonlinear feedback and feedforward networks generating and being generated by the developing organism. Consequently, the usual idea of Genetic Primacy is rendered incoherent.

In order to substantiate and defend this conception of epigenetics, and to show how it differs from standard accounts, it is helpful to indicate how it differs as well from the alternative views of critics. Following the work of developmental systems theorists, Mahner and Bunge, for instance, claim that a genes-plus approach to ontogeny unfortunately and illegitimately privileges one factor in a complex network of interacting factors. In order to avoid this result, they argue that "all developmental processes of biosystems are controlled or regulated through the systemic and lawful interaction of (the members of) its genome, its extragenomic composition, and its environment", concluding that "there is no exclusive (or sufficient, or privileged) control system of an organism's development, such as its genic system".[75]

Similarly, control does not reside in the extragenomic epigenetic system, either, as against the perspective of, e.g., Mae-Wan Ho. "Forever exorcised from our collective consciousness is any remaining illusion of development as a genetic programme involving the readout of the DNA 'master' tape by the cellular 'slave' machinery. On the contrary, it is the cellular machinery that imposes control over the genes .... The classical view of an ultraconservative genome [as] the unmoved mover of development is

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for (only) one polypeptide – at least not in the sense of the classical-molecular gene concept. Therefore, this gene concept is no longer useful; it is 'dead'".

[74]Neumann-Held (1999), p. 129; see also Griffiths and Neumann-Held (1999). Neumann-Held's "developmental process gene" concept stops at the polypeptide chain; in extending the notion to the folded structure, I am adopting the critique of Bob Perlman (personal communication) that polypeptide chains do not actually exist, but are merely convenient (and sometimes inconvenient) fictions.

[75]Mahner and Bunge (1997), pp. 284-286.

completely turned around".[76] Despite her wishful thinking that the idea of a genetic program is no longer with us, this idea that exclusive control resides within one component of a developing system is in direct conflict with the basic sense that development is in fact *co*actional. For even according to (most versions of) the Modern Consensus view, there are both cytoplasmic and nuclear switches.

But on both sides of the debate, theorists often suggest that either genes or cellular environments are more important; this is especially so in the case of gene-centrists, who tend to proceed in their experiments as though the genes were crucially and predominantly important (*genes-for*), and relegate the other necessary factors to background or standard conditions. This is an instance, in my view, of not taking development seriously by refusing to grasp the constitutive nature of epigenetics (and the creative nature of epigenesis). So Sterelny and Kitcher, for example, define the notion of an *allele-for*, while assuming a standard environment. Of course, there is nothing wrong as such with backgrounding the environment; "to be sure, when describing the development of biosystems, the environment can often be regarded as constant, so that the gene is the variable, that is, the 'thing that makes the difference'". Woodger called this the 'constant factor principle', but he issued along with it the following caveat: "if we ... omit reference to the [environment] ... because it is constant and common to all our experiments, we must obviously not slide into the assumption that the [environment] 'plays no part' in the processes involved".[77] And therein lies the error of primacy theorists of any stripe (though my principal concern is with theorists of genetic primacy).

For instance, the developmental systems theorist Russell Gray has shown that we could just as easily construct a definition of an *environment-for*, given standard genes and cellular apparatus. For that matter, Mahner and Bunge wonder why we do not just settle for the notion of a *cytoplasmic-constitution-*

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[76]Bidell and Fischer (1997), p. 200, citing Mae-Wan Ho, "Environment and Heredity in Development and Evolution", in Ho and P.T. Saunders (eds.), *Beyond Neo-Darwinism: An Introduction to the New Evolutionary Paradigm* (San Diego: Academic Press, 1984), pp. 267-289, at p. 285.

[77]Sterelny and Kitcher (1988); Woodger (1952); both as discussed by Mahner and Bunge (1997), p. 286.

for, given the right genotype and environment? Again, as a methodological and epistemological simplifying strategy, the constant factor principle may be effective; but as is evidenced by the slipperiness of the *gene-for* trope, it too often carries over into an unjustifiable thesis about ontological (and causal) primacy. "Since genetic determinism or genetic reductionism ... confers such ontic priority upon genes, it is a scientifically and metaphysically unsound thesis".[78]

But, in following Woodger, do Mahner and Bunge go far enough here? Is it merely the case that an appropriate environment *plus* a relevant gene (or gene network) *plus* an appropriate cytoplasmic constitution will generate (or, alternatively, adequately account for) the organismal state in question? Or is the additivity inherent in such a perspective itself problematic?

Consider the theoretical elaboration of developmental systems theory (DST) offered by Eva Neumann-Held, elements of which I have incorporated into Epigenetics_6. She holds that DST (as instantiated, for instance, by Gray and Oyama) grants too much to genetic primacy theorists in focusing mainly on the *functional* aspect of the classical-molecular gene concept, and ignoring problems with the *structural* aspect of the concept. "In modern textbooks of molecular biology a gene is defined as a certain segment (that might be interrupted) of the DNA, which has the function to code for a linear polypeptide chain, regardless of how complex the mechanism of expression might be". Gray adopts this textbook perspective: "the nucleotide sequence does specify the primary structure of a protein", thereby assuming a (more or less) simple correspondence between a DNA segment and a linear polypeptide chain. So, too, does Oyama, who notes that "it makes sense in general to say that the primary structure of a polypeptide is encoded on the chromosomes". But Neumann-Held contends that, given current results in molecular biology, "it is not necessary to make any concessions to the structural aspect of the gene concept", especially since any such concession may be interpreted as an implicit endorsement that structure

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[78]Gray (1992); Mahner and Bunge (1997), pp. 286-287.

determines function (as against the grain of DST).[79]

Neumann-Held shows that the very structure of genes is deeply context-dependent, due to such processes as mRNA[80] processing and mRNA editing. The phenomenon of mRNA processing shows that "DNA is not the sole carrier of information in the process of expression" – a simple example will suffice: "In eukaryotes, the so-called 5'end of the transcript is 'capped' by methylated Guanine, whereas the other end of the transcript, the 3'end is shortened by a few nucleotides, whereafter a tail of about 200 adenine nucleic acids is added (polyadenylation). These modifications, which are catalyzed by specific enzymes, are not prescribed in the DNA. However, they are essential for further processing (including translation) of the mRNA in the eukaryotic cell".[81]

Meanwhile, though we find it convenient to think that something as basic as the sequence of nucleic acids of DNA is given (hence the Human Genome Project), Neumann-Held underscores that, "as a matter of fact, it is not. Probably the most unbelievable kind of obtaining different polypeptides from the same DNA segment is mRNA editing in mitochondria and chloroplasts", and it has also been "shown in Physarum polycephalum, mammals, viruses and higher plants". The phenomenon of mRNA editing can be divided into two distinct kinds of phenomena. "In one kind, nucleotides are inserted into or removed from the mRNA. The second kind converts nucleotides, for example, C(ytosine) in[to] U(racile) (and the other way around). ... These processes [of mRNA editing] can only be described in the following way: environmental (developmental) conditions, primary mRNA, and processes such as mRNA editing, are in reciprocal ways contingent on each other in the determination of the structures that become translated".[82]

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[79]Neumann-Held (1999), p. 114; Gray (1992), p. 170; Oyama (1985), p. 70; Neumann-Held (1999), p. 115.

[80]"mRNA" refers to "messenger ribonucleic acid", which carries information to ribosomes during transcription.

[81]Neumann-Held (1999), p. 121.

[82]Neumann-Held (1999), pp. 122, 123-124.

On the basis of her discussion of mRNA processing and mRNA editing and other elements of the mechanics of transcription and translation, Neumann-Held concludes that "regulatory sequences and coding regions do not exist in the DNA or mRNA independently of the system. ... On the contrary, regulatory elements and coding regions are co-constructed (in a structural and functional sense) in reciprocal contingency by the components of the systems in succeeding processes" – in other words, the very structure as well as the ontogenetic 'meaning' of a stretch of DNA is constituted by the (spatial, historical, temporal, environmental, organismal) interactive developmental context in which it finds itself.[83] The genome simply does not precede any (additional) element of the developing organism, nor is it ever identical with the organism. The organism, therefore, as well as the evolutionary history of its species, precedes the genome, with which it immediately enters a complex array of constitutive epigenetic interactions. The organism (in context) was there all along. Hence E.S. Russell's prescient observation, cited above: "the unity of the organism is not something which comes to be during the course of development, but is there *ab initio*". That is the only primacy thesis worth defending.

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[83]Neumann-Held (1999), p. 124.

Chapter Four – Schizophrenia Epigenesis?

> Developmental biologists and geneticists usually focus on different aspects of genes (*translation versus transmission*). The geneticist uses a particular view of genes as units of heredity (i.e. transmission to the next generation) and may neglect the role of genes in development. Consequently, the developmental biologist may ask whether the distinction between genotype and phenotype advances genetics by leaving out development. Does evolutionary genetics provide a sufficient theory of morphological evolution? The mapping function from genotype to phenotype is not one-to-one. A gene may affect multiple structures (pleiotropy) and traits are often affected by many genes (polygeny). Furthermore, the mapping of gene effects on phenotype may be nonlinear. Because gene action during development is a cyclic series of gene-cell interactions, genes are just one element in the developmental process. Thus *the nature of interactions is the primary issue in development.*
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> – *S.J. Arnold* et al.[1]

4.1. The Putative Hereditary Basis of Schizophrenia

In this chapter, I discuss the case of the genesis of schizophrenia in an effort to demonstrate the differences in orientation, method, and ontology between the standard behavioural genetics approach to schizophrenia and the general approach to ontogenesis I am urging in this dissertation. I begin by examining how schizophrenia research is largely motivated by genetics, and raise both familiar and relatively novel criticisms of the evidence putatively supporting the genetic basis of schizophrenia. Then I demonstrate the impoverished nature of the reigning understanding of development in psychiatric genetics. Moreover, I attend to those schizophreniologists who presume a genetic basis for schizophrenia and then seek the 'schizophrenic genotype' in the absence of an adequate phenotype. I demonstrate the necessity of a sustained effort at characterizing the phenotype of schizophrenia as an enabling condition for the whole enterprise of psychiatric genetics – and for psychiatry itself. Without a clear picture of the

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[1]Arnold *et al.* (1989), p. 406; emphasis added.

organism-level phenotype, research at the level of genes will remain unproductive – assuming of course that research at the genetic level is appropriate at all.

A principal investigator in the Danish adoption studies of schizophrenia, Seymour Kety, enthusiastically proclaimed twenty-five years ago that "if schizophrenia is a myth, it is a myth with a strong genetic component!"[2] Since then, a number of critics have convincingly argued that the evidence for the genetic cause of schizophrenia is equivocal at best.[3] Nevertheless, research into molecular aspects of schizophrenia continues unabated, motivated by a positive assessment of the classic twin and adoption studies.[4] Just why is that? A likely explanation for the proliferation of molecular research into schizophrenia – despite the fact that this research has thus far proven unsuccessful, and despite the further fact that the classical basis on which it rests is profoundly unstable – is that some schizophreniologists work with an inadequate understanding of ontogenesis, one which unjustifiably privileges genes as necessarily aetiologically foundational. In this chapter, I will worry both the standard conception of gene action in ontogenesis, and the common sense of the role of genetics in psychiatry.

"The genetic contribution to schizophrenia is the most clearly established etiologic factor. Sadly, this seemingly impressive statement is simply another way of admitting that we know disturbingly little about the causes of schizophrenia".[5] The reasons are quite clear: while classical studies have contributed to the conviction that there is indeed a genetic influence on the development of schizophrenia, these

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[2]Kety (1974), p. 961.

[3]See, for instance, Rose *et al.* (1984), Marshall (1990, 1985); Boyle (1990).

[4]For economy's sake, I will refer to the family, twin, and adoption studies of schizophrenia as 'classical studies', though some authors prefer the phrase 'epidemiological studies'. Consideration of what may more properly be called 'epidemiological studies' of schizophrenia – namely, population studies of incidence such as the World Health Organization ten-country study (Jablensky *et al.* 1992) – is beyond the scope of this chapter. For summaries of the classical studies, see, e.g., Gottesman and Shields (1982); Andreasen *et al.* (1988); Cardno and McGuffin (1994).

[5]Murray *et al.* (1986), p. 3.

studies are problematic in a variety of ways.[6] Family, twin, and adoption studies do not indicate which specific genes are culpable, and molecular geneticists have as yet not succeeded in their efforts to reliably link genes with the illness. Further still, it is clear that schizophrenia does not follow a clear pattern of inheritance. So while schizophrenia – like Protestantism – seems to run in families, that appears to be virtually all we know about the aetiology of the illness.

I will not dwell on the details of the family studies, primarily because familiality – as established through the family studies – may imply either a genetic theory, a nongenetic biological theory, an environmental theory, or (more plausibly) some hybrid epigenetic theory: familiality does not by itself necessarily imply a genetic basis for schizophrenia.

Genes are thought to be implicated more directly by the twin studies approach. The method is straightforward. Identical twins derive from a single zygote; they are thus monozygotic (MZ) and share identical genes. Fraternal twins are dizygotic (DZ), sharing less than 100% of their genes (as do other full siblings). Given that identical twins share identical DNA while fraternal twins do not, we would expect MZ twins to be more concordant for a genetically determined trait than DZ twins. An immediate problem arises, however, for it is enormously difficult in practice to abstract the *genetic* identity of MZ twins from their nearly identical *physical* appearance. The result is that throughout their lives many MZ twins have very likely been treated in much the same way by many of the same people; some even ape each other, perhaps in an effort to confound those who would tell them apart. Consequently, in addition to sharing genes, MZ twins share environments. That they may be more concordant for a given trait might just as easily be the result of their environmental similarity rather than their genes. Twin researchers brush off these and other methodological difficulties, and conclude that as MZ twins are more concordant for

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[6]This conclusion is, of course, not surprising, given the role of genes in the development of almost all human traits from the simplest to the most complex! Difficulties arise only in trying to tease apart the relative contributions of genes and environments construed as independent determinants of traits.

schizophrenia than are DZ twins, or any other relatives, schizophrenia has a genetic basis.[7]

A further difficulty is that various twin investigators have used various criteria in diagnosing their probands (subjects with schizophrenia) and co-twins; some studies have used a pairwise concordance, others a probandwise concordance;[8] some have only a small number of index cases while other studies are massive by comparison; and some investigators provide inadequate case details, especially regarding the determination of zygosity in the twins. The result is that different literature surveys and commentaries deem different studies methodologically sound (or merely adequate, acceptable, and so on) and hence provide (sometimes very) different average concordance rates for MZ and DZ twins.

Gottesman drawing on data from Gottesman and Shields, arrives at a concordance rate of 48% for MZ twins and 17% for DZ twins (we can presume Gottesman is using the probandwise method). Kringlen bases his average concordance rates only on the register-based studies from the Nordic countries. He reports 30% MZ and 10% DZ (pairwise) and 40% MZ and 15% DZ (probandwise) concordance rates.

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[7]See Kendler and Gardner (1998) for a recent defense of twin studies in schizophrenia research, particularly of the equal environment assumption (that MZ twins experience an [external] environment no more similar than that experienced by DZ twins); though Kendler and Gardner dismiss criticisms of this approach, their discussion is remarkable in that they caution researchers not merely to assume the validity of the equal environment assumption, but rather to evaluate its merits and demerits. Nevertheless, the equal environment assumption is insensitive to the differences between MZ and DZ twins in their internal (*in utero*, e.g.) environments which may well contribute to the excess resemblance of MZ twins as compared to DZ twins.

[8]In the case of pairwise concordance, concordant twins are counted as one pair in the numerator and one pair in the denominator. In the case of probandwise concordance, twins who are both schizophrenic – as long as they were individually located (e.g., independently identified from a register of schizophrenics) – are counted as two pairs in the numerator and two pairs in the denominator (Gottesman 1991). Boyle (1990) notes that these two methods of measuring concordance ask different questions of the data: the pairwise method asks "in what proportion of pairs are both called schizophrenic?" while the probandwise method asks "in what proportion of pairs is there a 'schizophrenic' co-twin?" (Boyle uses the scare-quotes to signify what is for her the questionable status of the concept of schizophrenia). If A and B are schizophrenic twins and are both found during the initial search for probands, they will be counted as one pair according to the pairwise method (A and B are concordant), and two pairs according to the probandwise method (A is concordant with B and B is concordant with A). There is a debate over which method is preferable. According to Gottesman (1991), the probandwise method is technically more correct, and also more genetically informative – though he offers no argument for this claim. For a discussion of this dispute, see Boyle (1990). For a criticism of the method Gottesman champions, see Marshall (1985) and Marshall and Pettit (1985).

