Beyond Theoretical Reduction and Layer-Cake Antireduction

How DNA Retooled Genetics and Transformed Biological Practice

C. Kenneth Waters

Minnesota Center for Philosophy of Science,

Department of Philosophy,

University of Minnesota

1. Introduction

Watson and Crick's discovery of the structure of DNA led to developments that transformed many biological sciences. This much seems obvious. But what were the relevant developments and how did they transform biology? Typically, it is taken for granted that the developments were theoretical. According to the popular view, which is frequently advanced by scientists and science writers, a new fundamental theory of molecular biology, constructed in the decades following Watson and Crick's discovery, transformed biology by providing a basis for explaining a wide variety of phenomena. Some philosophers agree with this assessment. They argue that explanations provided by this DNA-centered theory "reduce" previous explanations that focused on entities at higher levels of organization. Other philosophers disagree. Some claim that reductionism failed biology because some phenomena are best explained at levels of organization higher than the molecular level. In this chapter, I will argue that discussions about whether molecular biology provides the fundamental theoretical basis for transforming biological sciences is based on a false premise. The developments following Watson and Crick's discovery that mattered were not primarily theoretical. It is not the fundamental theory of molecular biology, if indeed such a theory exists, that revolutionized genetics and transformed biological sciences. What changed biology so dramatically was a retooling of the investigative strategies used in genetics.

Much of the philosophical discussion concerning what Watson and Crick's discovery did for biology can be organized around two opposing views:

theoretical reductionism and layer-cake antireductionism. As is often the case with philosophical dichotomies, the most compelling arguments in this literature are those aimed against one or the other position, not those aimed in favor of a position. This suggests that it is time to move beyond the dichotomy. But we shouldn't move too quickly; there are lessons to be learned from the reductionism debate. The first aim of this chapter is to diagnose where the two opposing views go astray. My diagnosis suggests that philosophical attention should be shifted from theory to practice. The second aim is to identify what Watson and Crick's discovery did for the practice of genetics and to explain how the resulting changes in genetics transformed practice throughout many biological sciences.

Theoretical reductionism alleges that the relevant developments in genetics were a theoretical triumph. Before Watson and Crick, genetics was a science that explained patterns of trait transmission by appealing to a classical theory of the gene. The classical theory included the idea that genes are located on chromosomes, various principles about chromosomal mechanics, and principles about relationships between genes and outward phenotypic traits. Watson and Crick's discovery, according to this view, led to a deeper and more fundamental, molecular-level theory. The new theory allegedly improves upon higher-level explanations of the classical theory by explaining its core theoretical principles in terms of molecular processes.

The picture of genetics that emerges from the view called "theoretical reductionism" is of a two-tiered science: an upper tier of theoretical principles associated with the classical theory of genetics and a lower tier of theoretical principles about molecular processes involving DNA. This picture can be extended to all of biology: A fundamental theory of biology centered on DNA deepens biological knowledge because its theoretical principles can ultimately explain or reduce the explanatory principles of all higher-level theories. The research program is to transform biology by reducing all biological theorizing to the fundamental theory associated with molecular biology. The success of DNA-based research, on this account, follows from the fundamental truth that all biological processes are ultimately directed or programmed by genes and DNA.

I call the opposing view "layer-cake antireductionism." It also begins with the premise that Watson and Crick's discovery led to a new DNA-based theory. But the phenomena explained by the DNA-based theory, according to this view, are not the same phenomena explained by the higher-level theory of classical genetics. Moreover, the molecular theory, which according to antireductionism is *not* more fundamental, does not explain the central theoretical principles of the higher-level theory; what it explains are peripheral principles. Hence, the molecular theory couched in terms of DNA does not actually improve upon the explanations of classical genetics; it contributes to genetics by adding explanations of phenomena that were not previously explained.

The picture of genetics that emerges from this antireductionist view is also of a two-tiered science: an upper tier of theoretical principles aimed at explaining transmission phenomena and a lower tier of theoretical principles aimed at explaining other phenomena, such as the replication and expression of the genetic material (i.e., DNA). This picture, like the reductionist one, can also be extended to all of biology: The sciences of biology are like the layers of a cake, with each layer aimed at explaining the phenomena that are best explained at the level of organization corresponding to that layer. On this view, it cannot be the case that all life processes are directed by DNA because many phenomena cannot be explained at the molecular level. The take-home lesson of layer-cake antireductionism is that the DNA revolution is deeply problematic because it is based on a falsehood, not on a fundamental truth. It has been argued that a more-balanced research program that did not focus so much attention on genes and DNA would yield a truer, more holistic, and multileveled understanding of life.[1]

It is worth noting two features that theoretical reductionism and layer-cake antireductionism share. First, both advance "layer-cake" pictures. Not all reductionists accept the layer-cake image (e.g., Weber 2005), and some antireductionists seem more interested in advancing holism than multileveled holism (e.g., various contributors to Oyama et al. 2001). Nevertheless, many philosophers cling to the idea that biology is organized into separate sciences, each of which is focused on a particular level of organization. The second feature that these opposing views share is that they are almost exclusively focused on theory. Theory bias is ubiquitous, not just among theoretical reductionists and layer-cake antireductionists, but among philosophers of science in general.[2] Removing this bias will enable us to look beyond the layer-cake image and see what Watson and Crick's discovery did for genetics and how the resulting development in genetics transformed scientific practice throughout much of biology.

This chapter starts with a review of the relevant theories of classical genetics and molecular biology. I begin my diagnosis of the reductionism debate by showing that the chief reasons offered in favor of layer-cake antireductionism do not correspond to the realities of genetics, and hence the antireductionist critique of theoretical reductionism is mistaken. Then I turn my attention to theoretical reductionism and show that the real problem with this view is that it fails to identify developments that are vital to genetics or

[1] This theme runs throughout much of the most-recent philosophical literature on molecular biology, even literature that does not directly engage the views about reductionism discussed here (e.g., see Oyama et al. 2001).

