Introduction

This book discusses reasoning strategies for discovery that are exemplified in numerous biological cases. Scientific discovery should be viewed as an extended, piecemeal process with hypotheses undergoing iterative refinement. Construction, evaluation, and revision are tightly connected in ways that philosophers of science have often not recognized, given their neglect of reasoning in hypothesis construction and revision. Examination of historical cases from twentieth-century biology reveals reasoning strategies that could have produced the changes that did occur. Such critically examined reasoning strategies constitute compiled hindsight gleaned from these past episodes. Examples come from the fields of molecular biology, biochemistry, immunology, neuroscience, and evolutionary biology. Making reasoning strategies explicit shows that they are not merely descriptions of unique historical changes or unwarranted overly general prescriptions. They are advisory. They may be of use as metascientific hypotheses in philosophical and historical analyses of scientific reasoning, of use in future empirical and computational biological research, and of use in science education. Hence, one goal of this book is to make explicit reasoning strategies for construction, evaluation, and revision of scientific hypotheses.

Biologists often seek to discover mechanisms. Knowing what is to be discovered aids the extended process of discovery. The examination of the nature and means of representing biological theories aids analysis of reasoning in their discovery. What play the roles of theories in molecular biology, for example, are diagrammatically represented sets of mechanism schemas for such widely found mechanisms as DNA replication, protein synthesis, and many varieties of gene regulation. Hence, another goal of this book is to find reasoning strategies for discovering such mechanisms.

Sometimes scientific discoveries occur entirely within one field. In other cases, two or more scientific fields contribute to a scientific discovery in

various ways. Two fields may both seek to discover the same mechanism, investigating different modules of the mechanism using different techniques. Another field may supply items for the construction of an intrafield theory. Two fields may be bridged by an interfield theory. A multifield theory may integrate views of hierarchically nested mechanisms. An abstract mechanism schema from one field may be used analogically to construct a similar type of theory in another field. Hence, another goal of this book is to demonstrate the role of interfield relations in biological discoveries.

Much of the previous work in philosophy of science has been hampered by an overly sharp dichotomy between discovery and justification and by viewing scientific discovery as a mysterious process. Accounts of "aha" experiences, while entertaining, are not adequate descriptions of the reasoning in extended episodes of scientific innovation. Also, the prescriptions in philosophy of science of methods for confirmation or Karl Popper's (1965) of falsification have been shown to be too simplistic. Multiple factors play roles in the evaluation of scientific knowledge claims (both in assessing theories and credentialing empirical evidence). Some failures on some evaluative dimensions call not for complete rejection of a hypothesis but for its refinement. Surprisingly few philosophers of science have paid attention to reasoning in the revision of scientific hypotheses that face anomalies. Consequently, an alternative perspective, as I have also argued elsewhere (Darden 1991), needs to replace the simplistic dichotomy of irrational discovery followed by logically characterized justification (or falsification). Further, neglect of revision should be remedied. Science should be viewed as an error-correcting process and philosophers should seek to find reasoning strategies that constrain and guide that process. Hence, another goal of this book is to find strategies for anomaly resolution, viewed as diagnostic and redesign processes.

Some philosophers of science are what Tom Nickles (1980c) called "friends of discovery" (e.g., Hanson 1958, 1961; Schaffner 1974a; Buchanan 1982, 1985; Kleiner 1993), while others have recognized the importance of mechanisms in science, especially biology (Wimsatt 1972; Brandon 1985; Burian 1996a; Glennan 1996, 2002, 2005). Only a few have investigated reasoning in the discovery of mechanisms. Rom Harré was an early advocate: "Generally speaking, making models for unknown mechanisms is the creative process in science" (Harré 1970, p. 40). He emphasized the role of analogies in discovering mechanistic models. Harré also endeavored to find an analysis of causality compatible with his mechanistic view (Harré and Madden 1975). For numerous biological cases, William Bechtel and Robert Richardson showed how the heuristics of decomposition and localization aided the discovery of "mechanistic explanations" in the "dynamics