Torrey, a sometime collaborator of Gottesman's, has more reservations than Gottesman. Torrey considers the concordance rates produced only by those studies which employed representative samples and in which zygosity was reliably determined. He arrives at pairwise concordance rates of 28% for MZ twins and 6% for DZ twins.[9]

But these various rates may inflate the differences between MZ and DZ concordance. A recent hypothesis suggests that twin studies may have misled investigators into inferring a genetic basis of disease. We tend to assume that MZ twins share both an identical prenatal and identical postnatal and childhood environment, while DZ twins share similar (but not identical) prenatal and postnatal environments – but this assumption is inaccurate in a number of respects. Consider that dizygotic twins are the result of the fertilization of two ova; further, each twin-embryo develops within the confines of its own set of fetal membranes. DZ twins are thus dichorionic (DC); that is, they each enjoy their own chorionic sac. But while MZ twins develop from a single zygote, they do not necessarily share the same fetal membranes; that is, MZs might be monochorionic (MC) or they might be DC. When twinning occurs at an early stage (usually during the first 4 days after fertilization), the resulting MZs will be dichorionic (DC-MZ) and *in this respect will resemble DZ twins and not MZ-MC twins.* Their fetal circulation will almost never be connected. Approximately 33-40% of all MZs are DC. The rest of the MZ twins will be monochorionic. That is, they will share the same chorionic membrane and placenta, and occasionally a single amnion. In about 90% of these MC-MZs, fetal circulation is shared.[10]

This point about shared fetal circulation, chorion, and placenta is crucial: MC-MZ twins share a more similar prenatal environment than do DC-MZ twins; MC-MZs are, for instance, more likely to share infections than are DC-MZ twins. Should MC-MZ twins be more concordant for schizophrenia than DC-

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[9]Gottesman (1994); Gottesman and Shields (1982); Kringlen (1993); Torrey (1992). The studies with "representative samples" summarized by Torrey are Slater (1953); Tienari (1963); Kringlen (1967); Fischer (1973); Gottesman and Shields (1977); Kendler and Robinette (1983); and Onstad *et al.* (1991).

[10]Phillips (1993); Davis and Phelps (1995).

MZs (as they are), then one explanation would not invoke a genetic aetiology at all. A mother's exposure to infectious disease might increase the risk of later schizophrenia in her children.[11]

Davis and Phelps outline a very complex strategy for retrospectively determining placentation status. They err on the side of conservatism to avoid inflating their results. They determine that 60% of MC-MZs are concordant for schizophrenia, compared with 32% of DC-MZs. In a further study with another colleague, they refine the process of determining the placentation status, with nearly identical results. They thus conclude that it is very likely that the subset of MC-MZ twins inflates the MZ concordance rates in twin studies.[12]

Franz Kallmann reported long ago an MZ concordance rate for schizophrenia of 86%, compared with 15% for DZ twins. In 1991, Walker *et al.* reported on a meta-analysis of 21 studies: they found pairwise concordance rates of 25% (MZ) and 7% (DZ). Now we find, through Davis and colleagues that even this drop of 61 points in MZ concordance and 8 points in DZ concordance (and so 53 points in the difference between MZ and DZ concordance rates) may not be enough if it is the case that MC-MZ twins artificially inflate MZ concordance.[13] The twin-study evidence for a genetic basis for schizophrenia is thinning indeed.

A further problem with inferring a genetic aetiology for schizophrenia on the basis of twin-studies is that, as Rose *et al.* indicate, though DZ twins experience environments less similar than those that MZ twins experience, we would nonetheless expect DZ twins to experience more similar

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[11]Davis and Phelps (1995). The evidence for viewing schizophrenia as caused by an infection is equivocal. Some (e.g., Adams *et al.* 1993) hold that schizophrenia is caused (in some cases at least) by a maternal viral infection, and they offer the 1957 influenza epidemic as evidence for their claim; Crow (1994) is critical of these studies. Davis and Phelps (1995) do not specify a particular kind of infection. Ewald has long promoted infection as the cause of schizophrenia and other illnesses (see Hooper 1999). Suvisaari *et al.* (1999) have shown an association between the incidence of paralytic poliomyelitis and the subsequent incidence of births (five months later) of individuals who eventually were diagnosed with schizophrenia.

[12]Davis and Phelps (1995); Davis *et al.* (1995).

[13]Kallman (1938); Walker *et al.* (1991); Davis and Phelps (1995); Davis *et al.* (1995).

environments – both *in utero* and in the world – than other siblings. The upshot is that "from an environmental [nongenetic] viewpoint – and only from such a viewpoint – we would expect concordance among DZs to be higher than among ordinary sibs". As it turns out, this is indeed the case: DZ twins are more concordant for schizophrenia than are ordinary siblings; and so it would be eminently plausible to infer that the still higher concordance of monozygotic twins ought to be attributed not to genes but rather to their even greater environmental similarity.[14] That twin investigators ignore these difficulties is evidence of a *gene-centric approach*, whereby any difference in MZ-DZ concordance is immediately explained by invoking genes.

This gene centrism is bolstered by the adoption studies, which Gottesman and Shields refer to as "the straw that broke the environmentalist's back". Solomon Snyder called the first adoption studies "the best work that's been done" in biological psychiatry. "They take out all the artifacts in the nature vs. nurture argument".[15] Yet these studies are no less problematic than the twin studies. There are three types of adoption studies: first, studies examining the biological and adoptive relatives of adoptees; secondly, studies examining the offspring of schizophrenic biological parents; thirdly, so-called cross-fostering studies, in which the biological parents are not schizophrenic, though their child has inadvertently been placed with an adoptive parent later diagnosed as schizophrenic.

Rose *et al.* describe the details of a study of the first type, that of Kety *et al.* carried out in Denmark.[16] The Danish Adoption Studies (DAS) are commonly thought to provide definitive evidence of the biological heredity of schizophrenia. With 34 schizophrenic adoptees as index cases and 34 control adoptees with – in Gottesman's words – "clean pedigrees," Kety *et al.* traced 150 biological relatives of the index cases and 156 biological relatives of the controls. Rose *et al.* indicate numerous methodological

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[14]Rose *et al* (1984), p. 218.

[15]Gottesman and Shields are cited in Boyle (1990); Snyder is cited in Rose *et al.* (1984).

[16]Rose *et al* (1984); Kety *et al.* (1968).

problems with this study, primary among them the paucity of straightforwardly diagnosable *schizophrenics* among the relatives of either the index cases or the control cases. There was, it seems, exactly one "chronic schizophrenic among the index relatives and one among the controls".[17]

Kety *et al.* formulated a 'schizophrenic spectrum of disorders' comprising numerous illnesses (including chronic schizophrenia, borderline state, inadequate personality, uncertain schizophrenia, uncertain borderline schizophrenia, and uncertain borderline state). Even then, the authors found nine index cases with at least one schizophrenia spectrum diagnosis among their biological relatives, compared to only two such control cases. As Rose *et al.* remark skeptically: "That difference is the supposed evidence for the genetic basis of schizophrenia" – without the schizophrenia spectrum, Kety *et al.*'s study would have revealed no important genetic influence. Moreover, in their 1975 study, Kety *et al.* excluded the diagnosis of 'inadequate personality' from the schizophrenia spectrum, presumably because it was diagnosed equally frequently in index and control groups. Had the 1968 definition of the schizophrenia spectrum omitted the diagnosis of 'inadequate personality', the results would have lacked statistical significance.[18]

An additional difficulty with the adoption studies is ambiguity as to whether interviews were conducted with living subjects, or were rather reconstructions from the hospital records of dead relatives. Consider an example discussed by both Rose *et al.* and Marshall, that of a subject diagnosed with 'inadequate personality' in the 1968 study. Since that diagnosis falls within the boundaries of the 1968 definition of the schizophrenia spectrum, this subject contributed to the conclusion that schizophrenia has a genetic aetiology. This same subject was re-diagnosed for the purposes of the 1975 study with 'uncertain borderline schizophrenia' – that is, she no longer had an 'inadequate personality' (a diagnosis which was by 1975 no longer part of the schizophrenia spectrum), but rather was re-diagnosed with a

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[17]Marshall (1990), p. 108; Gottesman (1991), p. 103; Rose *et al.* (1984), p. 222.

[18]Rose *et al.* (1984), p. 222; Kety *et al.* (1975); Marshall (1990).

within-the-spectrum disorder, and thus continued to help demonstrate the genetic basis of schizophrenia. But as Rose *et al.* discovered, this subject, having committed suicide, was in fact never interviewed by the DAS investigators; rather, her two different diagnoses in 1968 and 1975 were reconstructed from hospital records – which indicated that she had actually been diagnosed by hospital physicians with manic depression! Rose *et al.*, astonished by their discovery, remark that "we can only marvel at the fact that the American diagnosticians, analyzing abstracts of these same records, were twice able to detect – without ever seeing her – that she really belonged within the shifting boundaries of the spectrum".[19]

Having considered these and other difficulties with the adoption-study methodologies, Rose *et al.* conclude that the weaknesses of the DAS are striking indeed, and wonder how such deep problems could have escaped the notice of those – like Snyder or Gottesman and Shields – who celebrate the conclusiveness of the adoption studies. A French meta-analysis reaches a similar conclusion. Cassou *et al.* set out to examine the scientific evidence for a genetic effect in schizophrenia. The ten reviews they selected for investigation declared unequivocally that the significance of genetic factors had been established. Yet after a meticulous analysis of each of the references in each of ten literature reviews, the authors conclude that there is *no evidence for a genetic effect in schizophrenia.*[20] Such a conclusion may be exaggerated, for the reasons to be examined below; but the study by Cassou *et al.* serves as an important counterpoint to the enthusiasm expressed by Kety and many other schizophreniologists. The truth lies somewhere between these two extremes – which, of course, is to say that we still know too little about the origins of schizophrenia.

4.2. Epigenesis And Schizophrenia

Nonetheless, schizophreniologists are convinced of the genetic basis of schizophrenia despite the

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[19]Rose *et al.* (1984), pp. 224-225; see also Marshall (1990).

[20]Cassou *et al.* (1980).

difficulties of the classical studies. A good instance is Gottesman's conclusion – which is the converse of Cassou *et al.*'s – that familiality is due largely to shared genes, more than shared pre- and postnatal environments. We have, Gottesman claims, "cumulative credible evidence" for "a large, rather specific, and important genetic factor(s), in conjunction with putative, unspecified nongenetic factors in most cases, lead[ing] to the development, over varying lengths of time, of varying severities of schizophrenia(s)".[21] But even in a passage such as this, full of qualifications and ambiguities, Gottesman overstates his case. He has no idea of the relation between genes and what might be called the schizophrenia spectrum; this is the reason he parenthetically pluralizes both "factor" and "schizophrenia" itself. Furthermore, his choice of language is particularly telling. Gottesman describes the genetic influence as "large", "rather specific" and "important", in contrast to the merely "putative" and "unspecified" nongenetic factors; such emphases suggest Gottesman's gene-centric agenda. Along with others convinced of the value of behavioral genetics, despite a wealth of criticism, Gottesman finds that the evidence from the family, twin, and adoption studies is methodologically adequate and that it consistently, though perhaps indirectly, points to a major genetic influence in the aetiology of schizophrenia. The hereditary basis of psychiatric genetics is established more by fiat than deduced from solid evidence.

The doctrine of gene centrism to which I have alluded is the *a priori* endorsement of the foundational, fundamental, preeminent role of genes in every aspect of human being. Gottesman and others demonstrate singular determination in their quest for the gene (or genes) causing schizophrenia. In order to convince those (justifiably) skeptical about our knowledge of schizophrenia, these gene centrists seek a schizophrenic genotype which will answer all doubters. Psychiatrists have grown weary of defending their discipline – in particular, they are tired of responding to critiques that mental illness is not "real" (and thus that psychiatry is not real medicine). Schizophrenia is probably the most contested of contemporary psychiatric diagnoses, a fact that has left schizophrenia researchers emboldened and

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[21]Gottesman (1991), p. 216.

embittered. If they could simply identify a 'gene for' schizophrenia, then they would silence the skeptics once and for all.[22] A well-established subfield of psychiatric genetics would raise the prestige of psychiatry as a medical specialty;[23] identifying a schizophrenia genotype would provide something tangible to point to when dealing with skeptics.

Of course, psychiatric geneticists are fully cognizant of the poverty of strictly genetic accounts of schizophrenia, and none proposes that a single gene of major effect, acting in virtual isolation, causes the disorder.[24] Gottesman himself remarks that a genetic diathesis-environmental stressor approach is accepted by a majority of schizophrenia researchers, and that this sort of "interactionist stance" (Gottesman's phrase) was already institutionalized by 1967.[25] Yet as Susan Oyama has asked of the nature-nurture debates as a whole, if we are all interactionists, then what's the problem? As she and others have observed, the trouble is with the very slipperiness of the concept of 'interaction' as such.[26]

For instance, interaction may occur at both populational (analysis of variance) and individual-developmental (analysis of causes) levels. In terms of populations, the task is to explain differences in

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[22]Gottesman (1994) is particularly annoyed by this dimension of the dispute: "in modern times at least, research into the causes of coronary heart disease, non-insulin dependent diabetes and Alzheimer's disease has not had to contend with the assertion that these diseases are 'myths', or are 'labels' used to maintain an unfair social class structure, or result simply from one or another kind of psychic stress traceable to how your mother raised you or how your parents communicated with each other in your presence". In response to such criticisms as he has noted, Gottesman is reduced to hurling epithets, claiming that the trouble is with "marxist philosophers, orthodox psychoanalysts, and assorted ideologues" who "would rather grind their own axes than further the impartial quest for the causes of schizophrenia". Which is, of course, to beg the question.

[23]Gaines (1991).

[24]See, e.g., Weinberger (1999).

[25]As Gottesman (1991, p. 83) remarks, "largely as a consequence of the Dorado Beach conference [Puerto Rico, 1967], the entire field of schizophreniology was converted, at least in public pronouncements, to some kind of interactionist stance for advancing against the common enemy – ignorance about the true causes of schizophrenia".

[26]Oyama (1985), p. 5. I am grateful to Lisa Gannett for encouraging me to try to be clearer about the various senses of 'interactionism' which are occasionally conflated in the literature. She also graciously supplied a very helpful unpublished manuscript.

traits in a population; that is, to account for phenotypic variation in terms of environmental variation, genetic variation, or both. From this perspective, interaction may be understood in two ways, additively (genes + environment = phenotype) or nonadditively (genes × environment = phenotype). (Additivity in this context refers to the aggregation of independent influences; the contribution of the genotype is insensitive to any environmental factor, and the contribution of the environment is not influenced by the genotype.[27]) There is a longstanding dispute between those who downplay nonadditive interaction and emphasize additivity, for whom therefore the partitioning of individual, independent influences is relatively straightforward; and those who recognize significant nonadditive interaction, and therefore contend that the interdependent variables cannot be meaningfully disentangled.

The situation is equally charged in the context of individual development, where the task is to explain the source not of differences in traits but rather of the traits themselves. A significant source of disagreement involves conceptual slippage from the level of populations to the level of individual organisms. Though there is an obvious difference between understanding statistical variance-in-traits and understanding ontological causes-of-traits, we sometimes confuse the two and partition traits into genetic and nongenetic components, just as we partition variation into genetic and environmental influences. That is a mistake, according to some interactionists, while it is perfectly acceptable to others (e.g., Scarr). Does ontogenetic interaction therefore refer to a thesis about genes (primary) and environments (secondary) as relatively independent factors, whereby genes are environmentally activated to produce the phenotype from what is thought to be 'latent in the genotype' (the Modern Consensus)? Or is ontogenetic interaction somehow more complex, consisting in a broader range of comparably important inherited and noninherited factors (DNA, cytoplasmic characters, nutrients, and so on), characterized by their context sensitivity (e.g., to temperature), developmental history, and spatiotemporal position in the cell and the organism, interacting in interdependent ways in the constitution of the phenotype? On the former

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[27]Wahlsten and Gottlieb (1997); Lewontin (1974).

account, interaction amounts to ontogenetically specific information-bearing genes being expressed as a result of (usually nonspecific) nongenetic triggering; genes are primary, requiring but activation for ontogenesis to take place, and the phenotype is only the simple result of the foundational genes. On the latter account, the developmentally specific information resides not in the genes but in the spatiotemporally delimited developing system, which is therefore the ontogenetically primary unit. Accordingly, interaction is not limited to gene-activation but implicates positive and negative feedback loops, at a variety of levels within and without the developing organism, which contribute to the constitution of the organism. Note that there is a qualitative difference between these two alternatives (which certainly do not exhaust the field of possibilities): the latter is not a more detailed presentation of what is implicit in the former, but rather a rejection of its basic premise of gene centrism and its ostensible oversimplification of the nature of interaction.

