1 Introduction

The year 1953 is one of iconic significance in the history of modern biology, perhaps even as important as 1858, when Darwin and Wallace first presented the theory of evolution by natural selection. On April 25, 1953, James D. Watson and Francis H. C. Crick published a two-page letter to *Nature* proposing a double-helix model for the structure of DNA, the icon alluded to in the last sentence.[1] The structure was constructed by piecing together an unprecedented variety of evidence: (diffraction) scattering patterns of X-rays from crystals of DNA; changes in these patterns brought about by the presence of water; knowledge that the two nucleotide base pairs, adenine (A) and thymine (T), cytosine (C) and guanine (G) (which are all components of DNA) occur in 1:1 ratios in the DNA of all species without known exception; knowledge of the lengths and strengths of chemical bonds, and so on. Equally important, the double helix was ''derived'' using physical models built of cardboard, wire, and wood, with hydrogen, carbon, nitrogen, oxygen, phosphorus, and other atoms simply being represented as solid balls with different radii. This modeling technique had entered the biological arena fewer than five years earlier, when Linus Pauling and Robert B. Corey had used it to propose a structural model for proteins that consisted of helical chains of the amino acid residues that composed them.[2] The success of this modeling strategy, which was widely recognized by the late 1950s and 1960s, represented the coming-of-age of the new discipline of molecular biology. Today, for good or for bad, depending on one's point of view, most of biology is molecular biology. Pauling's modeling strategy remains central to the field, though computer graphics have replaced the cardboard, wire, and wood.

The term ''molecular biology'' was introduced by Warren Weaver in 1938 in an internal report of the Rockefeller Foundation: ''And gradually there

is coming into being a new branch of science—molecular biology— … in which delicate modern techniques are being used to investigate ever more minute details of certain life processes.''[3] The next decade saw the steady increase in the use of these ''delicate'' techniques, in particular, X-ray crystallography, to study biological macromolecules ''minutely,'' increasingly with an emphasis on proteins. The central problem was the elucidation of the three-dimensional structures (the relative positions of the atoms) of biological macromolecules. Proteins were singled out because they were believed to be the most important of these macromolecules. In particular, since the founding of biochemistry as a self-standing scientific discipline in the 1920s, enzymes and their interactions had been held to be the key to understanding metabolism (the catch-all term for the complex chemical reaction systems that characterize life).[4] All enzymes are proteins. Until the early 1940s it was believed that the hereditary material (of the genes) was also likely to be composed of proteins. (The nucleic acids, constructed out of only four base types, were believed to be insufficiently complex to be able to specify the immense variety of known genes.)

What is philosophically most important about Pauling's modeling strategy is that, in a sense, its success apparently resolved, for once and for all, the long-standing question of whether biology (at least at the organismic level) can be reduced to physics and chemistry. The resolution was in favor of a thoroughgoing physical reductionism, which forms an underlying theme of most of the discussions of this book. However, this resolution raises foundational questions that remain pertinent today. The next section of this introduction (sec. 1.1) sets the context for three essays exploring reductionism (chapters 2–4). It discusses in some detail both the history of reductionism in biology and the developments within molecular biology that have made reductionism more plausible than ever before in the history of biology. All three chapters argue that what is both scientifically and philosophically interesting about reductionism are not such formal issues about the logical structure of explanations but, rather, substantive claims about the world that are of far-reaching significance. Can wholes be successfully decomposed into parts in models of biological systems? Do properties of the parts alone explain all properties of wholes? Such parts–wholes reductionism receives a mitigated defense in these chapters for the case of biology, while its failure at lower levels of organization (for instance, in quantum physics) is duly noted. However, a reduction to molecular inter-

actions is not necessarily a reduction to genetics, once the dream of the hereditarian program in the biology of the twentieth century. All three chapters are skeptical of such genetic reductionism (that is, the thesis that genes alone bear the weight of explanations at the molecular level). The success of physical reductionism should not be misinterpreted as a triumph of genetic reductionism. Molecular biology provides no added ammunition to the hereditarian program in biology. Rather, molecular details show that the claims of both hereditarianism and environmentalism are misplaced. Molecular biology may be reductionist, but it is not simplistic.

As in all other areas of biology, function ascriptions are ubiquitous in molecular biology. Functional *explanations* are typically offered to answer questions of origin: why some biological feature exists (or is the way that it is). The second section of this book (chapters 5–7) turns to the analysis of function ascriptions, mainly exploring the challenge presented by functional explanations to reductionism. Chapter 5 tries to clarify exactly how functional explanations pose a problem for reductionism. It argues that functional explanations are usually invoked to answer questions of origin rather than the questions of mechanism that form the staple of molecular biology. Thus, even if there is a conflict between functional explanation and reductionism, that conflict may be confined to a narrowly circumscribed set of questions. Chapter 5 also sketches a model that provides a potential resolution of this conflict. Chapter 6 gives more details of that model. However, both chapters may be criticized for using a narrow evolutionary concept of function, which may have to be broadened to capture many functional attributions in molecular biology. Meanwhile, chapter 7 notes that concern for function—often taken to be definitive of the practice of biology—may not capture all the aims of biological research. Following analytic techniques to the limits of their power (the scientific equivalent of formalism in the visual arts) may also guide research programs. The quest for sequences in the Human Genome Project may perhaps best be understood in this way, rather than in terms of any epistemological benefit it may provide. This chapter was written as a contribution to a conference on the role of aesthetics in science, and its conclusions remain rather tentative. Section 1.2 of this introduction puts the discussions of chapters 5 through 6 in context mainly by analyzing whether they take too narrow a view of function to capture all function ascriptions in molecular biology; no final resolution of this issue is offered (as is typical

of most discussions in this introduction). Section 1.2 also puts the more speculative observations of chapter 7 in context by defending the view that aesthetic considerations have always been part of scientific heuristics and the motivations that lead to the pursuit of science in the first place.

Part of the historical importance of the double-helix model was that it opened up a radically new possibility for the foundations of biology, one based on the concept of information. Section 1.3 of this introduction turns to the question of how the informational interpretation of biology interacts with the reductionist program (see chapters 8–10). Information is not a physical parameter (that is, one that occurs in physical theory),[5] and thus the stage is set for a potential conflict with reductionism. But is informational talk necessary in molecular biology? Worse, is information in molecular biology merely a metaphor masquerading as a theoretical concept? Chapter 8 summarizes the biological reasons for skepticism about information. Chapter 9 lays out the philosophical ramifications and argues that either all talk of information should be abandoned in favor of a thoroughgoing physicalism, or, a concept of information adequate for molecular biology should be properly explicated. Although both options are left open, the first is presented as being more plausible. Nevertheless, chapter 10 begins an exploration of the second option, after carefully delimiting the scope of informational talk in molecular biology. Section 1.3 provides a new analysis of the cognitive reasons for the perceived significance of the DNA double-helix model when it was first constructed. It also emphasizes problems with the highly popular but conceptually misleading metaphor of DNA as language.

''Nothing in biology makes sense except in the light of evolution,'' as Dobzhansky famously quipped.[6] At one level, Dobzhansky is obviously correct: without the context of the evolutionary history of any taxon, its biological features—in particular, those features that make it distinct from other taxa—are almost impossible to understand. Nevertheless, molecular biology provides a different type of unity, a different unifying framework for biology at the level of basic physical constitution and mechanisms. This perspective currently cohabits biology in uneasy tension with the received framework of evolutionary theory that was first constructed in the 1930s. The last four essays of this book (chapters 11–14) explore that tension. The first three concern one rather specialized topic: whether the molecular complexities of mutagenesis can be straightforwardly accommodated in

the received framework of evolutionary theory. Chapters 11 and 12 analyze the controversy that erupted in the early 1990s about the possibility of directional mutagenesis in bacteria. In retrospect, given that the claimed phenomena were delimited to microorganisms, the vehemence of that controversy remains a topic to be explored by historians and sociologists.[7] Chapter 13 attempts to summarize the state of the controversy some fifteen years afterward—it is likely that this chapter will also be controversial. Finally, chapter 14 touches on what molecular biology, especially the developments of the last five years, may contribute to the transformation of evolutionary theory to take into account morphogenetic development: it is an essay in the emerging field of developmental evolution. These essays barely scratch the surface of the evolutionary implications of postgenomic molecular biology. Were it not likely that such an observation would be quoted out of context and otherwise misused by miscreants such as Intelligent Design creationists, one would be tempted to quip (against Dobzhansky) that much of the received framework of evolution makes no sense in light of molecular biology.

1.1 Reductionism

As chapter 2 notes, the program of reductionism in the natural sciences goes back to the mechanical philosophy of the seventeenth century, which required that all physical laws be explained by local contact interactions between impenetrable particles of matter. Mechanical explanations replaced ones involving complicated combinations of Aristotelian elements and qualities. Reduction, as mechanical explanation, is thus a type of explanation. Reductionism is the doctrine that such explanations should be pursued because they are likely to be forthcoming. Sometimes, that doctrine also encompasses the view that these explanations will exhaust all interesting phenomena; this stronger version of the doctrine will not be assumed here.

Discussions of reductionism (see sec. 1.1.1) formed an integral part of natural philosophy, especially in the nineteenth century. The linguistic turn taken by logical empiricism in the 1930s led to the demise of traditional natural philosophy—or at least its demotion to the minor leagues—and its replacement by an anorexic philosophy of science in which the only legitimate questions were those that could be reduced to questions of

syntactic or semantic form.[8] This context strongly influenced the tenor of subsequent discussions of reductionism, beginning with Ernest Nagel and Joseph Henry Woodger in the late 1940s. In effect, Nagel and Woodger assumed that explanation was adequately explicated by the covering law model popularized by Hempel.[9] Reduction then becomes a form of intertheoretic explanation, in which the *explanans* and *explanandum* are both theoretical laws. This model of reduction implicitly assumes: (i) theories play a central role in reduction; and (ii) all philosophically interesting questions about reduction should be formulated as questions about various components of formal models of reduction. These assumptions dominated discussions of reduction in the 1960s and 1970s.

