Thinking About Mechanisms*

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The concept of mechanism is analyzed in terms of entities and activities, organized such that they are productive of regular changes. Examples show how mechanisms work in neurobiology and molecular biology. Thinking in terms of mechanisms provides a new framework for addressing many traditional philosophical issues: causality, laws, explanation, reduction, and scientific change.

1. Introduction. In many fields of science what is taken to be a satisfactory explanation requires providing a description of a mechanism. So it is not

*Received November 1998; revised July 1999.

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‡We thank the following people for their help: D. Bailer-Jones, A. Baltas, J. Bogen, R. Burian, G. Carmadi, R. Clifton, N. Comfort, S. Culp, F. di Poppa, G. Gale, S. Glennan, N. Hall, L. Holmes, T. Iseda, J. Josephson, J. Lederberg, J. E. McGuire, G. Piccinini, P. Pietroski, H. Rheinberger, W. Salmon, S. Sastry, K. Schaffner, R. Skipper, P. Speh, D. Thaler, and N. Urban. Lindley Darden's work was supported by the General Research Board of the Graduate School of the University of Maryland and as a Fellow in the Center for Philosophy of Science at the University of Pittsburgh; Carl Craver's work was supported by a Cognitive Studies Postdoctoral Fellowship of the Department of Philosophy of the University of Maryland. Both Lindley Darden and Carl Craver were supported by a National Science Foundation Grant (SBR-9817942); any opinions, findings and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect those of the National Science Foundation.

Philosophy of Science, 67 (March 2000) pp. 1–25. 0031-8248/2000/6701-0001$2.00

surprising that much of the practice of science can be understood in terms of the discovery and description of mechanisms. Our goal is to sketch a mechanistic approach for analyzing neurobiology and molecular biology that is grounded in the details of scientific practice, an approach that may well apply to other scientific fields.

Mechanisms have been invoked many times and places in philosophy and science. A key word search on "mechanism" for 1992–1997 in titles and abstracts of *Nature* (including its subsidiary journals, such as *Nature Genetics*) found 597 hits. A search in the *Philosophers' Index* for the same period found 205 hits. Yet, in our view, there is no adequate analysis of what mechanisms are and how they work in science.

We begin (Section 2) with a dualistic analysis of the concept of mechanism in terms of both the *entities* and *activities* that compose them. Section 3 argues for the ontic adequacy of this dualistic approach and indicates some of its implications for analyses of functions, causality, and laws. Section 4 uses the example of the mechanism of neuronal depolarization to demonstrate the adequacy of the mechanism definition. Section 5 characterizes the descriptions of mechanisms by elaborating such aspects as hierarchies, bottom out activities, mechanism schemata, and sketches. This section also suggests a historiographic point to the effect that much of the history of science might be viewed as written with the notion of mechanism. Another example in Section 6, the mechanism of protein synthesis, shows how thinking about mechanisms illuminates aspects of discovery and scientific change. The final sections hint at new ways to approach and solve or dissolve some major philosophical problems (viz., explanation and intelligibility in Section 7 and reduction in Section 8). These arguments are not developed in detail but should suffice to show how thinking about mechanisms provides a distinctive approach to many problems in the philosophy of science.

Quickly, though, we issue a few caveats. First, we use "mechanism" because the word is commonly used in science. But as we shall detail more precisely, one should not think of mechanisms as exclusively mechanical (push-pull) systems. What counts as a mechanism in science has developed over time and presumably will continue to do so. Second, we will confine our attention to mechanisms in molecular biology and neurobiology. We do not claim that all scientists look for mechanisms or that all explanations are descriptions of mechanisms. We suspect that this analysis is applicable to many other sciences, and maybe even to cognitive or social mechanisms, but we leave this as an open question. Finally, many of our points are only provocatively and briefly stated. We believe there are full arguments for these points but detailing them here would obscure the overall vision.

2. Mechanisms. Mechanisms are sought to explain how a phenomenon comes about or how some significant process works. Specifically:

> Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions.

For example, in the mechanism of chemical neurotransmission, a presynaptic neuron transmits a signal to a post-synaptic neuron by releasing neurotransmitter molecules that diffuse across the synaptic cleft, bind to receptors, and so depolarize the post-synaptic cell. In the mechanism of DNA replication, the DNA double helix unwinds, exposing slightly charged bases to which complementary bases bond, producing, after several more stages, two duplicate helices. Descriptions of mechanisms show how the termination conditions are produced by the set-up conditions and intermediate stages. To give a description of a mechanism for a phenomenon is to explain that phenomenon, i.e., to explain how it was produced.

