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Stud. Hist. Phil. Biol. & Biomed. Sci. 36 (2005) 349–371
Studies in History and Philosophy of Biological and Biomedical Sciences
www.elsevier.com/locate/shpsc

Relations among fields: Mendelian, cytological and molecular mechanisms

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Abstract

Philosophers have proposed various kinds of relations between Mendelian genetics and molecular biology: reduction, replacement, explanatory extension. This paper argues that the two fields are best characterized as investigating different, serially integrated, hereditary *mechanisms*. The mechanisms operate at different times and contain different working entities. The working entities of the mechanisms of Mendelian heredity are chromosomes, whose movements serve to segregate alleles and independently assort genes in different linkage groups. The working entities of numerous mechanisms of molecular biology are larger and smaller segments of DNA plus related molecules. Discovery of molecular DNA mechanisms filled black boxes that were noted, but unilluminated, by Mendelian genetics.

Keywords: Mechanisms; Mendelian genetics; Molecular biology; Discovery; Theory reduction; Interfield relations

1. Introduction

Philosophers of biology have debated the nature of the relations between Mendelian genetics and molecular biology for some fifty years. They have proposed a variety of relations between the fields, including reduction, replacement, and

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1369-8486/$ - see front matter
doi:10.1016/j.shpsc.2005.03.007

explanatory extension. This paper proposes a new analysis: the two fields discovered separate but serially connected mechanisms. These hereditary mechanisms have different *working entities* and the mechanisms operate at different times in an *integrated temporal series of hereditary mechanisms*. This analysis better characterizes the practice of biologists than previous accounts, as evidenced both by the historical development of the two fields and by presentations of the results of the two fields in contemporary textbooks.

Accounts of formal reduction played many roles in philosophical analyses of science in the second half of the twentieth century. Reduction was seen both as the relation among theories at different levels of organization at a given time (sometimes called 'microreduction') and as the relation among predecessor theories and successor theories. Furthermore, reduction was tied closely to explanation. The connection between what was to be explained (the *explanandum*) and what did the explaining (the *explanans*, usually general laws) was claimed to be (usually) deduction (Hempel, 1965). Hence, the deduction of the reduced theory (or the observations that it explained) from the reducing theory in formal reduction permitted the claim that the reducing theory explained the reduced theory (or its observation statements). The status of the reduced theory after a reduction was different in different accounts of formal reduction. In some accounts of reduction (e.g., Kemeny & Oppenheim, 1956; Oppenheim & Putnam, 1958), the reduced theory was eliminated; the reducing theory explained all the observations previously explained by the eliminated theory. In other accounts (e.g., Nagel, 1961), one theory was derived from another, but the reduced theory might still be useful in some way. Scientific progress was viewed as carrying out more and more reductions to lower levels of organization (Oppenheim & Putnam, 1958).

In analyses of the relations between Mendelian genetics and molecular biology, these roles for reduction have been criticized. Progress seemed to have occurred with the development of molecular biology, but how was this progress to be characterized? Did molecular biology microreduce Mendelian genetics or was it a successor that replaced Mendelian genetics? Could all the findings of Mendelian genetics be best explained at the molecular level? Did such molecular explanations entail the deduction of Mendel's laws from general laws of molecular biology? What were these general laws of molecular biology? Were the theories in the fields best characterized as consisting of laws? After the development of molecular biology, what was the status of Mendelian genetics?

Attempts to answer these questions about the relations between Mendelian genetics and molecular biology have been fraught with difficulties. It is argued here that integration of a temporal series of mechanisms with different working entities is the appropriate way to characterize the relations between Mendelian genetics and molecular biology. Cytology furnished the mechanisms of Mendelian heredity. The discovery of new mechanisms by molecular biology might be considered explanatory extension of Mendelian genetics, but this analysis differs from a previous account, as we will see. This extension occurred as a result of the discovery of mechanisms that illuminated *black boxes* noted by Mendelian geneticists but not accessible by Mendelian/cytological techniques. These molecular mechanisms occur

before and after the chromosomal mechanisms, including the mechanisms of DNA replication, mutation, and protein synthesis.

Furthermore, this paper argues that this analysis in terms of mechanisms provides alternative accounts of the following issues. The structure of biological theories in these fields is best analyzed by appeal to mechanism schemas, and not by appeal to sets of laws or argument schemata. Further, explanations of various phenomena consisted of describing the mechanisms that produced them, not of logically deducing anything from anything. Progress occurred in this case, not by reduction or replacement, not by adding premises to argument schemata, not by appeal to the smallest size components, but by discovering mechanisms with working entities of different sizes.

The following sections elaborate and support this analysis of the relations between Mendelian genetics and molecular biology in terms of serially integrated mechanisms. Section 2 characterizes the fields to be discussed. Section 3 criticizes a selection of previous philosophical analyses and critiques. Section 4 characterizes mechanisms, mechanism schemas, sketches, and working entities. Section 5 is a historical account tracing the discovery of mechanisms in Mendelian genetics, cytology, and molecular biology. Section 6 provides evidence for the contemporary integration of hereditary mechanisms by examining an exemplary contemporary molecular biology textbook.

2. The fields of Mendelian genetics, molecular biology, and their neighbors

As the topic here is the relation between the fields of Mendelian genetics and molecular biology, a few words about the identification of these fields and their neighbors are in order. Although the institutional and professional aspects of scientific disciplines are frequently complex, the conceptual components of scientific fields can often be delineated. These include the central problem, a domain of phenomena related to the problem, techniques and methods, and general knowledge encapsulated in concepts, laws, theories, or mechanism schemas that aim to provide solutions to the central problem (cf. Darden & Maull, 1977, p. 44).

Several fields are at issue here. The field of *classical Mendelian genetics* emerged in 1900 and developed through the 1920s. Its central problem was the explanation of patterns of inheritance of characteristics. The technique used was artificial breeding of organisms with variant characteristics. Empirical regularities were explained by appeal to the two Mendelian laws of segregation and independent assortment, which state regularities in the behavior of hypothetical genes. By 1926, T. H. Morgan's theory of the gene also included claims about linkage of genes arranged linearly in groups and crossing over between alleles in the same linkage group (e.g., Morgan, 1926, p. 25; Darden, 1991).

In the nineteenth century, the central problem of the field of *cytology* was to find the basic units of organisms. Cell theory solved that problem; the field moved on to the microscopic study of stained cells and their components. The study of chromosomes (darkly staining string-like structures in the nucleus) began in the late

nineteenth century and details about chromosomal behavior in normal cell division (mitosis) and meiosis (formation of gametes in which the chromosome number is halved) were available in the early twentieth century (see, e.g., Wilson, 1900; Hughes, 1959). Chromosomal behavior during meiosis, it will be argued below, provided the mechanisms producing the regularities noted in Mendel's laws. *Cytology* became *cell biology* in the 1950s and 1960s when new techniques provided ways of studying the functions of newly observed ultrastructure of cells (Davis, 1980, p. 209). The field underwent further change after the rise of molecular biology.