[2] Hacking (1983) identifies a general theory bias in history and philosophy of science and argues that it provides a distorted account of science. Rheinberger (1997) avoids this theory bias in his account of the historical development of molecular biologists' understanding of the expression of DNA.

relevant to the transformation of other biological sciences. My diagnosis will show that layer-cake antireductionism and theoretical reductionism lead philosophical attention astray by focusing on explanatory theories rather than research practices. Turning my attention to practice, I describe how research in classical genetics was organized by an integration of modest explanatory reasoning (associated with the transmission theory) and bold strategies for investigating phenomena, including the "genetic approach." Next, I show how the genetic approach has changed since Watson and Crick's discovery by examining a recent gene-centered investigation. This example illustrates how molecular biologists have retooled genetics by integrating the genetic approach of classical genetics with physically based methods of biochemistry and new methods based on recombinant DNA and RNA interference technologies. I conclude that it is this kind of retooling, not the construction of a new fundamental theory, that has transformed so much of biology.

2. The basic theory of classical genetics

The basic theory that layer-cake antireductionists and theoretical reductionists associate with classical genetics explains the transmission of traits from parents to offspring. Classical geneticists, starting with Thomas H. Morgan (1926) and his collaborators, explained the transmission of phenotypic differences by following the distribution of gene differences from generation to generation and attributing the presence of alternative phenotypic traits to the presence of alternative forms of genes (called "alleles"). Their theory depended on the idea that genes are located in a linear fashion on chromosomes, on principles about the transmission of genes that were grounded in cytological processes such as meiosis, and on the principle that differences in genes cause differences in phenotypes.

I will illustrate the classical mode of explanatory reasoning with a simple historical example involving the fruit fly *Drosophila melanogaster*. The mode of reasoning illustrated here is still an important part of genetics today. The experiment entailed breeding flies for several successive generations to produce distinctive inheritance patterns involving several different phenotypic traits (such as wing form), each of which was associated with a different gene. The basic aim of the experiment was to investigate the precise locations of the underlying genes. But it is unnecessary for my purposes in this section to describe the investigative reasoning or the intricate explanation of the complex inheritance patterns involving the transmission of several traits over a half dozen generations. It suffices to examine only a fragment of the explanation involving the transmission of one of the traits over a single generation.

Let us examine how Morgan explained the transmission of eye color when red-eyed females crossed with purple-eyed males produced all red-eyed offspring. Investigators knew from previous experiments that red eye was

dominant to purple eye. That is, they knew that flies containing a copy of the purple allele on one of their chromosome IIs (or "second chromosomes") and a copy of the red ("wild-type") allele on their other chromosome II (pr / +) exhibited the trait associated with flies homozygous for the red allele (+ / +). They also knew that all female parents used at this stage of the experiment were homozygous for the red-eye allele (+ / +), and all males were homozygous for the purple-eye allele (pr / pr).

The explanation of why crossing these red-eyed females with purple-eyed males yielded only red-eyed progeny proceeds, as do all classical explanations of inheritance patterns, in two stages. The first stage accounts for the distribution of genes and goes as follows: Each offspring received one copy of chromosome II from each parent. The maternally derived chromosomes must have contained the wild-type allele (since both second chromosomes of every female parent used in the experiment contained the wild-type allele). The paternally derived chromosomes must have contained the purple allele (since both second chromosomes of every male parent contained the purple allele). Hence, all offspring were heterozygous (pr / +).

The second stage of the explanation uses the result of the first stage, the genotypic makeup of the progeny, to draw an inference about their phenotypic appearance. Since all offspring were heterozygous (pr / +), and since purple is recessive to wild-type, all offspring had red eye color (the wild-type character).

This explanation depends only on the ideas that copies of the gene are distributed from generation to generation and that a difference in the gene (i.e., the difference between pr and +), whatever this difference is, causes the phenotypic difference in eye color. The idea that the gene is the difference maker needs to be qualified: Differences in the gene cause phenotypic differences in particular genetic and environmental contexts. This idea is so crucial and so often overlooked that it merits articulation as a principle:[3]

> *Difference principle*: Differences in a classical gene cause uniform phenotypic differences in particular genetic and environmental contexts.

It is also worth noting that the difference principle provides a means to explain the transmission of phenotypic characteristics from one generation to the next without explaining how these characteristics are produced in the process of an organism's development. The classical theory does not include and did not depend upon ideas about what genes are, how genes are replicated, what genes do, or how differences in genes bring about differences in phenotypic traits.

[3] See Waters 1994 for a fuller discussion.

3. The basic theory of molecular biology

The basic theory that emerged after Watson and Crick's discovery of the structure of DNA, which theoretical reductionists said would one day reduce the theory of classical genetics, provides an understanding of what classical genetics did not. It offers ideas about what genes are, how genes are replicated, what genes do, and how differences in genes bring about differences in phenotypic traits. According to this theory, genes are linear sequences of nucleotides in the double-helical molecules of DNA. Of course, not every string of nucleotides in DNA is a gene; segments of DNA are identified as genes according to what they do. Roughly speaking, genes serve as templates in the synthesis of RNA molecules. The result is that the linear sequence of nucleotides in a newly synthesized RNA molecule corresponds to the linear sequence of nucleotides in the DNA segment that served as the template.

Different RNA molecules play different functional roles in the cell, and an important class of RNA molecules, called messenger RNA (mRNA), play the role of template in the synthesis of polypeptide molecules. Newly synthesized polypeptides are linear sequences of amino acids that constitute proteins, and proteins play a wide variety of functional roles in the cell and organism (and environment). The ability of a polypeptide to function in specific ways depends on the linear sequence of amino acids of which it is formed. And this linear sequence corresponds to the linear sequence of triplets of nucleotides in RNA (codons), which in turn corresponds to the linear sequence of nucleotides in segments of DNA. This latter segment is the *gene* for that polypeptide.[4]

It is important to distinguish the *basic* theory of molecular biology, sketched in the paragraphs above, from *fundamental* theories that all biological processes are ultimately directed or programmed by genes (I will return to this idea in section 8). The basic theory, which states that genes are segments in a DNA double helix, suffices to explain how genes are replicated. Genes are replicated when the paired chains of a DNA molecule unwind and new chains are formed alongside the separating strands by the pairing of complementary nucleotides. When the process is complete, two copies of the original double helix have been formed, and hence the genes in the original DNA molecule have been effectively replicated.