Mechanisms are composed of both *entities* (with their properties) and *activities*. Activities are the producers of change. Entities are the things that engage in activities. Activities usually require that entities have specific types of properties. The neurotransmitter and receptor, two entities, bind, an activity, by virtue of their structural properties and charge distributions. **A** DNA base and a complementary base hydrogen bond because of their geometric structures and weak charges. The organization of these entities and activities determines the ways in which they produce the phenomenon. Entities often must be appropriately located, structured, and oriented, and the activities in which they engage must have a temporal order, rate, and duration. For example, two neurons must be spatially proximate for diffusion of the neurotransmitter. Mechanisms are regular in that they work always or for the most part in the same way under the same conditions. The regularity is exhibited in the typical way that the mechanism runs from beginning to end; what makes it regular is the ***productive continuity*** between stages. Complete descriptions of mechanisms exhibit productive continuity without gaps from the set up to termination conditions. Productive continuities are what make the connections between stages intelligible. If a mechanism is represented schematically by A→B→C, then the continuity lies in the arrows and their explication is in terms of the activities that the arrows represent. A missing arrow, namely, the inability to specify an activity, leaves an explanatory gap in the productive continuity of the mechanism.

We are not alone in thinking that the concept of "mechanism" is central to an adequate philosophical understanding of the biological sciences. Others have argued for the importance of mechanisms in biology (Bechtel and Richardson 1993, Brandon 1985, Kauffman 1971, Wimsatt 1972) and molecular biology in particular (Burian 1996, Crick 1988). Wimsatt, for example, says that, "At least in biology, most scientists see their work as

explaining types of phenomena by discovering mechanisms . . ." (Wimsatt 1972, 67). Schaffner often gestures to the importance of mechanisms in biology and medicine, but argues, following Mackie (1974), that talk of causal mechanisms is dependent upon prior and more fundamental talk of "laws of working" (Schaffner 1993, 287, 306-307). Elsewhere Schaffner claims that "mechanism," as used by Wimsatt and others, is an "unanalyzed term" that he wishes to avoid (Schaffner 1993, 287).

When the notion of a "mechanism" has been analyzed, it has typically been analyzed in terms of the decomposition of "systems" into their "parts" and "interactions" (Wimsatt 1976; Bechtel and Richardson 1993). Following in this "interactionist" tradition, Glennan (1992; 1996) defines a mechanism as follows:

> A mechanism underlying a behavior is a complex system which produces that behavior by . . . the interaction of a number of parts according to direct causal laws. (Glennan 1996, 52)

He claims that all causal laws are explicated by providing a lower level mechanism until one bottoms out in the fundamental, non-causal laws of physics. We find Glennan's reliance on the concept of a "law" problematic because, in our examples, there are rarely "direct causal laws" to characterize how activities operate. More importantly, as we argue in Section 3, the interactionist's reliance on laws and interactions seems to us to leave out the productive nature of activities.

Our way of thinking emphasizes the *activities* in mechanisms. The term "activity" brings with it appropriate connotations from its standard usage; however, it is intended as a technical term. An activity is usually designated by a verb or verb form (participles, gerundives, etc.). Activities are the producers of change. They are constitutive of the transformations that yield new states of affairs or new products. Reference to activities is motivated by ontic, descriptive, and epistemological concerns. We justify this break from parsimony, this dualism of entities and activities, by reference to these philosophical needs.

3. Ontic Status of Mechanisms (Ontic Adequacy). Both activities and entities must be included in an adequate *ontic* account of mechanisms. Our analysis of the concept of mechanism is explicitly dualist. We are attempting to capture the healthy philosophical intuitions underlying both substantivalist and process ontologies. Substantivalists confine their attention to entities and properties, believing that it is possible to reduce talk of activities to talk of properties and their transitions. Substantivalists thus speak of entities with capacities (Cartwright 1989) or dispositions to act. However, in order to identify a capacity of an entity, one must first identify the activities in which that entity engages. One does not know that aspirin

has the capacity to relieve a headache unless one knows that aspirin produces headache relief. Substantivalists also talk about interactions of entities (Glennan 1996) or their state transitions. We think state transitions have to be more completely described in terms of the activities of the entities and how those activities produce changes that constitute the next stage. The same is true of talk of interactions, which emphasizes spatiotemporal intersections and changes in properties without characterizing the productivity by which those changes are effected at those intersections.