The field that came to be called *molecular biology* emerged in 1953, I argue, with the discovery of the double helix structure of DNA. The term 'molecular biology' was coined in 1938[1] and was used by some X-ray crystallographers to label their work on the three-dimensional structure of macromolecules. However, in the 1950s and 60s, the field of molecular biology drew not only on X-ray crystallography and structural chemistry to study the structure of macromolecules, but also on theoretical work on the genetic code to find relations between nucleic acids and proteins, as well as genetic breeding techniques applied to microorganisms. The central problem of this post 1953 early molecular biology was the nature of the gene—how it replicates, mutates, and produces proteins. Molecular biologists solved these problems about the gene by finding mechanism schemas for DNA replication, point mutation, protein synthesis, and gene regulation, emphasizing weak forms of bonding, such as hydrogen bonding, and by using microorganisms as model organisms (see e.g., Watson, 1965; Morange, 1998).

The field of *biochemistry* emerged in the early twentieth century with a focus on proteins and enzymes, as well as other chemical components in the metabolism of living things. In the 1930s, when enzymes were found to be proteins and proteins were found to be macromolecules, one of biochemistry's many problems was the discovery of the different amino acids composing proteins. An associated problem for some biochemists was to understand the energetics of the chemical reaction that produces the strong covalent bonds between amino acids to form peptide bonds. Thus, although the two fields of early molecular biology and biochemistry investigated molecules within a similar size range, their problems, techniques, and hypothesized mechanisms were, and to some extent still are, different (see e.g., White et al., 1954; Kohler, 1982).

By about 1970, early molecular biology had solved its central problem about the nature of the gene, at least in procaryotes (microorganisms, such as bacteria, without an organized nucleus or chromosome). In its next phase, molecular biology added the study of eucaryotes (organisms with an organized nucleus and chromosomes). This later phase merged with *cell biology* (see e.g., Alberts et al., 1983). Its central problem was, and continues to be, to elucidate the molecular structures and

[1] In 1938, Warren Weaver of the Rockefeller Foundation coined the term and some of the early X-ray crystallographers used it to refer to their work on the structure of biological macromolecules, such as hair, according to Olby (1994). However, the field, as codified in Watson's *Molecular biology of the gene* (1965), began in 1953. The term 'molecular biology' came into widespread usage after the founding of the *Journal of Molecular Biology* in 1959.

mechanisms within and between cells. Especially relevant for our purposes here, for example, is the mechanism of crossing over between homologous chromosomes.

Molecular biology developed a repertoire of techniques for manipulating the genetic material that enabled other fields to 'go molecular'. Such expansion of molecular biology into cell biology and other areas has led some to distinguish *molecular genetics* from molecular biology. Philosophers (e.g., Kitcher, 1984) often use 'molecular genetics' synonymously with early molecular biology. Alternatively, 'molecular genetics' may refer only to results produced by cross-breeding variants to produce hybrid organisms (a usage extended from techniques of Mendelian genetics to genetic manipulations in bacteria). Another usage of 'molecular genetics' is to refer to any study of genetics at the molecular level, that is any study of the molecular biology of the gene. Whether biologists' usage of 'molecular genetics' has any identifiable historical trajectory is unclear.

'Molecular biology' is the name of the historical field with relations to Mendelian (sometimes called 'classical') genetics. Historians have chronicled its history (e.g., Morange, 1998); scientists in the period we will discuss often called themselves 'molecular biologists'. Francis Crick, for example, said: 'I myself was forced to call myself a molecular biologist because when inquiring clergymen asked me what I did, I got tired of explaining that I was a mixture of crystallographer, biophysicist,[2] biochemist and geneticist, an explanation which in any case they found too hard to grasp' (quoted in Stent, 1969, p. 36).

Not only is it important to identify the fields at issue here, we also need to delineate the theories, theoretical entities, and size levels. Sometimes philosophers assumed that one could identify a theoretical entity, which was used in a theory appropriately located at a level of organization for any given scientific field, or even a larger branch of science. For example, the units—atom, molecule, cell—figured in atomic theory, chemical theory, and cell theory, which corresponded to the branches of science—physics, chemistry, and biology (see e.g., Oppenheim & Putnam, 1958). The view that theories at lower levels would explain all the observations at higher levels constituted a reductive account of the goals of, and progress in, science.

However, this over-simplified identification of units, theories, fields, and levels breaks down for the fields of interest here. It is difficult to see at what level in a hierarchy Mendelian genetics, with its study of phenotypic characters and hypothetical genes, is to be placed, when compared to cytology and the study of chromosomes. Genes were claimed to be parts of chromosomes, but no one suggested reducing cytology to genetics (or vice versa). Furthermore, molecular biologists and biochemists investigated many of the same units and reactions at roughly the same size level, but used different techniques and perspectives. Molecular biologists and biochemists sometimes found their work to be complementary, such as work on the role of RNAs in the mechanism of protein synthesis (see Darden & Craver, 2002), and sometimes used their differing techniques to compete, such as the biochemical (e.g., Nirenberg & Matthaei, 1961) verses genetic (e.g., Crick et al., 1961) work on the genetic code

[2] On the usage of the term 'biophysics' at Cambridge University in England, see Chadarevian (2002).

(Kay, 2000). Although Mendelian genetics could be analyzed as having two laws as part of the theory of the gene, molecular biology did not fit this account of theory structure. Nothing was found to fill the role of general laws of molecular biology. As we will see, problems of identifying levels, fields, theories, laws, and units plagued the attempts to analyze the relations between fields in terms of reduction. These problems spawned new accounts of theory structure and explanation.

3. Previous work on the relations between Mendelian genetics and molecular biology

Kenneth Schaffner used and developed Ernst Nagel's (1961, Ch. 11) analysis of derivational theory reduction to argue for the reduction of classical Mendelian genetics to molecular biology and refined it over many years (summarized in Schaffner, 1993). The goal of formal reduction was to logically deduce the laws of classical genetics from the laws of molecular biology. Such a derivation required that all the terms of Mendelian genetics not in molecular biology be connected via 'correspondence rules'. Hence, Schaffner endeavored to find molecular equivalents of such terms as 'gene', as well as 'predicate terms', such as 'is dominant'. (One allele of a gene is said to be 'dominant' over another if the character associated with that gene appears in the hybrid offspring of a cross between pure breeding parents. For example, in a cross between tall and short pea plants, tall is dominant over short.)