Nevertheless, there were several attempts by both biologists and philosophers to move discussions of reduction beyond these two limiting assumptions.[10] Chapter 2, first published in 1992, attempts a taxonomy of all the then-extant models of reduction. With hindsight, it uses a category of ''explanatory reductionism'' to capture those models that focus on the substantive rather than formal assumptions involved in reductionist explanation. Chapters 3 and 4, written a decade later, incorporate a sharp distinction between formal and substantive issues and focus on the latter. They defend a model of ''strong'' reduction in which properties of wholes are explained entirely through properties of their parts. However, these chapters gloss over some of the subtleties of the substantive assumptions made in molecular biology; section 1.1.1 tries to remove this lacuna while providing the historical context of these assumptions. Chapter 3 also argues against a facile genetic reductionism; section 1.1.2 elaborates on that point. Finally, chapter 4 uses the model of reduction developed here to analyze reductionism in other areas of biology.

1.1.1 Wholes and Parts

Mechanical explanation entered the life sciences in 1628 when Harvey described the circulatory system of animals and argued that the heart was a pump. Harvey described how arteries pumped blood from the heart, veins returned blood to the heart, and valves in veins prevented blood from flowing in the wrong direction. The new picture displaced the one inherited from Galen (ca. 130–ca. 200) in which new blood was created at the heart. Harvey's model was instrumental in providing specific support for the view, also associated with Descartes, that the body of a living organism

can be viewed as a machine.[11] Mechanical explanation, and the associated program of mechanism, allowed only for what were traditionally called "efficient causes" (which temporally precede their effects) and, moreover, required that all causes be mediated entirely by local (spatially and temporally contiguous) interactions. The mechanical philosophy irreversibly altered the course of physics and chemistry.

The mechanistic view of living organisms gained support over time, but it remained controversial up to the early twentieth century. However, what was allowed to be a mechanism became broadened to include not only contact interactions, but also central forces, and eventually all chemical and physical interactions.[12] In the eighteenth century, vitalists challenged mechanism on ontological grounds by positing vital interactions in organisms beyond those that operated in inanimate matter. In the mid-nineteenth century, mechanism was challenged by the so-called teleomechanists who admitted the power of mechanistic explanations but argued that they remained incomplete for living phenomena, which required their supplementation by a teleological principle.[13] This teleological principle did not involve any ontological assumption about the existence of special substances or interactions. Rather, claiming to follow Kant's *Critique of Judgement*, teleomechanists argued that the "efficient causation" of mechanistic explanation would not suffice to explain the goal-directedness of biological organisms. Mechanistic explanation must thus be epistemologically supplemented by a teleological principle. Variants of teleomechanism, unlike their vitalist predecessors, remained influential in biology until the beginning of the twentieth century.

In the late nineteenth century, some physiologists, including Claude Bernard and Christian Bohr, also argued that the self-regulative goal-directedness of living phenomena and the "cooperativity" of the parts of organisms would not entirely succumb to mechanistic explanation. In 1904, Bohr reported the so-called the Bohr effect, which epitomizes cooperativity:[14] at very low oxygen concentration, the binding of oxygen with hemoglobin is low. However, it increases sharply as the oxygen concentration increases before leveling off, resulting in a sigmoid-shaped curve. Hemoglobin shows "cooperative" behavior: when some of it binds oxygen, it helps more hemoglobin also to bind oxygen, until saturation is reached. For antimechanists, cooperative behavior is supposed to be inexplicable using only individual properties of parts and without invoking collective

properties of the whole: the sigmoid binding curve is supposed to show that ''the whole is more than the sum of its parts.''

Traditional mechanism is what is here being called ''strong reductionism,'' or, more succinctly, ''reductionism.''[15] By the time Jan Christian Smuts coined the term ''holism'' in 1926 to describe the antimechanist project,[16] it had become reasonable to think that mechanism would finally emerge triumphant in this long-running dispute. As early as the first decade of the twentieth century, Jacques Loeb had laid out the mechanistic program in full detail.[17] Meanwhile, between 1900 and 1920, Frederick Gowland Hopkins, an avowed mechanist, had established biochemistry as a discipline in its own right, centered around the study of enzymes. While some physiologists such as J. S. Haldane continued to espouse the holist alternative, other biologists equally versant in physiology, such as Lancelot Hogben, were adamantly in favor of a mechanistic interpretation of all of biology.[18] By the 1930s, within biology, the philosophical dispute between mechanism and holism had become replaced by experimental research programs designed to explore the structure of biological materials at increasingly finer resolutions. Central to these was the X-ray crystallography of biological macromolecules, pioneered by J. D. Bernal, which was exploited brilliantly by Pauling and those who followed him.

For reductionists, structures were interesting because they formed the basis for biological explanations. The double helix illustrates this point beautifully. In the double helix, two phosphate chains, running antiparallel to each other, form the backbone of the helix. The DNA bases, A, C, G, and T, are stacked inside the backbone. Because of restrictions on possible hydrogen bonds, A is always coupled with T, and C with G, which explains the base pairing (or 1:1 ratios) mentioned earlier. These ratios had been reported by Chargaff in 1950;[19] for the first time they were explained. Other than base pairing, there is no restriction in the arrangement of the bases. One sequence (along one of the helices) can be entirely arbitrary; because of base pairing, it then completely determines the sequence along the other helix. Thus, a practically unlimited variety of DNA sequences and therefore of genes is possible. This explains how macromolecules built from only four nucleotide bases can specify the thousands of known genes. Finally, the structure immediately suggests how it can be reproduced: by base pairing, each helix can serve as a template for the formation of a new replica.

In the double-helix model, wholes are explained in terms of their parts, exactly as reductionism demands. Here, some care must be taken to make sure that the reductionist claim does not become philosophically vacuous. As noted before, since at least the nineteenth century, antireductionists generally do not make any ontological claim beyond those that are admitted by reductionists. They do not claim the existence of vital forces or peculiarly living components of matter.[20] What is at stake is the epistemological question of what can legitimately be invoked in an explanation. Here, the reductionist has a more restricted repertoire available than the holist. For an explanation to be reductionist, two criteria must be satisfied:

(i) the properties invoked in explaining some feature of a whole must be properties of the parts alone, each definable without reference to some other part;[21] and

(ii) the *weight* of the explanation must be borne by these properties of the parts. The relevant explanatory factors do not include every factor that has some influence on the behavior being explained. The context determines what is explanatorily relevant, that is, what bears the weight of explanation.[22] Within epistemology, this concept of explanatory weight has proved notoriously difficult to explicate. It will be assumed here that some sort of substitutional insensitivity criterion will be adequate. If some factor in an explanation can be substituted for without significant change of behavior, that factor does not bear explanatory weight.[23]

That reductionist explanation in molecular biology can potentially fail shows that, at the very least, reductionism is not an empty doctrine.

Such "structural" reductionist explanation implicitly invokes four seemingly innocuous rules about the behavior of biological macromolecules in this context:

(i) the *weak interactions* rule: the interactions that are critical in molecular interactions are very weak;[24]

(ii) the *structure-function*[25] rule: the behavior of biological macromolecules can be explained from their structure as determined by techniques such as crystallography;

(iii) the *molecular shape* rule: these structures, in turn, can be characterized entirely by molecular size and, especially, external shape, and some general properties (such as the hydrophobicity) of the different regions of the surfaces;

(iv) the *lock-and-key fit* rule: in molecular interactions, molecules interact only when there is a lock-and-key fit between the two molecular surfaces. There is no interaction when these fits are destroyed. A lock-and-key-fit thus based on shape is one way of achieving specificity, that is, that a biologically active macromolecule interacts exactly with one (or at most a very few) other entities.

Because they explain specificity, the molecular shape and the lock-and-key fit rules are probably the most important of these rules. These four rules are all rules of macromolecular physics. They are at best only approximately derivable from physics at lower levels of organization. Thus this success of reductionism cannot be taken as a vindication of any type of fundamentalist physicalism that requires that fundamental physics at the lowest level of organization provides explanations of phenomena at all higher structural levels.[26] This situation merits much more philosophical reflection than has so far been afforded to it. Should the triumph of reductionism here be regarded as only a pyrrhic victory, at best? Or, is it that there is something very peculiar about the macromolecular and some higher levels of organization that permit the success of reductionism? Is there any connection between the ability to analyze wholes into parts successfully and the emergence of the complicated phenomena associated with life?

It is truly remarkable how powerful these apparently innocuous rules are. Only two examples will be further analyzed here, both selected because they deflate cherished examples from the holists' repertoire:

(i) Recall the discussion of the Bohr effect, in which cooperativity between the parts is supposed to show that the whole is more than the sum of the parts. In the early 1960s, in another of early molecular biology's most significant achievements, Jacques Monod and Francois Jacob developed a model of ''allostery'' that dispelled any doubt that such cooperative phenomena could be given standard reductionist explanations.[27] Protein molecules such as those of hemoglobin are ''oligomers'' consisting of several ''protomers,'' which are single polypeptide chains. Hemoglobin, for instance, has four protomers. The allostery model starts with the spatial structure of the oligomer and makes four assumptions: (a) identical protomers occupy equivalent positions in the oligomeric protein; (b) each protomer contains exactly one receptor site for the reactant; (c) the oligomer

has at least two distinct conformations available to it—the affinity of the receptor sites for the reactant may be different in these two conformations; and (d) this affinity depends on the conformational state of the oligomer and, therefore, the protomers, but not on the occupancy of the neighboring sites. From these assumptions, using standard chemical kinetics, it is trivial to derive the sigmoid binding curve of the Bohr effect. Had (d) not been satisfied, then the explanation would not have been accomplished using properties of the parts alone; there would then have been some solace for holists.

(ii) Lactose digestion in the bacterium, *Escherichia coli*, is negatively regulated by feedback. The enzyme, β-galactosidase, which digests lactose, is produced by *E. coli* only in the presence of that substrate. Feedback regulation, which used to be called ''homeostasis'' by physiologists, was also traditionally part of the holists' repertoire.[28] Systems exhibiting feedback regulation were supposed to have such complex interactions that it would be impossible to explain the systems' behavior by (conceptually) dissociating the systems into parts and invoking only the properties of those parts. Explanations were supposed to have to refer irreducibly to states of the whole. In the late 1950s, in yet another of molecular biology's early triumphs, Jacob and Monod constructed the ''operon'' model to explain feedback regulation.[29] The first critical assumption in this model is a distinction between structural and regulatory loci. Structural loci produce proteins, whereas regulatory loci are involved in the control of protein production at structural loci. In the operon model, a regulator locus is responsible for the synthesis, at a slow constant rate, of a repressor molecule (which is usually also a protein). The repressor molecule binds to an operator locus in the absence of the inducer molecule, in this case, lactose. Presumably because of steric hindrance, when the repressor molecule is bound to the operator locus, synthesis of β-galactosidase does not take place. In the presence of the inducer molecule, because of interactions between it and the repressor molecule, the latter is no longer bound to the operator locus and β-galactosidase can be produced by the usual cellular transcription and translation processes. When all the lactose has been digested, the repressor molecule binds to the operator site again, and the production of β-galactosidase stops. The operon model provides a trivial mechanistic explanation of something that holists found mysterious.