Substantivalists appropriately focus attention upon the entities and properties in mechanisms, e.g., the neurotransmitter, the receptor, and their charge configurations or DNA bases and their weak polarities. It is the entities that engage in activities, and they do so by virtue of certain of their properties. This is why statistical relevance relations (cf. Salmon 1984) between the properties of entities at one time and the properties of entities at another (or generalizations stating "input-output" relations and state changes) are useful for describing mechanisms. Yet it is artificial and impoverished to describe mechanisms solely in terms of entities, properties, interactions, inputs-outputs, and state changes over time. Mechanisms do things. They are active and so ought to be described in terms of the activities of their entities, not merely in terms of changes in their properties.

In contrast to substantivalists, process ontologists reify activities and attempt to reduce entities to processes (cf. Rescher 1996). While process ontology does acknowledge the importance of active processes by taking them as fundamental ontological units, its program for entity reduction is problematic at best. As far as we know, there are no activities in neurobiology and molecular biology that are not activities *of* entities. Nonetheless, the process ontologists appropriately highlight the importance of active kinds of changing. There are kinds of changing just as there are kinds of entities. These different kinds are recognized by science and are basic to the ways that things work.

Activities are identified and individuated in much the same way as are entities. Traditionally one identifies and individuates entities in terms of their properties and spatiotemporal location. Activities, likewise, may be identified and individuated by their spatiotemporal location. They also may be individuated by their rate, duration, types of entities and types of properties that engage in them. More specific individuation conditions may include their mode of operation (e.g., contact action versus attraction at a distance), directionality (e.g., linear versus at right angles), polarity (attraction versus attraction and repulsion), energy requirements (e.g., how much energy is required to form or break a chemical bond), and the range of activity (e.g., electro-magnetic forces have a wider influence than do the strong and weak forces in the nucleus). Often, generalizations or

laws are statements whose predicates refer to the entities and properties that are important for the individuation of activities. Mechanisms are identified and individuated by the activities and entities that constitute them, by their start and finish conditions, and by their functional roles.

Functions are the roles played by entities and activities in a mechanism. To see an activity as a function is to see it as a component in some mechanism, that is, to see it in a context that is taken to be important, vital, or otherwise significant. It is common to speak of functions as properties "had by" entities, as when one says that the heart "has" the function of pumping blood or the channel "has" the function of gating the flow of sodium. This way of speaking reinforces the substantivalist tendency against which we have been arguing. Functions, rather, should be understood in terms of the activities by virtue of which entities contribute to the workings of a mechanism. It is more appropriate to say that the function of the heart is to pump blood and thereby deliver (with the aid of the rest of the circulatory system) oxygen and nutrients to the rest of the body. Likewise, a function of sodium channels is to gate sodium current in the production of action potentials. To the extent that the activity of a mechanism as a whole contributes to something in a context that is taken to be antecedently important, vital, or otherwise significant, that activity too can be thought of as the (or a) function of the mechanism as a whole (Craver 1998, Craver under review).

Entities and a specific subset of their properties determine the activities in which they are able to engage. Conversely, activities determine what types of entities (and what properties of those entities) are capable of being the basis for such acts. Put another way, entities having certain kinds of properties are necessary for the possibility of acting in certain specific ways, and certain kinds of activities are only possible when there are entities having certain kinds of properties. Entities and activities are correlatives. They are interdependent. An ontically adequate description of a mechanism includes both.

3.1. Activities and Causing. Activities are types of causes. Terms like "cause" and "interact" are abstract terms that need to be specified with a type of activity and are often so specified in typical scientific discourse. Anscombe (1971, 137) noted that the word "cause" itself is highly general and only becomes meaningful when filled out by other, more specific, causal verbs, e.g., scrape, push, dry, carry, eat, burn, knock over. An entity acts as a cause when it engages in a productive activity. This means that objects *simpliciter,* or even natural kinds, may be said to be causes only in a derivative sense. It is not the penicillin that causes the pneumonia to disappear, but what the penicillin does.

Mackie's (1974) attempt to analyze the necessity of causality in terms

of laws of working is similar to our analysis in many ways. He stresses that laws of working must be discovered empirically and are not found a priori (213, 221). He also claims that counterfactuals are supported by the inductive evidence that such basic processes are at work (229). However, he wants to analyze causality in terms of qualitative or structural continuity of processes (224), and more vaguely in terms of "flowing from" or "extruding" (226). It is unclear how to apply such concepts in our biological cases. But perhaps he is trying to use them to refer to what we call "activities" and to capture what we mean by "productivity."