David Hull (1974) criticized formal reduction, argued against Schaffner's claims, and suggested, instead, that perhaps molecular biology replaced classical genetics. Hull's critiques focused on the problem of connectibility of terms. A close look at their dispute showed that it hinged on debates about mechanisms of gene expression. Hull said:

> Even if all gross phenotypic traits are translated into molecularly characterized traits, the relations between Mendelian and molecular predicate terms express prohibitively complex, many–many relations. Phenomena characterized by a single Mendelian predicate term can be produced by several different types of molecular mechanisms. Hence any reduction will be complex. Conversely, the same types of molecular mechanisms can produce phenomena that must be characterized by different Mendelian predicate terms. Hence, reduction is impossible. (Ibid., p. 39)

Schaffner criticized Hull for claiming that the same molecular mechanism could give rise to phenomena labeled with different Mendelian terms. 'Different molecular mechanisms can appropriately be invoked in order to account for the same genetically characterized relation, as the genetics is less sensitive. The same molecular mechanisms can also be appealed to in order to account for different genetic relations, but only if there are further differences at the molecular level', such as different initial conditions (Schaffner, 1993, p. 444). Empirical investigation was required to determine the molecular mechanisms of gene expression (ibid., p. 439).

One artifact of the connectibility of terms required in formal reduction was that philosophers focused so much attention on dominance. The dominance of one allele

over another during gene expression was found to have many exceptions. In 1926, when T. H. Morgan stated the theory of the gene, dominance was not included as a component of the theory (Morgan, 1926, p. 25). Finding molecular mechanisms for dominance, which was later called 'dosage effect' (Darden, 1991, p. 72), was not a central problem in early molecular biology, as we will see. Such connectibility of terms, and other items requiring attention in a formal reduction analysis were peripheral to the concerns of scientists, as both Schaffner (1974) and Hull (1974) realized. The idealized formal reduction relation, even if it could have been imposed on some version of the historically developing fields (or some logical reconstruction of their theories), did not serve to capture the practice of scientists. (As an aside, we may note that when scientists use the term 'reduction', they mean something different from that captured in the formal philosophical account; exactly what they mean has not been adequately analyzed.)

Note that the mechanisms at issue in the Schaffner–Hull debate were located in the black box in Figure 1 labeled gene expression. Mendelian genetics had no account of the mechanisms producing gene expression. It is not surprising that studying molecular mechanisms of gene expression produced refinements in the

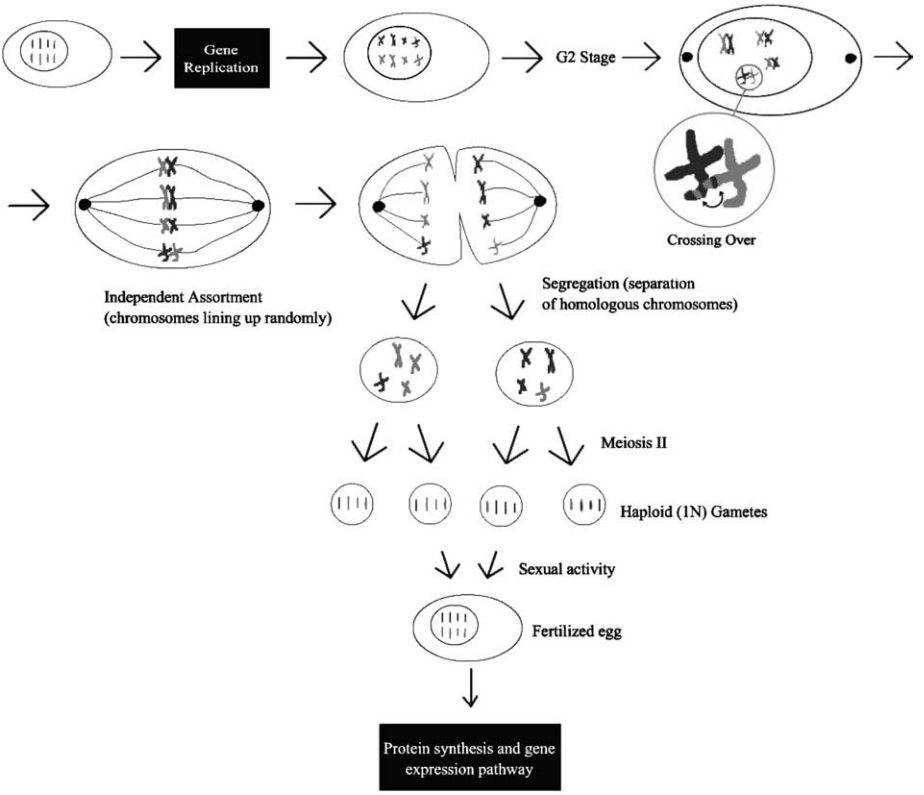

Fig. 1. Mechanisms of heredity.

understanding of the network of relations among gene products during the production of the phenotypic traits that were accessible to Mendelian geneticists. Such illumination of a black box is not appropriately analyzed as either replacement or formal theory reduction.

Wimsatt (1976) analyzed Schaffner and Hull's dispute. He strengthened the argument for the peripherality of the formal model of reduction to the practice of science. He noted: 'At least in biology, most scientists see their work as explaining types of phenomena by discovering mechanisms, rather than explaining theories by deriving them or reducing them to other theories, and *this* is seen as reduction, or as integrally tied to it' (ibid., p. 671). Wimsatt proposed that 'explanatory reduction' (microreduction) should be recast as a search for lower-level mechanisms to explain upper level phenomena. As will be argued below, a characterization of mechanisms and their working entities shows that one does not always move down to a lower size level to find the mechanism producing a phenomenon.

Responding to Wimsatt's critique, Schaffner (1993, pp. 490–499) analyzed relations between the 'causal/mechanical' view of reduction and the 'generalized reduction/replacement' model:

> reductions in science frequently have two aspects: (1) ongoing advances that occur in piecemeal ways, for instance, as some features of a model are further elaborated at the molecular level or perhaps a new 'mechanism' is added to the model, and (2) assessments of the explanatory fit between two theories (viewed as a collection of models) or even between two branches of science. (Ibid., p. 495)

But Schaffner expressed concern about the use of 'mechanism', an 'unanalyzed term' (ibid., p. 287).[3]

Darden and Maull (1977) focused attention on the bridges between fields as an important locus of new discoveries in science. The bridges, we claimed, might be identities (required of correspondence rules in the formal reduction model), but they might be other kinds. Interfield relations included part–whole relations (e.g., genes are parts of chromosomes), structure–function relations (e.g., an identified molecule functions as the repressor in gene regulation), and cause and effect relations. Sometimes the relations were elaborated in an 'interfield theory', such as the chromosome theory of Mendelian heredity (genes as parts of chromosomes). What was important, we argued, was to find the relations, not to formally derive anything from anything. However, we missed the importance of mechanisms in our analysis.