1.1.2 Genes

Proteins and nucleic acids received equal attention in the molecular biology of the 1950s and 1960s, but, since the 1970s, nucleic acids have been at the center of research in molecular biology, even as the sway of molecular genetics has been replaced by that of genomics.[30] A central concern of the philosophy of biology in the late 1960s and early 1970s was whether classical genetics was being reduced to molecular genetics (see chapter 2). Antireductionists usually argued that either classical genetics was being replaced by molecular genetics, or molecular genetics involved an extension of classical genetics that is not correctly viewed as a reduction.[31] Over the years, some measure of consensus has been reached on four points:

(i) If reduction is viewed as necessarily a relation between theories, as construed by logical empiricists, there is no question of a reduction of classical genetics to molecular genetics. The latter does not have laws and theories (as these are formalized by logical empiricists—see chapter 2); for some antireductionists even classical genetics lacks laws of the relevant sort.[32] A search for intertheoretic reduction has not played any significant role in the research strategies of molecular biology.[33]

(ii) There is no question of molecular genetics replacing classical genetics, particularly the use of Mendel's rules, not only to predict patterns of gene transmission into the future, but also retrospectively to infer patterns of evolutionary change in the past. Molecular detail—variation at the level of protein and DNA sequences—permits such retrospective inferences with greater precision than any method previously available.

(iii) There is similarly little question that molecular genetics provides explanations of classical regularities, including Mendel's rules.[34] Moreover, the molecular mechanisms that are operative also show the rather unexpected extent to which these rules may be violated. As is commonplace among reductions, the reducing rules, besides explaining, partly correct the reduced rules.

(iv) The critical problem in interpreting the development of molecular genetics as a reduction is that of providing a molecular "definition" of the classical gene. Ever since it became clear that there was no one-to-one correspondence between genes and DNA sequences (see chapters 4, 8, and 9), it also became clear that any molecular "definition" of the classical gene

cannot have the logical form of a biconditional. However, biconditionals are not necessary for explanations of classical regularities from the molecular level even if explanations are supposed to have the form required by Hempel's covering law model.[35]

The upshot of these developments is that, if reduction is construed necessarily as an intertheoretic relation, and theories are construed in the traditional manner of logical empiricism, there are problems with the reduction of classical genetics to molecular genetics. However, there would also be almost no successful reduction anywhere in the history of science. If, however, attention is focused on substantive issues—as is argued for throughout this book—the case for successful reduction is compelling.

Far more philosophically interesting than these somewhat arcane questions about definability and reductionism, though surprisingly rarely discussed by philosophers, is molecular biology's contribution to the nature–nurture dispute. Chapter 4 details how the success of molecular genetics led to the hope that developmental genetics will provide a sound theory of development. Proponents of the Human Genome Project exploited that hope to initiate massive blind DNA-sequencing projects: the full sequencing of entire genomes without prior concern for the functions of the sequences.[36] The same hope led to numerous, often irresponsible, claims that complex human behaviors (including male sexual orientation, schizophrenia, alcoholism, autism, reading disability, bipolar affective disorder [or manic depression], neuroticism, adolescent vocational interests, spatial and verbal reasoning, alleged differences in intelligence, etc.) had genetic etiologies.[37] From this perspective, phenotypic traits are being explained from a genetic basis: the framework is one of genetic reductionism. Not one of these claims of genetic etiology has survived further experimentation and scrutiny (as chapter 4 notes), though it would also be irresponsible to argue that inherited biological constitution has no role in the etiology of human behavior.

As chapter 4 records, the failures of genetic reductionism are fairly transparent. Nevertheless, two points deserve more emphasis than they receive there:

(i) Molecular biology has little to do with the claims of genetic etiology mentioned in the last paragraph. They were based on classical genetic methods, sometimes using molecular markers, that is, molecular types, to

distinguish phenotypes. Such a use of markers, however, does not involve explanation at the molecular level.

(ii) Molecular biology has done much to demonstrate that genetic reductionism itself is sterile by showing how complex the path is from DNA sequence to phenotype, even for ordinary morphological phenotypes, let alone complex behavioral ones. From the molecular perspective, simple genotype-phenotype determinations are exceptional; phenotypic plasticity is ubiquitous.[38] In the proteomic era, toward which postgenomic biology seems to be heading (see chapter 14), genes are but one of many interacting resources participation in the construction of phenotypes.

Finally, given what has so far been said, it may be tempting to conclude that the advent of molecular biology has shown that the traditional nature–nurture dispute itself is sterile. However, any such claim would be premature, involving an illegitimate conflation, though it may turn out to be correct in the future. Molecular developments have shown that the construction of phenotypes can receive neither a genetic nor an environmental etiology alone. Thus, there is more to biology than genetics, and the two should not be conflated. Identifying the natural with the genetic is illegitimate. However, suppose that the "nature" of the nature–nurture dispute refers to a putative biological substratum, a result of the interactions between the genes and environmental factors during development, that can be operationally distinguished from cultural factors. To the extent that such a distinction can be usefully maintained, nature–nurture questions may not be entirely misplaced.

1.2 Functions

The somewhat eccentric English naturalist and traveler, Charles Waterton, lived in what was British Guiana (now Guyana) from 1804 to 1812, returning there in 1816, 1820, and 1824.[39] Watertown was fascinated with sloths and even kept one (presumably a three-toed sloth, *Bradypus tridactylus*[40]) in his room for several months. Waterton's initial description of a sloth, in his entertaining 1825 travelogue, *Wanderings in South America*, emphasized its apparent maladaptiveness:

> On comparing him to other animals . . . , you could perceive deficiency, deficiency and super-abundance in his composition. He has no cutting teeth, and though four

stomachs, he still wants the long intestines of ruminating animals. He has only one inferior aperture, as in birds. He has no soles to his feet, nor has he the power of moving his toes separately. His hair is flat, and puts you in mind of grass withered by the wintry blast. His legs are too short; they appear deformed by the manner in which they are joined to the body . . . , and his claws are disproportionately long. Were you to mark down upon a graduated scale, the different claims to superiority amongst the four-footed animals, this poor, ill-formed creature's claim would be the last upon the lowest degree.[41]

But, Waterton wisely observes later: "This singular animal is destined by nature to be produced, to live and to die in the trees; and to do justice to him, naturalists must examine him in his upper element."[42] Once the arboreal perspective is adopted, the sloth's apparent malformations are recognized as functional for a life largely spent hanging from branches. Waterton proceeds to give one of the first reasonably accurate descriptions of the natural history of sloths and justly takes the Comte de Buffon to task for assuming that the sloth must live its life in misery because of the poverty of its design. Modern research has fully vindicated Waterton's assessment.[43]

That organismic features, the color, shape, size, and organization of parts, as well as behaviors, often serve functions was recognized at least as early as Aristotle. Ever since then, considerations of function have played a central role in analyzing biological systems. Function ascriptions are ubiquitous in molecular biology, as they are in every other area within biology. Also going back to Aristotle is the tradition of using the function of some feature to explain its origin, why it is there in the sense that it has the specific properties that it has. That tradition continues to this day, even in molecular biology, as chapter 5 attests. Arthropods (including insects) usually have a hardened cuticle with waxy waterproofing. They have them because these cuticles functioned to protect the body from desiccation when the first arthropods invaded the land after their evolutionary origin in the oceans.[44] Many mammals sweat, but humans sweat most profusely and efficiently. Sweating functions for heat tolerance.[45] Among mammals, probably only camels are more heat tolerant than humans. Questions of origin, whether of arthropod cuticles or human sweating behavior, thus receive functional answers.[46] The important distinction, here, is between such *why*-questions and *how*-questions. The latter probe how some feature is brought about, what mechanism leads to its production. For Aristotle, how-questions were to be answered by appeal to efficient causes; why-questions

by appeals to final causes. This distinction is periodically rediscovered, apparently independently. For Mayr, writing in 1961, the same distinction is one between ''proximate'' and ''ultimate causes.''[47]

The distinction here is between reductionist explanations, which invoke only temporally antecedent conditions, and functional explanations, which refer to the future. The function of a feature refers to some future effect of that feature's being there. Resistance to desiccation is a result of arthropods already having hardened cuticles with waxy waterproofing. Efficient cooling is a result of the human ability to sweat profusely. However, not all effects of the possession of a feature are functions: the waxy surface of arthropod cuticles also make them light-reflective, but that is not one of its functions. Sweating temporarily reduces the weight of human bodies (though only marginally) but this reduction of weight is not one of its functions. Only those effects that somehow seem to serve a future purpose can constitute functions. Functional explanations thus seem to violate any requirement that adequate explanations must refer only to antecedent conditions. This requirement amounts to denying that there are purposes in nature, that is, denying that nature is in any fundamental sense goal-directed. Ever since the rise of the mechanical philosophy in the seventeenth century this requirement has been a metaphysical presupposition of the physical sciences. Its justification has been the spectacular success of those sciences under the new metaphysics, compared to what had been achieved in the centuries spent under the banner of teleology. This metaphysics was systematically extended to cover the biological sciences during the last few centuries with equal success, particularly with the advent of molecular biology in the mid-twentieth century. But functional attributions remained part of biology. The task of establishing consistency between functional and reductionist explanation is the problem of naturalizing function.

1.2.1 Broad-sense Functions

For most philosophers of biology, the problem of naturalizing function was effectively solved by Darwin and Wallace's theory of natural selection, though the details of various proposed solutions vary. Roughly, the solution is simply that some effect of a feature is function if it is associated with an increased fitness. Effects that do not increase fitness are not functions. Because of this increase in fitness, a feature with a function is retained

during evolution once it arose by blind variation; a feature with only nonfunctional effects is not similarly retained. In fact, with continued selection, any feature with a function is likely to become more ubiquitous in that species. In this sense the function of a feature explains why it is there, thus answering the question of its origin.[48] Functions are thus intimately tied to fitness enhancement. Here, these functions will be called ''functions in the narrow sense'' or, simply, ''narrow-sense functions.'' They solve the problem of restricting explanations to antecedent factors, because a feature's potential to increase fitness in a given environment is present temporally before any effect of a feature is expressed. This is the etiological view of biological functions. It is assumed in chapters 5 and 6.