Our emphasis on mechanisms is compatible, in some ways, with Salmon's mechanical philosophy, since mechanisms lie at the heart of the mechanical philosophy. Mechanisms, for Salmon, are composed of processes (things exhibiting consistency of characteristics over time) and interactions (spatiotemporal intersections involving persistent changes in those processes). It is appropriate to compare our talk of activities with Salmon's talk of interactions. Salmon identifies interactions in terms of transmitted marks and statistical relevance relations (Salmon 1984) and, more recently, in terms of exchanges of conserved quantities (Salmon 1997, 1998). Although we acknowledge the possibility that Salmon's analysis may be all there is to certain fundamental types of interactions in physics, his analysis is silent as to the character of the productivity in the activities investigated by many other sciences. Mere talk of transmission of a mark or exchange of a conserved quantity does not exhaust what these scientists know about productive activities and about how activities effect regular changes in mechanisms. As our examples will show, much of what neurobiologists and molecular biologists do should be seen as an effort to understand these diverse kinds of production and the ways that they work.

3.2. Activities and Laws. The traditional notion of a universal law of nature has few, if any, applications in neurobiology or molecular biology. Sometimes the regularities of activities can be described by laws. Sometimes they cannot. For example, Ohm's law is used to describe aspects of the activities in the mechanisms of neurotransmission. There is no law that describes the regularities of protein binding to regions of DNA. Nonetheless, the notion of activity carries with it some of the characteristic features associated with laws. Laws are taken to be determinate regularities. They describe something that acts in the same way under the same conditions, i.e., same cause, same effect. (Schaffner 1993, 122, calls these "universal generalizations$_2$.") This is the same way we talk about mechanisms and their activities. A mechanism is the series of activities of entities that bring about the finish or termination conditions in a regular way. These regularities are non-accidental and support counterfactuals to the extent that

they describe activities. For example, if this single base in DNA were changed and the protein synthesis mechanism operated as usual, then the protein produced would have an active site that binds more tightly. This counterfactual justifies talking about mechanisms and their activities with some sort of necessity. No philosophical work is done by positing some further thing, a law, that underwrites the productivity of activities.

In sum, we are dualists: both entities and activities constitute mechanisms. There are no activities without entities, and entities do not do anything without activities. We have argued for the ontic adequacy of this dualism by showing that it can capture insights of both substantivalists and process ontologists, by showing how activities are needed to specify the term "cause," and by an analysis of activities showing their regularity and necessity sometimes characterized by laws.

4. Example of a Mechanism (Descriptive Adequacy). Consider the classic textbook account of the mechanisms of chemical transmission at synapses (Shepherd 1988). Chemical transmission can be understood abstractly as the activity of converting an electrical signal in one neuron, the relevant entity, into a chemical signal in the synapse. This chemical signal is then converted to an electrical signal in a second neuron. Consider Shepherd's diagram in Figure 1.

The diagram is a two-dimensional spatial representation of the entities, properties, and activities that constitute these mechanisms. Mechanisms are often represented this way. Such diagrams exhibit spatial relations and structural features of the entities in the mechanism. Labeled arrows often represent the activities that produce changes. In these ways, diagrams represent features of mechanisms that could be described verbally but are more easily apprehended in visual form.

In Shepherd's diagram, the entities are almost exclusively represented pictorially. These include the cell membrane, vesicles, microtubules, molecules, and ions. The activities are represented with labeled arrows. These include biosynthesis, transport, depolarization, insertion, storage, recycling, priming, diffusion, and modulation. The diagram is complicated in its attempt to represent the many different mechanisms that can be found at chemical synapses. We use the first stage of this mechanism, *depolarization,* to exhibit the features of mechanisms in detail.

Neurons are electrically polarized in their resting state (i.e., their resting membrane potential, roughly -70 mV); the fluid inside the cell membrane is negatively charged with respect to the fluid outside of the cell. Depolarization is a positive change in the membrane potential. Neurons depolarize when sodium (Na^+) selective channels in the membrane open, allowing Na^+ to move into the cell by diffusion and electrical attraction. The resulting changes in ion distribution make the intracellular fluid pro-