of theory development" (Bechtel and Richardson 1993, pp. xii–xiii). Bechtel and Abrahamsen (2005) discussed a variety of experimental procedures for discovering the parts of mechanisms, their operations, and their organization. Paul Thagard, long interested in reasoning in discovery (e.g., Thagard 1992; Holyoak and Thagard 1995), turned his attention to the discovery of mechanisms in the biomedical sciences: "Discovery of a pathway provides a mechanism that describes the productive activity that enables the cell to perform tasks . . . " (Thagard 2003, p. 239). Then, he continued, the discovery of such molecular cell mechanisms aids medical discovery: "Many diseases can be explained by defects in pathways, and new treatments often involve finding drugs that correct those defects" (Thagard 2003, p. 235). Some philosophers examined the dynamics of scientific change during anomaly characterization and error correction (e.g., Wimsatt 1987; Allchin 2002; Elliott 2004).

Hence, an important goal here is to integrate work on biological mechanisms and reasoning in discovery. The chapters of Part I, "Biological Mechanisms," focus on the characterization of biological mechanisms and the roles of reasoning strategies and techniques from different fields in their discovery, with examples from Mendelian genetics, molecular biology, and neurobiology. The chapters of Part II, "Reasoning Strategies: Relating Fields, Resolving Anomalies," discuss ways of representing biological theories, as well as reasoning strategies in finding interrelations between biological fields and in resolving anomalies for biological theories. These chapters add examples from evolutionary biology and immunology. Part III, "Discovering Mechanisms: Construction, Evaluation, Revision," integrates the earlier parts and expands the discussion of reasoning in discovering mechanisms. Chapter 12 responds to some of the criticisms of earlier work, elaborates the features of mechanisms that need to be discovered, and elaborates reasoning strategies for discovering mechanisms during construction, evaluation, and revision.

In our collaborative work, beginning in 1997, my colleagues Peter Machamer and Carl Craver and I analyzed aspects of mechanisms in biology. Peter Machamer brought his insights about seventeenth-century mechanisms (e.g., Machamer and Woody 1994; Machamer 1998). Carl Craver's ideas were informed by his work in neurobiology and mine by examination of molecular biology. Our collaborative chapters in Part I analyze these issues: characterization of biological mechanisms in molecular biology and neurobiology, constraints on an adequate description of a mechanism, some reasoning strategies for the discovery of mechanisms, and interfield integration in mechanism discovery.

Chapter 1, "Thinking About Mechanisms" with Peter Machamer and Carl F. Craver, was originally published in 2000. We refer to this paper as "MDC."

It provides a characterization of mechanisms that produce phenomena in terms of entities, activities, and their productive continuity. The activities in twentieth-century mechanisms are much more varied than the contact action of geometrico-mechanical seventeenth-century clockwork mechanisms. Especially important for molecular biological mechanisms are the activities of chemical bonding, especially weak hydrogen bonding. This chapter is programmatic, suggesting a new mechanistic approach for philosophy of biology that may be applicable to fields beyond molecular biology and neuroscience. It sketches analyses of mechanistic explanation, theory structure, theory change, causality, the unimportance of universal laws and derivational reduction, as well as interrelations among fields of biology. (Section 12.2 responds to critiques of this MDC characterization of mechanisms and I develop it further there; cf. Machamer 2004; Bogen 2005.)

Chapter 2, "Discovering Mechanisms in Neurobiology: The Case of Spatial Memory" with Carl F. Craver, elaborates constraints that an adequate description of a mechanism should satisfy, including componency, spatial, temporal, and hierarchical constraints. Another topic is finding experimental strategies for investigating mechanisms. Given an experimental setup with a running mechanism, one can intervene via inhibition or excitation and, then, detect the downstream effect. We argue that the neurobiological case study shows the hierarchical integration of work at different levels on mechanisms of spatial memory. The mechanistic approach in cases from neurobiology has been further developed by Craver (2001, 2002a, 2002b, 2003, 2005). (In Part III, I slightly expand what I there call "the features of mechanisms.")