A different narrow-sense view of function, but one also tied to increased fitness, is the propensity theory, according to which the functions of a feature are its adaptive effects (that is, those that increase fitness) rather than the effects for which it is an adaptation (effects favored by natural selection because of which the feature exists).[49] The propensity theory effectively denies that functional attributions arise as answers to questions of origin. Though these two views are usually presented as alternatives, there is no contradiction between the two views because they emerge from two different questions: the etiological theory asks why a trait arose irrespective of what it does, and the propensity theory asks what it does no matter how it arose. Moreover, in an important sense, the etiological view is reducible to the propensity view. Faced with a question of origin—for instance, why do birds have feathers?—the propensity view can invoke past functions that were functions at the relevant past times because they then enhanced fitness. In the early evolution of birds, feathers helped in thermal regulation and thus enhanced fitness. The etiological view thus consists of the reconstruction of past functions that may be quite heterogeneous—from helping in thermal regulation, feathers eventually came to help achieve buoyancy for flight.[50] This heterogeneity is a result of the assumption that functional attributions are necessarily made in response to answers to questions of origin.

The propensity view allows a broader category of function than the etiological view. Moreover, the propensity view has another advantage over the etiological view: it seems to have the potential to capture the common practice in biology (and elsewhere, for instance, psychology) of making functional attributions from present roles with no reference to evolutionary history.[51] Nevertheless, there is at least one reason to suspect that

narrow-sense function, even with the propensity rather than the etiological view, does not fully capture such usage. Ernst Mayr, for example, distinguishes between functional biology and evolutionary biology and claims: ''[t]he functional biologist is vitally concerned with the operation and interaction of structural elements, from molecules up to organs and whole individuals. His [*sic*] ever-repeated question is 'How?' How does something operate, how does it function?''[52] It is the ''functional'' biologist who is concerned with proximate causes. Functions, in this sense, refer to roles played by particular mechanisms in the networks of interactions by which organisms carry out their typical activities.[53] Mayr had molecular biology in mind in the passage quoted above. The function of the gene (allele) for sickle-cell hemoglobin is to encode that hemoglobin irrespective of whether it increases fitness (as, for instance, in heterozygotes for whom it reduces susceptibility to malaria) or decreases fitness (in homozygotes in whom it results in sickle-cell disease). In mammals, the function of the heart is to pump blood even in females well past their reproductive age: this function clearly does not enhance fitness.[54] Narrow-sense function is so closely tied to adaptation that it makes it impossible to attribute functions to any feature that is not adaptive. If it turns out to be true that, at the molecular level, many features of organisms are not fitness-enhancing, as the neutral theory of molecular evolution holds, there can be very few attributions of function at that level. Even at higher levels of organization, the extent to which organismic structures and behaviors are adaptations is a matter of ongoing controversy.[55] Using ''function'' only in its narrow sense would require a radical revision of the customary linguistic practice of contemporary biology, especially molecular biology.

Thus what seems to be required is a broader sense of ''function'' (''broad-sense function'') so that all customary uses of the term in contemporary biology may be captured. The problem, once again, is that of naturalizing function—distinguishing functional features from nonfunctional ones and doing so with reference only to factors that are temporally antecedent to functional attributions. One possible solution—which requires much more careful elaboration than can be attempted here—is to invoke a principle of persistence: an effect of some structure, A, is a function if it contributes to the persistence of some system, B, of which A is a part; the persistence of B is to be defined contextually to allow for some state changes and disallow others.[56] Thus the function of the heart is to pump blood even in mammals past reproductive age because it contributes to the persistence of the

individual with the heart. For broad-sense function, the principle of persistence plays the role that the principle of natural selection plays for narrow-sense function.[57] Note, *critically*, that the principle of persistence is also less problematic than the principle of natural selection from the perspective of having a reputable physical basis: organisms are structures that tend to persist because of their physical constitution. The mechanisms responsible for the persistence of organisms are precisely the ones that are being elaborated by molecular biology. Finally, narrow-sense function is a subcategory of broad-sense function: organisms must persist in order to reproduce and evolve by natural selection.

Recourse to broad-sense function constitutes a departure from usual practice in the philosophy of biology, but it has the advantage of keeping the discussions closer to scientific practice. Without some expansion beyond the narrow sense, it is likely that a sense of function (for instance, that used in chapters 5 and 6) cannot do justice to functional ascriptions in molecular biology.

As a final caveat, it is also not clear that, in answering questions of origin, the sharp distinction between ''proximate'' and ''ultimate'' factors will continue to be helpful. Consider a crystal: any answer to a question of its origin will refer only to the efficient mechanisms by which it was brought about. The why-question has no different answer than the how-question. In the context of biological features, the distinction between proximate and ultimate answers depends heavily on the assumption that why-questions traditionally receive a radically different answer from how-questions. Answering why-questions involves recourse to the theory of natural selection, which is conceptually disparate from the physical and chemical theories that are invoked to answer how-questions. There are two related reasons why this situation may change:

(i) If it turns out that adaptation is not quite as ubiquitous as it has traditionally been assumed, then appeal to natural selection will not provide an answer to all questions of origin. There will still be an evolutionary story to be told, but the factors invoked, such as chance production and survival or physical rules of body construction, will often be the usual proximate factors that are used to answer questions of mechanism.

(ii) Even in the presence of adaptation, recent attempts to understand development in an evolutionary context have begun to integrate these proximate factors into a theory of phenotypic evolution that looks very

different from the traditional genetic theory of natural selection that goes back to the late 1920s and 1930s (see sec. 1.4 below). In contemporary evolutionary biology, the distinction between proximate and ultimate factors is becoming blurred. The loss of this distinction affects only the analysis of narrow-sense function in terms of adaptive value; the status of broad-sense function is not affected.

1.2.2 Biology beyond Functions

The original aim of the Human Genome Project (HGP) was to sequence the entire human genome with no concern for the function of any part of the sequence.[58] The project was soon expanded to include the sequences of several other species. Why bother? Going beyond the explicit epistemic aims of the HGP's proponents (about which there has always been ample room for justified skepticism), chapter 7 suggests that part of the HGP's appeal was aesthetic. However, the operative aesthetic motivation was not some ascription of beauty or taste. Rather, it was the pursuit of a technique (a ''formalism''), in this case, sequencing, to its limit. Just as formalism in the visual arts of the 1920s was supposed to reveal deep features of the human spirit, the sequence was supposed to reveal the essence of humanity.

Given the dearth of work on the aesthetics of science—even while it is freely acknowledged that scientists routinely and explicitly appeal to aesthetic norms—it is hard to evaluate the soundness of the argument of chapter 7 is. Suffice it here to note that there is another interpretation of the initiation of the project that does not appeal to the explicit epistemological aims of the HGP's proponents. The various genome-sequencing projects can also be viewed as a continuation of the descriptive project of biology that goes back at least to Aristotle: describe every organism in excruciating detail simply because it is there, no matter whether the description seems capable of providing any further insight. Part of the motivation—and value—of such descriptive projects has been that such detailed descriptions have often eventually yielded other insights, as has also been claimed for the HGP.[59]

1.3 Biological Information

As noted at the beginning of this introduction, chapters 8 through 10 concern biological information. All three chapters are concerned with the

question of whether the concept of biological, in particular, genetic, information is coherent. Chapter 8 may be regarded as an extended abstract of chapter 9 (which is rather long). Chapter 8 was commissioned as a generally accessible summary of chapter 9; there is thus much in common between the two chapters. Chapter 10 brings those discussions up to date. Consequently, this section of the introduction will turn to two other issues regarding the informational interpretation of biology, rather than elaborate on the material presented in chapters 8 through 10.

1.3.1 The Double-helix Model Revisited

This introduction started with the observation that the DNA double-helix model has iconic status in contemporary biology. Typical explanations of this status refer to the alleged beauty of the model, the popularity of Watson's entertaining and irreverent—as well as exceptionally fictionalized—account of its discovery,[60] as well as the epistemic reasons connected to reductionism discussed earlier (sec. 1.1.1). However, there are even deeper epistemic reasons why the double-helix model was so important, and these reasons shed considerable light on the use of models in science, especially how they may contribute to theoretical unification. The emergence of the informational interpretation of biology is central to this story.

What is critical about the double-helix model is that it provides a point of contact between four different research programs:

(i) Classical transmission genetics, as practiced during the first half of the twentieth century, made no commitment to the physical nature of the gene.[61] As noted earlier (at the beginning of this introduction), until the 1940s, genes were generally believed to be specified by proteins, but this was no ground for cognitive or epistemic dissonance with the rest of what was known about biology. According to the received view of evolution (see sec. 1.4.1 below), the classical gene must satisfy three constraints: (a) it must be capable of being duplicated during reproduction; (b) its duplication and transmission must obey Mendel's rules in diploids; and (c) it must be capable of occasional mutation. The received view implicitly assumed the primacy of the gene, that is, that genes produce traits. However, as with the physical nature of the gene, it was silent about how traits were so produced.

(ii) However, starting in the 1930s, and both conceptually and organizationally independent of the research program of transmission genetics,

there emerged a program of studying gene action. This program began largely within biochemistry and can be interpreted as a rudimentary attempt to incorporate some developmental biology into classical genetics. From this program two new constraints were imposed on the chemical gene: (d) it was required to be connected by chemical mechanisms to other chemical constituents of cells; and (e) since the late 1930s it was becoming clear that there must be a specific relationship between genes and enzymes. What deserves emphasis is that there was potential for considerable tension—if not downright contradiction—between the classical gene (as conceptualized by the transmission geneticists) and the chemical gene (of the biochemists).

(iii) Yet another constraint was imposed on the gene by a third research program. The biophysical structural studies mentioned earlier (sec. 1.1.1) required of the physical gene that: (f) it satisfy all bond length and other stereochemical restrictions between atoms discovered from crystallographic studies.

(iv) To confound the matter further, a fourth set of constraints emerged, not from a well-defined research program, but from sporadic theoretical work from a variety of sources. These constraints were clearly articulated by Erwin Schrödinger in *What Is Life?* in 1944:[62] (g) from a physical perspective, the gene is unusually stable, remaining constant over hundreds of generations. It is more similar to an inorganic crystal than to the usual organic matter studied by biochemistry; but, (h) nevertheless, the structure of the gene must permit almost infinite variability to account for the known diversity of genes. Schrödinger presciently proposed a combinatorial solution to this problem, speculating on the possibility of a ''hereditary code-script.''