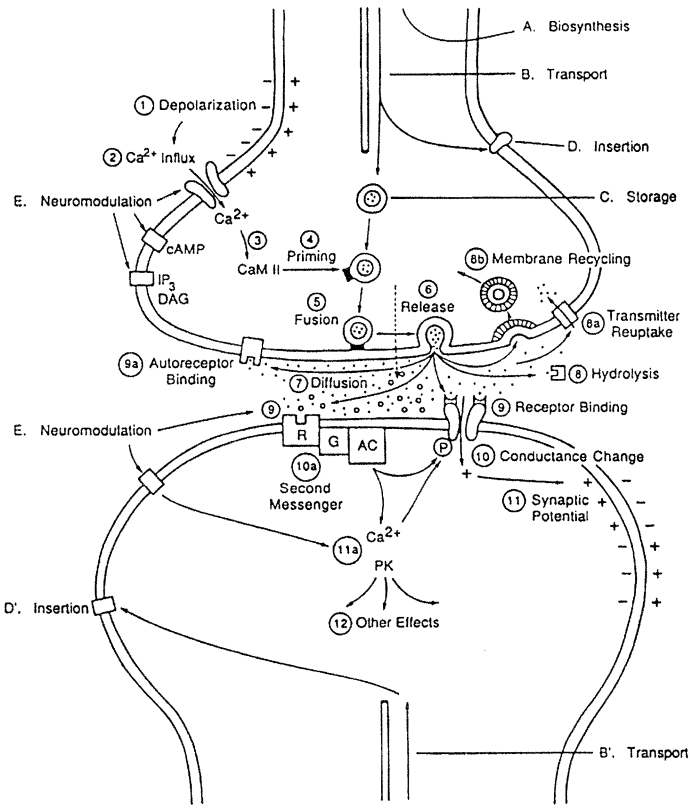

Fig. 4.8 A summary of some of the main biochemical mechanisms that have been identified at chemical synapses. A–E. Long-term steps in synthesis, transport, and storage of neurotransmitters and neuromodulators; insertion of membrane channel proteins and receptors; and neuromodulatory effects. ①–⑫. These summarize the more rapid steps involved in immediate signaling at the synapse. These steps are described in the text, and are further discussed for different types of synapses in Chapter 8. Abbrevations: IP_3, inositol triphosphate; CAM II, Ca/calmodulin-dependent protein kinase II; DAG, diacylglycerol; PK, protein kinase; R, receptor; G, G protein; AC, adenylate cyclase.

Figure 1. Biochemical mechanisms at chemical synapses. From Gordon M. Shepherd, *Neurobiology*, 3/e; © 1994 by Oxford University Press, Inc. Reproduced by permission.

gressively less negative and, eventually, more positive than the extracellular fluid (peaking at roughly +50 mV). Shepherd represents this change in the top left of Figure 1 with pluses (+) inside and minuses (−) outside the membrane of the presynaptic cell. Figure 2, which we have drawn from Hall's (1992) verbal description of the voltage sensitive Na^+ channel, is an idealized close up of the mechanism by which the pluses in Figure 1 (actually Na^+ ions) get inside the neuronal membrane. The panels in Fig-