Moving beyond debates about formal theory reduction, Kitcher (1984, 1989) and Waters (1990, 2000) advanced the discussion about the relations between the fields of Mendelian genetics and molecular biology. Kitcher criticized a reductive approach and Waters defended 'informal' aspects of reduction.

Developing an analysis of theory structure in terms of argument schemata, Kitcher argued that the relation between Mendelian and molecular genetics was 'explanatory

[3] I thank Jim Tabery for the plausible interpretation of Schaffner's (1993), Ch. 6, 'Explanation and causation', as Schaffner's own attempt to analyze causal mechanisms, using Salmon's and Mackie's work, and connect causal mechanistic explanation with explanation via generalizations.

extension' (Kitcher, 1984, p. 371). The theory of molecular genetics provided a refined and expanded set of premises when compared to the argument schemata of classical genetics (Kitcher, 1989, pp. 440–442). However, classical genetics retained its own schema. For example, the independent assortment of genes (Mendel's second law) was objectively best explained, according to Kitcher, by instantiating a pairing and separation schema, thereby showing that chromosomal pairing and separation was a unifying natural kind. Such unification would be lost if attention was focused on the gory details at the molecular level. The cytological level thus constituted an 'autonomous level of biological explanation' (Kitcher, 1984, p. 371).

On the other hand, in order to solve problems of gene replication, mutation, and action, Kitcher claimed that the 'gory' molecular details were required, and were part of the expanded premise set of the schema labeled 'Watson–Crick' (Kitcher, 1989, p. 441). Among the premises of the 'Watson–Crick' schema, for example, were 'transcription, post-transcriptional modification and translation for the alleles in question', along with details of 'cell biology and embryology' for the organisms in question (ibid., pp. 440–442). An explanation of a particular pattern of distribution of progeny phenotypes in a genetic cross resulted from instantiating the appropriate schema: the variables were filled with the details from the particular case and the conclusion derived from the premises.

Waters (1990) criticized Kitcher's arguments. First, Waters noted that other instances of pairing and separation processes, other than the separation of paired chromosomes, were only hypothetical. It was difficult to see what was achieved by unifying chromosomal processes with other imagined pair separations, carried out by other kinds of hypothetical forces, in a pair-separation schema. Second, Waters criticized Kitcher's claim that the 'gory' molecular details did not improve the relevant explanation. In contrast, Waters claimed that our understanding was enhanced by the molecular models for the mechanism of crossing over, and that such increased understanding constituted 'informal reduction' as opposed to formal, derivational reduction.

In the remainder of the paper, I argue for a different view in which mechanisms play a prominent role. I argue that the two fields of Mendelian genetics and molecular biology investigated separate but serially connected mechanisms with different working entities that operate at different times in (what is now known to be) an integrated temporal series of hereditary mechanisms. One explains, for example, a particular distribution of phenotypic traits from a genetic cross as resulting from a series of mechanisms connecting parent(s) to offspring. Along with Kitcher, I argue that the phenomena summarized in Mendel's laws of segregation and independent assortment were (and are) explained by the behavior of chromosomes. However, the reason has nothing to do with unification into a natural kind of pair-separation processes, but is because the chromosomes are the working entities of the mechanisms of meiosis. The analysis of working entities in a mechanism provides an alternative to Kitcher's analysis, but also serves to block the reductive move that one always gains understanding by investigating the gory details of the smallest entities present.

Waters correctly noted that the molecular level is the appropriate one for finding the mechanism(s?) of crossing over. However, the molecular mechanism of crossing

over operates at a stage in a temporal sequence of hereditary mechanisms between the pairing and then the separation processes that Kitcher discussed. Kitcher and Waters were talking past each other because they were not arguing about the same mechanisms. Different genetic mechanisms, as we will see, have different working entities and operate at different times; tasks in discovering mechanisms are to find the working entities at whatever level of organization and the temporal sequence in which they act.

Also with Kitcher, I argue for abstract schemas of varying scope as a way of representing general knowledge in these fields. However, the schemas are not argument schemata, but mechanism schemas. (I use 'schemas' rather than 'schemata' as the plural of 'schema'.) Rather than premises and conclusions, mechanism schemas describe the mechanism's entities and activities and their productively continuous organization from beginning to end. Mechanism schemas are often depicted in diagrams. Diagrams perspicuously show the structures of the entities, as well as spatial arrangements and temporal stages. Furthermore, mechanism schemas have various degrees of abstraction (Darden, 1996), not merely the two place relation of a variable and its value.

This mechanistic analysis, I claim, better captures the practice of biologists, with their frequent talk and diagrams of mechanisms, than do the analyses of the relations between the fields in terms of formal reduction, informal reduction, replacement, and explanatory extension via expanded argument schemata.

With Wimsatt, I argue that biologists often explain phenomena by describing mechanisms. 'Mechanism' is no longer an unanalyzed term. The analysis to be discussed below differs in some respects from the decompositional view in Wimsatt (1976) and developed by Glennan (1996, 2002). For them, the behavior of the system was to be explained by decomposing a system into its parts and explaining its behavior by the interactions of its parts. Instead, I argue, finding the mechanism that produces a phenomenon may require not further decomposition of a system, but instead going 'up' in size level. For example, finding the mechanism for the segregation of genes did not require decomposing genes into their parts, but required finding the wholes, the chromosomes, on which the parts, the genes, ride. (For comparisons of the decompositional and this alternative view of mechanisms, see Machamer, Darden, & Craver, 2000; Tabery, 2004.) To this analysis we now turn.

4. Mechanisms, mechanism schemas, mechanism sketches

This analysis of the relations between Mendelian genetics and molecular biology makes use of several concepts, some analyzed in previous work, such as *mechanism*, *mechanism schema*, *mechanism sketch*, and others introduced here, such as *working entities*. This section discusses these concepts and then uses them to explicate the relations between these fields.

Mechanisms have components that work together to do something. One identifies some phenomenon of interest (in the sense of Bogen & Woodward, 1988), or some

task that is carried out (Bechtel & Richardson, 1993). One then seeks the mechanism that produces the phenomenon or carries out the task. Previous work on the concept of mechanism provides this characterization:

> Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions. (Machamer, Darden, & Craver, 2000, p. 3).

Types of entities include macromolecules (such as proteins and the nucleic acids, DNA and RNA); sub-cellular structures, such as ribosomal particles (composed of RNA and proteins); chromosomes (composed of DNA and proteins); and cells. Types of activities include geometrico-mechanical activities, such as lock and key docking of an enzyme and its substrate; and chemical bonding activities, such as the forming of strong covalent bonds and weak hydrogen bonds. The entities and activities are organized in *productive continuity* from beginning to end, that is, each stage gives rise to the next. Entities having certain kinds of activity enabling properties allow the possibility of acting in certain ways, and certain kinds of activities are only possible when there are entities having certain activity enabling properties (Darden & Craver, 2002; Darden, 2002).