This is all very abstract, to be sure, and it is therefore important to consider an example. For the remainder of this section, I will criticize the first interpretation of population-level interaction, and defend the second interpretation of interaction at the level of individual ontogenesis, against the current of much research in schizophrenia genetics.

The challenge to quantitative genetic efforts to disentangle the relative effects of genes and environments is many decades old. The model employed by behavioral geneticists assumes that hereditary factors are of necessity genetic factors, and presumes further that genes and environments act separately and additively, so that their respective contributions to a trait can be separated statistically.[28] The standard tools of statistical and population-genetic analyses either assume additivity, or do not detect nonadditive interaction and therefore presume that it does not exist. But it has been repeatedly shown that the statistical analysis of variance (ANOVA) does not detect nonadditive interaction not because it is not

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[28]Wahlsten and Gottlieb (1997), p. 163.

there, but rather because the test is insensitive.[29] Thus, the presumption of additivity is misguided; meanwhile, research on large populations of different strains of laboratory animals has demonstrated that nonadditive interaction is the rule rather than the exception.[30]

Nevertheless, the presumption of additive interactions prevails in psychiatric genetic research, and has contributed a sense of urgency to efforts to decompose mental illness into individual and relatively independent genetic and environmental components. The problem is attributable in part to the neglect of developmental biology in the Modern Synthesis.[31] Aetiological models of schizophrenia, motivated by population-level measurements of heredity that are insensitive to gene-environment interaction, reduce the interaction of genes and environment to the (secondary) environmental stimulation of predisposing genes. Consider the diathesis-stressor model upon which many schizophreniologists base their aetiological understanding of schizophrenia. In a standard diathesis-stressor model, *diathesis* denotes a predisposition while *stressor* refers to the event(s) which trigger(s) the schizophrenic episode. What counts as a stressor might be a single event or a series of them, and the stressor(s) must be understood in context; as Gottesman notes, "how one event affects an individual depends not only on how it is perceived by that individual and on what events have preceded it, but also on when the events happened and on individual differences in the person's vulnerability at each of those times". It is accurate to characterize a diathesis-stressor model as a genes-*plus* model of schizophrenia, for it 'adds on' environmental influences (as stressors) to the underlying (genetic) predisposing substrate.[32]

Gottesman refers to such a model as an 'epigenetic' account of schizophrenia. It is unclear what

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[29]Hogben (1933); Wahlsten (1990); Strohman (1993); Wolf (1995); Wahlsten and Gottlieb (1997); Sarkar (1996a; 1998; 1999).

[30]The research on laboratory animals is summarized in Wahlsten and Gottlieb (1997). See Sarkar (1998), chapter 4, for a trenchant critique of quantitative genetic efforts to separate genetic and environmental influences.

[31]Wahlsten and Gottlieb (1997); Gottlieb (1995).

[32]Gottesman (1991), p. 150; Alper and Natowicz (1993).

exactly he means by this plastic term which, as is evident from the previous chapter, has many interpretations in contemporary and historical biological literature. As I explained in Chapter Three, the term 'epigenesis' dates back at least to William Harvey writing in 1601, but Aristotle is often referred to as the first epigenecist. The basic idea of epigenesis is that the traits of organisms are not preformed *in utero*, but rather emerge anew during the developmental process. As noted in the previous chapter, C.H. Waddington updated the concept of epigenesis for the twentieth century with his notion of 'epigenetics', combinging the classical notion of epigenesis with classical and, later, molecular genetics. A modern definition in this vein is that "epigenetics" refers to "the multiple genetic and nongenetic factors that influence or regulate gene activity during development". A plausible conjecture, then, is that for Gottesman the schizophrenic is not preformed, not curled up in the zygote, but rather the predisposition for schizophrenia exists preformed in the genes from conception, and emerges epigenetically under the 'right' developmental conditions.[33]

On this account of epigenetics, the primary emphasis is on the 'genetics', not the 'epi', and epigenetic control takes the genotype as its starting point and the phenotype as its endpoint.[34] As Gottesman concludes, the presumably relatively low prevalence of the predisposing genes, compared with the presumably broad range and variety of environmental risk factors or triggers, indicates that the fundamental causes of schizophrenia must be genetic.[35] The corollary is thus that environmental causes are secondary to the primary role of (as yet undiscovered) genes. The environmental triggers unleash the schizophrenogenic potential inherited in the DNA.

But, there are ways of interpreting 'epigenetics' and 'epigenesis' (and the epigenesis of schizophrenia) without recourse to the causal, methdological, or ontological primacy of the genes. For

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[33]Needham (1959); Waddington (1940; 1975); Thom (1989); Hall (1998), p. 114-115.

[34]Hall (1998), p. 114.

[35]Gottesman (1991).

instance, unlike Gottesman, Waddington was not a gene centrist. Genes were important only as part of a complex developing organism not reducible to its genes.[36] The 'epi' was just as important as the 'genetics'. From this point of view, the appropriate domain of epigenetics is not the space between genotype and phenotype, but rather that between egg and developing organism, in sociocultural context. On such an account, epigenetic processes become coextensive with ontogenesis as a whole, and cannot be reduced to mere gene activation. Furthermore, note the corollary: 'heredity' cannot be reduced to genes alone, for we inherit much more than a genome at conception. Accordingly, to interpret the classical studies of schizophrenia as showing not merely that schizophrenia runs in families but that it is a genetic disorder is to step unwisely.

An alternative position is advanced by proponents of developmental systems theory (DST).[37] According to DST, the secondary epigenetic triggering of a preformed, encoded, inherited genetic predisposition misconstrues organismic development altogether. Genes-plus theories make the mistake of relegating developmental processes and life experiences to the role of expressing, translating, or otherwise mediating the underlying, preestablished genetic program. This idea that phenotypes are transmitted through coded instruction sets is misguided, according to DST, for phenotypes are not transmitted at all but rather "constructed anew" in each individual life-cycle through strong organism-environment interactions throughout development. The unit of development is not the epigenetically regulated genetic program, but the organism-in-an-environment system whose various multileveled components interact nonadditively over time in the production of the mature organism.[38]

For adherents to DST, development is, therefore, not genes-plus anything; it is strongly interactive, not additive. Schizophrenia, like any other trait, complex or simple, is not unleashed, but is

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[36]See, e.g., Gilbert (1991) and Needham (1986).

[37]Oyama (1985; 1998); Gottlieb (1995); Gray (1992); Griffiths and Gray (1994); Neumann-Held (1999).

[38]Mahner and Bunge (1997), pp. 304-309.

rather "constructed epigenetically through ontogeny". Genes are surely a relevant factor in schizophrenia – as in most human characters – but they are not primary, not foundational, not fundamental. Commentators such as Oyama insist that development ought to be thought of as "a contingent series of constructive interactions, transformations, and emergences" not reducible to preformed informational genes and their epigenetically mediated products.[39]

Eva Neumann-Held's criticism of standard concepts of the gene foregrounds many of the concerns of DST. She underscores how the meaning and function of a given gene are necessarily context-dependent – dependent, that is, on a variety of ontogenetic processes in the developing organism. But Neumann-Held takes the additional step of arguing that the *structure* of a gene is itself context-dependent, subject to and so constitutively contingent upon a wide variety of contextual factors in development. "Independently of context and system, the DNA has neither structure, nor function, nor program, nor information".[40] The focus on genes as preformed determinants – even as parts of complex networks of genetic and nongenetic partial determinants – is therefore misguided. Genes do not exist in isolation – there is no such thing as a genome without a system; neither are genes somehow prior to the developing organism, awaiting epigenetic activation. The implication of developmental systems theory, especially as elaborated by Neumann-Held, is that the very idea of genes-plus-anything as a cause of ontogeny is a mistake.

Gottesman acknowledges the validity of certain crucial elements of the DST account, for instance that "gene expression is always environmentally mediated". To his credit, at no point does Gottesman fail to recognize (he calls it a truism) that behavioral phenotypes are necessarily produced by both genes and environments – the basic presumption of all forms of interactionism.[41] But he does not seem to fully

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[39]Gray (1992), p. 167; Oyama (1998), p. 69.

[40]Neumann-Held (1999), p. 119; see also Sarkar (1996b).

[41]Goldsmith *et al.* (1997), p. 375.

appreciate the limitation that interaction imposes on behavior genetics, namely, that, as Gray notes, "it is not possible to assign causal primacy nor to dichotomise developmental causation into internal and external components".[42]

Gottesman's most recent proposal is to underscore that "there may be *partially* genetically influenced *predispositions* for basic behavioral tendencies, that under certain experiential contexts, make the *probability* of developing psychopathology higher for individuals who possess greater rather than lesser degrees of such behavioral tendencies".[43] But if that is all that psychiatric genetics can tell us, then its medico-scientific import is ambiguous at best, and Gottesman's middle-way is something of a dead end. For virtually all of the characters of organisms are in this way genetically influenced; no one doubts that. It is unclear, therefore, what practical or therapeutic end is served by focusing on genes and not the complex behaviors or behavioral processes themselves.[44] Meanwhile, many of Gottesman's colleagues are not likely to admit (and even less likely to take seriously) the limitations of genetic explanations of behavior.

Consider, for instance, the representative remarks of Anne Farmer and Michael Owen:

> The Human Genome Project is the enabling technology by which the genes contributing to the genetic aetiology of common familial disorders, including the major psychiatric disorders, will be identified. We may be uncertain precisely how quickly and by what means such discoveries will be made but there is little doubt that they will happen and that the knowledge gained will radically alter clinical practice. ... The accuracy of diagnosis of major psychiatric disorders will be greatly enhanced and the complex interplay between environment and genotype will be increasingly understood.[45]

Such faith in the promise of the Human Genome Project (HGP) is commonplace among psychiatric

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[42]Gray (1992), p. 175; see also, e.g., Lewontin (1983; 1991; 1992; 1995); Strohman (1993); Wolf (1995).

[43]Goldsmith *et al.* (1997), pp. 383-384; italics (unbelievably) in the original.

[44]Aside from the fact that, that, thanks to funding decisions and the particular interests of geneticists, the genes may be more experimentally tractable. See e.g. Gannett (1999); Schaffner (1998); and Griffiths and Knight (1998).

[45]Farmer and Owen (1996), p. 135. They refer to Owen and McGuffin (1992).

geneticists. Gottesman, for instance, holds that the identification of "genes that contribute to the etiology of behavioral disorders ... will inevitably follow from the results of the Human Genome Project".[46] But if we take seriously the challenge of developmental systems theory, then we must recognize just how far removed the HGP's official human genome is from the actual complexity of the interactive, spatiotemporally delimited, context-dependent developmental processes occurring within organisms which in fact co-determine both the structure and function of genes.[47] We must admit that the HGP's preformed, informational, context-free, static official genome is an abstraction; indeed, "the" human genome is a fiction, for there is no genome independently of a developing organism and, further, no single genome could be representative of the species.[48] At best, the HGP may produce a false model which may still have some heuristic value as a means to improve theories of development.[49] But let us not pretend that the HGP will permit us to hold "nature" constant while solving for "nurture"[50] – the two are inextricable. "Developmental information is not *in* the genes, nor is it *in* the environment, but rather it develops in the fluid, contingent *relation* between the two".[51] It is by no means obvious therefore how the production of a one-dimensional readout of As, Cs, Ts, and Gs – frozen in time, abstracted from developmental context – will improve our understanding of ontogeny, or of the aetiology of disease.[52]

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[46]Goldsmith *et al.* (1997), p. 380.

[47]Neumann-Held (1999).

[48]See e.g. Tauber and Sarkar (1993); Robert (1996), chapter two.

[49]Wimsatt (1987).

[50]As in, for instance, Bodmer and McKie (1994).

[51]Gray (1992), p. 177. By the same token, a predisposition is neither in the genes nor in the environment, but rather in their more-or-less fortuitous interaction.

[52]Rose (1997), p. 157.

4.3. Nosology

Yet schizophreniologists make an additional set of claims about the future benefits of research into the genetics of schizophrenia. They contend that the identification of some underlying schizophrenic genotype will help to refine psychiatry's entire nosological system, making it at once more scientific, more objective, and more valid than it is presently. Thus, the idea that schizophrenia has a strong genetic component persists as an accurate portrayal of the Gestalt of psychiatric geneticists, despite the methodological and inferential problems with the classical studies. My contention is that the epidemiological motivation for psychiatric genetics, at least in the case of schizophrenia, is assumed rather than demonstrated – notwithstanding Gottesman's admonition that anyone who criticizes this perspective must be acting for reasons of ideology and not rationality.[53] And while we know surprisingly little about the aetiology of schizophrenia, we know even less about its clinical phenomenology. Consequently, given the methodological flaws (inconsistencies, contradictions, conflations, ambiguities) of the epidemiological studies, the search for schizophrenia genes is not well-motivated.

But there arises another possible explanation for the persistence of genetic research into complex behaviours such as schizophrenia: "genetic strategies and inferences about the etiology, course, and outcome of schizophrenia are much easier to devise than are those required to detect psychosocial and physical-environmental factors".[54] That is, it is easier to study genes as putative aetiological factors than it is to study anything else. Of course, the heuristic (if not ontogenetic) primacy of genes may very well be an artefact of a more basic sense that genes really are ontogenetically foundational which has fostered the

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[53]Above, I cited the middle part of a passage from Gottesman, within which he summarizes the results of his review of the classical literature. The full passage is as follows: "unbiased readers of this text will have to conclude that, based on the cumulative credible evidence, a large, rather specific, and important genetic factor(s), in conjunction with putative, unspecified nongenetic factors in most cases, leads to the development, over varying lengths of time, of varying severities of schizophrenia(s). Resistance to such a balanced conclusion, when it appears, must be based on ideological reasons" (Gottesman 1991, p. 216).

[54]Gottesman (1991), p. 150.

development of a wide range of tools to investigate the genetic contribution to traits! But then the decision to inquire into the alleged genetic basis of schizophrenia is not made for the value-free, unbiased reasons that Gottesman supposes. Instead, the merest suggestion that genes are causally primary leads to the search for disease-causing genes which reinforces the sense the genes are causally primary which forces researchers to redouble their investigative efforts, on and on in a self-fulfilling prophetic cycle.[55]

Hence, schizophreniologists are seeking to identify a 'gene for' schizophrenia – "an important step in the reification of psychiatric disease concepts"[56] – which would be the salvation of schizophreniology, and would validate the basic sense that schizophrenia is a real, objective diagnostic category. I suggest that, if current trends continue, the best that psychiatric nosologists can hope for is the discovery of some genes implicated in some cases of schizophrenia-type illnesses. But even those most strongly against genetic reductionism will grant that there surely do exist genes implicated in cases of schizophrenia, for humans are mutually determined by genetics, environment, and a plastic neurology; all three, in complex interplay, are implicated in all aspects of human behavior. The dispute is over whether (and how) localizing those genes is important to – or even sufficient for – identifying, diagnosing, understanding, or treating the disorder. The answer is dependent on just how much we take the genes to explain, and there is a consensus position somewhere between the unacceptable extremes of "nothing" and "everything". But how to stake out this middle ground?

In the psychiatric and philosophical literature there are two ways – moderate and strong – of interpreting the potential role of genetics in psychiatric nosology. Moderate: molecular genetics will help to refine often-confused higher-level disease categories. Strong: the fate of psychiatric nosology ultimately rests on advances in molecular genetics. Following discussion of these alternatives, I will

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[55]See, e.g., Gannett (1999, pp. 359, 370): "By electing to control for environmental factors in the laboratory, genes are rendered the target of causal investigation. ... It is not surprising that from laboratory contexts that treat genes as active causes and nongenetic factors as background conditions emerge theories that increasingly understand traits and diseases as genetic".

[56]Harris and Schaffner (1992), p. 145.

advance a third interpretation, weaker than the strong one, and even qualitatively weaker than the modest one: sometimes feedback and feedforward loops between clinical phenomenology and molecular genetics may influence the disease classification, *but only if the clinical description is relatively robust and reliable in the first place.*

Both moderate and strong interpretations are motivated by a sense of the primacy of genes, and consequently are characterized by a certain optimism about the prospects of molecular genetics in psychiatry. Regarding the movement toward "a more biological basis for psychiatric diagnosis", Harris and Schaffner write that "it can be anticipated that molecular genetics will make a very substantial contribution to this movement. As genetic markers play an increasing role in diagnosis, new disease classes may emerge that replace or significantly modify old ones".[57] Tsuang *et al.* are even more enthusiastic: "the new tools of molecular and statistical genetics promise to build an enduring theoretical and empirical structure that will house solutions to many questions of etiology, pathophysiology, diagnosis and treatment". But while Tsuang *et al.* are concerned to facilitate this process by attempting to define "genetically meaningful diagnostic categories", Harris and Schaffner indicate the importance of ensuring that great care be taken to make certain that "what is lost by these approaches to diagnosis does not outweigh the conceptual simplification or explanatory force that is gained".[58]

Allow me first to address the strong interpretation. Tsuang endorses a "psychiatric genetic nosology" – "a scientific nosology created from psychiatric genetic data" – which "seeks to classify patients into categories that correspond to distinct genetic entities". In other words, "instead of using predefined categories, these methods attempt to define new phenotypes that maximally correspond to the

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[57]Harris and Schaffner (1992), pp. 128-129. It is worth noting that Schaffner's optimism has apparently been tempered by his recognition of the complexity of developmental processes, even at the molecular level. See, e.g., Schaffner (1999).