What is remarkable about the double-helix model is that it simultaneously satisfied all eight constraints seamlessly (that is, there was no post hoc approximation required to meet the constraints). In this sense, it is a *confluent* model (standing at the confluence of four different research programs). The unpacking of the DNA strands of the double helix immediately suggested a mechanism for the satisfaction of constraints (a) and (b). An occasional change of base sequence provided a mechanism for satisfying (c). Constraints (d) and (e) could be interpreted as that of deciphering the chemical properties of DNA sequences. All physical assumptions of the

double helix model satisfy the stereochemical constraints (f). With the nucleotide bases protected inside the core of the helical cylinder, the double helix was believed to be a model of stability (constraint [g])—it was realized only much later that maintaining the structural integrity of the double helix requires a formidable array of repair mechanisms. Finally, the combinatorial explosion of possible sequences accounts for (h).

Confluent models establish a certain kind of consistency between different research programs without epistemically privileging any of them. Each program can now pursue its own agenda without worry that results from one of the others would contradict its core assumptions and render it unviable. The double helix permitted biochemical genetics to flourish without the specter of biophysics or transmission genetics haunting it, and so on, for the other research programs. Moreover, in the case of those constraints that were yet to be embedded in an identifiable research program (the fourth set above), the confluent model provided the impetus for such a program to be created—chapters 8 through 10 record the vagaries of that program. Finally, the double helix furthered Pauling's strategy of model construction, as was emphasized earlier in this introduction. It should come as no surprise that the double helix was recognized for its importance right from the beginning.

It is an open question how often confluent models occur in the history of science. Within molecular biology, both the allostery and the operon models played significant confluent roles, though not to the same extent as the double helix. The former established consistency between biophysical structural studies and a long-term research program within physiology, dating back to the 1890s. The latter established consistency between, once again, biophysical structural studies and a research program within biochemistry studying enzymatic adaptation (see chapter 9). (Beyond biology, Maxwell's mechanical models of the electromagnetic field provide one obvious example.) However, confluent models provide an epistemic account of theoretical unification very different from any that would be obtained by a focus on theories as linguistic structures. (Obviously, such an account is also fundamentally *not* a sociological one.)

1.3.2 DNA as Language

One result of the informational interpretation of molecular genetics has been a set of linguistic metaphors that pervades contemporary biology:

deletion, (RNA) editing, frameshift (mutations), insertion, messenger (RNA), missense (mutations), nonsense (mutations), open reading frames (in DNA), (DNA) proofreading, reading frames (for DNA), readthrough (of termination codons), sense and nonsense (DNA strands for transcription), translation (from DNA to protein), transcription (from DNA to RNA); and only a very few others that are not derived as directly from linguistic contexts, for instance, chaperones, housekeeping (genes), orphan (genes), and (RNA) splicing.

These metaphors congeal into an overarching metaphor of DNA as a language (or, sometimes, as the language of the genes). Even in the context of development, about which early molecular biology—like classical genetics before it—could say very little, as early as 1965, John Tyler Bonner argued that ''all cells contain the directions for all cell life, written in DNA.''[63] Several technical as well as popular books have been written that explicitly endorse the linguistic metaphor.[64] It also forms the basis of the discipline that calls itself ''biosemiotics.''[65] However, probably because molecular biology came of age simultaneously with the advent of digital computation, the metaphor of language was usually taken to refer not to natural languages—in which case compelling disanalogies would probably soon have been recognized—but to computer languages. To invoke yet another metaphor, the genome was supposed to contain a program for development. In 1961, Mayr explicitly argued that an individual was programmed by natural selection through its genome.[66] Almost simultaneously, introducing the operon model, Jacob and Monod argued that the ''discovery of regulator and operator genes ... reveals that the genome contains not only a series of blue-prints but a coordinated program of protein synthesis and the means of controlling its execution.''[67] And in Monod's later words: ''The logic of biological regulatory systems abides not by Hegelian laws but, like the working of computers, by the propositional algebra of George Boole.''[68]

The three metaphors—genetic information, DNA or genes as language, and the genetic program—reinforce each other since they are mixed and matched without producing cognitive dissonance: computer programs are written in artificial languages constructed on principles originally abstracted from natural languages, and all languages trivially facilitate the transmission of information, no matter how ''information'' is construed. Chapters 8 and 9 challenge the use of the metaphor of genetic information. However, following one of the strategies suggested in chapter 9, chapter 10

attempts to convert the metaphor into a model by providing a new account of what it means for DNA to encode information for traits. Chapter 10 also argues for the increasing epistemic irrelevance of the concept of information as levels of organization higher than proteins become the foci of interest. Chapter 14 argues against the relevance of the metaphor of a genetic program, noting its epistemic incompetence not only when confronted with the phenomena of development but also at the level of DNA and protein. The metaphor of DNA as language is perhaps even less compelling though it has presumably done less harm because, when it comes to designing research protocols, molecular biologists are well aware that DNA is a molecule, a physical structure, not a linguistic one. Returning to the molecular biology of the 1960s, the linguistic metaphor could perhaps be defended insofar as it suggested research programs designed to decipher the code, establish translation rules, and so on. But the unexpected complexity of eukaryotic genetics has prevented the straightforward extension of those programs beyond prokaryotes. The linguistic metaphor no longer suggests interesting research programs—consequently, in contemporary molecular biology, it is of little relevance.

Meanwhile, the main harm of the linguistic metaphor is that it obfuscates the physical complexity and developmental contingency of gene expression. The DNA sequence is not a book waiting to be read unless, perhaps, the metaphor is intended to refer to a work of fiction or to a religious text, the deep meaning of which can be understood only by detailed knowledge of context. (Defending the HGP, Walter Gilbert endorsed such an interpretation by describing the human DNA sequence as the Holy Grail of biology.)[69] The linguistic metaphor suggests far too static a picture of the genome than is warranted; it ignores the dynamic use, conversion, and transformation of DNA and its immediate products during even the production of protein from DNA (as chapter 14 will detail). At the level of traits further removed from DNA, there is no question of encoding or translation (see chapter 10). But, perhaps most unfortunately, the linguistic metaphor also suggests an unsound determinism in which all biological features are supposed to be dependent on the DNA sequence. As section 1.4 (sec. 1.4.3) will emphasize, part of the conceptual excitement of genomics has been that, especially from an evolutionary point of view, the organization of DNA can be understood only from the perspective of the evolving organism.

1.4 Evolution

The evolution of populations requires the existence of variation, as well as change in the intensity and extent of this variation. Conceptually, for evolution to occur, there is no requirement of statistical independence between the production of variation, its intensity (in different ''individuals'' of a population), and its extent (that is, its frequency in the population). As chapter 12 notes, Lamarck's evolutionary model posited a positive correlation between all three factors. In contrast, Darwin's original (1859) model of evolution by natural selection (which is equally due to Wallace) explicitly assumed independence between the first and third factors.

Darwin's model of evolution by natural selection makes three assumptions about the process of the change of the extent of variation:[70]

(i) intrapopulation variation: that such variation exists at the level of entities or ''individuals'' within a population. (these ''individuals'' could be cells, organelles, biological individuals, groups, etc. Although Darwin focused mainly on biological individuals, the model is not committed to any single level of selection);

(ii) differential fitness: that different variants contribute different numbers of offspring to the next generation; and

(iii) inheritance of fitness-determining properties: that there is a correlation between parent and offspring in the properties that, by varying, produce differential fitness.

It is instructive to note what this model does not assume: (a) any particular mechanism of hereditary transmission.[71] Darwinian evolution by natural selection can even occur through the cultural inheritance of traits. Moreover, it does not assume (b) a genotype-phenotype distinction, which Mendel implicitly introduced in 1866 by distinguishing between characters and factors (which were transmitted during reproduction and were responsible for producing the corresponding characters). The modern form of the last distinction was introduced only around 1909 by W. Johannsen, who conceptualized the genotype as an abstract entity defining the total genetic profile of an individual organism.[72]

1.4.1 Mathematical Mendelism

The received view of evolution, sometimes called neo-Darwinism (or the ''Modern Synthesis''), emerged in the late 1920s and early 1930s primarily

through the work of three individuals, R. A. Fisher, J. B. S. Haldane, and Sewall Wright.[73] At the core of the received view are mathematical models of heredity; for diploids these are based on Mendel's rules as modified by linkage. For expository simplicity, attention will be restricted here to the diploid case.[74] These models predict evolutionary stasis in the null model when reproduction takes place in isolated populations large enough for chance effects to be irrelevant, no variation through mutation, and no selection: this stasis is captured by the Hardy–Weinberg rules, which state that allelic frequencies do not change from generation to generation. For a single locus, if mating is random with respect to that locus, genotypic frequencies also do not change. These other factors that can lead to change are modeled as deviations from Hardy–Weinberg predictions. It is more accurate to call the received framework of evolution mathematical Mendelism rather than neo-Darwinism (in contrast to the proposal of chapter 12), because the Hardy–Weinberg rules are a result of Mendelian inheritance, not Darwinism in general.[75] Philosophers have paid little attention to how this framework fares in the light of modern molecular biology when the abstract genotype is confronted with the dynamics of the material genome.

Going beyond Darwin's original model, neo-Mendelism assumes:

(i) a sharp genotype–phenotype distinction, with inheritance occurring only through the genotype, thus usually preventing the inheritance of acquired characters;

(ii) that transmission of hereditary material between generations is governed by Mendel's rules for diploids, and by their analogues in the case of haploids or polyploids;

(iii) that variation arises through mutations in the genotype;

(iv) that these mutations are "random" or "blind" in the sense that the mechanisms responsible for mutagenesis are equally likely to produce a mutation in contexts where that mutation enhances or diminishes fitness;[76] and

(v) evolutionary dynamics is adequately modeled in genotypic space, which assumes that phenotypes may be predictively tracked from genotypic space; thus phenotypic evolution is reducible to genotypic evolution.