Working entities engage in activities within a mechanism. Various general features of entities (whether working or not) aid in identifying the working entities of a mechanism. An entity may have a spatio-temporal location. An entity may have a clear boundary, such as a membrane bounding it. An entity may be composed of chemically bonded subparts that are not similarly bonded to the parts of other entities. It may be composed of specific chemicals that differ from chemicals in the surroundings. It may be robustly detectable, that is, accessed by using different techniques (Wimsatt, 1981). It may be stable over some period of time, as are chromosomes, or it may be rapidly synthesized and degraded, as are some messenger RNAs. It may have a developmental history, that is, it may be formed during embryological development. It may have an evolutionary history, that is, it may be a descendant in a lineage.

In addition to these general features of entities, working entities in mechanisms have additional features. A working entity *acts* in a mechanism. It may move from one place to another. It has activity enabling properties. It may have one or more *localized* active sites. For example, the centromeres of chromosomes are active sites that attach to the spindles during the mechanisms of meiosis. Similarly, enzymes have localized active sites that bind to substrates. Alternatively, the active sites may be *distributed* throughout the entity, as are the slightly charged bases along the entire double helix, which serve as the active sites in DNA replication.

Working entities in a given mechanism may be, and often are, different sizes. For example, ions, macromolecules, and cell organelles may all be working entities in the same mechanism, such as the mechanism of protein synthesis. Because working entities in a given mechanism may be of different sizes, mechanism levels may not correspond tidily to size levels. Of course, all biological entities are composed of smaller parts; however, most subcomponents do not change during the activities of the working entities of which they are parts. For example, atomic nuclei are parts

of working entities, but merely stable subcomponents. Atomic nuclei are not *working* entities or active sites in the DNA replication mechanism. They are parts of the structure, buried away behind electrons from active sites. In other conditions, nuclei of atoms can become working entities, for example, in nuclear fission mechanisms when atoms are split. But during DNA replication, atomic nuclei are not working entities. Similarly, genes outside the centromere are just along for the ride on the chromosomes during meiosis; they only become working entities during the operation of developmental mechanisms occurring later.

Perhaps surprisingly, genes are not the working entities in any of the hereditary mechanisms except gene expression. Genes have no 'role function' (Craver, 2001) in the mechanisms of chromosomal pairing and separation. Like atomic nuclei in the mechanism of DNA replication, genes are buried within chromosomal packaging during chromosomal pairing and separation. Genes are along for the ride, like passengers on a train; they are not working entities, as those mechanisms operate. The entire chromosomes are the working entities, and their centromeres are the active sites.

Similarly, in DNA replication the entire DNA molecule is the working entity, with the polar charges of individual bases as the active sites. The genes are not working entities or active sites during DNA replication.

Only during the mechanisms of gene expression do genes become working entities; they are working segments of DNA molecules (except in RNA viruses) that are active in mechanisms for the transcription of DNA segments into RNA. Individuating genes can be problematic. Bacterial genes are easier to individuate because they are usually continuous segments of a DNA molecule. Because eucaryotic genes have introns (as well as other complicating factors), identifying the DNA segments making up the genes has proved a challenging task. What one needs to know in order to reliably identify a gene is the mechanism in which it participates. Sometimes one reasons backward from a gene's product, such as a protein, to locate the DNA segment(s) that produced it. (For numerous kinds of mechanisms involved in gene action, see Fogle, 2000.)

One form of a structural gene is a linear sequence of bases that is transcribed into messenger RNA, whose linear sequence of bases is translated into the linear sequence of amino acids in a protein (see Figure 3). Other genes are transcribed into RNAs that play other roles, for example, transfer RNA and ribosomal RNA. Debate has occurred as to whether regulatory elements should be called genes (Waters, 1994). This is just a terminological dispute; what is important is what the DNA segment does in the transcription mechanism. Some segments of DNA work as part of the control mechanism, while others are transcribed. Subsequently, in organisms with introns, some regions of the pre-messenger RNA are spliced out to produce messenger RNA. One need not argue about whether the gene includes regulatory and intronic regions, as long as the particular roles of these DNA segments in the transcription mechanism are understood. The role in a mechanism is what is important.

Scientists rarely depict all the particular details when describing a mechanism; representations are usually schematic, often in diagrams. A *mechanism schema* is a

truncated abstract description of a mechanism that can be instantiated by filling it with more specific descriptions of component entities and activities. An example is a slightly simplified version of James Watson's (1965) diagram of his version of the central dogma of molecular biology:[4]

DNA → RNA → protein

This is a schematic representation (with a high degree of abstraction) of the mechanism of protein synthesis, which can be instantiated with details of DNA base sequence, complementary RNA sequence, and the corresponding order of amino acids in the protein produced by the mechanism (see Figure 3).

In contrast, a mechanism *sketch* cannot (yet) be instantiated. Components are (as yet) unknown. Sketches may have *black boxes* for missing components whose function is not yet known. A more developed sketch may have boxes whose functional role (Craver, 2001) is known or conjectured, but what specific entities and activities carry out that function in the mechanism are (as yet) unknown. Sketches guide further work to fill the black boxes. (Biologists may use the term 'model' to refer to a schema, a sketch, or an instantiation of a schema.)

Mendel's laws sketched regularities found to be produced by chromosomal mechanisms during meiosis. The general knowledge in molecular biology is best characterized not in terms of laws or a theory but as a set of mechanism schemas (Machamer, Darden, & Craver, 2000; Craver, 2002). These are schemas for such mechanisms as DNA replication (and repair), protein synthesis, and gene regulation. They have domains of applicability of varying scope, from the widely found mechanism of protein synthesis, to the myriad different mechanisms of gene regulation.

An adequate description of hereditary mechanisms shows the wider context into which any given mechanism fits. Hereditary mechanisms operate in a temporal series stretching from parent(s) to offspring. A goal in understanding heredity is to find well supported schemas for the mechanisms of heredity, as depicted in Figure 1.

5. Historical developments: discovering hereditary mechanisms

This section discusses one way to identify the relations between fields—by tracing the historical discoveries of hereditary mechanisms in the twentieth century in the fields of Mendelian genetics, cytology, and molecular biology. This history provides evidence for the claim that the relations among these fields is best understood from the perspective of the relations among the mechanisms they discovered.