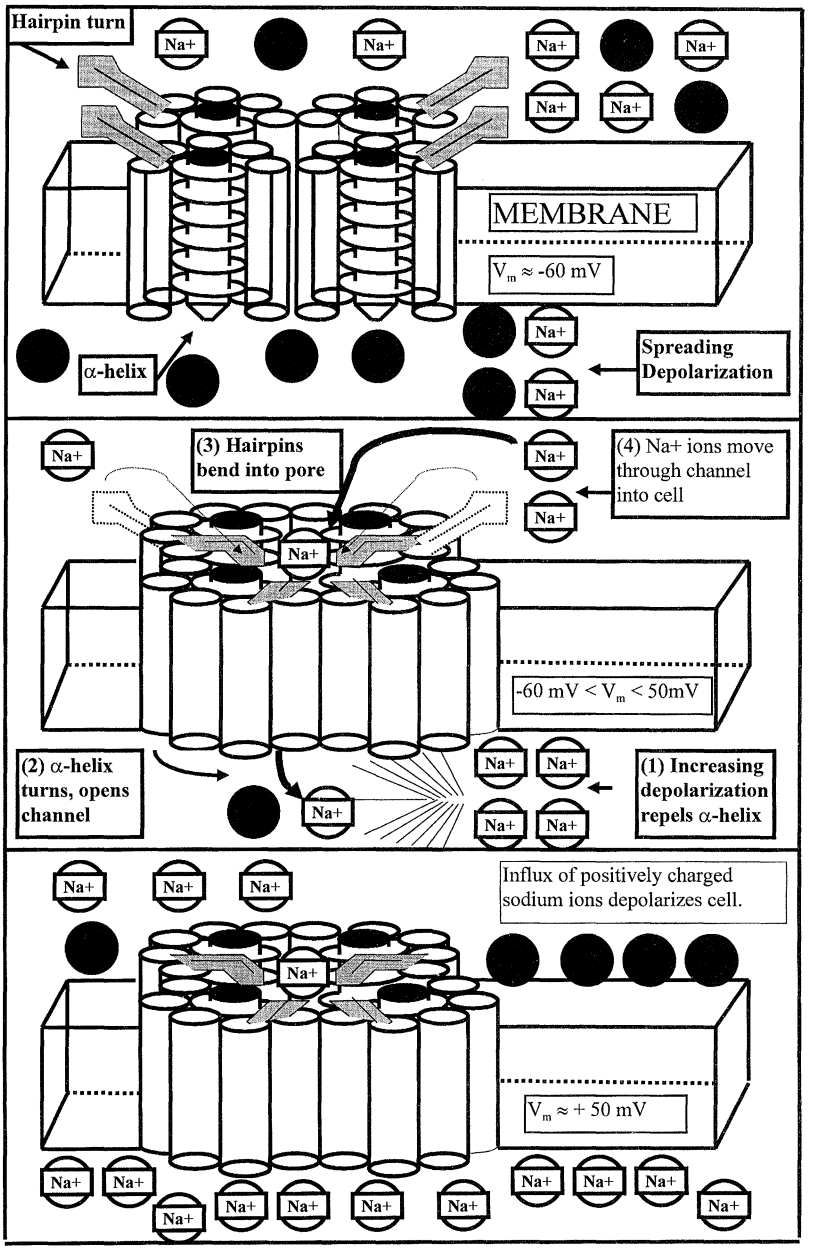

Figure 2. An idealized voltage-sensitive Na + channel and the mechanisms of depolarization. Panels (top to bottom) represent set-up conditions, intermediate activities, and termination conditions (modeled on verbal description in Hall 1992).

ure 2 represent, from top to bottom, the set-up conditions, intermediate activities, and termination conditions of the depolarization mechanism.

4.1. Set-Up Conditions. Descriptions of mechanisms begin with idealized descriptions of the start or set-up conditions. These conditions may be the result of prior processes, but scientists typically idealize them into static time slices taken as the beginning of the mechanism. The start conditions include the relevant entities and their properties. Structural properties, spatial relations, and orientations are often crucial for showing how the entities will be able to carry out the activities comprising the first stage of the mechanism. The set-up also includes various enabling conditions (such as available energy, pH, and electrical charge distributions). For simplicity in, e.g., textbook descriptions, many of these conditions are omitted, and only the crucial entities and structural descriptions appear. Among relevant entities and properties, some are crucial for showing how the next step will go. The bulk of the features in the set-up (spatial, structural, and otherwise) are not inputs into the mechanism but are parts of the mechanism. They are crucial for showing what comes next; thus we avoid talk of "inputs," "outputs," and "state changes" in favor of "set-up conditions," "termination conditions," and "intermediate stages" of entities and activities.

The lines of pluses and minuses along the membrane at the top of the Shepherd diagram represent the spreading depolarization of the axon, a crucial set-up condition for the depolarization of the axon terminal. This set-up condition is labeled in the top panel of Figure 2.

Also crucial are the locations, orientations, and charge distributions of the components of the Na^+ channel and the differential intra- and extracellular concentrations of Na^+. Two structural features of the Na^+ channel are crucial; each is depicted in the top panel of Figure 2. The first is the corkscrew shaped portion of the protein (an alpha helix) known as the "voltage gate." It contains evenly spaced, positively charged amino acids. The second is a hairpin turn in the protein, known as the "pore lining," that has its own particular configuration of charges. Other factors important for the activity of the mechanism include temperature, pH, and the presence or absence of pharmacological agonists or antagonists; such factors are the contents of the *ceteris paribus* clauses often implicit in descriptions of the channel's activity. The structural and spatial set-up conditions are not inputs to the mechanism; neither are temperature and pH. Yet these factors and relations are crucial to seeing how the mechanism will go.

4.2. Termination Conditions. Descriptions of mechanisms end with finish or termination conditions. These conditions are idealized states or parameters describing a privileged endpoint, such as rest, equilibrium, neu-

tralization of a charge, a repressed or activated state, elimination of something, or the production of a product. There are various reasons why such states are privileged. For example, the end product may be the production of a particular kind of entity or state of affairs that we set out to understand or create. Or, it may be the final stage of what is identified as a unitary, integral process. The termination conditions are most often idealized as end points or final products; misleadingly, they are called "outputs."

In the case of the depolarization mechanism, we take the termination condition to be an increase in intracellular Na^+ concentration and a corresponding increase in membrane voltage. This is illustrated in the bottom panel of Figure 2. This condition is privileged, and so a termination condition, because it is the end of what is taken to be a unitary process, namely, the depolarization of the axon terminal. This is illustrated in the bottom panel of Figure 2 as the Na^+ channels lining up against the intracellular membrane surface. Calling this termination stage the "output" inaccurately suggests something comes out.