Chapter 3, "Strategies in the Interfield Discovery of the Mechanism of Protein Synthesis" with Carl F. Craver, uses the mechanistic approach to illuminate the extended discovery of the mechanism of protein synthesis. Molecular biologists and biochemists worked on different ends of the mechanism. The molecular biologists began with the genetic material, DNA, while biochemists studied peptide bond formation between activated amino acids in proteins. Their work converged in the middle of the mechanism, with the discoveries of the types and roles of RNAs. In this case of interfield interaction, researchers in two different fields worked to understand the same mechanism. This case exemplifies two strategies for discovery: schema instantiation, and forward/backward chaining. (These strategies are put into a larger context of reasoning strategies of construction, evaluation, and revision in Part III.)

In Chapter 4, "Relations Among Fields: Mendelian, Cytological, and Molecular Mechanisms," I criticize earlier philosophical claims about relations between the fields of Mendelian genetics and molecular biology. I argue that these relations should not be analyzed in terms of reduction, replacement,

or (one form of) explanatory extension. Instead, the two fields are shown to have investigated different, serially integrated, hereditary *mechanisms*. The mechanisms operate at different times and contain different working entities. Molecular biological mechanisms filled black boxes that were noted, but unilluminated, by Mendelian geneticists. (For another argument against reduction from his multilevel mechanistic perspective, see Craver 2005.)

The chapters in Part II extract additional reasoning strategies for problem solving from extended discovery episodes. Chapter 5, "Interfield Theories" with Nancy Maull, discusses cases in which interfield theories, bridging two fields, solve problems that could not be solved within a single field alone. Interrelations among fields, even if not developed into a full-fledged interfield theory, may provide new ideas for one or both of the bridged fields. I examine the chromosome theory of Mendelian heredity bridging genetics and cytology. Nancy Maull's cases are the operon theory of gene regulation, bridging genetics and biochemistry, and the theory of allosteric regulation bridging biochemistry and physical chemistry. (Compare additional analyses of interfield relations in, e.g., Bechtel 1984, 1986; Darden 1991; Craver 2005.)

Chapter 6, "Theory Construction in Genetics," contrasts the vague analogies used by William Bateson with the interfield relations that proved fruitful in T. H. Morgan's development of the theory of the gene. Analogies may serve as a source for new ideas; however, this chapter argues, interfield relations, if available, are likely to be more fruitful. (The extended discovery of the theory of the gene and reasoning strategies it exemplified were discussed in more detail in Darden 1991.)

Sometimes, hypotheses about mechanisms at several hierarchical levels can be integrated in a multilevel theory, as in the synthetic theory of natural selection. Chapter 7, "Relations Among Fields in the Evolutionary Synthesis," discusses the integration of mechanisms at three levels in the work of Theodosius Dobzhansky (1937). Genetics and cytology study mutations and chromosomal changes in organisms, which are the raw material for evolutionary change. Population genetics studies the impact of the environment on populational changes via, for example, selection or migration. Finally, evolutionary biology studies speciation mechanisms, investigating the study of isolating mechanisms that prevent interbreeding and thereby produce new species. (Compare the case of multifield integration in neuroscience in Craver 2005 and discussion of speciation mechanisms in Baker 2005.)

Once a new theory has been constructed, it may be seen as representative of a type. Joseph A. Cain and I discuss one prevalent type in Chapter 8, "Selection Type Theories." Abstracting (namely, eliminating details) from

the theory of natural selection provides a schema for selection type theories. In contrast to the more usual analysis of selection in terms of replicators and interactors (Hull 1980), this selection schema relegates replication to a more minor role, a possible downstream benefit. The first step in a schema for a selection mechanism is the production of a population of variants. Even if this step is stochastic, as long as it provides variants for the next stage, it fulfills its appropriate role in the selection mechanism. (The related issue of possible mechanisms for producing adaptive mutations is the subject of Chapter 11.) The second step in the Darden and Cain schema is the crucial, difference-making step – the interaction of the variants with a critical environmental factor. The next step abstractly characterizes the result of the selective interaction – some variants benefit and others suffer. These terms are sufficiently abstract that many different kinds of outcomes can count as benefits. In Darwinian natural selection, a short-range benefit is survival and a longer range benefit is increased reproduction of the successful variants. Such a schema – variants, interaction, benefit – can be used to guide the construction of other selection type theories to solve adaptation problems. Once selection had been discovered in evolutionary biology, it became available as an analogy for other fields. Chapter 8 includes the historical examples of the clonal selection theory in immunology and the more speculative neural Darwinism. (Compare the further development of this schema as a mechanism schema in Skipper 1999, 2001; and critiques in Skipper and Millstein 2005. Also see the critique of the peppered moth example in Rudge 1999.)