Seminal publications are good sources for tracing the development of fields. The field of classical Mendelian genetics began in 1900 with the rediscovery and reinterpretation (de Vries, 1966 [1900]; Correns, 1966 [1900]) of Gregor Mendel's 1865

[4] For differences between Watson's and Crick's versions of the central dogma, see Darden (1995) and Keyes (1999a, 1999b).

paper. The field developed significantly in the hands of T. H. Morgan and his colleagues, whose early work was presented in their book *The mechanism of Mendelian heredity* (Morgan et al., 1915). The culmination of that work can conveniently be marked with Morgan's publication of a book in 1926.

The primary technique of classical Mendelian genetics was cross-breeding of variants of plants and animals, noting the distributions of the variant phenotypic characters through several generations, and, finally, making inferences about hypothetical genes associated with those characters. Geneticists made two inferences about genes (and their alleles), namely that they exhibited segregation and independent assortment, called 'Mendel's first and second laws'. In order to state these laws, it is useful to consider a typical breeding experiment. Suppose pure breeding tall and short pea plants are crossbred.[5] The hybrid offspring are called the 'F_1 generation', for the 'first filial generation'. All the F_1 plants are tall. Consequently, tall is said to be 'dominant' over short. When the plants in the F_1 generation are allowed to self-fertilize, then the F_2 plants occur in the ratio of 3 tall to 1 short. The short ones thereafter breed true, but the tall split in the next generation into a 1:2 ratio of pure breeding tall to those that again behave as hybrids. Such 3:1 ratios in the F_2 generation are an empirical regularity that was observed by early geneticists in many species of plants and animals. One variant dominating over the other in the F_1 generation was found only in some cases; sometimes the character of the hybrid might be a blend form intermediate between the two parents or look quite different from the parents. Thus, dominance was not a general empirical regularity (Darden, 1991), nor was it listed as a component of the theory of the gene by Morgan (1926, p. 25).

To account for the regular 3:1 ratios, geneticists sketched aspects of the mechanism operating during the formation of gametes (sperm and eggs in animals) of the hybrid. A relationship between a phenotypic character and an allele of a gene was assumed; for example, one allele is associated with the tall character in peas and its corresponding allele with the character for short. Usually in a sexually breeding organism there are two alleles of a given gene. During the formation of gametes, the two alleles separate, that is, segregate, so that each gamete receives one but not the other. This regularity is 'Mendel's first law'. This law thus sketches the behavior of some sort of mechanism operating during the formation of gametes to separate the paired alleles of a gene.

When two traits in peas are followed through two generations, during an experiment such as the one above, the regularity in the F_2 generation is found to be 9:3:3:1. For example, if a tall plant that produces yellow peas is crossed with a short plant that produces green peas, the two traits behave independently. At the beginning of Mendelism, no separate law was formulated to express this independence. Segregation just seemed to be operating in each trait separately. Only after exceptions were found was Mendel's second law explicitly formulated.

[5] For the contrast between Gregor Mendel's historical work and this account in, for example, Morgan (1919), see Darden (1991), Ch. 4.

In 1906, Bateson and his associates found a case in which two traits exhibited segregation but the traits did not produce the expected 9:3:3:1 ratios (Bateson et al., 1906). Bateson referred to the phenomenon as 'coupling', because the mechanism that he proposed consisted of some 'allelomorphs' (as he called them) being attracted to others. However, Morgan renamed the phenomenon 'linkage' (e.g., Morgan & Lynch, 1912) when he and his colleagues proposed an alternative mechanism. They explained the lack of independent assortment as due to the anomalous genes being linked on chromosomes. In 1919, Morgan explicitly separated Mendel's two laws and formulated 'Mendel's second law' as the claim that genes in different linkage groups assort independently during the formation of gametes (Morgan, 1919; Monaghan & Corcos, 1984; Darden, 1991). The regular behavior of chromosomal mechanisms produced the phenomena encapsulated in Mendel's two laws of segregation and independent assortment of different linkage groups. The Morgan group was able to make use of work on chromosomes already carried out by cytologists (Wilson, 1900).

By 1900, cytologists had shown that microscopically visible chromosomes occurred in pairs that separated during the formation of gametes, so that each gamete had one half the usual parental number. Independently, Walter Sutton (1903) and Theodore Boveri (1904) proposed that the hypothetical hereditary factors exhibiting Mendelian segregation were in or on the chromosomes. The chromosome theory of Mendelian heredity was thus an interfield theory, postulating a part–whole relation between visible chromosomes and hypothetical genes, and thereby integrating findings from the fields of cytology and genetics (Darden & Maull, 1977).[6]

Morgan (1909, 1910a) had originally opposed the chromosome theory, arguing that the amount of correlation of characters expected if they were linked on chromosomes had not been found. He changed his view in 1910 as a result of his work on the fruit fly *Drosophila* (Morgan, 1910b, 1911). Patterns of inheritance allowed Morgan to infer that sometimes pieces were switched between homologous chromosomes. This mechanism of crossing over occurred after pairing but prior to separation; it served to produce less correlation of characters because alleles were reshuffled. As a result, Morgan abandoned his objection to the chromosome theory.

Morgan, with his students Calvin Bridges, A. H. Sturtevant, and H. J. Muller, actively pursued the relations between chromosomes and 'factors' (in 1917, Morgan adopted Johannsen's 1909 term 'gene'). In 1915, in *The mechanism of Mendelian heredity*, they stated: 'the chromosomes furnish exactly the kind of mechanism that the Mendelian laws call for' (Morgan et al., 1915, p. viii).

Key hereditary problems unsolved by Mendelian geneticists and unilluminated by drawing on cytology were the chemical nature of genes (speculated to be proteins), how genes replicated, how genes mutated and then faithfully reproduced those mutations,

[6] Although our concern here is with the way geneticists used findings from cytology, inferences went both ways, as is often a mark of interfield theories, as discussed in Darden & Maull (1977). New claims were made about chromosomes, namely their random assortment, based on the connection to genetics; also, new uses were made of the mechanisms of meiosis to explain Mendel's laws.

and how genes related to phenotypic characters. The black boxes of Figure 1 show the mechanisms not illuminated by Mendelian/cytological techniques.

The modern field of molecular biology began, I argue, in 1953 with the discovery of the DNA double helix by James Watson and Francis Crick (Watson & Crick, 1953a,b; Olby, 1994; Judson, 1996; Morange, 1998). The new field drew on work in several other fields, in order to solve the questions about genes unsolved by Mendelian genetics. These fields included X-ray crystallography, for determining the structures of macromolecules; structural chemistry, especially Linus Pauling's work on weak forms of chemical bonding, such as hydrogen bonding (e.g., Pauling, 1939; Pauling & Corey, 1950); and to a much lesser extent biochemistry, for its study of the chemical analysis of proteins and nucleic acids, as well as energy requirements of strong covalent bonding.