4.3. Intermediate Activities. Obviously, mechanisms are made up of more than their set-up and termination conditions. In addition, complete descriptions of mechanisms characterize the intervening entities and activities that produce the end from the beginning. A description of a mechanism describes the relevant entities, properties, and activities that link them together, showing how the actions at one stage affect and effect those at successive stages. In a complete description of mechanism, there are no gaps that leave specific steps unintelligible; the process as a whole is rendered intelligible in terms of entities and activities that are acceptable to a field at a time. In the simplest case, the stages of a mechanism are organized linearly, but they also may be forks, joins, or cycles. Often, mechanisms are continuous processes that may be treated for convenience as a series of discrete stages or steps.

Look again at the depolarization example. The activities by which the cell will depolarize are presaged in the set-up conditions. These intermediate activities are presented in the central panel of Figure 2. The spreading depolarization from the axonal action potential (1) repels the positive charges in the alpha helix voltage gates, (2) rotates them about their central axis and opens a pore or channel through the membrane. The resulting conformation change in (or bending of) the protein (3) moves the extracellular hairpins into the pore. The particular configuration of charges on this pore lining makes the channel selective for Na^+. As a result, (4) Na^+ ions move through the pore and into the cell. This increase in intracellular Na^+ concentration depolarizes the axon terminal (see the final panel, Figure 2). Although we may describe or represent these intermediate activities

as stages in the operation of the mechanism, they are more accurately viewed as continuous processes. As the axonal depolarization spreads, the repulsive forces acting on the positive charges in the corkscrew are increasingly pushed outward, rotating the helix and opening the Na^+ selective channel pore.

The activities of the voltage-sensitive Na+ channel are thus crucial components in the depolarization mechanism. It is through these activities of these entities that we understand how depolarization occurs.

5. Hierarchies, Bottoming Out, Mechanism Schemata, and Sketches. Mechanisms occur in nested hierarchies and the descriptions of mechanisms in neurobiology and molecular biology are frequently multi-level. The levels in these hierarchies should be thought of as part-whole hierarchies with the additional restriction that lower level entities, properties, and activities are components in mechanisms that produce higher level phenomena (Craver 1998, Craver and Darden forthcoming). For example, the activation of the sodium channel is a component of the mechanism of depolarization, which is a component of the mechanism of chemical neurotransmission, which is a component of most higher-level mechanisms in the central nervous system. Similar hierarchies can be found in molecular biology. James Watson (1965) discusses mechanisms for forming strong and weak chemical bonds, which are components of the mechanisms of replication, transcription, and translation of DNA and RNA, respectively, which are components of the mechanisms of numerous cell activities.

5.1. Bottoming Out. Nested hierarchical descriptions of mechanisms typically *bottom out* in lowest level mechanisms. These are the components that are accepted as relatively fundamental or taken to be unproblematic for the purposes of a given scientist, research group, or field. Bottoming out is relative: Different types of entities and activities are where a given field stops when constructing mechanisms. The explanation comes to an end, and description of lower-level mechanisms would be irrelevant to their interests. Also, scientific training is often concentrated at or around certain levels of mechanisms. Neurobiologists with different theoretical or experimental interests bottom out in different types of entities and activities. Some neurobiologists are primarily interested in behaviors of organisms, some are primarily interested in the activities of molecules composing nerves cells, and others devote their attention to phenomena in between. The fields of molecular biology and neurobiology, in 1999, do not typically regress to the quantum level to talk about the activities of, e.g., chemical bonding. Rarely are biologists driven by anomalies or any other reason to go to such lower levels, although some problem might require it. Levels below molecules and chemical bonding are not fundamental for the fields

of molecular biology and molecular neurobiology. But remember, what is considered the bottom out level may change.

In molecular biology and molecular neurobiology, hierarchies of mechanisms bottom out in descriptions of the activities of macromolecules, smaller molecules, and ions. These are commonly recognized as bottom out entities; we believe that we have identified the most important types of bottom out activities. These bottom out activities in molecular biology and molecular neurobiology can be categorized into four types:

(i) geometrico-mechanical;
(ii) electro-chemical;
(iii) energetic;
(iv) electro-magnetic.

(i) Geometrico-mechanical activities are those familiar from seventeenth-century mechanical philosophy. They include fitting, turning, opening, colliding, bending, and pushing. The rotation of the alpha helix in the sodium channel and the geometrical fitting of a neurotransmitter and a post-synaptic receptor are examples of geometrico-mechanical activities.