The basic theory also explains how differences in genes can bring about differences in phenotypic traits. A difference in the nucleotide sequence of a gene will result in the difference in the nucleotide sequence of RNA molecules. Differences in mRNA molecules can in turn result in a difference in the amino acid sequence of a polypeptide. Differences in the linear sequences of amino acids in polypeptides (and in the linear sequences of nucleotides in functional RNA molecules) can affect the roles they play in the cell and organism, sometimes having an effect that is observable as a phenotypic difference. The

[4] See Waters 1994 and 2000 for a more-detailed account.

mutations (differences in genes) identified by the Morgan group (e.g., the purple-eye mutation) have been routinely identified as differences in nucleotide sequences in DNA.

4. Layer-cake antireductionism

Layer-cake antireductionism is the dominant view among philosophers interested in this debate, so it is appropriate to begin with this view.[5] According to layer-cake antireductionism, classical genetics will never be reduced, eliminated, or explained away because its central theory explains kinds of phenomena that are best explained at the level of classical genes and chromosomes. There are a number of arguments in the philosophical literature offered in support of this kind of view, but I will focus on two. First, it is claimed, genes cannot be conceived at the molecular level. Hence, explanations of classical genetics, which rely on principles about genes, will never be explained in terms of molecules. This argument alone does not rule out the possibility that classical genetics will be eliminated. Perhaps explanations couched in terms of genes will be discarded and all of the phenomena of genetics will be explained in terms of the physicochemical principles of molecules such as DNA, RNA, and polypeptides. Antireductionism rules out this possibility with a second claim: Classical genetics offers objectively better explanations of certain transmission phenomena than any molecular-level explanation could ever provide.

4.1. Two unconnectable tiers of theoretical discourse

The most rigorous formulation of the unconnectability idea can be found in the early writings of Alex Rosenberg, who formerly contended that there is an unbridgeable conceptual gap between the classical and molecular theories of genetics (1985, 1994). In support of this claim, he argued that relations between the gene concept of classical genetics and the concepts of molecular genetics are hopelessly complicated "many-many" relations that will forever frustrate any attempt to systematically connect the two theories. Rosenberg began his analysis by pointing out that, in classical genetics, genes are identified by way of their phenotypic effects. Classical geneticists identified

[5] Kitcher (1984) offers the fullest account of this position, which is reprinted in prominent anthologies without rejoinder (e.g., in volume 7 of *The Philosopher's Annual* (Atascadero, Calif.: Ridgeview Publishing Company, 1984); in Richard Boyd, Philip Gasper, and J. D. Trout (eds.), *Readings in the Philosophy of Science* (Cambridge, Mass.: Bradford Books, MIT Press, 1991); and in Martin Curd and Jan Cover (eds.), *Philosophy of Science: The Central Issues* (New York: Norton, 1998). Although not everyone agrees with Kitcher's entire account, various aspects of the position are supported by considerations that can be found throughout much of the literature. For example, see Wimsatt (1976a, 1976b), Darden and Maull (1977), Burian (1986, 1996), Collier (1988), and Dupré (1993).

the gene for purple eye color, for example, by carrying out carefully orchestrated breeding experiments and following the distribution of eye-color phenotypes in successive generations of a laboratory population. The reason classical genetics will never be reduced to a molecular-level science, according to Rosenberg (1985), is that there is no manageable connection between the concept of a Mendelian phenotype and that of a molecular gene:

> *The pathway to red eye pigment production begins at many distinct molecular genes and proceeds through several alternative branched pathways.... The pathway from the [molecular] genes also contains redundant, ambiguous, and interdependent paths. If we give a biochemical characterization of the gene for red eye color either by appeal to the parts of its pathway of synthesis, or by appeal to the segments of DNA that it begins with, our molecular description of this gene will be too intricate to be of any practical explanatory upshot.* (Rosenberg 1985, 101)

Rosenberg concluded that, since the relation between molecular genes and Mendelian phenotypes is exceedingly complex, the connection between any molecular concept and the Mendelian gene concept must also be exceedingly complex, thereby blocking any systematic, reductive explanation of classical genetics in terms of molecular-level theory.[6]

4.2. Why transmission phenomena are (allegedly) best explained at the chromosomal level

The idea that the phenomena explained by the upper-tier theory of classical genetics cannot be better explained by the lower-tier theory of molecular genetics is clearly articulated by Philip Kitcher and can be found in several of his writings (e.g., Kitcher 1984, 1989, 2001). Following David Hull (1974), Kitcher assumes that classical genetics is transmission genetics. The classical theory explains the transmission of phenotypic traits, not the connection between genes and phenotypes nor the development of phenotypic traits in individual organisms. So, the special domain of phenomena explained by the upper-tier theory is the domain of transmission phenomena, the patterns of inheritance discussed in section 2 above. And transmission phenomena, on Kitcher's account, are best explained at the level of cytology:

> *The distribution of genes to gametes is to be explained, not by rehearsing the gory details of the reshuffling of the molecules, but*

[6] Rosenberg has subsequently changed his position on this issue, largely on the grounds that technical advances in information storage and processing "may substantially enhance our capacity to understand macromolecular processes and their combinations" (Rosenberg 2006, 14).

> *through the observation that chromosomes are aligned in pairs just prior to the meiotic division, and that one chromosome from each matched pair is transmitted to each gamete*. (Kitcher 1984, 370)

Kitcher states that the pairing and separation of chromosomes belong to a natural kind of pair-separation process; that is heterogeneous from the molecular perspective because different kinds of forces are responsible for bringing together and pulling apart different paired entities. The separation of paired entities, he claims, "may occur because of the action of electromagnetic forces or even nuclear forces; but it is easy to think of examples in which the separation is effected by the action of gravity" (Kitcher 1984, 350). For this reason, he concludes, the classical transmission theory will never be reduced or eliminated by the lower-level theory of molecular genetics. The lower-level theory, Kitcher says, is important because it explains what the classical theory cannot (see section 2). But what the classical theory can explain is not better explained by the molecular theory.