The model organisms of early molecular biology were bacteria (procaryotes) and their viruses. Choice of such model organisms, which lacked a nucleus and organized chromosomes, indicated that the central problems addressed by the field in its early days were not problems about the molecular details of chromosome pairing, crossing over, and separation, as one would expect on a reduction analysis. Instead, the molecular biologists tackled the problems of finding the nature of the genes (nucleic acids, not proteins) and the mechanisms for gene replication, mutation, and expression.

As Watson and Crick (1953a) noted, the structure of DNA immediately suggested a copying mechanism. Their 1953 sketch served as the framework for the discovery of the DNA replication mechanism. The DNA helix opened, they suggested, to serve as two templates for the assembly of their complements (see Figure 2). The structure also immediately suggested one way that mutations might form, what we now call 'point mutation'. An error in copying occurs when a base substitution was made that departs from the usual A–T, G–C base pairing during DNA replication.

Interestingly, genes proved not to be the working entities of either gene replication or gene mutation. The working entity of the mechanism of gene replication was found to be an entire DNA double helix molecule. As in the chromosomal mechanisms of meiosis, the genes were found to be just along for the ride during the replication of helices. Moving down in size, the working entity for the formation of a point mutation was found to be the single base of a DNA double helix, smaller than a DNA segment constituting a functional gene. The genes became the working entities only in the mechanisms of gene expression.

The efforts of early molecular biologists in investigating the mechanisms of gene expression began with work on the mechanism of protein synthesis and its regulation. One part of this work resulted in the discovery of the mechanism sketch DNA → RNA → protein. This sketch was elaborated into a detailed understanding (see Figure 3) of the mechanism of protein synthesis (Darden & Craver, 2002) and the reading of the genetic code (Kay, 2000). Another part of this work resulted in the understanding of some mechanisms of gene regulation, especially the mechanism of derepression in the *lac* operon of *E. coli*, that served to turn a group of genes (an operon) on and off, depending on environmental conditions (Jacob & Monod, 1961; Morange, 1998).

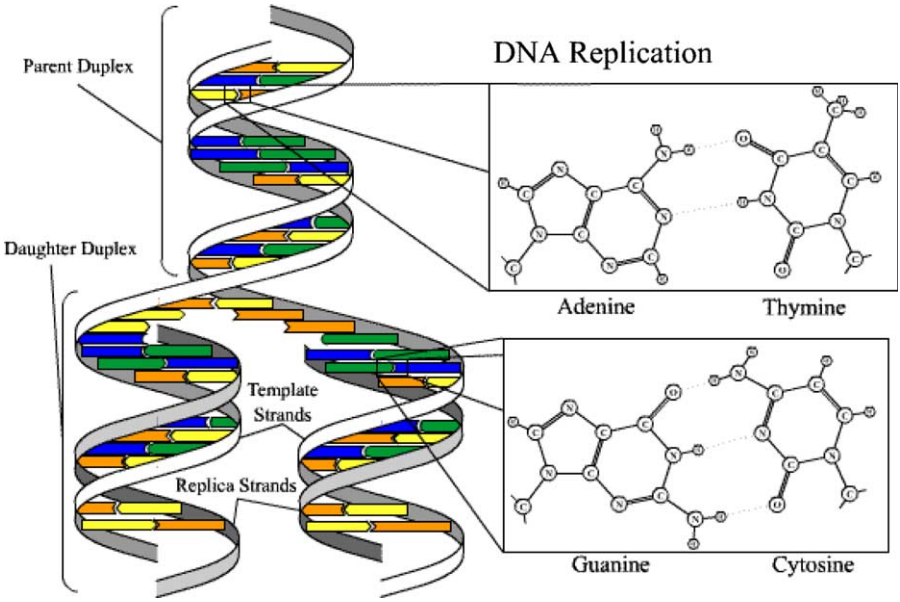

Fig. 2. DNA replication.

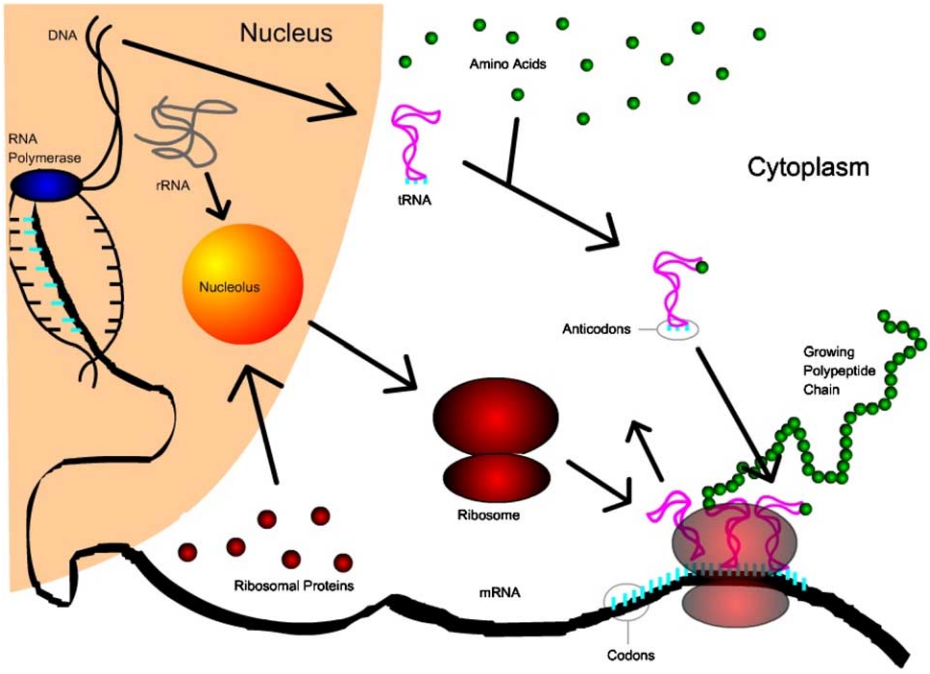

Fig. 3. Diagrammatic schema for protein synthesis.

This brief account of the development of the field of molecular biology from 1953 to 1970 showed that early molecular biologists discovered different mechanisms than the Mendelian/cytological ones operating during meiosis in eucaryotes. They focused on the nature of the gene rather than seeking the molecular details about chromosomal mechanics. They concentrated on filling the black boxes totally unilluminated by Mendelian and cytological techniques: gene replication, mutation, and expression. Their work served to elucidate mechanisms more universally found (in both procaryotes and eucaryotes), namely, mechanisms of DNA replication, point mutation, and protein synthesis.