Developments within molecular biology have challenged all these assumptions. Historically, the identification of DNA as the genetic material, and the informational interpretation of the gene (see sec. 1.3), led to the interpretation of genotypic inheritance as inheritance of DNA sequences

alone. All forms of epigenetic inheritance (for instance, the inheritance of methylation patterns of DNA) then violate assumption (i). Several biologists have pointed out that some types of epigenetic inheritance can be interpreted as the inheritance of acquired characteristics. In particular, Eva Jablonka and Marion Lamb have urged the evolutionary significance of epigenetic inheritance. However, they have also generated confusion by claiming to defend Lamarckianism.[77] As chapter 12 notes, Lamarck was not unique in assuming that acquired characteristics are inherited—in fact it is a mistake (unfortunately, one prevalent among biologists) to associate Lamarck with that position. Rather, Lamarck's name should be associated with the position that the generation of hereditary variation itself is preferentially adaptive. Moreover, as noted at the beginning of this section, the inheritance of acquired characteristics is logically consistent with Darwin's own model of evolution by natural selection. Such inheritance falls afoul of the received view, not of Darwinism.[78]

Most types of epigenetic inheritance also violate assumptions (ii) and (iii). Those who would hold that the received view of evolution requires no major modification in light of the molecular data can perhaps argue that epigenetic inheritance may be of only limited importance to evolution. But assumptions (ii) and (iii) are also routinely violated at the level of DNA. Three examples will be noted here, each consisting of phenomena recognized during the era of classical genetics but regarded as being anomalous and probably of no great evolutionary significance:

(a) As early as 1951, Barbara McClintock reported the presence of transposable DNA elements in maize that inserted themselves into different regions of the genome,[79] violating (ii), and generated new genotypes, violating (iii). McClintock's original report was greeted with skepticism bordering on derision.[80] In the molecular era, mobile genetic elements (such as transposons) have been found in virtually every species examined, prokaryotic or eukaryotic.[81] They result in chromosome rearrangements and enable horizontal gene transfer. In bacteria, they enable the rapid spread of antibiotic resistance.

(b) Meiotic drive, or the preferential transmission of one of the two homologous alleles, in violation of Mendel's rule of independent segregation, has been known since 1928.[82] Thus, assumption (ii) of the received view is violated. Meiotic drive systems can be chromosomal or genic.[83] In the

former case, some property of the entire chromosome must give one homologue a replication or orientation advantage in the spindle during meiosis. This chromosome is preferentially represented in the gametes. In the latter case, gametes containing the relevant allele are at an advantage over other gametic types. Most cases of genic meiotic drive are believed to be explained by the segregation distortion model. Most proponents of the received view of evolution see meiotic drive as an instance of intragenomic conflict, also showing that selection acts at different levels of organization. Even if this interpretation is accepted, it nevertheless requires an expansion of the received view beyond assumption (ii). More than Mendel's rules are necessary.

(c) Gene conversion, defined as the nonreciprocal transfer of ''information'' between homologous DNA sequences, has been known since Carl Lindegren's work on the yeast *Saccharomyces cerevisiae* in the 1950s.[84] Unlike crossovers, in which the exchange of DNA between homologous chromosomes is reciprocal, in gene conversion, one chromosome may donate its sequence while the other loses its sequence, during meiosis (and, more rarely, mitosis). Assumption (ii) of the received view is violated; arguably, so is assumption (iii), at least on those occasions when the resulting genotype is new. Mechanistic models of meiotic gene conversion go back to a model by Robin Holliday in 1964.[85] One major effect of gene conversion is that it enables concerted evolution: that duplicated (paralogous) sequences within a species become more closely related to each other than to orthologous sequences from other species. Gene conversion is one of two mechanisms that lead to the situation in which repeated homologous sequences within a genome tend to get homogenized.[86] There are at least three ways in which this process is evolutionarily significant and will require moving beyond the received view of evolution: conversion can facilitate the spread of a mutation in a population; it erases that trace of evolutionary history from the genome that consists in the use of the extent of divergence to estimate the time of the duplication; and it decreases intraspecific divergence while potentially increasing interspecific divergence.

Molecular biology also calls assumption (iv) into question—this issue is dealt with in chapters 11 through 13.

Finally, one topic that is not broached in this book is the neutral theory of evolution, the first challenge presented by molecular biology to the

received view of evolution. In the early 1960s, the development of gel electrophoresis led to the realization that variation at the level of proteins was ubiquitous in natural populations.[87] Given the degeneracy of the genetic code, this observation implied that variation at the DNA level was even more pronounced. In 1968 Motoo Kimura argued, on the basis of J. B. S. Haldane's thesis of there being a cost to selection (in terms of the required loss of the less fit individuals), that natural selection could not maintain this degree of variation.[88] Much of this variation must, therefore, be neutral. A year later, drawing on Kimura's calculation, J. L. King and T. H. Jukes announced the advent of a ''non-Darwinian'' model of evolution in which drift of neutral alleles replaced selection as the driving force of evolutionary change.[89] Partly because of King and Jukes's rhetoric, there immediately began an acrimonious debate about the etiology of molecular variation in natural populations, which has not ended yet.

However, the received view of evolution does allow for the existence of other factors of evolutionary change, besides selection, including random change (called ''drift''). Consequently, in one straightforward sense, Kimura's position is one that can be formulated within the received view: it states that drift rather than selection best explains the patterns of diversity and variation seen at the molecular level. The conflict is between neutrality and selectionism, the latter being the position that selection is the dominant mechanism of evolutionary change at all levels of organization. Both positions are correctly viewed as alternatives within the received view.

As such, Kimura's theory contrasts earlier alternative global theories of evolution proposed by R. A. Fisher and Sewall Wright to account for the patterns of change seen during evolutionary history.[90] Fisher argued for the importance of selection acting on individual mutations with small fitness effects in large panmictic populations, whereas Wright emphasized the importance of population structure and, to some extent, drift in small populations. Kimura and most other neutralists have also maintained that neutrality at the molecular level is compatible with ubiquitous selection at higher levels of organization; however, since entities at these higher levels of organization are composed of their constituent molecules, there is a paradox here. For future reference, this will be called the ''neutrality paradox.'' Any resolution of this paradox probably requires that development screens off the molecular level from the effects of selection acting, for instance, on entire organisms, a position that is not inconsistent with the

received view of evolution, though only because the latter is entirely silent about development—a point emphasized in chapter 14.

1.4.2 Developmental Evolution

A theory of development was the central goal of several research programs of nineteenth-century biology. As chapter 14 notes, in 1926, T. H. Morgan initiated an operational divorce between studies of heredity (that is, the new science of genetics) and development on the basis of the assumption (justified in its own context) that Mendelism could be pursued using traits that had a simple genotype–phenotype relationship. Three consequences of this strategy are worth emphasis: (i) the received view of evolution, which emerged from the genetics of the 1920s, largely ignored development (as noted at the end of sec. 1.4.1); (ii) attention came to be restricted to those traits that did not display complex developmental origins;[91] and (iii), partly as a result of (ii), genetic reductionism (which has already been criticized in sec. 1.1.2) gained plausibility within biology.

In contrast, by elucidating the complexity of the molecular mechanisms required for gene expression, let alone the control of phenotypic expression at even higher levels of organization, molecular biology has shown the potential complexity of the relationship between phenotypes and genotypes. Developmental genetics, starting in the 1960s, promised to bring some simplicity and theoretical order to the field by pursuing explanations from a genetic basis, but it promised much more than it ever came close to delivering. Until the 1990s there seemed to be little plausible prospect for a theoretical understanding of development.

Although it would be rash, even now, to suggest that a *theory of development* is forthcoming in the foreseeable future, a suite of related recent results makes it plausible to expect that there will at least be piecemeal theoretical insights into development. First, there has been a shift of focus from the DNA to the cellular level, with proteins dominating attention at the latter (see sec. 1.4.4). Second, partly as a result of this shift, it has been realized that there is a convergence—or universality—of molecular structures and mechanisms at the cellular level that is not discernible at the DNA level. Third, this universality holds across wide classes of taxa. For instance, there are hundreds of different genes and their primary products that are known to be involved in transducing signals across the plasma membranes of cells; yet the mechanisms of signal transduction can all be

classified into only sixteen signaling systems in metazoans.[92] At least arguably, taxa are more similar at the level of cells and protein-mediated biochemical mechanisms than at the level of their DNA sequences. Thus, and this point has not been widely appreciated, the new molecular biology resolves the neutrality paradox mentioned earlier (sec. 1.4.1): neutral variation at the molecular level (in particular, the DNA level) may be consistent with selection for the small number of possible functional complexes at the cellular and higher levels of organization.

The emergence of these molecular insights into development has been accompanied by the resurgent hope that the time has come for reconciliation, an end to the divorce between development and evolution promulgated by Morgan by the contruction of an integrated framework for both disciplines. Several variant research programs have emerged that all embody this hope in different ways:[93]

(i) studies of the evolution of development,[94] perhaps intellectually the most traditional of these programs, which treats developmental features (such as life-history traits) as standard phenotypes to be studied using the usual techniques of the received view of evolution;

(ii) evolutionary developmental biology,[95] which uses phylogenetic relationships to elucidate developmental mechanisms in individual species; and

(iii) developmental evolution, intellectually the most radical of these programs,[96] which calls for the modeling of which calls for the modeling of evolution in phenotypic space (besides genotypic space) to incorporate constraints and opportunities for phenotypes; it thus denies assumption (v) of the Mendelian received view of evolution (described in sec. 1.4.1).

Only one of the many innovations of developmental evolution will be noted here: in that research program, the genotype–phenotype relationship itself becomes a target of evolutionary change. For instance, mutational bias because of physical constraints on chromosomal dynamics may lead to directional evolution in infinite populations in the absence of selection, a phenomenon not permitted by the received view.[97] The program of developmental evolution offers perhaps the most hope for constructing an evolutionary theory that gives a detailed account of phenotypic evolution (including both morphology and behavior). Although the hope of such a theory is hardly new—Darwin clearly stated it and attempted to

construct such a story for many special cases, including the functional morphology of orchids[98]—it is only since the early 1990s that there has been some plausible prospect of success.

1.4.3 From Genetics to Genomics

As chapter 14 records, the massive human and other genome sequencing projects of the 1990s have led to an unexpected transformation of the conceptual terrain of molecular biology. The sequencing projects were supposed to inaugurate a triumphant new era of genetic reductionism in both biology and medicine. Instead, the sequences that emerged exposed the impotence of sequence-gazing.[99] The study of DNA migrated from genetics to genomics, with an emphasis in the latter on computational tools and informatics. One fact has become clear: the peculiar properties of eukaryotic genomes—in particular, the G-value paradox (that there is no clear correlation between the number of genes and organismic complexity)[100]—seem to require the formulation of a framework for the study of heredity very different from classical genetics, in which genes are seen as indivisibile units generally posited to have one-to-one maps to proteins (if not more complex phenotypes).