4.3. Extending the layer-cake image

The image of genetics that emerges from the antireductionist literature is of a two-tiered science composed of two discrete theoretical discourses, one grounded in principles about entities at the cytological level (such as chromosomes) and the other grounded in principles about entities at the molecular level (such as nucleotide sequences in DNA). This image is then extended to all of biology. Again, Kitcher is the most articulate proponent:

> *[A]nti-reductionism emerges as the thesis that there are autonomous levels of biological explanation. Anti-reductionism construes the current division of biology not simply as a temporary feature of our science stemming from our cognitive imperfections but as the reflection of levels or organization in nature. Explanatory patterns that deploy the concepts of cytology will endure in our science because we would foreswear [sic] significant unification (or fail to employ the relevant laws, or fail to identify the causally relevant properties) by attempting to derive the conclusions to which they are applied using the vocabulary and reasoning patterns of molecular biology*. (Kitcher 1984, 371)

According to layer-cake antireductionism, different biological sciences relate to particular levels of organization. Sciences aimed at levels of organization higher than molecular biology will endure, the antireductionists claim, because some phenomena are better explained at those higher levels of organization.

4.4. What's wrong with layer-cake antireductionism

The chief arguments offered in favor of layer-cake antireductionism in genetics fail to correspond to the actual science. This should have been apparent in the mid-1980s and is certainly evident today. Consider the argument that the two tiers of discourse corresponding to classical and molecular genetics cannot be systematically connected because claims made in terms of genes cannot be connected to claims couched in terms of DNA. This argument rests on the assumption that, in classical genetics, the relationship between a gene and a phenotypic trait is taken to be simple. But classical geneticists knew better. Consider what Sturtevant, one of Morgan's star students and collaborators, had to say about genes and eye color:

> *The difference between normal red eyes and colorless (white) ones in Drosophila is due to a difference in a single gene. Yet red is a very complex color, requiring the interaction of at least five (and probably of very many more) different genes for its production. And these genes are quite independent, each chromosome bearing some of them. Moreover, eye-color is indirectly dependent upon a large number of other genes such as those on which the life of the fly depends. We can then, in no sense identify a given gene with the red color of the eye, even though there is a single gene differentiating it from the colorless eye. So it is for all characters.* (quoted from Carlson 66 69; my emphasis)

Sturtevant's quotation suggests that the relationship between gene and eye color in classical genetics exhibited the same complexity that Rosenberg discussed at the molecular level (compare Sturtevant's quotation to that of Rosenberg 1985 presented in section 4.1). It is not the case that the genotype-phenotype relationships appear simple and uniform at the level of classical genetics and complicated and disunified at the molecular level. The situation appears similarly complex at both levels of analysis.

Classical genetics nevertheless finds a simple way to explain transmission phenomena by appealing to the difference principle, according to which particular *differences* in particular genes cause particular *differences* in phenotypic traits in particular contexts (see section 2). Sturtevant alludes to this principle in the first sentence of the quotation above and again in the emphasized clause. So the question arises: Can this relationship be captured at the molecular level? And the answer is yes. The differences used by classical geneticists to explain inheritance patterns have been routinely identified at the molecular level by contemporary geneticists.

The claim that the phenomena explained by classical genetics cannot be better explained at the molecular level fares no better. Antireductionism claims that the cytological level allegedly provides the best level of explanation

because explanations at this level uniformly account for a wide range of cases that would look heterogeneous from a molecular perspective. Kitcher claims that meiosis exemplifies this kind of situation. The uniformity of pair-separation processes is evident at the cytological level, but is lost in the gory details at the molecular level where the process "may occur because of the action of electromagnetic forces or even of nuclear forces" (Kitcher 1984, 350). But it is unclear what Kitcher has in mind. The molecular mechanisms underlying the pairing and separation of chromosomes are remarkably uniform in creatures ranging from yeast to human beings; it is not the case that some involve electromagnetic forces and others involve nuclear forces. Kitcher's claim that "it is easy to think of examples in which the separation is effected by the action of gravity" has no basis in what molecular biologists have learned about the pairing and separation of chromosomes. In fact, in the two decades since Kitcher's "Tale of Two Sciences" was first published, biologists have learned a lot about the pairing and separation of chromosomes and what they have learned does not support his contention that the processes are realized by different forces in different cases.

Meiosis is an unpromising candidate to advance the idea that what appears uniform at the level of classical genetics turns out to be heterogeneous at the molecular level. But this idea is illustrated by other genetic phenomena. Consider the phenomenon of genetic dominance. In classical genetics, examples of complete dominance are treated alike for the purposes of explaining transmission phenomena. But contemporary genetics reveals that there are several very different mechanisms underlying different instances of dominance. According to Kitcher's unificationist theory of scientific explanation, the classical account of dominance provides an objectively better basis for explaining transmission phenomena because it provides a more unified organization of the phenomena. But this would imply that the shallow explanations of classical genetics are objectively preferable to the deeper explanations provided by molecular theory.

In sum, layer-cake antireductionism holds that biology will always be organized into layers with the theories of each layer representing different levels of organization. The layers will allegedly endure because some phenomena are, objectively speaking, best explained in terms of one level of organization and other phenomena are best explained at higher or lower levels. Genetics is often cited as a case in point. Classical genetics explains transmission patterns in terms of cytological processes, such as meiosis, which antireductionists argue cannot be adequately represented or explained at the molecular level. In contrast to these claims, molecular biologists are investigating processes, such as meiosis, at the molecular level. When one examines the results of this research, the antireductionist suggestion that these investigations are not producing better explanations of chromosomal processes, such as the pairing and separation of chromosomes, is simply false. Focusing attention at the molecular level, and on DNA, has been extremely fruitful for

research across a broad range of biological phenomena, including the phenomena behind the core theoretical principles of classical genetics. Layer-cake antireductionism cannot offer a tenable account of what happened to biology after Watson and Crick discovered the structure of DNA.

5. Theoretical reductionism

Layer-cake antireductionism emerged in response to Kenneth Schaffner's claim that genetics was in the process of being reduced to physics and chemistry (1969). He characterized this alleged reduction in terms of Thomas Nagel's model of theoretical reduction. According to Nagel's model, the reduction of one science to another science entails the reduction of the central *theory* of one science to the central *theory* of the other. Nagel believed that this kind of reduction led to progressive changes in scientific knowledge, including the establishment of more-accurate experimental laws that can explain a broader range of facts and the discovery of surprising connections among these laws. Schaffner claimed that this kind of reduction was currently taking place in biology where a theory aimed at a higher level of organization was being reduced to a theory aimed at a lower level of organization. The higher-level theory was the transmission theory of classical genetics; the lower-level theory was a newly emerging theory of molecular genetics.