Chapters 9, 10, and 11 categorize types of anomalies and refine strategies for anomaly resolution. Chapter 9, "Strategies for Anomaly Resolution: Diagnosis and Redesign," argues that anomaly-driven scientific change can be viewed as, first, a diagnostic reasoning process. A failure in a theory must be localized in a theoretical component. This analogy between localization of an anomaly and diagnostic reasoning is a fruitful one that allows philosophers of science to make use of the extensive work on reasoning in diagnosis. Second, fixing the failed component(s) of the system is a redesign process. Steps and strategies for localizing and fixing anomalies for scientific theories are outlined. A simulation model represents a Mendelian breeding experiment. The model is systematically debugged as an illustration of anomaly localization in a computational philosophy of science experiment. (For further development of the computational perspective for discovering mechanisms, see Darden 2001.)

Chapter 10, "Exemplars, Abstractions, and Anomalies: Representations and Theory Change in Mendelian and Molecular Genetics," shows that representations of scientific theories are closely tied to reasoning strategies for

theory change. One way a scientific theory may be represented is by a set of concrete exemplary problem solutions. Alternatively, a theory may be depicted in an abstract schema, which, when its variables are filled with constants, becomes a particular explanation. The exemplars and abstractions may be depicted diagrammatically, as they are in the cases from Mendelian genetics and molecular biology. One way that a theory grows is by adding new types of exemplars to its explanatory repertoire. Model anomalies show the need for a new wide-scope exemplar; they turn out to be examples of a typical, normal pattern that had not been included in the previous stage of theory development. The discovery of the linkage of genes resulted from the resolution of a model anomaly. In contrast, a special-case anomaly indicates the need for a new exemplar or abstraction with only a small scope of applicability. The discovery of reverse transcriptase provided a special-case anomaly for the central dogma of molecular biology, which is a mechanism schema for protein synthesis with wide scope: DNA –>RNA –>protein. For retroviruses, an additional step was added to the beginning of this mechanism schema: RNA –>DNA. Neither the linkage anomalies nor the reverse transcriptase anomaly could be barred as a monster that did not require theory change. (For more on Temin's discovery of reverse transcriptase, see Marcum 2002.)

Chapter 11, "Strategies for Anomaly Resolution in the Case of Adaptive Mutation," examines the controversial anomaly of directed or adaptive mutations. The anomaly has received many diverse responses, beginning in 1988 with radical challenges to the theory of natural selection and the central dogma of molecular biology. The hypothesized instructive mechanisms to produce directed mutation provide a contrast to selection mechanisms. As of 2003, this anomaly appears to be resolvable by appeal to operation of known types of mechanisms. Examination of this anomaly allows refinement of strategies for anomaly resolution.

Finally, Part III, Chapter 12, "Strategies for Discovering Mechanisms: Construction, Evaluation, Revision," summarizes and extends analyses in earlier chapters. A few criticisms of our MDC characterization of mechanism are briefly addressed. The list of features of mechanisms is expanded. Reasoning strategies for discovery of mechanisms via iterative refinement are discussed. The categories of strategies are construction, evaluation, and revision. Guidance in construction may be provided by the reasoning strategies of schema instantiation, modular subassembly, and forward/backward chaining. Evaluation strategies serve to assess adequacy. Evaluation detects the incompleteness in mechanism sketches. Proposed mechanism schemas are transformed as various evaluative strategies are employed, moving from how possibly, to how plausibly, to how actually the mechanism works. Anomaly

resolution strategies guide diagnosis and repair during revision of mechanism schemas and sketches.

Thus, these chapters extract reasoning strategies for biological discovery from episodes in the history of biology. They may be useful for philosophers and historians of science interested in reasoning in discovery. They may serve as heuristics for scientists in lab meetings. They may serve as guides for educators who teach scientific reasoning. They may be of use for building computational systems to make biological discoveries.

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