[58]Tsuang *et al.* (1993), p. 131; Harris and Schaffner (1992), pp. 146-147.

genetic component of psychiatric illnesses".[59] Yet this notion of tailoring clinical diagnoses to suit genetic data does not establish – but rather begs the question of – the genetic basis of the disorder. If there is reason to doubt that, say, schizophrenia or bipolar disorder has a genetic basis, then it is not obvious why we should seek to define these disorders in terms of their (possibly non-existent) genotype. But Tsuang has no doubt that schizophrenia is heavily genetically influenced. In an editorial in the *American Journal of Psychiatry*, he claims, completely uncritically, that

> epidemiology has played a unique role in psychiatry's quest to validate its diagnoses and treatments with the scientific method. Epidemiologic studies yielded rigorous definitions of disorders that enabled international teams to show how disorders like schizophrenia were not artifacts of culture but diseases like any other. Genetic epidemiologic studies provided the first real clue that psychiatric disorders had a biological basis. Indeed, the classic family, twin, and adoption studies of schizophrenia planted the seeds of biological psychiatry, whose fruits are enjoyed regularly in this journal and elsewhere.[60]

Hence Tsuang's endorsement of the necessity of a schizophrenic genotype. But several questions immediately arise; for instance, if no schizophrenia genes are found, are we to conclude that schizophrenia is not a proper mental illness? But if schizophrenic genes are found, why should we trust them to indicate a diseased person in the pre-symptomatic stage when no other phenotypic indicators of illness are present? Meanwhile, since no schizophrenia genes have been found to date, what are we to infer about the current status of the clinically defined diagnostic category?

But there is an even deeper concern here. It has often been suggested that a psychiatry built upon a scientific nosology would enjoy increased prestige and credibility. Kendler asserts that "the application of the scientific method should make our nosology better, moving it away from our preconceptions toward a more accurate and valid description of clinical reality".[61] The suggestion is that the genetic diagnostic categories would be objective in precisely the way that mere clinical judgments – the target of resounding

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[59]Tsuang *et al.* (1993), p. 131; Tsuang (1994), p. 4; Tsuang *et al.* (1993), p. 136.

[60]Tsuang (1994), p. 3.

[61]Kendler (1990), p. 970.

criticism – fail to be. So psychiatric diagnoses, based in experimental genetics, would ostensibly be just as scientific, objective, non-normative, and value-neutral as any other biomedical diagnosis.

But, to be sure, the move toward a psychiatric genetic nosology does not do away with preconceptions. As Lisa Gannett has persuasively argued, in both physiology and molecular genetics knowledge of the normal follows upon knowledge of the pathological, and any values (e.g., about normalcy, health, and illness) that are present at the level of individuals are imported to the level of the genome.[62] Since those same values abound in the genotypic realm, the process of identifying a schizophrenic genotype simply is no less value-laden than the process of identifying a schizophrenic phenotype. In fact, the process of identifying a schizophrenic genotype may be even more value-laden than the process of identifying a schizophrenic phenotype, in assuming that schizophrenia is a *genetic* disorder rather than something else. In short, then, genetic normality is no more value-neutral than phenotypic normality. To 'go genomic' is just to push the matter down a level.[63]

Despite the belief that a more scientific psychiatry is more credible than earlier psychiatries, I am not confident that a genetic approach is any more *scientific* than, e.g., a neurological approach. And since the idea that schizophrenia has a genetic basis is deeply ingrained in schizophrenia research, we must bear in mind that this presupposition need not lead to the inference that the entire psychiatric nosologic system ought to be at the mercy of advances in molecular genetics. Let us then briefly consider two versions of the more moderate interpretation of the role genetic approaches should play in psychiatric research, particularly regarding schizophrenia.

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[62]Gannett (1998).

[63]Philosophers of science have long contended that no scientific theories are perfectly value-free; this is certainly the case with biomedical theories, insofar as diagnoses of illness inherently make value judgements about the state of the patient's body as compared to a normal body. Psychiatry could perhaps be rendered less (ostensibly) subjective by appeal to biological markers – that is the point of using, e.g., neurological testing as a means of determining what sort of disorder a particular patient suffers from. But insofar as biological markers are themselves normative, the hope of value-freedom in psychiatric diagnosis is a false hope, in the same way that such a hope is false also in the case of other biomedical diagnoses – none of which is to say that biomedical diagnoses are subjective.

Tsuang and colleagues describe one variant of the moderate interpretation (though they refer to the stronger interpretation as being "closer to a true psychiatric genetic nosology"), a method which begins with "known psychiatric or neurobiological categories" and reorganizes them "in a fashion that maximizes the usefulness of family data for genetic linkage studies".[64] Insofar as this approach conceives the genotypic entity as the standard to which the phenotypic category must adhere, and therefore assumes that identifying schizophrenia genes is somehow more objective than identifying schizophrenics at the level of phenotypes, it encounters the same difficulties about putative value-neutrality as the strong approach.

Harris and Schaffner's alternative version of a modest proposal is more successful. They identify two possible influences of genetic approaches on psychiatric nosology: "Traditionally distinct DSM-III-R [now DSM-IV] categories may be merged by the reduction of diverse clinical syndromes that have common genetic markers. Alternatively, diagnostic categories thought to represent single diseases may be subdivided into multiple disease entities having different genetic patterns".[65] As this approach implies, a psychiatric genetic nosology is not forced on us by the nature of psychiatric disease; rather, we may choose, when appropriate, to integrate the results of methodologically sound and genuinely informative genetic research. This appropriateness criterion is akin to recognizing that some nosological questions may be "fundamentally nonempirical"[66] – not decided by facts, but rather by at least partially pragmatic considerations.[67]

In this regard, Kendler underscores that "one important limitation of a scientific nosology is that it cannot address the validity of a psychiatric disorder where there is disagreement about its proper

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[64]Tsuang *et al.* (1993), p. 136; Tsuang *et al.* (1993), pp. 132-133.

[65]Harris and Schaffner (1992), pp. 140-141.

[66]Kendler (1990), p. 972.

[67]I use "pragmatic" here in the sense intended by Gannett (1999).

construct. That is, data can only provide an answer if there is an agreement about what the question is".[68] I worry that Harris and Schaffner, and certainly Tsuang, do not attend sufficiently to this consideration about the initial characterization of the phenotype. The success of genetic studies of schizophrenia will depend on possessing an adequate phenotype in the first place;[69] that we lack one helps to explain the failure to identify linkage between particular genes and schizophrenia.[70]

Genetic linkage studies are carried out in families with a large proportion of afflicted members. If an unknown disease gene[71] and a known genetic marker are located close together on a chromosome, then they are likely – in violation of Mendel's law of independent assortment – to be inherited together. Two types of linkage studies are (1) those premised on the roughly 30 or 40 classical genetic markers (e.g., blood group antigens, human leukocyte antigens), and (2) those exemplary of the new genetics, premised on the techniques of recombinant DNA. These newer techniques have allowed for the introduction of a massive number of markers consisting in, for instance, DNA fragments known as restriction fragment length polymorphisms. If a marker is shared between affected family members, additional and increasingly sophisticated tests may allow the gene itself to be identified.[72]

That genes are the cornerstones of the aetiological "puzzle of schizophrenia" is self-evident to any number of schizophrenia researchers, as well as to geneticists, physicians, and lay people;[73] and so schizophreniologists have sought to identify linkage between particular chromosomal loci and aspects of

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[68]Kendler (1990), p. 970.

[69]Kringlen (1993), p. 79.

[70]Of course, another possibility is that there are no such things as 'schizophrenia genes'.

[71]This is, of course, an odd locution; the idea is that if investigators find the same gene near the marker in a number of afflicted relatives (and, ideally, not in those not afflicted), then that is the 'gene for' schizophrenia.

[72]Cardno and McGuffin (1994).

[73]Tsuang (1994); for a recent example of popular attention to the quest for schizophrenia genes, see Nicol (1999).

the schizophrenic phenotype. The researchers operate under the presumption that replicated genetic linkage studies "will shed enormous light on the genetic aspects of mental illness, because they will turn the circumstantial evidence of genetic involvement gained from population genetic strategies into hard, physical evidence".[74] Unfortunately, molecular geneticists have so far been unable to ascribe particular roles to specific genes in the development of schizophrenia.[75] Some researchers, such as Tsuang, are astonished by these failures: "surprisingly, despite decades of epidemiologic research pointing to genes as an etiologic mechanism for schizophrenia, application of the sophisticated methods of molecular and statistical genetics that are now available has not revealed which genes are involved and how gene products lead to the disorder".[76] But, as I will show, this result is in fact not surprising at all.

Four conditions must be met for linkage to be successful: the disorder must be caused by a single gene of major effect; the disorder must be homogeneous in the family under study; the (approximate) mode of inheritance must be known; and the diagnostic criteria of the disease must be relatively straightforward. Schizophrenia meets none of these conditions: every genetic model is at least oligogenic; the afflicted relatives of schizophrenics are most likely not to be schizophrenics themselves, but rather to have schizophrenia-spectrum disorders; the mode of inheritance is unknown; and the diagnostic signs of schizophrenia have expanded and contracted throughout the twentieth century.[77]

It is therefore surprising to find Tsuang claiming, in a passage cited above, that epidemiological studies have generated "rigorous definitions" of psychiatric disease entities; such a claim is patently false in the case of schizophrenia. As Andreasen *et al.* say:

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[74]Gottesman (1991), p. 93.

[75]See, e.g., Moldin (1999); DeLisi and Crow (1999); Crow and DeLisi (1998).

[76]Tsuang (1994), p. 3.

[77]For the first three conditions, see Cardno and McGuffin (1994), pp. 345-346; for the fourth condition and additional discussion, see Billings *et al.* (1992), pp. 232-237, and Andreasen and Carpenter (1993). Note that concerns about the first condition may be addressed by more recent work on quantitative trait locus (QTL) mapping.

> Studies that invest heavily in the collection of biological or outcome measures are penny wise and pound foolish if they scrimp on the phenomenological description of patients. This is particularly important because we do not know the definition or boundaries of schizophrenia. The process of understanding the definition and boundaries must resonate back and forth between good phenomenology and good biological measures.[78]

The most promising orientation to defining the role of genetics in psychiatric nosology therefore would invoke multidirectional feedback between genes and larger phenotypic elements in the eventual refinement of a robust diagnostic category – but then we cannot rely strictly or even primarily on genetic studies to supply the 'interactive phenotype', as it were.

4.4. Reorienting Schizophreniology

Beginning in 1982, the United States National Institute of Mental Health's journal, *Schizophrenia Bulletin*, ran a series of unsolicited articles by leading schizophrenia researchers under the title "What is Schizophrenia?" As one might imagine, the opinions of the researchers varied greatly. Yet many of them expressed optimism regarding the future of psychiatry. Meltzer was especially hopeful: "in the year 2000, an essay such as this might be able to discuss when in the developmental cycle specific genes and their products, in response to specific exogenous insults or stresses, produced various biochemical and electrophysiological abnormalities that, in turn, were the basis for specific abnormal behaviors in the numerous subtypes of schizophrenia. What a joy it will be to read, what an even greater joy to write, such an essay".[79] These millenarian hopes have not come to fruition; allow me to suggest a reason why they have not been realized.

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[78]Andreasen *et al.* (1988), p. 361 – note that Tsuang is one of the eleven authors of this report. The authors continue: "The ability to advance our knowledge about schizophrenia has been partially handicapped by our inability to define it precisely and consistently. There is no question that schizophrenia is a 'real disorder' that produces severe and often persistent disabilities. For a variety of historical and conceptual reasons, however, there has been disagreement among clinicians and investigators as to the best ways to define this disorder" (Andreasen *et al.* 1988, p. 345). Hence, "the student of schizophrenia pursues a moving target" (Andreasen and Carpernter 1993, p. 200). For further discussion, see, e.g., Boyle (1990) and Andreasen (1997).

[79]Meltzer (1982), p. 434.

In 1974, the American Psychiatric Association (APA) appointed Robert Spitzer as head of its Task Force on Nomenclature.[80] The mandate of the Task Force was to develop and issue the third edition of the APA's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*). Wanting (with some justice) a clean break from *DSM-II*, Spitzer demanded of the APA Board of Trustees a Task Force whose membership comprised no one who had helped to create the earlier manual. He chose as Task Force members psychiatrists and psychologists "committed to diagnostic research and not to clinical practice," intellectually rooted in St. Louis and not Vienna – more interested in biological substrates than in clinical phenotypes, or "phenomenotypes".[81]

This focal shift in schizophrenia research helped to facilitate the conceptual and practical slide from the apparent heredity of schizophrenia (based on the indirect and circumstantial evidence of the family, twin, and adoption studies) to genes-plus aetiological models. That is, thanks in part to these changes in psychiatric orientation, the merest suggestion that schizophrenia is inherited led to the judgment that genes, when environmentally triggered, cause schizophrenia. Then, given this latter conviction, research attention was diverted from the clinical phenomenology of schizophrenia and directed toward its biological substrates, including its putative genetic basis, according to which the aetiology of the disorder is almost universally construed in terms of a diathesis-stressor model.

As should by now be evident, the imperative to investigate the biological substrates and genetic aetiology of, disorders is deeply embedded in contemporary psychiatry; as Louis Sass has observed, the "tendency to neglect careful description and analysis of abnormal psychological phenomena in favour of a too-quick and too-exclusive focus on etiology or causation" is "a great weakness of twentieth-century

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[80]In the following paragraphs, I draw on the discussion of Young (1995), pp. 99*ff.*

[81]Millon (1986); Bayer and Spitzer (1985), p. 188. The term "phenomenotypes" is used by Andreasen (1987).

psychiatry and psychology".[82] And this is so despite the claimed aetiologically atheoretical approach of the *DSM-III-R* and *DSM-IV*. The current repudiation of phenomenology (that is, the current lack of attention to description and analysis at or near the level of the observed behavioral phenomena) is the lasting legacy of the biological, and more recently genetic, revolution in psychiatric research and, I contend, helps to explain our failure to understand schizophrenia. The classical motivation for the aetiological imperative is anaemic at best, and "none of the evidence for a biological mechanism responsible for schizophrenia or any of its symptoms is conclusive. Interest in genes involved in various neurodevelopmental process is based on incomplete evidence and circumstantial inferences".[83] It may be time, then, to dislodge the aetiological imperative, especially in its genetic incarnation.

My contention is that the quest for schizophrenia genes in the absence of an adequate conception of its phenotype may result in a more rather than less value-laden diagnostic classification. One reason for this consequence is that a prejudice toward a genetic model is built into the 'most genetic' phenotype – that phenotype which corresponds best to some underlying genetic anomaly. A second, more fundamental reason is that the genotype cannot be accessed in multiple interdependent ways, and thus the diagnostic category cannot be subject to triangulation.[84] We are supposed, on certain accounts of the proper role of genetics in nosology, to presume *a priori* that a genetic classification is somehow more objective than a higher-level classification; but that is a biased presumption. What makes a diagnostic classification valid is its multiple determination;[85] therefore psychiatric genetics cannot by itself establish the (independent) validity of disease constructs.

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[82]Sass (1994), p. x. To be sure, the central focus on aetiology was a problem with the pre-genetic era in psychiatry, as well; proponents of psychoanalytic approaches were preoccupied with establishing a causal and explanatory framework for interpreting mental illness (Harris and Schaffner 1992, p. 137).

[83]Weinberger (1999).

[84]Crano (1981).

[85]This is an inference I draw from the work of Wimsatt on robustness; see Wimsatt (1994), (1981), (1976), and (1974).