Nagel described the ideal of theoretical reduction by specifying two formal requirements satisfied by successful reductions. In specifying these requirements, he made two assumptions. First, he assumed that theories consist of "laws." Second, he assumed that explanations work by using laws to derive statements describing the phenomena to be explained.

One of the two formal requirements set out by Nagel held that the "laws" of the reduced theory must be derivable from the laws and associated coordinating definitions of the reducing theory. This deducibility requirement was intended to capture the idea that the explanatory principles (or laws) of the reducing theory ought to explain the explanatory principles (or laws) of the reduced theory. Nagel's second formal requirement, the connectability requirement, was that all essential terms of the reduced theory must either be contained within or be appropriately connected to the terms of the reducing theory by way of additional assumptions.

Although nearly all discussions of Nagel's model focus exclusively on these formal requirements, Nagel himself acknowledged that the formal conditions "do not suffice to distinguish trivial from noteworthy achievements" (Nagel 1961, 358). Nagel's informal discussion of the thermodynamics case indicates that noteworthy reductions are marked by fruitfulness in inquiry.

Schaffner (1969) modified Nagel's formal model by incorporating the idea that what the reducing theory actually derives (and hence explains) is a

corrected version of the reduced theory, not the original form of the theory. He argued that this revised model better captures reductions in the physical sciences. He intended to apply his model to biology by showing how the transmission theory of classical genetics was being corrected and reduced to a new theory of molecular genetics.

Schaffner claimed that, as the molecular theory of genetics developed, the laws of classical genetics, such as the law of dominance, would be revised in ways such that they would be derived from physicochemical laws of the molecular theory. His idea was that the revised laws would be more accurate than the laws postulated by classical geneticists. Schaffner was not arguing that the classical theory would be eliminated; he was arguing that it would be made more accurate and that it would be explained in terms of physicochemical principles. Hence, he was advancing a layer-cake view. In subsequent works, Schaffner has maintained, in the face of considerable criticism,[7] that *in principle* at least, the project of theoretical reduction in genetics could be completed.

5.1. What's wrong with the theoretical reductionist account of genetics

The problem with the theoretical reductionist account is that it focuses on something that is peripheral to advancing scientific research. Geneticists are not interested in explaining the principles of classical genetics in terms of physicochemical principles of molecular biology. As Schaffner admits:

> *Jacob and Monod did not, in their research program, aim initially at providing chemical characterizations of the entities with which they worked, even though methods for at least beginning such characterizations were available. Such chemical analyses were extremely tedious and probably would not have provided any information about the interactions of the genes and their expression for a very long period of time. Accordingly, we can conclude that we have before us a paradigmatic example of theory construction in an area that is usually termed molecular biology or molecular genetics but that found many of the methods that would yield physicochemical characterizations of its elements irrelevant to its development. The short-term aim of Jacob and Monod was not to reduce genetics to physics and chemistry; it was to determine the principle governing the causal interactions of the entities responsible for enzyme induction and repression and for*

[7] Schaffner's position has been criticized by a number of philosophers, including David Hull (1974), William Wimsatt (1976a, 1976b), Lindley Darden and Nancy Maull (1977), Philip Kitcher (1984), Richard Burian (1986, 1996), John Collier (1988), John Dupré (1993), Alexander Rosenberg (1985, 1994), and Russell Vance (1996).

> *phage synthesis and latency*. (Schaffner 1993, 512, footnote deleted)

From a philosopher's point of view, geneticists are frustratingly unprincipled. They are not driven by epistemological ideals, such as theoretical reductionism. They conceive of biological entities in loose molecular terms when it serves their proximate interests, and they do not see the point in systematically casting their explanations in physicochemical terms. Schaffner does not deny that developments stemming from Watson and Crick's model of DNA were useful to Jacob and Monod's research. But he seems to concede the point that his model of theoretical reduction does not help to reveal what the developments were or why they were useful.

One might try to rescue theoretical reduction by pointing out that, although the lower-level theory of molecular biology may not be couched in physicochemical terms, it is nevertheless couched in macromolecular terms. Hence, Jacob and Monod's failure to explain their results in terms of chemistry would not count against reduction to molecular biology; it would only count against reduction to chemistry. But Schaffner's "peripherality thesis" exposes a more-fundamental problem with the theoretical reductionist account of genetics. The real problem with the account is that it focuses attention on something peripheral to the achievement that has turned out to be so fruitful for biological research.

If our aim is to understand what DNA did for genetics and to identify the development in genetics that transformed many biological sciences, then the model of theoretical reduction won't help. The problem isn't that biologists cannot better explain at the molecular level what was once explained at the cytological level. Current research on processes such as meiosis and mitosis is being conducted at the molecular level and is yielding better explanations of these processes than can be offered at the cytological level. The problem is that seeking and obtaining these better explanations is not the development in genetics that has transformed biology.

6. Beyond theoretical reduction and layer-cake antireduction

Both the reductionist and antireductionist views assume that the relevant developments in genetics were theoretical (or explanatory). But neither offers a real explanation of how the theoretical developments transformed so much of biology. The development identified by theoretical reductionism, the explanation of higher-level theoretical principles in terms of lower-level principles, is tangential to the revolution in genetics. It is unclear how this tangential theoretical development could possibly be responsible for the transformation of biology. Layer-cake antireductionism alleges that the developments in genetics have yielded a divided science, one part aimed at

explaining transmission phenomena and another part aimed at explaining developmental phenomena. By extension, it seems to imply that biological disciplines established before 1953 should exhibit multiple theoretical tiers. But contemporary biology does not take the form of a layer cake. Furthermore, even if biology did consist of multiple levels of autonomous theories, it is quite unclear how a theory at the bottom of the cake could transform theories at higher levels unless something along the lines of theoretical reductionism was correct.

Layer-cake antireductionists might respond that the DNA-based theory at the bottom of the cake should not have transformative effects on the rest of biology. They could insist that molecular biology is destined to explain the leftovers and gory details of fields like physiology or embryology, which should keep their focus on higher-level principles. On this account, the DNA revolution represents a reductionist diversion that privileges phenomena that are best explained in terms of molecules and obscures phenomena best explained at higher levels of organization. A shortcoming of this view is that it lacks a compelling argument. We have seen that the argument from extension based on genetics won't work (section 4.3). Neither does the abstract argument from multiple-realizability (see Sober 1999). Another problem with this view is that it does not explain why a theoretical layer under classical genetics ought to have a transformative effect on a different area, say, physiology. Something happened to genetics after 1953 that transformed much of biology. What was it?