Now that we have discussed early molecular biology, we can situate historically the molecular work on some of the details of chromosomal mechanisms found in hereditary mechanisms of sexual reproduction that had been studied by Mendelism and cytology. Only after the molecular biology of the *gene* (Watson, 1965) was elucidated did attention turn to the molecular biology of the *cell* (Alberts et al., 1983). The later work on structures and mechanisms of the cell resulted in the hypotheses about the molecular mechanism of crossing over in eucaryotes. These mechanisms were found in domains of smaller scope, namely only in sexually breeding organisms with organized chromosomes, in contrast to the more widely found mechanisms of DNA replication and protein synthesis. The molecular biology of the cell contributed to solving the problem of embryological development in multicellular eucaryotes that undergo such changes. Yet to be fully elucidated are all the steps in mechanisms of gene expression between gene(s) and phenotypic character(s).

Looking back at the history of Mendelian genetics, cytology, and molecular biology, it is amazing that the classical geneticists were able to infer as much as they did about genes simply by following the transmission of phenotypic characters through several generations. That they were able to detect crossing over, segregation, linkage, and independent assortment of different linkage groups was perhaps attributable to these phenomena resulting from chromosomal mechanisms. In the mechanisms of gene replication, mutation, and expression, the molecules and their parts become the working entities. These molecular mechanisms were unilluminated by the breeding techniques of Mendelian genetics or the tracing of chromosomal mechanics by cytologists. These molecular mechanisms served to fill some of the gaps between the inferred genes and their phenotypic characters studied by Mendelian genetics.

6. Contemporary account of the relations among hereditary mechanisms

The historical development of the two fields discussed in the previous section provides one form of evidence for the claim that the two fields studied different mechanisms in a integrated, temporal series of hereditary mechanisms. Examination of an exemplary contemporary textbook of molecular biology provides another form of evidence for this claim and, furthermore, shows that the meiotic chromosomal mechanisms of Mendelian heredity have not been eliminated but have been integrated with the prior and subsequent molecular ones (again see Figure 1).

The first edition of James Watson's *The molecular biology of the gene* (1965) codified the newly emerged field of molecular biology. This seminal text, after two more editions (Watson, 1970, 1977), culminated in a multiauthored work (Watson et al., 1988). Chapter 1, 'The Mendelian view of the world', opened with a discussion of meiosis. Mendel's crosses and Mendel's laws were diagramed, and they were explained, the authors claimed, by the 'chromosome theory of heredity'. Recounting Sutton's work, the authors noted: 'He postulated that the yellow- and green-seeded genes are carried on a certain pair of chromosomes and that the round- and wrinkled-seeded genes are carried on a different pair. This hypothesis immediately explains the experimentally observed 9:3:3:1 ratios' (ibid., p. 12). Again in the summary of the chapter:

> Mendel proposed that a hereditary factor (now known to be a gene) for each hereditary trait is given by each parent to each of its offspring. The physical basis for this behavior is the distribution of homologous chromosomes during meiosis: One (randomly chosen) of each pair of homologous chromosomes is distributed to each haploid cell. . . . For many years, the structure of genes and the chemical way in which they control cellular characteristics were a mystery. (Ibid., p. 23)

Later chapters detailed the mechanisms of DNA replication (including mutation and repair) and the associated molecular mechanisms of recombination in crossing over. For example, after discussing competing hypotheses about crossing over: 'In retrospect it is obvious what mechanism most precisely aligns DNA molecules in crossing over, because we can hardly imagine any other: Complementary base-pairing between strands unwound from two different chromosomes puts the chromosomes in exact register' (ibid., p. 316). An entire part of the book was devoted to the 'Steps in protein synthesis'. This was followed by discussion of gene expression mechanisms, first in the regulation of protein synthesis in bacteria and then a final part indicating the black boxes associated with 'Facing up to eucaryotic cells'.

This textbook account supports the analysis of contemporary understanding of the mechanisms of heredity. The black boxes of Figure 1 were filled, in part, by the mechanisms depicted in Figures 2 and 3. The mechanisms for sexually breeding organisms occur in a temporal sequence of DNA replication, chromosomal duplication, crossing over, chromosomal random assortment, chromosomal segregation, germ cell formation, organismal mating, gametic fertilization, and, finally, gene expression during development, thereby producing phenotypic characters.

7. Conclusion

To return to the philosophical analyses, we see that Mendelian genetics has not been reduced to molecular biology nor replaced by it. As both Schaffner and Hull realized, the formal model of reduction does not capture the practice of biologists, either in the way the two fields developed historically or as depicted in an influential contemporary textbook. As Kitcher argued, the appropriate explanatory level for pairing and

separation was, and is, that of the chromosomes. As Waters argued, the molecular level was the appropriate one for finding the mechanism of crossing over. That mechanism operates after chromosomes pair, but before they separate. As Kitcher argued, molecular biology was an explanatory extension of Mendelian genetics and cytology.

What now needs to be added to this analysis is the view for which this paper has argued. The fields of Mendelian genetics and molecular biology are best characterized as investigating different, serially integrated hereditary mechanisms. The mechanisms operate at different times and are composed of different working entities of different sizes. One does not always make progress by moving to lower size levels. The important interfield bridge between Mendelian genetics and cytology was neglected by most previous philosophical accounts. The working entities of the mechanisms of Mendelian heredity are chromosomes, whose movements serve to segregate alleles and independently assort genes in different linkage groups. The regularities captured in Mendel's laws of segregation and independent assortment were, and still are, explained by the chromosomal mechanisms of meiosis, as the Morgan group's work showed and as depicted in textbooks today. The behavior of chromosomes in meiosis provide 'the mechanisms of Mendelian heredity'. The working entities of numerous mechanisms of the molecular biology of the gene are larger and smaller segments of DNA plus related molecules. Molecular DNA mechanisms filled black boxes unilluminated by Mendelian/cytological techniques. Progress in genetics occurred, not by reduction or replacement, but by discovering new mechanisms and integrating them into the temporal series of hereditary mechanisms.

Acknowledgements

This work was supported by the National Science Foundation under grant SBR-9817942, and by an award from the General Research Board of the Graduate School at the University of Maryland. Thanks to David Hull and Ken Schaffner, my teachers, who introduced me to this problem many years ago; to David Didion, who pointed out that independent assortment occurs prior to segregation and drew some of the diagrams; to Jonathan Roy for his work as my research assistant; to Joan Straumanis for the metaphor—genes on chromosomes like passengers in a train; to Carl Craver, whose insights about mechanisms pervade all that I write and who provided helpful comments on several drafts of this paper; to the DC History and Philosophy of Biology discussion group and colleagues at the University of Pittsburgh, whose comments forced clarifications; to Nathaniel Goldberg, Nancy Hall, Greg Morgan, Rob Skipper, Jim Tabery, Ken Waters, and an anonymous reviewer for helpful comments.

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