It is fair, I think, to suggest that, given the failure to establish the putative genetic mechanisms responsible for schizophrenia, the molecular strategy has reached a crossroad: either we persist in genetic reductionism and continue to search for genetic influences, or turn attention toward the phenotype of schizophrenia as a necessary condition for any future genetic (or environmental) studies. Cardno and McGuffin appear to support the former alternative. They contend that while the boundaries of the concept of schizophrenia are unclear, the homogeneity of the illness is debated, and the mode of inheritance remains unknown, we ought nonetheless to conclude that the techniques of molecular genetics, especially those based on recombinant DNA technology, are our best hope for future success in schizophrenia research. Farmer and Owen reach a similar conclusion about the prospects of the HGP.[86]

For the reasons elucidated in this chapter, I cannot share their optimism, nor can I encourage their persistence. Rather, I concur with the conclusion reached by Tim Crow and Lynn DeLisi after summarizing the results of both the 1997 and 1998 Chromosome Workshops at the Vth and VIth International Congresses of Psychiatric Genetics:

> Perhaps one should conclude from current [unsuccessful] attempts to map genes for schizophrenia and bipolar disorder that it is time to return to hypotheses that relate to the nature of psychosis and what is known or may be hypothesized about its pathology.[87]
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> At present, the linkage strategy is not yielding the strong and consistent leads that had been hoped for 5 to 10 years ago. Other approaches, e.g., through pathophysiological mechanisms, may have to be pursued. Without a hypothesis there may be no way ahead.[88]

Others, including Andreasen, Kringlen, and Lander, acknowledge this fundamental point that "good genetics requires good phenotypes".[89] For any substantial progress to be made in understanding the

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[86]Cardno and McGuffin (1994); Farmer and Owen (1996).

[87]Crow and DeLisi (1998).

[88]DeLisi and Crow (1999).

[89]Andreasen *et al* (1988); Andreasen *et al.* (1999); Kringlen (1993); Lander (1988), p. 106.

aetiology of schizophrenia, "knowing how to describe, define, and recognize it is a necessity".[90] That is, for molecular genetics to contribute to psychiatry in any important way, we must refine the phenotype of schizophrenia such that we might be better equipped to investigate the possible existence of molecular aetiological mechanisms – assuming that we have good evidence for supposing their existence, and assuming that we have a sufficiently rich model of ontogenesis, that is, one not always or entirely reducible to differential gene expression.

In this regard, let us bear three points in mind: to begin, as I have suggested throughout this dissertation, we must be careful not to overstate the role of genes in development. Though it *may* be methodologically appropriate to focus on genes as *primus intra pares*,[91] it is by no means clear that it is ontologically,[92] epistemologically,[93] or even ethically appropriate.[94] But, secondly, also as I indicated above, in order for the (heuristic) focus on genes to be informative, we must recall the need for an adequate clinical phenomenotype in the first place. We must emphasize clinical phenomenology, else we will never home in on schizophrenic genotypes (assuming they exist). Thirdly, then, a crucial element in elaborating phenomenotypes is attention to the prime matériel of the psychiatrist: unhappy people who behave bizarrely. The person, her/his behaviour, context and life circumstances, must all be part of our analysis. As it stands, we have removed the clinic from psychiatric nosology, and thus we have removed patients as well, replacing them by their blood, sweat, urine – and DNA.[95] Consequently, we have tended

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[90]Andreasen *et al.* (1988), p. 345.

[91]Schaffner (1998); but see Griffiths and Knight (1998, p. 255) for sceptical considerations.

[92]Mahner and Bunge (1997).

[93]Sarkar (1998).

[94]van der Weele (1999).

[95]As Young (1995, p. 283) puts it, in the case of post-traumatic stress disorder, "to obtain facts and findings, researchers now interrogate blood and urine rather than men". On the replacement of the clinic by the lab, see, e.g., Wilson (1993).

to overlook a rich and important phenotypic feature of psychiatric patients – their own narrative of the disorder, their own experience of its various, variable symptoms – while presuming that the "true disease"[96] is at the level of genes and not of persons.

To be sure, the point of the foregoing is not to deny the importance of biological aspects of mental illness; it is instead to begin to understand mental illness at an appropriate level of complexity. As indicated, any success in behavioral genetics requires more than linkage analysis, for one of the keys to linkage success is an adequate clinical phenomenology. Hence the need for a dialectical approach between good phenomenology, scientific but nonmolecular aspects of nosology (such as biometric and neurological approaches), and molecular genetics, in an effort to describe the clinical, personal, and biological reality of schizophrenia as accurately as possible, and to understand its aetiology as fully as possible.[97]

I thus encourage the return to phenomenology construed as a dialectical interplay between (*a*) the study of the clinical presentation of schizophrenia (that is, of the actual schizophrenic individual in all his complexity, and not merely his blood, tears, and DNA) , *(b)* scientific but nonmolecular aspects of nosology (such as biometric and neurological approaches), and – eventually – (*c*) the use of strategies of molecular genetics and 'human social ecology', if and where appropriate.

Allow me to substantiate my proposal with an illustration of a robust – or at least proto-robust – schizophrenic phenotype, drawing on some recent research that approximates the perspective I envision as most promising in psychiatry. I have noted that the clinical heterogeneity of schizophrenia is very widely accepted. Two schizophrenics can each present with a number of the *DSM-IV* symptoms of schizophrenia, and yet in fact share none of these symptoms with one another. One consequence is that there is some debate, both historical and contemporary, as to whether schizophrenia should be understood

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[96]The phrase belongs to Tsuang *et al.* (1993), p. 136.

[97]For similar remarks, see Andreasen *et al.* (1988).

as a single disease entity, or in terms of dimensions, or rather in terms of categorical subtypes.[98] Moreover, schizophrenia has no objective marker comparable to plaques in Alzheimer's disease. The clinical diversity and diagnostic ambiguity of schizophrenia have confounded research at two levels of investigation, the micro-level of genetic mechanisms and the macro-level of observed symptoms. Research into biological substrates of certain symptoms has tended "to focus on one aspect of the disorder while ignoring others (e.g., accounting for hallucinations by invoking the temporal lobe but failing to explain why delusions or various negative symptoms are also present)".[99] Meanwhile, the search for schizophrenic genes has been hampered by the lack of a discrete phenotype. The recent work of Andreasen and her colleagues is designed to redress these concerns.

Andreasen *et al.* direct their energy at an intermediate level, proposing that neither the symptoms nor their alleged genetic determinants are primary. Instead, they argue, the phenotype of schizophrenia is best understood as a neurodevelopmental cognitive abnormality – a timing aberration in a fundamental, highly contextual, extremely sensitive feedback loop; this defect in timing affects a basic neurodevelopmental process upon which memory, attention, and language, for instance, are based, with the result of producing the severe heterogeneous symptoms characteristic of schizophrenia.

Andreasen *et al.* develop their model of cognitive development and function/malfunction on an analogy with the development of motor activity:

> In the motor system, synchrony of movement occurs as a consequence of very rapid on-line processing and feedback between the sensory-motor cortex and the cerebellum, mediated through the thalamus. This feedback loop permits constant checking and updating of input and output at the nanosecond level, and facilitates the rapid and smooth execution of complex motor acts such as hitting a baseball or catching a pass in football.[100]

An alteration in the timing of these processes (motor dysmetria) leads to lack of motor coordination and

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[98]For recent comments on this general topic, see, e.g., Andreasen *et al.* (1999); Kendler *et al.* (1998); Crow (1998); Andreasen (1997).

[99]Andreasen (1999), p. 908.

[100]Andreasen *et al.* (1999), p. 911.

consequently, such abnormalities as dysdiadokokinesia or inability to achieve tandem gait. Andreasen *et al.* name this feedback circuit after its multiple nodes: the cortico-cerebellar-thalamic-cortical circuit (CCTCC). Drawing on research in neuroanatomy and the tools of neuroimaging, they propose that:

> cognitive dysmetria is the cognitive or mental equivalent of motor dysmetria: a disruption in the fluid coordination of mental activity that is the hallmark of normal cognition. ... The CCTCC performs a similar function in monitoring and coordinating the fluid execution of mental activity (synchrony) and that a disruption in the activity of this circuit leads to cognitive dysmetria, and ultimately, to the disordered cognition and the clinical symptoms of schizophrenia.[101]

In order to explain this consequence, Andreasen *et al.* invoke the metaphor of attempted information transfer between computers with mismatched baud rates:

> [An] individual with mistimed information transfer may incorrectly connect perceptions and associations and misinterpret both external and internal processes, leading in turn to delusions or hallucinations (e.g., a neutral perception will be associated with a frightening affective association, internal thoughts or vocalizations may be attributed to others). Defects in coordinating language production will lead to "thought disorder". In addition, the flow of information through the system may become paralyzed, leading to "negative symptoms" such as alogia or affective blunting.[102]

Thus do Andreasen *et al.* propose an understanding of schizophrenia immune to the criticisms raised in this chapter. Notice three key features of their model of the schizophrenic phenotype. First, this research does not draw its motivation from flawed family, twin, and adoption studies; though cognitive dysmetria may very well turn out to be inherited, this is as yet an open question, one not predecided by prior commitment to a hypothesis about its transmission – and therefore one not saddled with the impetus to find schizophrenia genes. (And even if it is inherited, bear in mind the caveat that it may not be inherited *genetically*.) Secondly, though Andreasen *et al.* do not focus on the genetic level, it is inappropriate to thereby infer that the genetics of the CCTCC are unimportant or irrelevant, for deeply "generatively entrenched" mechanisms involved in the development of fundamental motor and cognitive

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[101] Andreasen *et al.* (1999), p. 911.

[102] Andreasen *et al.* (1999), p. 916.

activity in humans are surely partly determined by the activities of genes-in-developmental-context.[103] This admission has no bearing on the appropriate methodology for investigating such mechanisms; the CCTCC certainly does not require, *a priori*, a lower-level explanation, least of all one based on genes. As Andreasen *et al.* evince, the CCTCC is worth investigating on its own terms, for the reinterpretation of the symptoms of schizophrenia as sharing an underlying phenotypic (endophenotypic) – though perhaps not genotypic – substrate is an important advance in schizophrenia research. Meanwhile, schizophreniologists, no longer constrained by the search for nonspecifically triggered predisposing genes, may attend as well to the search for specific higher-level (e.g., environmental or possibly social) causal determinants of cognitive dysmetria.

This is a third advantage of Andreasen *et al.*'s proposal: this meso-level phenotype – identified through clinical observation, theoretical neurobiology and neuropathology, and neuroimaging techniques – is robust, and permits the elucidation of a robust disease category that may put to rest long-standing debates over the appropriate interpretation of the schizophrenia construct. It will surely generate additional research into the intricate neurodevelopmental processes involved in the aetiology of schizophrenia. In particular, the cognitive dysmetria phenotype may be elucidated in detail so as to facilitate new studies in both human social ecology and in molecular genetics, though we must keep in mind the challenge of developmental systems theory to any simplistic model of gene action. Note as well that the explicit focus on neurological development is an enormous advance over the usual focus on identifying ostensibly causally responsible agents without attending (at least not presently) to the actual

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[103]"Generative entrenchment" is a notion developed by Wimsatt; see Wimsatt (1999a; 1999b; 1986); Schank and Wimsatt (1986); and Wimsatt and Schank (1988). For Wimsatt, generatively entrenched mechanisms – stable, persistent, and *de facto* foundational mechanisms productive of important 'downstream' effects – may well be inherited, but they are not as a result necessarily gene-like. Wimsatt's recent extension of generative entrenchment to the realm of cultural heredity (as in his 1999a) may prove helpful in trying to understand why psychiatric nosologists have trouble abandoning, or at least abandoning faith in, the quest for the genetic underpinnings of psychiatry – for deeply held beliefs which generate research strategies and hypotheses and experiments may be preserved, effectively guarding against 'downstream' disciplinary mayhem.

development of the disorder beyond the genome.

Regarding psychiatric nosology as a whole, the use of multiple indicators – measurement scales, diagnostic questionnaires, family histories, patient narratives, the art of clinical observation, neurological assessments, biological assays, molecular techniques, neuroimaging, treatment-response – taken together may help to triangulate on and multiply determine the objectivity and validity of a psychiatric disease classification, and foster appropriate interventions. The techniques of molecular genetics, and the Human Genome Project, may well eventually contribute to our overall understanding of schizophrenia, but only in the context of a sufficiently well-elaborated phenotype; a genuine openness to the possibility of specific nongenetic determinants of schizophrenia; an analytical emphasis on developmental mechanisms; and an appropriately robust psychiatry concerned, first and foremost, with environmentally embedded organisms and not merely their DNA. This is the surest route to the scientific credibility of the discipline and its practitioners – and to a consistently positive impact on the lives of those who turn to them for help.

Chapter Five – Creative Epigenesis: Toward Genuine Synthesis

> The cell is to evolutionary developmental biology as the gene or species is to evolution and as embryos are to development. Epigenetics is to evolutionary developmental biology as natural selection is to evolution and as differentiation, morphogenesis and growth are to development.
> – *Brian K. Hall*[1]

5.1. Trimming the 'Hedgeless Hedge'

Susan Oyama has made an insightful observation about responses to her own and others' work in developmental systems theory (DST). Oyama reports that "a fairly common reaction to DST is 'That's a completely crazy idea, and besides, we already knew it'". She elaborates: "theorists are exasperated to be told what they have 'always known'. Yet there is a difference between knowing in a parenthetical, 'of course it's important' way about the intimacy and reciprocality of organism-environmental exchanges in development and evolution, say, and incorporating the knowledge in models and explanations, research and theory".[2] This notion that what critics of certain strains of current biology are annoyingly complaining about is common knowledge, even though it is knowledge not worth dwelling upon or even incorporating into models, is reminiscent of McCain's notion of the "hedgeless hedge" tactic, which he thought was a major problem besetting sociobiological thinking.[3] I would like to extend the applicability of his metaphor.

According to the hedgless hedge, "one admits the existence of an anomaly or problem of theory and then proceeds as though one had not. If one is then accused of neglecting the anomaly, one then

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[1]Hall (1998), pp. 400-401.

[2]Oyama (1999), pp. 80, 88.

[3]McCain (1980).

produces the admission of its existence as conclusive evidence of one's innocence of the charge".[4] Examples of this kind of thinking abound in biological, psychological, and psychiatric research. They are instances of paying lip service to the developmentalist challenge, while proceeding as if development is irrelevant, or something pesky to be explained later, or even as if the developmentalist challenge is a mere semantic squabble. Consider the rationale for the Human Genome Project, which solves first for structure, then for function, in complete isolation of developmental processes which are themselves constitutive of both structure and function.[5] Or consider Gottesman's nonchalant – but rhetorically significant – slide from the epigenesis of schizophrenia to the genesis of schizophrenia and then back to the epigenesis of schizophrenia without changing his mind one iota about the (foundational) significance of gene action in the aetiology of the disorder.[6] The difference between standard epigenetics (or genes-plus-(epigenetic)-regulation) and constitutive epigenetics (as discussed in Chapter Three) turns out to be the difference between pretending to take and actually taking development seriously.

Gilbert Gottlieb has recently called attention to a similar problem; in a paper critical of the discipline of developmental behavioural genetics, Gottlieb places 'developmental' in scare quotes in his title in order to draw attention to the possibility that 'developmental' behavioural genetics is not in fact

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[4]McCain (1980), p. 126.

[5]In 1992, a biotechnology serial ran an advertisement for the *Encyclopedia of the Mouse Genome*. The advertisement read: "The Complete Mouse (some assembly required)". As Gilbert and Faber (1996, p. 136) note, "the 'some assembly' is the entirety of development needed to go from genotype to phenotype. The whole field of embryology was trivialized in parentheses". I would go still further in that, as I have argued in previous chapters, the relevant developmental space ought not to be confined to that ostensibly between genotype and phenotype.

[6]Gottesman and Shields (1982), Gottesman (1991), Gottesman (1994); for commentary, see Robert (in press [a]). It is worth noting that when "epigenesis" or "epigenetics" is used carelessly – as, for instance, by Gottesman – it functions as a "plastic word" (Poerksen 1995); that is, a scientific-sounding though unfortunately vacuous word used to stymie critics by merely pretending to take seriously obvious problems with the speaker's enterprise (in Gottesman's case, the genetics of schizophrenia). The same is true of "interaction", as discussed in Chapter Four; given the "interactionist consensus" – no one denies that phenotypic traits are a joint genes-environment production – it is remarkable that these selfsame scientists actively seek to segregate complex traits into genetic and environmental components as if interaction amounted to nothing but mere aggregativity.

sufficiently attentive to the phenomena of development.[7] It is worthwhile to discuss Gottlieb's work in some detail, not only for the value of his critique, but also to enable me to demonstrate the differences between Gottlieb's positive proposal and my own.