A reductionist might respond to this quandary by seeking a new account of reduction, one that is not based on Nagel's idea that the fruitful developments involve the explanation of high-level explanatory principles in terms of lower-level principles. And indeed, philosophers have tried to identify the relevant developments in genetics by constructing models of reduction that depart from Nagel's. But, as I will show, the revisionists do not let go of Nagel's assumption that the reductive developments that increase the fruitfulness of research are theoretical or explanatory.

William Wimsatt (1976a) departs from Nagel's model by rejecting the assumption that scientific theories are sets of law-like statements and the idea that explanations are arguments in which the phenomena to be explained are derived from laws. He uses Salmon's account of explanation (Salmon 1971) to examine claims that molecular genetics offers reductive explanations. Likewise, Sahotra Sarkar (1998) rejects the account of theories and explanation presupposed in Nagel's concept of reduction. In fact, he explicitly avoids relying on any particular account of scientific theories or theoretical explanation. Instead, he assumes that reductive explanations are explanations without specifying what an explanation is, and then seeks to identify the features that set reductive explanations apart from other explanations.

Wimsatt, Sarkar, and others (including Kitcher 1984) have sought to replace Nagel's conception of reduction with a conception that does not

assume that scientific explanation involves subsumption under universal laws. In contrast, Weber (2005) seeks to replace Nagel's conception with one that retains this idea. What Weber rejects is the Nagelian notion that reductionism in biology involves explaining higher-level biological laws. He argues that, with some rare exceptions, biological sciences don't have laws. He contends that reductionism in biology involves explaining biological phenomena directly in terms of physical laws. Hence, he rejects the layer-cake conception of reduction implicit in Nagel's account. This marks an important advance, but it still keeps the focus on theory.

Wimsatt's writings on reduction (1976a, 1976b, 1978) emphasize the fruitfulness of attempting to achieve a reduction, even when a reduction is not achieved. He argues, for instance, that efforts to discover the molecular makeups of entities identified at higher levels is often fruitful, even when identities between levels cannot be found. Others have also argued that the role of reduction in science should emphasize the fruitfulness of reductive inquiry (Waters 1990; Sarkar 2000). But these accounts still have something in common with Nagel's: They focus on how geneticists explain or try to explain phenomena, not on how they manipulate or investigate phenomena. This is even true of Wimsatt's (1976a) account of heuristics, which stresses heuristics for explanation.

Russell Vance (1996) offers a more-thorough shift in attention from theory to investigative practice. He argues that there is only one contemporary science of genetics on the grounds that investigative methods of classical genetics are an essential part of the methodology of what is called molecular genetics. He concludes that reductionism fails because contemporary genetics still depends on methods of classical genetics involving breeding experiments. Vance's picture of genetics is compelling. The laboratory methods of classical genetics do indeed carry on, even as they are greatly extended, augmented, and often replaced by techniques involving direct intervention on DNA. But Vance's picture does not match the layer-cake image of a two-tiered science and the antireductionist contention that the explanatory principles of classical genetics (and the phenomena that they help to explain) cannot be better explained at the molecular level. Vance does not provide a defense of antireductionism. What he offers is a convincing reason to shift attention to investigative practice.

In the next two sections, I will show that conceiving science as an investigative practice involving an interplay of methodological and explanatory reasoning leads to a different image of genetics and a new idea about how it developed after Watson and Crick's discovery. The image is not of a two-tiered science, one (classical genetics) aimed at investigating and explaining transmission phenomena and another (molecular genetics) aimed at investigating and explaining developmental phenomena. Instead, there is one science that retains much of the investigative and explanatory reasoning of classical genetics by (a) reconceptualizing its theoretical basis modestly in molecular terms and (b) retooling its basic investigative approach by

integrating its methodologies with physically based methods of biochemistry and new methods of recombinant DNA and RNA interference technologies.

7. What was classical genetics?

Philosophical accounts of classical genetics reflect the way philosophers think about scientific knowledge. We typically analyze science by identifying central explanatory theories. Then, for each theory, we analyze its special concepts and principles (or laws), detail how it can be applied to explain various phenomena, reconstruct how it is justified, explore how it might be further developed or how its explanatory range might be extended (the so-called research program), and consider how it should be interpreted (e.g., instrumentally or realistically). This approach has yielded agreement about classical genetics: The science was centered on a theory of transmission genetics (the one developed by Morgan and his collaborators), and the research program was organized around efforts to improve this theory's explanations of heredity and to expand the range of inheritance phenomena that it could explain.

I will use a different, less theory-dominated philosophical approach in this section (see Waters 2004 for a fuller account). Instead of viewing classical genetics in terms of an organizing theory, I will view genetics as a science organized by an integration of explanatory reasoning (associated with a theory) and investigative strategies aimed toward developing knowledge about phenomena which fall outside the explanatory domain, even the potential explanatory domain, of any existing theory. I have already sketched parts of the explanatory reasoning in section 2. Now, it is time to turn to a central investigative strategy of classical genetics, the genetic approach. I will begin by describing an example, Sturtevant's investigation of reductions in the rate of chromosomal crossing over.

7.1. An integration of explanatory and investigative reasoning

The literature of classical genetics is quite complex, but the basic explanatory pattern remains the same: Patterns of inheritance are explained by tracing gene transmission and attributing the presence of alternative traits to the presence of alternative alleles. Sometimes, classical explanations become more complicated because the transmission of genes can involve intricate chromosomal processes. The process of crossing over, for instance, exhibits many variations. While early introductory textbooks often reported that the frequency of crossovers between any two loci was constant (e.g., Sturtevant and Beadle 1939), more technical reports indicated that crossover frequency varies with temperature, age of female parents, chromosomal context of the segment containing the loci, and the presence of mutant crossover reducers on

the same chromosome (e.g., Bridges and Morgan 1923). The explanation of the dramatic decrease in crossing over allegedly caused by the presence of mutant crossover genes illustrates how geneticists working on special problems nevertheless depended on the same basic explanatory pattern. More important, it reveals how "transmission studies" were carried out in order to investigate basic biological processes.