Enthusiasts of traditional genetic reductionism have not entirely disappeared. Even in 2003, in an introductory contribution to a book entitled *Behavioral Genetics in the Postgenomic Era*,[101] Watson endorses sociobiology and genetic reductionism, and, for good measure, indulges in an ad hominem attack on the political left: ''Though human twin studies ... had provided incontrovertible evidence for genetic involvement in personality and intelligence differences [by 1975, when E. O. Wilson's *Sociobiology* was first published], those on the radical left continued to shout 'not in your genes.' Sadly, many of their students enthusiastically accepted their antigenetics diatribes, wanting futures determined by free will as opposed to genetics.''[102] The bloated rhetoric is not matched by the substantive contributions in the book, which, by and large, while maintaining an official party line of the primacy of the gene, emphasize the complexity of genotype–environment interactions and unpredictability of individual behavior from DNA sequences.

By now, views such as Watson's border on scientific irrelevance. A recent encyclopedia article notes that, in fully sequenced microbial genomes, 30–60 percent of protein-coding regions (identified as open reading frames, or

ORFs) are ''orphan'' genes to which no function can be assigned: ''sequence information alone provides no clue as to the molecular or cellular functions of these hypothetical proteins.''[103] A new framework for the study of heredity must rescue such orphans and establish functional roles for them within cells. Inspection of genes alone, or even predominantly, holds little promise of success. The future will show what the new framework for modeling heredity looks like, how it embraces development, and whether it may even be regarded as a partial connotation of the older tradition of classical genetics. Chapter 14 presents one speculative model. It is likely that a period of intellectual ferment and excitement awaits the study of heredity and development during the first few decades of the twenty-first century. The likely center of that study is the new discipline of proteomics.

1.4.4 Toward Proteomics?

The term ''proteome'' was introduced only in 1994 to describe the total protein content of a cell produced from its genome.[104] Unlike the latter, it is not even approximately a fixed feature of a cell (let alone an organism), changing as it does during development. Deciphering the proteome, and following its temporal development during the life cycle of each tissue of an organism, has emerged as the major challenge for molecular biology in the postgenomic era.[105] The discovery of universality of developmental processes at the level of cells and proteins mentioned earlier (in sec. 1.4.2) has contributed to the perceived promise of proteomics. The emergence of proteomics in the wake of the various sequencing projects signals an acceptance of the position that studying processes largely at the DNA level will not suffice to explain phenomena at the cellular and higher levels of organization. Even genomics did not go far enough; a sharper break with the past will be necessary.

In one important sense, the emergence of proteomics recaptures the spirit of early molecular biology, when all molecular types, but especially proteins, were the foci of interest, and the deification of DNA had not replaced a pluralist vision of the molecular basis for life.[106] In the late 1960s, Sidney Brenner and Crick proposed ''Project K,'' ''the complete solution of *E. coli*.'' *E. coli* (strain K-12) was selected as a model organism because of its simplicity (as a unicellular prokaryote) and ease of laboratory manipulation. Project K included: (i) a ''detailed test-tube study of the structure and chemical action of biological molecules (especially pro-

teins)'';[107] (ii) completion of the models of protein synthesis; (iii) work on the structure and function of cell membranes; (iv) the study of control mechanisms at every level of organization; and (iv) the study of the behavior of natural populations, including population genetics. Once *E. coli* was solved, biology could move on to more complex organisms.

Notice that: (i) DNA receives no preferential attention at the expense of other molecular components in Project K; and (ii) the centrality of proteins as the most important active molecules in a cell is fully recognized. Project K accepts that there is much more to the cell than DNA; it accepts that no simple solution of the cell's behavior can be read from the genomic sequence. After a generation of infatuation with DNA—which chapter 3 interprets as an infatuation with genetic, rather than physical, reductionism—the aims of proteomics return in part to the vision of biology incorporated in Project K. However, in at least one important way, that project went beyond even proteomics as currently understood: it emphasized all levels of organization, whereas the explicit aims of proteomics are limited to the protein level. The future will probably require further expansion, consistent with Project K, but proteomics is a good beginning and serves as a healthy antidote to the deification of DNA. Physical reductionism is not abandoned in this vision; rather, it presumes that, unlike the myopic genetic reductionism of the last two decades, the physical reductionism of molecular biology will produce a complete theoretical biology, at least at the level of individual organisms. This is the biology of the future. The purpose of this book is to encourage philosophical reflection on it.

Acknowledgments

Thanks are due to Justin Garson and Alex Moffett for comments on earlier drafts of this chapter. This work was supported by the United States National Science Foundation, Grant No. SES-0090036, 2002–2003.

Notes

1. See Watson and Crick (1953). Judson (1979) provides a scintillating history.

2. Pauling and Corey (1950); this is so-called α-helix model of protein structure. Unlike the DNA double helix it is not nearly universal and is only one of several structural motifs found in proteins.

3. As quoted by Olby (1974, p. 442).

4. Kohler (1973) has emphasized the point that the study of enzymes was central to the establishment of biochemistry as a discipline separate from the older organic chemistry.

5. This is true, at least in the traditional intepretations of physics, notwithstanding the many attempts to apply information theory to physics—see, for instance, Brillouin (1956).

6. See Dobzhansky (1973).

7. See, in this context, Keller (1992).

8. It may seem odd to cast semantics as a study of form rather than content. However, formal semantics involves a reduction of questions of content to those of form—as the logician, Church (1956, p. 65) insightfully noted. See also Sarkar (1992).

9. See Nagel (1949, 1951, 1961), Woodger (1952), and Hempel and Oppenheim (1948). For a detailed historical analysis, see Sarkar (1989).

10. See, for instance, Kauffman (1972) and Wimsatt (1976).

11. See Harvey (1628). Descartes, of course, muddied this view by insisting that humans were special, insofar as they had a soul besides being machines.

12. This broadening reflected the ultimate failure of mechanism within classical physics itself: gravitation, the empirically most successful theory within classical physics, required action-at-a-distance and could not, even after many repeated attempts, be given an interpretation in terms of contact interactions of material particles.

13. For a history, see, for instance, Lenoir (1982).

14. See Bohr, Hasselbalch, and Krogh (1904); for a modern review, see Riggs (1988).

15. For other forms of reductionism, see chapter 4 and Sarkar (1998).

16. See Smuts (1926). No general history of the emergence of holism in biology exists.

17. See Loeb (1912); for historical details, see Pauly (1987).

18. See J. S. Haldane (1931) and Hogben (1930).

19. Chargaff (1950); Judson (1979) particulary emphasizes the significance of Chargaff's ratios as a constraint on model-building.

20. There are exceptions—see, for instance, Bergson (1911).

21. This does not mean that these properties do not depend on some other part: the weight of a piece of matter depends on the gravitational pull of other pieces of matter, but, nevertheless, it is definable by a single parameter referring to nothing else; this type of dependence does not force a relational defintion. However, consider some entity that is a member of a set of cardinality n, and consider some property of that entity that depends on n. A (not entirely unproblematic) biological example comes from population ecology when some property of an individual—say, its fertility—may depend on the density of the population in its habitat and, therefore, on population size. A reductionist explanation need not invoke entities only at the lowest possible level of organization. Reductionist explanation of cellular behavior need not invoke only individually defined properties of molecules; it can (and routinely does) refer to those of organelles within cells. But, to be a *reductionist* explanation of a cell, it may not refer to properties defined using the entire cell or entities at higher hierarchical levels.

22. The atomic weight of the carbon in it has some bearing on exactly how a strand of DNA behaves but, in most contexts, it does not bear explanatory weight. A different isotope of carbon would not have made any relevant difference. However, in the Meselson–Stahl experiment (Meselson and Stahl 1958) to demonstrate semiconservative replication, it is exactly the atomic weight that mattered. DNA composed of one radioactive and one nonradioactive strand migrated differently in the centrifuge from how DNA composed of two radioactive or two nonradioactive strands would have. The context determines what bears explanatory weight.

23. Suppose that a biological system consists of a network of reactions and some property it has is explained by the network topology. Then one may substitute individual molecular types without altering the behavior so long as the relevant topological features are maintained. In this case, the explanation of the whole is not in terms of its parts because individual properties of the parts do not bear the explanatory weight. One of the standard features of diploid organisms is that some traits show dominance. An unsolved problem of molecular biology is to provide an empirically adequate molecular account of dominance. None is immediately forthcoming. One intriguing proposal has been that what matters are not specific properties of alleles, or the proteins produced from them, but the toplogy of the reaction networks in which they participate (see Kacser and Burns 1981 and Kacser 1987). If this model is correct, it will provide a very interesting explanation of dominance but, nevertheless, not one that is reductionist in the sense being explicated here—and it will be the first such example in molecular biology.

24. For instance, covalent bonds of ordinary chemistry have a bond strength of about 90 kcal/mole. (It takes 90 kilocalories of energy to break 1 mole [6.022×10^{23}] of these bonds.) Covalent bonds help maintain the gross structure of biological macromolecules (for instance, the backbone of the DNA double helix), but these bonds are not of much explanatory relevance for the biological behaviors that are of

interest. Ordinary ionic bonds (in nonaqeuous environments) have a bond strength of about 80 kcal/mole. These bonds are also not usually of explanatory relevance. Rather, the bonds that are relevant are hydrogen bonds, ionic bonds in aqueous environments, and what are called hydrophic bonds but which are not actual bonds. They represent molecular regions brought into contiguity by the hydrophobic effect. In the aqueous cellular environment, hydrogen bonds have a strength of about 1 kcal/mole, and ionic bonds about 4 kcal/mole. Hydrophobic ''bonds'' have a strength of about 1 kcal/mole.

25. The term ''function'' is being used here because it is ordinarily so used in molecular biology—the philosophical significance of such ascriptions of function will be discussed in sec. 1.2.

26. Perhaps the clearest statement of such a position is Oppenheim and Putnam (1958).

27. Monod, Changeux, and Jacob (1963); the discussion in the text is based on Monod, Wyman, and Changeux (1965).

28. See, for instance, von Bertalanffy (1975).

29. See Jacob et al. (1960); the account here follows Monod (1971).

30. Perhaps, if, during the next few decades, proteomics becomes central to molecular biology, as many have predicted, proteins will once again return to center stage.

31. See, for instance, Hull (1972, 1974) and Kitcher (1984).

32. See, for instance, Kitcher (1984).

33. Schaffner (1974) was the first to emphasize this important point, while defending the view that what was (nevertheless) achieved constituted intertheoretic reduction.