Gottlieb's main target is the application to behavioural phenomena of development-free techniques of population-genetics analysis, such as the ANalysis Of VAriance (ANOVA). As Lewontin showed in 1974, and as Wahlsten has underscored more recently, ANOVA is insensitive to the interaction of putatively separable genetic and environmental contributors to development. According to Sarkar, this point was made as well by Lancelot Hogben almost seventy years ago: "phenotypic variation (as measured by variance) cannot be additively decomposed into genotypic and environmental parts because there is a variable interaction between the genotype and environment".[8] Gottlieb notes that "statistical procedures that *appear* to separate variance according to genetic and environmental causes do not provide a valid representation of physiological reality", because genes and environments are not independent, separate, or separable causes.[9]

Furthermore, in addition to artificially segregating genes and environment into two relatively independent classes of ontogenetic factors, proponents of the population genetics paradigm do not attend to what may be called a "third source of developmental differences" – properly neither genetic nor environmental, but rather *epigenetic*. The existence of this third source evinces the limits of the population genetic approach: "if there are three potential sources of individual variation, it is utterly impossible and illogical to prove that something is genetic by holding environment constant and vice versa".[10] Consequently, the basic schema of population genetics sketched in Chapter Three is clearly

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[7]Gottlieb (1995a).

[8]Lewontin (1974); Wahlsten (1990); Sarkar (1999), pp. 238-239; see also Sarkar (1998) for his detailed argument.

[9]Wahlsten and Gottlieb (1997), p. 178.

[10]Molenaar *et al.* (1993); Wahlsten and Gottlieb (1997), p. 180.

inadequate when appropriated for understanding ontogeny.

The third source of individual variation is located in, to use Keller's apt phrase, "that no man's land beyond the gene but beneath the skin",[11] and comprises what are sometimes chaotic and other times apparently programmatic epigenetic events generative of the developing organism.[12] Especially instructive is the work of Gaertner who, over a period of thirty years, developed genetically and environmentally identical strains of laboratory mice and rats that were, indeed, *non-identical*, thereby demonstrating the existence of a neither-genetic-nor-environmental source of ontogenetic variation. (Consider culture and a complex artifactual and biophysical ecology, and the situation for humans is that much more nebulous.) This is a very basic illustration of the main theme of this dissertation, namely, that development is not reducible to the environmental expression of genomic potential, no matter how tantalizingly elegant and apparently explanatory the statistical models may be. In short, insofar as 'developmental' behaviour (or medical) genetics relies on the sort of bipartite, additive model required, assumed, and implied by analyses of variance, the discipline is unable to make tenable inferences about either individual development or evolution.[13]

One is able to witness some impressive, though ultimately artless, hedgeless hedging in the various responses to Gottlieb's paper on the limits of 'developmental' behaviour genetics, although part of the difficulty is, as I will show below, attributable to Gottlieb himself (and Gottlieb himself hedges hedgelessly). Gottlieb's major theoretical contribution to the debates over the role of genes in ontogenesis is a distinction he draws between what he calls "predetermined epigenesis" and "probabilistic

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[11]Keller (in press), p. 7.

[12]These processes are sometimes referred to as 'randomness' or 'developmental noise', and described in terms of self-organization and non-linear dynamics. For extensive discussion, see, e.g., Wahlsten and Gottlieb (1997) and Molenaar *et al.* (1993).

[13]Gaertner (1990); Gottlieb (1995a); Wahlsten and Gottlieb (1997); see also Strohman (1995), (1994), and (1993) for germane criticisms of not only behavioural but also medical genetics.

epigenesis".[14] Predetermined epigenesis coheres with both the Modern Consensus and the "Central Dogma" of molecular biology, namely that there is one-way information flow from (preformed) DNA to (epigenetic) structure and function. According to this view, while genes do not act independently of the developing organism, the organism nonetheless exerts no specific control in the developmental process, for DNA is both instruction-set and master-crafter, the prime ontogenetic mover.[15] Variations on this theme do license some role for the developing organism – switching on the genetic program, for instance, and so permitting diathesis-stressor models of ontogenesis – but all specific ontogenetic information is supposedly contained in code form in the DNA.

In contrast, probabilistic epigenesis captures the insight that the genetic component of an organism is but one of its developmental components, all of which act contingently and in concert in the production of the developed organism. There is no prime ontogenetic mover, according to proponents of probabilistic epigenesis, for developmental regulation does not emanate strictly from the nucleus but rather is multidirectional across all components of the developing organism. Ontogenetic outcomes are not predetermined genetically, but rather emerge as a function of intersystemic activity, and so are irreducibly probabilistic.

The name "probabilistic epigenesis" creates difficulties.[16] In her scathing and uncharitable response to Gottlieb's paper, Scarr asserts that she is a probabilist to the core ("all developmental outcomes are probabilistic"), while nonetheless endorsing a position akin to predetermined epigenesis, leading to the inference that the difference between predetermined epigenesis and Gottlieb's preferred

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[14]E.g., Gottlieb (in press), (1998), (1995a), (1991), (1970).

[15]Gottlieb (1998); recall my citation from Schrodinger's *What is Life?* (1944) in Chapter One.

[16]Gottlieb (1998); Bidell and Fischer (1997, p. 208) rename Gottlieb's position "constructive epigenesis" in order to underscore the emergent self-construction of the organism from both genetic and nongenetic developmental material. I have rejected this euphemism in Chapter Three in favour of "constitutive epigenesis" which carries some similar connotations. But my position is more than semantically different from Gottlieb's and Bidell and Fischer's, as will become evident below.

alternative is not a matter of probability but rather of reciprocal causal contingency. In any event, Scarr claims – just as Oyama would have predicted – that developmental systems theory is redundant: "it states the obvious – to wit, that genes and environments must interact during an individual's development, and individual development depends on the interplay of both". But she also maintains that, at a population level, we can isolate (preformed) genetic and (epigenetic, probabilistic) environmental influences on development, and so achieve practically useful correlations within complexes of predictors and outcomes.[17]

The trouble is that Scarr, though she aims to distinguish between (for her, relatively unimportant) 'how?' questions about causal mechanisms (in which she claims Gottlieb is interested), and (for her, important) 'how much?' questions about sources of variation (in which she herself is interested), incautiously slips from variance to causation, committing the fallacy against which Lewontin and others have long since warned.[18] Consider Scarr's remarks about canalized developmental pathways, which she claims are representative of an organism's biases and tendencies toward particular developmental outcomes. Without much argument, Scarr concludes that "these biases are undoubtedly genotypic".[19] In so doing, Scarr easily (and unashamedly[20]) moves from an analysis of (populational) variance to an explanation of (individual) causation, in violation of Gottlieb's demonstration that causation in individual development simply cannot be inferred from (development-free) population-level analyses. Hence Scarr's hedgless hedging, her lip-service to the developmentalist challenge: 'of *course*, genes and environments

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[17]Scarr (1995), pp. 154, 156, 157.

[18]Lewontin (1974).

[19]Gottlieb (1995a), p. 133, citing S. Scarr-Salapatek, "Genetic Determinants of Infant Development: An Overstated Case", in L. Lipsitt (ed.), *Developmental Psychology: The Significance of Infancy* (Hillsdale, NJ: Erlbaum, 1976), pp. 59-79, at p. 63.

[20]"In fact, most developmental theory is about associations between complex sets of predictors and outcomes [references omitted] to which causal status is sometimes attributed without mechanistic analysis. ... The causal status of predictors in coreelational models can be questioned, but they often provide the only information we have about complex developmental phenomena" (Scarr 1995, p. 156).

interact in individual ontogeny – everyone knows *that* – but that's no reason to avoid inferring genetic causes of behaviour on the basis of population analyses of variance, however insensitive to gene-environment interaction such analyses have proven in fact to be!'

It is noteworthy that many of Scarr's objections to Gottlieb are either misinterpretation or *ad hominem*. (The same is true of both of the other responses to the article, to which I will shortly turn.) Scarr believes it to be a criticism of Gottlieb to assert that "multiple causation – both many genes and many environmental factors – is the rule for complex, socially important human phenotypes, such as intelligence, personality, and mental health. Neither single genes nor single environmental variables are likely to account for more than a tiny part of the complex causal web". She insists, again putatively in contrast to Gottlieb, that "research designed to isolate single causes" is somehow both "impossible and, in fact, unproductive".[21] Given Gottlieb's clearly articulated position that genes are an integral part of a multilevelled, contingently coactive developing system and so cannot be isolated as independent ontogenetic variables, it is difficult to discern the reasoning behind Scarr's patronizing dismissal of Gottlieb's perspective. *Prima facie*, in the remarks just cited, Scarr would appear to share in some aspects of Gottlieb's overall outlook on causal complexity in ontogenesis, though she apparently does not follow her own counsel by proceeding to make causal inferences about individual development on the basis of populational analyses of variance.

Equally troubling, but in another vein, is Scarr's use of *ad hominem* arguments to undermine Gottlieb's authority. For instance, she asserts that critics of the population genetics approach to behavior have succumbed to the rhetoric of 'political correctness' and so cannot see the empirical value of the science. Moreover, she refers to some putative character traits of Gottlieb's as being at the root of the problem. In particular, she has in mind his "arrogance", "intolerance" for differing points of view, and experimental dogmatism – his alleged exclusive preference for experimental manipulations with animal

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[21]Scarr (1995), pp. 155, 156.

populations – as obstacles to a genuinely productive pluralism in developmental psychology.[22] These are not merely academic disputes!

Similar hedging tactics and *ad hominem* arguments are employed by Turkheimer, Goldsmith, and Gottesman in their response to Gottlieb. Consider their passive-aggressive opening passage:

> We find ourselves in an unusual position of rhetorical asymmetry regarding Gottlieb's assault on the validity of our chosen field of study – behavioral genetics. We admire Gottlieb's empirical work, feel no need to 'impugn' it, and do not see it as incompatible with our own. We agree with many of the theoretical premises advanced by Gottlieb and recognize them as long-established principles of behavior genetics. We acknowledge some of the limitations of the current state of our methods and findings but do not see how they would lead a reasonable critic to the conclusion that the study of behavior genetics is without value to the fields of developmental psychology or biology.[23]

Herein they prepare two separate attacks on Gottlieb: first, by suggesting that they take development just as seriously as Gottlieb does and, secondly, by indicating that Gottlieb could not possibly be a "reasonable critic" in reaching the conclusions he reaches.[24] Setting aside the *ad hominem* charge, it is worth examining the former claim, their assertion that Turkheimer *et al.* subscribe to Gottlieb's theoretical premises.

In attempting to flesh out the similarities between their approach and Gottlieb's, Turkheimer *et al.* offer a pat statement of the interactionist consensus view that there is no linear relationship between genotype and phenotype because gene-expression is environmentally sensitive and because genes themselves interact with each other (epistatic interaction).[25] Note that the claim about gene-environment interaction is no more than the recognition that particular genes require environmental switches, which is only a relatively minor violation of the Central Dogma. As such, it represents only a tiny step in the

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[22]Scarr (1995), pp. 155, 157.

[23]Turkheimer, Goldsmith, and Gottesman (1995), p. 142.

[24]In this regard, they note their worry that Gottlieb is continuing in the tradition of the "ideology-as-science manner of long-time critics" (Turkheimer, Goldsmith, and Gottesman 1995, p. 142). For similar remarks, see Gottesman (1994), as discussed in Chapter Four of the present dissertation.

[25]Turkheimer, Goldsmith, and Gottesman (1995), p. 148.

direction of developmentalism, rather than full-fledged consanguinity. The distance between Gottlieb and Turkheimer *et al.* is more evident in the remainder of the passage in question, wherein the latter assert that "the environments provided to offspring are in part a reflection of the offspring's genotype"[26] and that "organisms seek out environments partly on the basis of their genetic endowment".[27] Exactly these sorts of assertions are expressly forbidden by Gottlieb's coactional approach, according to which putatively additive genetic and environmental effects cannot be meaningfully separated.[28]

But Turkheimer *et al.* go further still, and end up again stepping out of line with the overall developmentalist programme. They begin by briefly discussing what is apparently a hybrid predetermined-probabilistic epigenesis model of heart disease aetiology,[29] according to which an investigator engages in both 'top-down' (behavioural phenotype → organismal phenotype → physiological endophenotype) and 'bottom-up' (genes → gene products → physiological endophenotype) analysis of causes. Gottlieb would, I imagine, worry about whether either the uppermost or lowermost levels are construed predeterministically, but he also would (and does[30]) nonetheless appreciate their effort to work with a systems model.

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[26]Turkheimer, Goldsmith, and Gottesman (1995), p. 148, referring to R. Plomin and C.S. Bergeman, "The Nature of Nurture: Genetic Influence on Environmental Measures", *Behavioral and Brain Sciences* 14 (1991): 373-427.

[27]Turkheimer, Goldsmith, and Gottesman (1995), p. 148, referring to S. Scarr and K. McCartney, "How People Make Their Own Environments: A Theory of Genotype → Environment Effects", *Developmental Psychology* 54 (1983): 424-435.

[28]"The bedrock notion of the developmental systems concept is that interaction or coaction obtains everywhere and anywhere, so that, in any event, a simple summation of influences is psychologically and biologically invalid" (Wahlsten and Gottlieb 1997), p. 170.

[29]Turkheimer, Goldsmith, and Gottesman (1995), pp. 149*ff*; the model in question is that of C.F. Sing, S.L. Reilly, "Genetics of Common Diseases That Aggregate, But Do Not Segregate, in Families", in Sing and C.L. Hanis (eds.), *Genetics of Cellular, Individual, Family, and Population Variability* (New York: Oxford University Press, 1993), pp. 140-161.

[30]Gottlieb (1995b), p. 167. Gottlieb rightly and happily notes that in attempting to adapt this sort of model for behaviour genetics purposes, Turkheimer *et al.* are in fact *leaving behind* – however unintentionally – a straightforward population genetics approach to the genesis of behaviour.

Turkheimer *et al.*'s next move is to posit, again in apparent violation of Gottlieb's coactional model, that "twin studies have shown us that – however complex, interactive, and nonlinear the mechanisms may ultimately be – genotype bears some relationship to marital status, a relationship that can at least be modeled as linear". Exactly what that means is unclear – the very idea of "complex, interactive, and nonlinear" mechanisms prohibits a meaningful linear model, requiring something more like the nonlinear reaction-diffusion models discussed by Burgess and Molenaar in their response to Gottlieb (to be discussed momentarily). Nevertheless, Turkheimer *et al.* then return to the putatively coactional model they have adapted for behavioural genetics, and remark that:

> Widely endorsed, we have noted, is a 'systems model' of the social sciences, focusing on the specification of intervening mechanisms in the hierarchy of complexity between molecular events and sociocultural processes. This is an easy position to take, but what do we expect our eventual model of something as complex as marital status to look like? ... What is the 'cholesterol' of divorce? What sort of gene products should we look for to point us in that direction? To say we don't know is to put it politely; we don't know where to look. ... Can one even imagine a causal model of divorce that respects the complexity and humanity of the phenomenon while preserving the scientific rigor of Sing's models of heart disease?[31]

On the basis of such statements, a less charitable critic might suggest that we need look no further for an excellent (though inadvertent) *reductio ad absurdum* of behavioural genetics! Gottlieb is more sympathetic than that, however, and offers some suggestions (e.g., about incorporating longitudinal studies) for attempting more fully to model co-causal factors in divorce.[32]

What is nevertheless problematic is that both Scarr and Turkheimer *et al.* are committed to viewing genes and environment as separate (and separable) variables in development; only by so doing can Scarr claim that developmental pathways are genetically canalized and that genes "partly determine" an organism's choice of environment, and Turkheimer *et al.*'s remarks about the existence of some linear relationship between genes and divorce prerequires a commitment to the relative independence of genes and environments – despite their insistence that the nature-nurture debate has been settled in favour of

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[31]Turkheimer, Goldsmith, and Gottesman (1995), pp. 150, 151-152, 150, 152.

[32]Gottlieb (1995b), p. 167.

(some kind of) interactionism.[33] And neither Scarr nor Turkheimer and colleagues engages with the existence of a third (epigenetic) source of developmental difference which, all by itself, impugns the gene-environment dichotomy undergirding their work.

In the final commentary on Gottlieb's paper, Burgess and Molenaar advocate this latter idea that a tripartite approach is required, factoring in genetic, environmental, and epigenetic causes of ontogeny. They aim to extend Gottlieb's proposal by explaining epigenetic effects by appeal to chaos theory, a move that Gottlieb himself makes in a later work.[34] They support what they take to be Gottlieb's perspective on causal coactions in ontogenesis, and endorse a further conclusion of Gottlieb's that methodological systemism (as distinct from both methodological microreductionism and methodological macroreductionism) is a prerequisite for explanatory success in the case of complex systems.[35] Nevertheless, for Burgess and Molenaar the genotype remains a relatively independent, preformed, foundational ontogenetic factor: they write, for instance, of epigenetic processes as those which "translate genotypes into phenotypes"; more cryptically, they insist that nonlinear epigenetic events are those through which "genotypes are transformed into phenotypes"; and, somewhat surprisingly, they adopt the slippery trope of 'genes for' even in contexts of deeply culturally mediated phenotypic traits (such as lactose intolerance).[36] Thus, though they claim to support Gottlieb's overall approach – notwithstanding their rejection of his rejection of ostensibly 'developmental' behaviour genetics – their understanding of genes as the preformed basis of epigenetic events appears to run contrary to Gottlieb's programme. I fear, therefore, that they pay mere lip service to the developmentalist challenge, though they are considerably

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[33]Turkheimer, Goldsmith, and Gottesman (1995), p. 142.