The first crossover modifier found in *Drosophila*, *CIIIA*, reduced crossing over in the region around ebony in the third chromosome. This modifier did not reduce crossing over when present in homozygous form (Bridges and Morgan 1923, 89–92). After discovering *CIIIA*, geneticists discovered several additional crossover modifiers. At first, it was generally presumed that the modifiers were mutant genes, and geneticists mapped their locations. But Sturtevant noted that the dramatic decrease in crossover might be caused by an inverted section of the chromosome, rather than by a mutation in a single gene. He later mapped the region around the *CIIIB* modifier and showed that the order of the genes in the affected region was reversed (Sturtevant 1926). Crossing over was reduced in *Drosophila* heterozygous for *CIIIB* because genes in the inverted region of the *CIIIB* chromosome were not positioned across from the corresponding genes in the wild-type chromosome during meiosis. Crossing over was not reduced in flies homozygous for *CIIIB* because the order of the genes was the same in both third chromosomes of these flies.

In order to map the region around the *CIIIB* modifier region, Sturtevant conducted many carefully orchestrated breeding experiments. These experiments produced inheritance patterns, which he subsequently explained using the transmission theory (along the lines described in section 2). These explanations, however, were not what made Sturtevant's work on *CIIIB* important. Finding explanations for the complex inheritance patterns exhibited in his carefully arranged breeding experiments was the *means* rather than the *ends*. Sturtevant's research on *CIIIB* was important because of what it revealed about synaptic attraction between chromosomes during the process of meiosis. Hermann Muller had already pointed out that the most notable feature of genes, other than their autocatalysis, was "the highly specific attraction which genes (or local products formed by them) show for each other" (Muller 1922, 37). Muller explained that what was particularly remarkable about this mutual attraction was that

> *when the gene mutates, the forces become readjusted, so that they may now attract material of the new kind; this shows that the attractive or synaptic property of the gene, as well as its catalytic property, is not primarily dependent on its specific structure, but on some general principle of its make-up, that causes whatever specific structure it has to be auto-attractive (and autocatalytic).* (Muller 1922, 37–38)

Opponents of the Morgan school of classical genetics were skeptical of Muller's claims about the physical relationship between genes and chromosomes. Sturtevant's finding that chromosomal inversions reduced crossover was important because it favored the idea that mutual attraction between genes was responsible for the mutual attraction between homologous chromosomes during meiosis and because it suggested that the process of crossing over depended on the close affinity of homologous genes.

7.2. The genetic approach

Sturtevant's research on the crossover modifier illustrated a pattern of reasoning that was not just central to research in the later 1920s, '30s, and '40s, but is still central to the practice of genetics today. Biologists call it the "genetic approach." This approach, as exemplified in the research of the Morgan school, is to (a) identify naturally occurring or artificially produced mutants that exhibit a difference *relevant to some biological process of interest*, (b) carry out genetic analyses of the mutants, and (c) recombine the mutants to learn more about the process of interest. In a way, the strategy isn't new. Physiologists had long investigated various mechanisms, such as the mammalian circulatory system, by interfering with its parts and observing what happens. Home mechanics use this investigative approach to learn how machines work. What is new is the idea that one could tinker with a process, such as sex determination, by recombining genetic mutations.

The genetic approach had mixed success in classical genetics. It tended to be most successful in the study of chromosomal mechanics. For example, when Sturtevant applied the strategy to investigate the process of crossing over (section 2), he learned about the cause of dramatic decreases in crossover rates affecting various regions of the second and third chromosomes. More important, he also learned about the basic biological process of chromosome synapsis: His results supported ideas about the auto-attraction of genes and confirmed the notion that the mechanism of crossing over was facilitated by the matching of genes in homologous chromosomal segments.

The genetic approach for investigating biological processes was not confined to studies of chromosomal mechanics. It was also used to learn about gene action, mutation, development, and evolution. Mutants involving dosage effects and genetic mosaics were often investigated in order to shed light on gene action or on broader issues of development, such as sex determination. Interests in gene action also led researchers to investigate position effects. These studies often involved chromosomal aberrations. Generally, this research did not live up to the promise of yielding important new knowledge about gene action or development (at least in the short run). But chromosomal aberrations were also investigated to learn more about processes of chromosomal mechanics (e.g., translocation, unequal crossing over, nondisjunction, etc.) and evolution (e.g., speciation). As Robert Kohler (1994)

has astutely noticed, even when no light was shed on the phenomenon of interest, genetic studies still yielded publishable information about the existence and genetic location of new alleles and, we might add, about processes of chromosomal mechanics or evolutionary relationships. This helps to explain why the underlying investigative strategies have disappeared in hindsight. Whether successful or not, the investigative strategies of the genetic approach were an integral part of the reasoning of classical genetics.

8. The retooling of genetics

Developments following from Watson and Crick's discovery led to a retooling of the genetic approach, which I will illustrate with an investigation of neurons in *C. elegans*. A central aim in *C. elegans* research is to learn how the nervous system of this nematode works. The explanatory goal of the research program corresponds to what Robert Cummins (1975) calls a "functional analysis." Investigators want to explain how the nervous system works by finding out how parts of the nervous system contribute to its various capacities. Hence, when they ask, "what is the *function* of this structure in the nervous system?" they are seeking an account of how the structure contributes to one or another capacity of the system of which it is a part. The series of experiments I describe were aimed at determining the function of a protein, ß-spectrin, in neurons.

ß-spectrin is part of a spectrin-based membrane skeleton that exists as a cytoskeletal structure contained in most cells, but these experiments concerned the function of this protein in nerve cells. Prior experiments had revealed that organisms lacking ß-spectrin exhibit neuronal defects. In addition, biologists had already conducted imaging experiments to determine the distribution of this protein. They learned that it is contained in the growth cones of neurons, which indicated that this protein functions in the outgrowth of axons and dendrites. This study, conducted by Marc Hammarlund, Erik Jorgensen, and Michael Bastiani (2007), was aimed at learning more about the role of ß-spectrin.