34. Sarkar (1998, chapter 6) elaborates this point in detail.

35. Nagel (1961) explicitly recognized this elementary logical point though it was lost by almost all subsequent advocates of models of intertheoretic reduction. Sarkar (1998, chapter 2) emphasizes this point.

36. See Tauber and Sarkar (1992, 1993), which are highly critical of blind sequencing.

37. For a survey, including references to the literature, see Sarkar (1998, chapter 1).

38. See Pigliucci (2001) for an overview.

39. Among other things, Waterton, during his South American travels, transported a fourteen-foot ''Coulacanara'' snake in wreaths around his body and rode a cayman

along the bank of a river. For more on Waterton's eccentricities, see Barber (1980, chapter 7).

40. Waterton does not give scientific names of the species he describes. This identification is based on the geographical distribution of the various species of sloth (Eisenberg 1989, p. 56).

41. Waterton (1973, pp. 5–6).

42. Ibid., p. 93.

43. See Goffart (1971).

44. See Strickberger (2000, p. 382).

45. Human sweat is produced by eccrine glands and has low salt and almost no fat content compared to other mammals in which sweat is produced by apocrine glands. The low mineral content of human sweat and the general hairlessness of the human body ensure rapid evaporation of the sweat. The result is a very efficient way of cooling the body. See Baker (1992) for more detail.

46. Note, however, that this leaves open the logical possibility that functional attributions can also be made in other contexts, that is, not necessarily in response to a question of origin.

47. Mayr (1976, pp. 362–363).

48. See Wimsatt (1971), Wright (1973), Millikan (1989), and Neander (1991) for discussions of variants.

49. See Bigelow and Pargetter (1987).

50. Thus, the etiological view may fall back equally on adaptations and exaptations. See Gould and Vrba (1982).

51. However, this feature does leave the propensity account open to the charge of vagueness: at present there is no clear delimitation of what may be considered to be functional (see Millikan 1989).

52. Mayr (1976, p. 360).

53. To take such usage into account, some philosophers have argued for a ''causal role'' theory of function—see Cummins (1973), Godfrey-Smith (1993), and Amundson and Lauder (1994). As is often the case, the term ''causal'' here does no work: no particular explication of causality, or even a presumption that causal talk is necessary or justified, is required in the ''causal role'' theory.

54. Technically, the problem here is more with the propensity theory of narrow-sense functions than with the etiological theory since such effects are trivially no longer adaptive. But even the etiological theory has to explain why these effects

should be regarded as having arisen through selection since a female that no longer had a heart for pumping blood after the postreproductive period would be no more selectively favored than the one that did. (At best, the etiological theory can say that some selected features persist because of accident—but this brings the etiological theory close to the ''broad-sense'' account of function explicated later in the text.)

55. See Gould and Lewontin (1979) and Maynard Smith (1978).

56. For a similar account, see Nagel (1961, pp. 410–414). Note the contrast to Cummins (1973) who puts no restriction on what features (including potentially pathological behaviors) may be invoked when making functional ascriptions. The account given here is much more restrictive.

57. However, Wimsatt (1972) argues that such a position is too broad since it would allow function ascriptions to parts of inanimate entities such as autocatalytic reactions. From the perspective of the position being advocated here, this is a virtue, because there is no principled distinction between living and nonliving matter.

58. This was blind sequencing—see Tauber and Sarkar (1992, 1993). There were many problems with the original project, including the fact that the concept of *the* human genome is incoherent given the ubiquitous variation of intraspecific DNA sequences. See Sarkar and Tauber (1991).

59. See, for instance, Gilbert (1992).

60. See Watson (1968).

61. Sarkar (1998) emphasizes the point that classical genetics was a formal science based on statistical laws. This was explicitly recognized by the geneticists—see chapter 3 (sec. 3.2) of this volume. The best account of the conceptual structure of classical genetics in the 1940s, including the biochemical aspects referred to in the next paragraph, is Haldane (1942).

62. See Schrödinger (1944). There have been many historical assessments of this book; for a conceptual assessment of what it achieved, see Sarkar (1991).

63. See Bonner (1965, p. v).

64. At least four books use ''language'' and ''DNA,'' ''genes,'' or ''genetics'' in their titles—Beadle's (1966) *The Language of Life: An Introduction to the Science of Genetics*; Berg and Singer's (1992) *Dealing with Genes: The Language of Heredity*; Jones's (1994) *The Language of the Genes*; and Pollack's (1994) *Signs of Life: The Language and Meanings of DNA*. Restricting attention to just the last five years (since 1998), at least thirteen books invoke the ''language'' of ''genes''—Dikotter (1998, p. 73); Hademenos and Fried (1998, p. 98); Mawer (1998, p. 115); Coen (1999, pp. 37, 66, 54); Gross (1999, p. 62); Mahoney (1999, p. 166); McGinn (1999, p. 225); Enriquez (2001, p. 5); Fortey (2000, p. 87); Lock, Young, and Cambrosio (2000, p. 24); Martineau (2001,

p. 29); Bellavite, Signorini, and Steele (2002, p. 136); and Little (2002, p. 18). At least fifty books from the same period refer to DNA as providing a language.

65. See Hoffmeyer (1996) and Merrell (1996). Emmeche (1999) tries to address the criticisms made here and in chapter 9.

66. Mayr (1961); see chapter 14 for further discussion.

67. Jacob and Monod (1961, p. 354). For an interesting historical commentary, see Keller (2000, chapter 3).

68. Monod (1971, p. 77).

69. See Gilbert (1992).

70. This reconstruction of evolution by natural selection is a modification of the one originally proposed by Lewontin (1970).

71. Given that Darwin did not have any initial model of heredity, it was perhaps inevitable that the model of evolution in the 1859 (first) edition of the *Origin* was neutral about the nature of heredity.

72. See, for instance, Johannsen (1909).

73. This date (the late 1920s and early 1930s) is not universally accepted by historians, some of whom place it a decade later—see Sarkar (2004) for a critical perspective on the historiography of the received view. For the work that established the received view of evolution, see, in particular, Fisher (1930), Wright (1931), and Haldane (1932). Provine (1971) provides a succinct account of the developments until 1932. There is no reliable comprehensive history of later developments in evolutionary biology.

74. Other models of heredity, for instance, haploidy, sex-linked inheritance, and polyploidy, raise technical complications but no new conceptual problems.

75. From a historical perspective, it is also more accurate to describe the received view as Mendelism rather than Darwinism. Bowler (1989) emphasizes this point.

76. Note that this formulation is supposed to avoid the following problem: in chapter 12, a mutation is defined as random ''if and only if the probability of its occurrence in an environment has no correlation with the fitness of the phenotype associated with it in that environment.'' However, this definition falls afoul of the fact that most mutations are harmful, and that, consequently, there will be a negative correlation between mutations and the fitness changes they induce. The new formulation given in the text is supposed to be immune to this objection.

77. See, for instance, Jablonka and Lamb (1995). Despite the unfortunate use of ''Lamarckian'' in its title, this book remains an important theoretical contribution to evolutionary biology.

78. One of Darwin's immediate followers, George Romanes, fully appreciated this point, coining the term "neo-Darwinism" to distinguish between the position that denies the inheritance of acquired characteristics from Darwinism proper. See Romanes (1896).

79. See McClintock (1951).

80. See the discussion in Comfort (2001).

81. See Braam and Reznikoff (1998).

82. See Gershenson (1928) and Sandler and Novitski (1957).

83. See Lyttle (1993) for more details of the mechanisms being discussed.

84. See Lindegren (1953) and Hurles (2002).

85. This is the Holliday junction model, also used to explain recombination through crossovers without conversion. See Holliday (1964).

86. The other is unequal crossover, which can act only on tandemly duplicated repeats.

87. This was originally established by Lewontin and Hubby (1966) for *Drosophila pseudoobscura* and Harris (1966) for humans.

88. See Kimura (1968) and Haldane (1957).

89. See King and Jukes (1969), entitled "Non-Darwinian Evolution."

90. Kimura (1983) presents an early synthesis of the neutral theory.

91. As a result, for several generations, biology, especially in the West, ignored phenotypic plasticity (as, for instance, represented by variable norms of reaction)—see Sarkar (1999) for further discussion of this issue.

92. These are: (i) transmembrane tyrosine kineasas; (ii) receptors linked to cytoplasmic tyrosine kinases; (iii) transmembrane serine/threonine kinases; (iv) transmembrane protein phosphatases; (v) Wnt receptors; (vi) IL-1, toll receptors; (vii) G-protein linked receptors; (viii) hedgehog receptors; (ix) Notch/Delta; (x) nuclear hormone receptors; (xi) integrins; (xii) ligand-gated cation channels; (xiii) gap junctions; (xiv) nitric oxide receptors; (xv) cadherins; and (xvi) receptor guanylate cyclases. See Gerhart and Kirschner (1997, pp. 102–103).

93. For a historical discussion, see Sarkar and Robert (2003).

94. See, for instance, Purugganan (1998).

95. See Hall (1998, 2000) and Arthur (2002) for a slightly varying statement of this program.

96. See Wagner (2000, 2001) for a statement of the program.

97. See Stadler et al. (2001) and Garson, Wang, and Sarkar (2003). Of course, what still remains subject to debate is the relative significance of such a departure from the received view.

98. See Darwin (1862); Hall (1998) and Sarkar and Robert (2003) provide histories.

99. See, for instance, Stephens (1998).

100. See Hahn and Wray (2002). The G-value paradox is the genomic analog of the earlier C-value paradox, that there is no correlation betwen organismic complexity and the size of the geonome (measured by the length of DNA sequences)—see Cavalier-Smith (1985). That paradox was resolved by the discovery of ubiquitous noncoding DNA in euklaryotic genomes.

101. See Plomin et al. (2003); the book's contributions come from a 2001 conference and are already outdated.

102. Watson (2003, p. xxi), referring to Wilson (1975). It is peculiar that the reference is to *Not in Our Genes* (Lewontin, Rose, and Kamin 1984), an author of which was one of the most prominent geneticists of his generation.

103. See Hung and Kim (2000), writing in the *Nature Encyclopedia of Life Sciences*.

104. See Williams and Hochstrasser (1997).

105. For an accessible overview, see Hung and Kim (2000).

106. For more on the deification of DNA, see Tauber and Sarkar (1992, 1993) as well as Lewontin (1992).

107. See Crick (1973, p. 67); this is the only published account of the project initially proposed to the European Molecular Biology Organisation (EMBO) by Brenner and Crick.

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