[34]Burgess and Molenaar (1995); Gottlieb (1998); see also Gottlieb (1995b).

[35]For further discussion, see, e.g., Mahner and Bunge (1997) and Robert (2000a).

[36]Burgess and Molenaar (1995), pp. 159, 162-163. Moreover, Burgess and Molenaar self-identify as genic selectionists (1995, pp. 162-163), at odds with proponents of developmental systems theory such as Griffiths and Gray. See, e.g., Griffiths and Gray (1994), Gray (1992).

more sophisticated than either Scarr or Turkheimer *et al.*

A nice instance of the limits of Burgess and Molenaar's approach is evident in their identification of a putative paradox:

> A paradox presents itself – one that, so far as we know, has not been noticed before. On the one hand, it is evident that the developmental 'distance' between initial genotype and realized behavioral and cognitive phenotypes is large – a distance that has to be bridged by a network of epigenetic systems whose nonlinear dynamics destroy genetically induced correlations. On the other hand, we observe in behavior genetic investigations that these phenotypes can show substantial *genetically induced* correlations between relatives, an observation in conflict with the presumed primacy of epigenetic systems in realizing the translation of genotype into phenotype. At present, the solution to this paradox is unclear.[37]

The interpretation of this state of affairs as a 'paradox' depends on two key assumptions: first, that epigenesis is no more than the expression of preformed genes (in particular environmental contexts); and, secondly, that similarities between relatives – hereditary similarities – must be genetic (and neither environmental nor epigenetic). Both of these assumptions are false, and a truly developmental (behaviour) genetics has no need for either of them.

In spite of their apparent engagement with the crucial developmental import of epigenetic events – which would, on its surface, indicate an openness to the kind of developmentalism I am advocating in this dissertation, – it turns out that Burgess and Molenaar succumb to the general thrust of the Modern Consensus. That is, they hold that though complex, nonlinear epigenetic processes are necessary for the expression of genotypic potential, nonetheless preformed genes are ontogenetically foundational. The irony, though, is that Gottlieb would appear, occasional protestations notwithstanding, to be under the same spell; in other words, though Gottlieb does not make the second assumption identified above,[38] he does indeed, and unfortunately, make the first.

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[37]Burgess and Molenaar (1995), p. 160.

[38]See, e.g., Gottlieb (1998) and Wahlsten and Gottlieb (1997).

5.2. Beyond the Modern Consensus

An analogy will prove instructive: Gregory Mikkelson has recently called into question the developmentalist critique of DNA as an instruction set for ontogeny. He has suggested that:

> in order for a book on home maintenance to have its intended effect, a large number of other factors must also cooperate, perhaps most saliently a person capable of reading, understanding, and putting into action the instructions. The book is just as 'inert' by itself, given meaning by the 'complex' 'environment in which it is embedded,' and activated by 'irreducibly spatiotemporal' processes, as is DNA. However, we still call the contents of the book 'instructions.' So how then do parallel considerations undermine DNA's status as a set of instructions?[39]

Of course, whether the home-maintenance manual is analogous to DNA is exactly what is in question here. If they are in fact analogous, then developmentalism is not very different from gene-centric accounts of ontogeny, for no one (neither gene-centrists nor developmentalists) denies that a complex organism is prerequired for the expression of its genome. If there is a disanalogy, however, then the distance between gene-centrists and developmentalists is great indeed. So, then, how successful is the putative analogy?

Not very. First, and minimally, books have a physical independence from readers that genomes do not have from organisms. That is, genomes are as *inter*dependent as books are *in*dependent. Secondly, this conception of DNA as preformed into meaningful sequences (words, letters, sentences, paragraphs) is not true to the reality of DNA as a jumble of nucleotides upon which order is imposed within the developing organism (that is the force of constitutive epigenetics). DNA simply is not preassembled into genes ready to be acted upon by some external agent in the way that a book is a cogent, intentional (and intensional) statement to be acted upon by a reader. A somewhat more apt analogy is proffered by Griffiths and Neumann-Held: "The sequence of DNA can ... be compared to a sequence of letters without spaces or punctuation marks. The state of the developmental system is then analogous to a scheme imposed on these letters – grouping letters into words, adding punctuation marks and editing notes. A

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[39]Mikkelson (2000); the portions in scare quotes are cited from Robert (2000b).

different developmental state imposes a different scheme over the letters, that is, over the DNA sequence".[40]

Mikkelson might retort that there is nothing in his analogy that rules out such alternative interpretive schemes: different readers may well bring different expectations, desires, background conditioning, and skill sets to their home-maintenance tasks. Indeed, he would be correct in that suggestion. But to defend the force of his analogy, he would nonetheless need to maintain that the book has some fixed meaning, some "intended effect", captured within the book itself (or, perhaps, within its author's aims). That is, insofar as the book is an instruction manual, it contains instructions – independently of particular readers – even though translation of the instructions requires particular literate, competent, and efficacious readers.[41] So the analogy goes for DNA: DNA contains preformed ontogenetic instructions requiring a complex organism for their translation and execution – roughly, the Modern Consensus view of ontogeny. The recognition of the need for a complex organism to interpret genetic instructions represents a small step toward genuine developmentalism, but involves some hedgeless hedging nevertheless. "Nowadays it seems that everybody is an 'interactionist'. Unfortunately, frequent incantations of the word 'interaction' and the familiar homily that, 'of course all phenotypes depend on both genes and experience', have not been enough to drive away the ghost of dichotomous views of development".[42]

How, then, does this bear on Gottlieb and his critics? Gottlieb laments the insistence of some

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[40]Griffiths and Neumann-Held (1999), p. 659.

[41]I should note that Mikkelson's analogy, as it stands, makes no room for developmental redundancy – the existence of multiple pathways toward an equifinal endpoint (or at least a functionally equifinal endpoint). The analogy could be modified, however, by including a 'choose-your-own-adventure' component, according to which the reader makes choices between predefined alternatives toward similar home-maintenance ends. Nevertheless, for Mikkelson (as for Scarr-Salapatek), the alternatives would have to be genetically predefined, as against the developmentalist notion that the pathways may very well be developmentally rather than genetically constrained.

[42]Gray (1992), p. 172.

researchers (notably Scarr) that we cannot get beyond an additive, dichotomous view of development.[43] But it is at least arguable that the reason that Turkheimer *et al.* and Burgess and Molenaar claim to be largely in agreement with Gottlieb is not that they misinterpret him, but rather that he does not go far enough, that he does not follow through on the implications of his own proposal. How much of Gottlieb's programme is captured in the analogy of DNA as an instruction manual? As it turns out, Gottlieb's view bears a strong affinity with that analogized by Mikkelson.

Gottlieb adopts several basic positions clearly endorsed by Turkheimer *et al.*, Burgess and Molenaar, and Mikkelson, which together coincide with central elements of the Modern Consensus. One is the view that genes, construed as stretches of DNA, produce proteins: DNA → RNA → protein. In this regard, Gottlieb does not appear to endorse that developmental information itself has an ontogeny. A second is that genes are not self-governing, for "their expression – whether they are active or inactive – is determined by influences from other levels of the system" – a thesis denied by no one. Thirdly, Gottlieb shares, I think, with the others the view that "the reductionistic-analytical approach has had great success in detecting and understanding genes at the molecular level but is far from adequate for understanding how a gene functions in the larger context, where there is a web of feedback relations, nonlinear interactions, and multifactorial contingencies". In other words, a strictly genetic account would be explanatorily impoverished; that is simply the fallout of the interactionist consensus.[44]

But as I hinted in Chapters Three and Four, developmentalists see ontogenesis as something more, and in fact as something other, than gene expression, however chaotic, nonlinear, or emergently epigenetic. As I mentioned above, developmentalists do indeed share with consensus interactionists the view that gene function is context-dependent all the way down; but some developmentalists go further in urging that gene *structure*, too, is dependent on developmental context. In part, this is the view of Eva

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[43]Gottlieb (1995b), p. 168.

[44]Wahlsten and Gottlieb (1997), p. 178; Gottlieb (1995a), pp. 132, 138; Wahlsten and Gottlieb (1997), p. 179.

Neumann-Held outlined in previous chapters. In an effort to demonstrate exactly how my proposal differs from Gottlieb's and from developmental systems theory more generally, I will now return to considerations initially raised in Chapter Three about the nature of developmental programs in the context of whole-organism biology.

I share with Keller a worry about the elision of the organismic body in modern biology. The body, when seen at all, is seen passively, as a nurturing environment for the active, ontogenetically and evolutionarily important work of the genes. To be sure, when we transcend the nature-nurture or gene-environment dichotomy in favour of a conjunction of the two, then we *prima facie* develop a concern for both genes and environments. But is the body best construed as an *environment* for genetic activity? Both Keller and I would take issue with this latter conjecture, and urge instead that the body be conceived more actively (and interactively) as a developmental agent.

Keller notes an ambiguity over identifying the "body", despite its crucial evolutionary and ontogenetic significance. It is something within an outer integument, of course, but is it the multicellular organismic body contained by the epidermis, the cellular body contained by the cell membrane, or the nuclear body contained by the nuclear membrane (in eukaryotes)? Keller chooses to focus on the cellular body at that time in the life cycle when it is coextensive with the organismic body – the zygote or fertilized egg, porous and permeable as it may be. Like Russell, she holds that "the true germ-plasm must be the cell-organism". The reason is that the cellular integument serves the vital function of holding things together in close proximity:

> Proximity is crucial for it enables a degree of interconnectivity and interactive parallelism that would otherwise not be possible, but that is required for what I take to be the fundamental feature of the kind of developmental system we find in a fertilized egg, namely, its robustness. Prior to all its other remarkable properties – in fact, a precondition of these – is the capacity of a developmentally competent zygote to maintain its functional specificity in the face of all the vicissitudes it inevitably encounters.[45]

Keller's ideas here bear some affinity to E.S. Russell's notion of the "autonomy" of the developing

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[45]Keller (in press); Russell (1930), p. 193; Keller (in press).

organism – its ability to reach a developed form despite, as it were, environmental vicissitudes.[46] But "robustness" is a better characterization, considering (a) the deep (even *autokoenomous*) interrelations – supportive, constitutive, and constraining cointeractions – between a developing organism and the diverse elements of its various developmental contexts; and (b) the existence of multiple developmental and regulatory pathways toward an equifinal endpoint.[47] So, according to Keller, the robust cell-organism ought to be deemed the unit of development, as against either the gene (or genome) or the developmental system.

Recall Keller's distinction between genetic programs and developmental programs. Within the cell-organism, the genome is of vital significance to a developmental program dispersed throughout the whole organism but, *contra* Mayr and others, the genome does not contain a program for development. As Keller shows, developmental information is not encoded in the genes but is instead "distributed throughout the fertilized egg" undergoing ontogenesis. The developmental program is not comprised of particular genetic entities, and it does not reside in the genome itself; rather, it consists and exists in "the cellular machinery integrated into a dynamic whole". Thus, Keller writes that "if we wish to preserve the computer metaphor, it would seem more reasonable to describe the fertilized egg as a massively parallel processor in which 'programs' (or networks) are distributed throughout the cell" processing nuclear and cytoplasmic and other bits of developmental data. The cell-organism is therefore both ontogenetic agent and a material source of developmental information. As against the Modern Consensus, then, the cell-organism is a contextualized generative structure conditioning, and only partly conditioned by, DNA. Accordingly, development is not a genetic process, but rather a function of the whole organism.[48]

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[46]Russell (1930), pp. 6-7, *et passim*.

[47]This point about developmental redundancy is underscored as well by Strohman (1993) and Gilbert, Opitz, and Raff (1996); the latter suggest that the morphogenetic field – a concept I will introduce momentarily – acts like an ecosystem (p. 367).

[48]Keller (in press); for Keller's reasons for wishing to preserve the computer metaphor, see her (1999).

Hence, creative epigenesis: drawing on the contextually conditioned nuclear and cytoplasmic structure it inherits, a developing organism constructs, processes, and regulates specific ontogenetic information[49] dispersed throughout itself and its environment. Development, to use Russell's phrase, is a "living, responsive activity of the organism".[50] In this sense, then, organismic development is an autopoietic[51] (self-constructive) process not only post-natally (when it is obvious that organisms creatively construct themselves and their environments), but also from conception. Development will only be taken with due seriousness when it is consistently acknowledged that organisms are not the product of epigenetically triggered, preformed genetic programs.

5.3. Beyond the Modern Synthesis

As I indicated in Chapter Three, development (as understood by embryologists) was left out of the Modern Synthesis. Development was reduced to differential gene expression and, consequently, organisms were seen as nothing but environments for the study of gene action and activation.[52] Gilbert, Opitz, and Raff summarize the neglect of development pithily: "to go from functional biology to evolutionary biology without considering developmental biology is like going from displacement to acceleration without considering velocity".[53] But are things really that bad?

Recall from Chapter One the discussion of attempts to reconcile developmental biology and molecular genetics. One recent effort deserves sustained attention here as I assess the potential impact of

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[49]Mahner and Bunge (1997) reject Information, because, as they argue, the notion of an informational instruction presupposes a being able to respond to that instruction. For Mahner and Bunge, there is no such being. But, in fact, there is, namely, the directive and responsive cell-organism as the unit of development.

[50]Russell (1930), p. 109.

[51]I owe the word and concept to Rose (1997), p. 18, who in turn owes it to Humberto Maturana.

[52]Rose (1997), p. 221.

[53]Gilbert, Opitz, and Raff (1996), p. 362.

creative epigenesis on research programmes in biology. Beginning in the 1980s, a new biological subdiscipline sensitive to both evolutionary and developmental considerations emerged.[54] Evolutionary developmental biology, sometimes referred to as "evo-devo", has in its best incarnations the virtue of considering "organisms as more than adults, embryos as more than means of making adults, and the phenotype as more than the physical expression of the genotype".[55] I will briefly sketch a rough outline of the field.

In a sense, the discipline has merely rejuvenated some very old ideas, though injecting them with empirical data from recent studies of ontogeny and phylogeny. Some of the old ideas are 'homology', 'macroevolution', and 'morphogenetic fields'. But a still more basic notion opens the logical and empirical space for evo-devo: heredity itself is a feature of the development of the organism. This is an idea advanced in the 1930s by E.E. Just and E.S. Russell, among others, as against those who would, for either practical or theoretical reasons, divorce heredity (transmission) from development.[56] Genes are not the only, or even the primary, object of evolutionary forces, for it takes much more than genes to make an organism, and much more than DNA is transmitted between generations at conception, birth, and beyond. Developmental mechanisms are themselves subject to evolutionary pressures, and not merely the genes which provide some of the ontogenetic matériel. As Adam Wilkins has noted, "mechanisms for ensuring developmental stability are as crucial for maintaining the continuity of a species as the basic information for encoding gene products in the DNA itself".[57]

This is also the perspective of the developmental systems theorists, such as Oyama, Griffiths, and

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[54]Scott Gilbert, John Opitz, and Rudolf Raff published a review of evolutionary developmental biology in 1996; Brian Hall published its leading textbook in 1992, now in a much expanded and improved second edition (1998).

[55]Hall (1998), p. 399.

[56]See also Griesemer (1998).

[57]Hall (1998), p. 197, citing A.S. Wilkins, "Canalization: A Molecular Genetic Perspective", *BioEssays* 19 (1997): 257-262, at p. 261.