Hammarlund, Jorgensen, and Bastiani implemented an enhanced version of the genetic approach. They manipulated the system under study by manipulating various genes, including the gene for ß-spectrin called *unc-70*. Their first goal was to determine whether ß-spectrin functions in axon outgrowth. They began by inserting a gene for green fluorescent protein (GFP) under the control of a regulatory region that distributed this protein in the growth cone of nerve cells. This enabled them to observe growth of nerve cells as they extended from the ventral side to the dorsal side during embryogenesis. Next, they used a mutation of *unc-70* to observe what happened to the growth pattern of these cells in the absence of ß-spectrin. They observed that the growth pattern was not disrupted. This result conflicted with the idea that the

function of ß-spectrin was to facilitate the outgrowth of axons and dendrites (since such growth occurred without the molecule). They obtained similar results when they conducted experiments on the extension of other neuronal processes. The investigators concluded that ß-spectrin does not contribute to the growth capacity of these neurons.

Hammarlund, Jorgensen, and Bastiani inferred that since axon outgrowth does not require ß-spectrin, neuronal defects that were observed in animals lacking ß-spectrin occur after outgrowth has occurred. They pursued this idea by observing axon morphology at different life stages. Again, they used the genetic approach, manipulating genes to insert reporter proteins so they could image neuronal extensions and to shut off the production of ß-spectrin. They observed the accumulation of a number of defects that had never been observed in wild-type animals, including breaks in the neuronal extensions (from ventral to dorsal), postembryonic growth cones, and aberrant branching of neuronal extensions. They observed similar accumulations of defects in processes of other types of neurons as well. Additional observations and considerations led them to the conclusions that the primary defect was the break in the long axon extensions and that the postembryonic growth cones and aberrant branching were consequences of the breaking. This suggested two possible functions of ß-spectrin in neurons:

> *First, ß-spectrin might be involved in the addition of membrane to axons during growth of the organism (Morris 2001). Because worms increase in length and circumference during development, failure to insert membrane into axons could cause them to break. Alternatively, ß-spectrin might protect neurons against the acute strains caused by movement*. (Hammarlund et al. 2007, 272)

To explore these two possibilities, they prevented the *unc-70* mutated worms from moving so the mutant axons would not experience the acute strains normally caused by movement. They prevented the worms from moving by using RNAi (interference RNA) to prevent the expression of a muscle myosin gene. That is, they used the genetic approach. In this case, they manipulated the functioning of one component in the system (myosin) to learn about the role of a different component (ß-spectrin). Although they did not directly manipulate the myosin gene itself, they manipulated its expression by directly manipulating a gene for RNAi. They used genes as investigative levers.

The experiment revealed that RNAi largely rescued the neuronal defects of animals lacking ß-spectrin. This indicated that, by preventing movement, experimenters also prevented the breakage of axons. However, there is another possibility. Perhaps the suppression of axon breakage resulted from some effect of RNAi other than paralysis. To test against this possibility, they manipulated the expression of a different gene, *Twitchin*, which rendered

mutant worms incapable of coordinated movements, such as deep body bends, the kind of movements that result in acute strains of axons. The result of this experiment was a partial rescue of the wild-type phenotype (i.e., a reduction in axon breakage in *unc-70* mutants). Hammarlund, Jorgensen, and Bastiani concluded that ß-spectrin's role is to "protect neurons against breakage cause[d] by movement-induced strain" (2007, 272). To express this conclusion in a causal role idiom: The function of ß-spectrin is to contribute to the structural integrity capacity of neurons to withstand acute, movement-induced strain.

The investigation of the role of ß-spectrin illustrates how genetics has developed since Watson and Crick's discovery of DNA and why this development has transformed much of biology. The development involved a new basic theory that recast ideas of classical genetics in terms of molecules (as described in section 3). What makes this theoretical recasting so important isn't that it improves upon the explanation of inheritance patterns or helps to explain causal regularities of classical genetics at a lower level of organization. It is accomplishing both of these, but these successes are peripheral to the development in genetics that has transformed much of biology. The recasting of the basic theory is important because it makes it possible for biologists to retool and build upon the basic investigative approach of genetics.

Old views die hard. Some might try to rescue the idea that the relevant development stemming from Watson and Crick's discovery must have been primarily theoretical, and insist that a new fundamental theory of biology has been established (e.g., along the lines of Rosenberg 2006). According to this view, which might be called "genetic reductionism," biologists have identified the fundamental units of life in DNA. These units—genes and extragenic regions of DNA—program development by directing the synthesis of RNA and polypeptide molecules. The reason this theoretical development has transformed biology is because a broad range of biological sciences has adopted the research program of completing the fundamental theory. This theory, the genetic reductionist might claim, can inform all biological research by providing the basic pattern of explanatory reasoning that can be filled out and applied to explain everything that happens in an organism.

The investigation of ß-spectrin described here shows what is wrong with this account. The development in genetics that advanced Hammarlund, Jorgensen, and Bastiani's investigation did not rest on any fundamental theory; the basic theory of molecular biology (described in section 3) sufficed. Furthermore, and this warrants particular stress, the basic theory of genetics was used only to help construct experiments and to explain experimental results. The explanation ultimately gained from the experimentation, the explanation concerning the role of ß-spectrin in the maintenance of neuronal structural integrity, does not even refer to genes or to DNA. So the idea that a fundamental theory of DNA is responsible for the remarkable success of DNA-centered research is not supported by this example. I submit that this study is

representative of much of the research in contemporary gene-centered investigations. Genes are used as levers to manipulate and investigate a wide variety of biological processes.[8]

9. Conclusion

What made the recasting of genetics in terms of DNA so important for genetics and transformative for biology? Recasting the basic theory meant that the interplay between theoretical reasoning and investigative strategies could yield new methodologies that greatly increased the investigative powers of the genetic approach. This was important for genetics because it dramatically increased its investigative utility. This has been transformative for biology because the genetic approach, and other strategies from genetics, can now be utilized in many different disciplines of biology. The key to understanding what DNA did for biology is to stop being distracted by theoretical sideshows and focus on the main event.

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[8] . It is also worth pointing out that Hammarlund, Jorgensen, and Bastiani's account of ß-spectrin's role and their explanation of neuronal structural integrity were cast at the molecular level. Hence, the failures of theoretical reductionism and genetic reductionism do not support layer-cake antireductionism.

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