Gray, whose work I have discussed throughout this dissertation. As Oyama has remarked, "transmission, which masquerades as a mechanism explaining the regularity of development, actually *presupposes* and *requires* reliable development. For a given DNA sequence or phenotypic feature to reappear in the next generation, both parent and offspring must have developed well enough to be viable and similar in the relevant ways". As against the usual story of the Modern Synthesizers, Oyama contends that:

> if transmitting or 'passing on' means 'delivering materially unchanged', then few if any developmental resources are transmitted across evolutionary time (depending on how you measure material change). If transmission means 'reliably present in the next life cycle', which is the biologically relevant meaning in DST, then an indefinitely large set of heterogeneous resources or means is transmitted, sought or produced by the organism itself, supplied by conspecifics or others, possibly through social processes and institutions. Although many developmentally important environmental features are exceedingly stable, others are noncontinuous, perhaps varying seasonally or geographically. Any definition of inheritance that does not privilege the nuclear or cell boundary *a priori* will be applicable to other constituents of the system. The developmental systems perspective stresses the processes that bring together the prerequisites for successive iterations of a life cycle.[58]

Hence the impropriety of separating ontogeny and phylogeny. Thus, development is "the immediate cause of introduction of variation at the level of the individual organism ... Central to understanding the role of development in evolutionary mechanisms must be the study of emergent and epigenetic properties of developing systems and their unique role in the processes by which variation is introduced among individual phenotypes".[59]

Yet, reverting momentarily to my discussion of Keller above, there is something of a difficulty

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[58]Oyama (1999), pp. 83, 86-87 (references omitted). Oyama's notion of 'reliable presence in the next life cycle' bears an affinity with King and West's notion of an 'ontogenetic niche', as described by Gottlieb (in press) – referring to M.J. West and A.P. King, "Settling Nature and Nurture Into an Ontogenetic Niche", *Developmental Psychobiology* 20 (1987), pp. 549-562. Gottlieb summarizes their view: "in addition to our genes, we not only inherit a fairly standard embryonic and fetal stimulative environment but also parents, peers, and the places they inhabit. They coined the term 'ontogenetic niche' to signify the species-typical ecological and social legacies that accompany genes". I would go a step further – genes themselves are not *accompanied by* these environments (too additive a conception); rather, the ontogenetic significance of genes is in fact co-constructed with and by a full range of nongenic developmental resources (Neumann-Held 1999).

[59]Hall (1998), p. 155, citing K.S. Thomson, *Morphogenesis and Evolution* (Oxford: Oxford University Press, 1986), pp. 16-17.

here, namely a dispute over the appropriate unit (or units) of evolutionary developmental biology. Thomson, in the passage just cited, slides from "individual organism" to "developing system" to "individual phenotype". While Mahner and Bunge would insist on the individual organism as the locus of evolutionary developmental biology, developmental systems theorists prefer the whole developmental system, which is superorganismal. Hall prefers the cell, as does Keller. And Gilbert, Opitz, and Raff opt for the morphogenetic field.[60] Is it possible to synthesize these alternatives? I believe that it is, and that the reconciliation I hereby propose helps to ensure that, within evolutionary developmental biology, genetics does not merely subsume embryological concerns, but rather attends to the complexity of developing organisms.

But first, a basic terminological question: what exactly is a 'morphogenetic field'? For sixty years, the phrase, and the concept, were at the periphery of biology. Gilbert, Opitz, and Raff have commented that "it was one of those notions that was so powerful as to be assumed rather than continually proven", and it served as the basic explanatory concept – and entity – in pre-molecular embryology. The morphogenetic field is a modular, physical web of embryological information defining cells and delimiting their interactions. There are eye fields and limb fields and heart fields, for instance, comprising and regulating particular collections of cells required for the morphogenesis of eyes, limbs, and hearts. Once upon a time, these fields were "innocent of genes", but now, in the genetic era, at least two distinct interpretations of morphogenetic fields are extant. Gilbert, Opitz, and Raff subscribe to a heavily genetically mediated notion of fields;[61] my own view is less gene-driven, according to which genes are but one, though important, determinant of morphogenetic fields. I will say more about the difference between these views momentarily.

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[60]Mahner and Bunge (1997); Oyama (1985); Hall (1998); Keller (in press); Gilbert, Opitz, and Raff (1996). Schwartz (1999) posits homeobox genes at the core of his synthetic biology, though he is not specifically interested in the units of evolution dispute.

[61]Gilbert, Opitz, and Raff (1996), pp. 359, 366-367.

Heart fields, eye fields, and limb fields are well-described as "secondary fields" – secondary, that is, to the "primary field": "the entire embryo during blastogenesis, before axis or cell determination".[62] At and prior to this same developmental stage, the developing system just is the fertilized cell – but it is also an organism, an embryo, *and* a morphogenetic field. Thus the four possibilities are linked into one.[63]

If the developing organism is characterized in a sufficiently robust way, as I contend that it should be, may we avoid following developmental systems theorists in invoking the superorganismal developmental system to avoid the analytical, theoretical, and empirical biases of *a priori* gene centrism? I am doubtful. Consider the DST position that the cell-embryo-organism-field is clearly organized in a systemic way; that is, the interrelations between the parts of this object are structured in positive- and negative-feedback systems. For developmental systems theorists, development is not guided uniquely or unidirectionally by genes or any other ontogenetic element; control is rather dispersed throughout the gene-in-an-organism-in-an-environment. Consider further the robustness of organisms: organisms are more than epiphenomena of genomes, more even than epiphenomena of genomes in particular structured environments. For a genome is in no sense prior to or separate from an organism, and an organism is in no sense prior to or separate from an environment. The organism is part of the environment (and the environment part of the organism), while the genotype is part of the phenotype; moreover, in fact, not only does an organism require an environment, so does a genome prerequire an organism for its very expression.[64] I have already mentioned the second primary sense in which organisms are robust, namely,

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[62]Gilbert, Opitz, and Raff (1996), p. 366.

[63]Burian (1997, pp. 244, 260-262), in his rejection of the morphogenetic field as an appropriate basis for evolutionary developmental biology, ignores this point that "earliest embryos" simply are primary morphogenetic fields.

[64]There are some surface similarities between this point of view and Dawkins's notion of the "extended phenotype" (Dawkins, 1982). Both recognise the blurriness of boundaries between organisms and environments, for instance, and both place "emphasis on complex ecological webs of interaction and dependence" (Gray 1992, p. 195). But there the similarities end, for Dawkins holds genes to be causally primary, while those more concerned about ontogeny see causality as diffused throughout the network of (relationships between) developmental resources within the organism robustly construed. Dawkins is

Kant and Russell's emphasis on the ability of organisms to develop toward an equifinal endpoint via alternative pathways where necessary.

Rather than rest comfortably with the idea of a structured-organism-in-an-environment, developmental systems theorists insist that we ought to be concerned with developmental *systems*, not organisms. A 'developmental system' is understood typically as encompassing "not just genomes with cellular structures and processes, but intra- and interorganismic relations, including relations with members of other species and interactions with the inanimate surround as well"[65] – culture, artifact, biogeography, and so on. While focusing on robust organisms is certainly an advance over focusing on genes or gene networks, we cannot ignore the rest of the developmental manifold. Depending on our explanatory goals, sometimes focusing on even robust organisms may not be enough; this is the pragmatic dimension of explanation, and so we must accept the need for multiple units at the core of evolutionary developmental biology.[66]

As I noted above, there are at least two ways of interpreting the role of genes in the production of morphogenetic fields. As against Gilbert, Opitz, and Raff, I contend that the primary morphogenetic field – the cell-organism-embryo – is not exclusively or even primarily genetically delimited; it is rather the product of constructive and constitutive cointeractions between evolutionary, ecological, and genetic agents and reactants, forces and resources. Much work in evolutionary developmental biology, including some conceptions of the morphogenetic field, is fully compatible with the Modern Consensus, and unfortunately so. In Chapter One, for instance, I discussed Walter Gehring's work on homeobox genes, which he interprets as showing that genes control development and evolution. It is more accurate, though, to interpret homeobox genes not as 'master control genes' but rather as crucial interactants in the

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quite happy to understand an extended phenotype as "the read-out from a one-dimensional string of A's and C's and G's and T's" (Rose 1997, p. 121); I am not so happy.

[65]Oyama (1985, p. 123.

[66]For discussion of pragmatics, see Oyama (2000), Gannett (1999), and van der Weele (1999).

primary morphogenetic field. Gilbert, Opitz, and Raff also prefer a less loaded euphemism for homeobox genes. Within the morphogenetic field, genes and gene products and other elements of the web work in concert to effect morphogenesis. No element of the web exerts a dominating influence – there is no room for so-called master genes; nevertheless, Gilbert *et al.* retain a focus on homeobox genes as of decisive importance within fields. They therefore conceive homeobox genes as selector or switch genes, themselves regulated and helping to initiate an effusion of interreactions.[67]

Depending on how the field concept is elaborated, this notion of switch or selector genes may or may not be satisfactory. Even in the careful hands of Gilbert, Opitz, and Raff, it is possible for notions of genetic control, though not of mastery, to intervene in morphogenetic fields: they write of "genetically defined interactions among cells", for instance.[68] Hall, too, insists that "the genetic basis for development lies preformed in the DNA of the egg and subsequently in the zygote", though he allows epigenetic events to direct developmental processes.[69] Consequently, I worry that some evolutionary developmental biologists ascribe too much of ontogenesis to genetics, without sufficient attention to constitutive epigenetic processes.

If evolutionary developmental biology aims to explain the evolution of development – and the development of evolution – in genetic terms, then it will be merely a shadow of what it could be. If evolutionary developmental biology interprets epigenetic events as nothing but the regulation of expression of genetic information, then it will provide no explanation of *development* as such, but only of *gene action and activation in development*, which is but a subsidiary question. In contrast, my notion of constitutive epigenetics forces a broader interpretation of evolutionary developmental biology, one according to which the development of whole organisms is taken seriously as a primary analysand, rather

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[67]Gilbert, Opitz, and Raff (1996), p. 367.

[68]Gilbert, Opitz, and Raff (1996), p. 367.

[69]Hall (1998), p. 113.

than as secondary to the 'epigenetic' expression of purely or primarily genetic potential.

Allow me to conclude with some remarks about an instance of a putative reconciliation between evolutionary, molecular, and developmental biology, one well characterized under the banner of subsumption as distinct from genuine synthesis. In Chapter One, I discussed the work of Jeffrey Schwartz, who argues that homeobox genes are pivotal in individual ontogeny, productive of both normal development and also, when their timing is off, monstrous macromutations which generate large-scale phylogenetic change resulting in new species and higher taxa. Schwartz contends that in ontogeny, "all that is necessary is that homeobox genes are either turned on or they are not" at the appropriate time.[70]

Schwartz could have suggested, plausibly, that homeobox genes are one of many factors in the production of macromutations at the level of organisms, and that the organismal level is the level at which (micro and/or macro) selection pressures are operative in the establishment of new species. Such a view would have been congruent with the perspective of evolutionary developmental biologists that variation between individual organisms is introduced ontogenetically, as a result of genetic-epigenetic-phenotypic-environmental interactive processes. Instead, Schwartz opts for an implausible suggestion: homeobox genes "control everything" and "run the whole show". Therefore, "the morphologies that make up an organism ultimately derive from the turning on and off of homeobox genes". According to Schwartz, then, "timing is everything": the timing of homeobox gene expression makes all the difference between eels and elephants, flies and frogs, humans and yeast.[71]

Graham Budd complicates this sort of story by noting some of the other transformations that would be required for a change in the timing of homeobox gene expression to have an evolutionary, or even an ontogenetically functional, impact. One of the examples he discusses is the feeding appendages of crustaceans; these are, like the vast majority of functional organismal features, intricate, integrated

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[70]Schwartz (1999), pp. 362, 368-369.

[71]Schwartz (1999), pp. 36, 34, 44, 280.

modules. If it were shown that an alteration in the timing of homeobox gene expression results in a homeotically transformed feeding appendage, an outstanding problem would remain, namely that of "the integration of the new morphology into the functional complex that is an animal as a whole". Not only would the new appendage need to be integrated with the other feeding appendages, so too would necessary correlated alterations in muscles and in the nervous system.[72] In other words, Schwartz's story ignores both modularity and integration. Budd proposes an alternative model of homeobox activity according to which evolutionary change is not initiated or driven by changes in the timing of the expression of these genes; rather they are employed to streamline developmental processes once gradual (microevolutionary) morphological change has occurred.[73] Whether Budd turns out to be right is an empirical question yet to be decided; at the very least, Schwartz's view is shown to be misguided.

Schwartz's problem is that he adopts a Modern Consensus view of development, according to which homeobox genes are foundational and the only foci of genuine evolutionary and ontogenetic interest; epigenetics, for Schwartz, is no more than the differential regulation and expression of homeobox genes; therefore, his is a genes-plus account of ontogenesis, according to which development is subsumed under genetics. Perhaps Schwartz is an easy target, though; his expertise is in paleoanthropology, not developmental biology. But developmental biologists Gilbert, Opitz, and Raff fare little better; though they replace the gene with the morphogenetic field at the heart of evolutionary developmental biology, their conception of morphogenetic fields nonetheless takes genes as basic and definitive, and they still attempt to explain development in genes-plus terms. Finally, because Hall keeps epigenetics separate from genetics (holding that epigenetics just is regulation of gene expression), his, too, is a genes-plus

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[72]Another of Budd's (1999, p. 327) examples is that of bithoracic flies, that is, flies with an extra pair of homeotically induced wings, who are nonetheless incapable of flying, and this for two reasons: the musculature of the fly is not accordingly altered homeotically to accommodate the extra wings and, more basically, the body plan of the fly is not aerodynamically suited to two pair of wings, but only to the usual single pair.

[73]Budd (1999), pp. 327, 329-330.

account.[74]

Given my arguments in favour of constitutive epigenetics and creative epigenesis, I would argue that a primary unit of evolutionary developmental biology is the cell-organism-morphogenetic field, which is at no point coextensive with the genome, nor is it somehow contained within the genome as 'preformed' developmental information. The morphogenetic field cannot be specified genetically, but is rather a basic product of organismal reproduction. This is not to suggest that DNA is not an important interactant in morphogenetic fields, but rather that DNA simply cannot be foundational. The genetic component of ontogenesis is constituted epigenetically during the development of the (primary) organism. In other words, if ontogenesis is an additive process, then it is an *organism*-plus process – the Modern Consensus has things the wrong way around! But just as genes cannot exist independently of organisms, so too can organisms not exist independently of genes; the privileging of either one over the other is therefore inappropriate, given their reciprocal contingency. The full range of developmental material is required, and its ontogenetic specificity is negotiated through spatiotemporally sensitive, contingent, constitutive cointeractions within the primary and, eventually, secondary morphogenetic fields. The result is the emergence of a developed organism bearing a remarkable resemblance to its parents – without recourse to anything like species-specific genetic programmes.

Richard Burian has warned that, in attempting a reconciliation of genetics and embryology, we must bear no allegiance to the basic precepts of either discipline; he therefore dismisses both master control genes and morphogenetic fields. Burian nevertheless, in concert with the Modern Consensus, ascribes to genes undue ontogenetic primacy and agency.[75] I lean in the other direction, preferring development as our focus in attempting to understand development. Of course, if we define development, with the Modern Synthesizers, as differential gene expression, then a genetic focus just is a developmental

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[74]Gilbert, Opitz, and Raff (1996), p. 368; Hall (1998), p. 114.

[75]Consider, for instance, his adherence – without critical engagement – to the genetic-triggering-of-developmental-cascades line (Burian 1997, p. 258, *et passim*).

focus; but I see no persuasive reason to define development in such limited – and limiting – terms.

Why should this debate over subsumption *versus* synthesis matter? It is because the answers we generate are predetermined in scope and in kind by the sorts of questions we ask. When we subsume development under genetics, we ask only about differential gene expression; but when we define development in organism- or system-level terms (depending on our ends), differential gene expression does not provide a complete explanation of development. This is not to say that genetics should have no bearing on developmental biology; the activity of homeobox genes surely contributes in important ways to development. That is not in question. Nor must we presume with Kant that organisms (and their development) cannot be explained at all – they cannot be explained mechanistically, perhaps, but they can indeed be explained systemically by appeal to constitutive relations between their composition, structure, and environment. This is a different kind of scientific explanation. What, then, of the relation between genetics and developmental biology?

In our efforts to reconcile disparate disciplines, at least three strategies are possible: assimilation (or subsumption), fusion, and contamination.[76] Contamination (which is not to be understood pejoratively) is unavoidable, as witnessed by the past one hundred years of the history of biology, wherein a genetic perspective has permeated every biological subdiscipline. The choice, then, is between fusion and assimilation. Burian favours fusion, according to which both disciplines lose their distinct identities and meld together seamlessly. Yet, as I noted, Burian's fusion is impure, tending too much toward assimilation. Assimilation is the aim of adherents to the Modern Consensus. As against both of these options, I prefer a fourth strategy – synthesis – in order to guard against both the pauperization of development and the hegemony of molecular biology.

Synthesis stems from the inevitability of contamination, but ensures its reciprocity. In so doing, it avoids the assimilation characteristic of biology since the Modern Synthesis. Yet it also avoids fusion's

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[76]I borrow these terms from David Ingram's (2000, p. 86) discussion of cultural identity.

melting-pot mentality, while building on its mutualism by permitting the division of biological labour into differentiative and integrative problem sets. Both of these are crucial in understanding and explaining developing organisms, but only when they condition each other.

After synthesis, neither genetics nor developmental biology will remain as it was, but both will be more than either could have been through any alternative reconciliation. The fruits of synthesis will be enjoyed not only in biology as such, but also in our currently ecologically and developmentally challenged medicine.

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