(ii) Attracting, repelling, bonding, and breaking are electro-chemical kinds of activity. Chemical bonding, such as the formation of strong covalent bonds between amino acids in proteins, is a more specific example. The lock and key docking of an enzyme and its substrate involves geometrical shape and mechanical stresses and chemical attractions. As we will see, the historical development of the mechanism of protein synthesis required finding an activity to order linearly the constituents of the protein, its amino acids; an early idea using primarily geometrico-mechanical activities was replaced by one involving, primarily, the weak electrochemical activities of hydrogen bonding.

(iii) Energetic activities have thermodynamics as their source. **A** kind of energetic activity involves simple diffusion of a substance, as, for example, when concentrations on different sides of a membrane lead to movement of substances across the membrane.

(iv) Electro-magnetic activities are occasionally used to bottom out mechanisms in these sciences. The conduction of electrical impulses by nerve cells and the navigational mechanisms of certain marine species are examples.

5.2. ***An*** *Historical Aside.* These categories of relatively fundamental activities suggest an historical strategy for examining the history of mechanisms. The discovery and individuation of different entities and activities are important parts of scientific practice. In fact, much of the history of science has been well written, albeit unwittingly, by tracing the discoveries of new entities and activities that mark the changes in a discipline.

The modern idea of explaining with mechanisms became current in the seventeenth century when Galileo articulated a geometrico-mechanical form of explanation based on Archimedes's simple machines (Machamer 1998). Soon an expanded version of this geometrico-mechanical way of describing and thinking about the world became widespread across Europe (and the New World) and was called the "mechanical philosophy."

In the eighteenth and nineteenth centuries, chemists and electricians began to discover and describe other entities and activities that they took as fundamental to the structure of the world, and so expanded the concept of what could occur in mechanisms. The nineteenth century also saw an emerging emphasis on the concept of energy and electromagnetism. These different kinds of forces acting were new and different kinds of activities.

In every case, scientists were compelled to add new entities and new forms of activity in order to better explain how the world works. To do this they would postulate an entity or activity, present criteria for its identification and recognition, and display the patterns by which these formed a unity that constituted a mechanism. These became the new laws or ways of working of the various sciences. Documenting such new entities and activities allows us to map out the changes that become the substance of the history of science.

This pastiche of history is a quick and simplistic way to show that the discovery of different kinds of mechanisms with their kinds of entities and different activities is an important part of scientific development. Contemporary sciences such as neurobiology and molecular biology are in this tradition and draw on the entities and activities made available through some of these historical discoveries.

The history of these changes implies that what count as acceptable types of entities, activities, and mechanisms change with time. At different historical moments, in different fields, different mechanisms, entities, and activities have been discovered and accepted. The set of types of entities and activities so far discovered likely is not complete. Further developments in science will lead to the discovery of additional ones.

5.3. Mechanism Schemata and Sketches. Scientists do not always provide complete descriptions of mechanisms at all levels in a nested hierarchy. Also, they are typically interested in types of mechanisms, not all the details needed to describe a specific instance of a mechanism. We introduce the term "mechanism schema" for an abstract description of a type of mechanism. A *mechanism schema* is a truncated abstract description of a mechanism that can be filled with descriptions of known component parts and activities. An example is represented in Watson's (1965) diagram of the central dogma of molecular biology (see Figure 3).

Schemata exhibit varying degrees of abstraction, depending on how

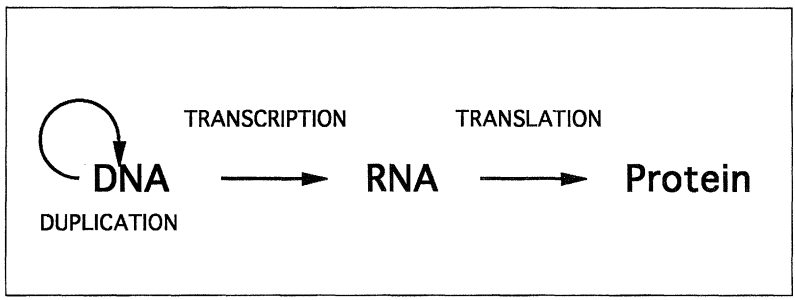

Figure 3. Watson's central dogma diagram (redrawn, based on Watson 1965).

much detail is included. Abstractions may be constructed by taking an exemplary case or instance and removing detail. For example, a constant can be made into a variable (Darden 1995). A particular DNA sequence may be abstracted to any DNA sequence. Often, scientists use schema terms, such as "transcription" and "translation," to capture compactly many aspects of the underlying mechanism. These may be characterized as activities in higher-level mechanisms.

Degrees of abstraction should not be confused with degrees of generality or scope (Darden 1996). Abstraction is an issue of the amount of detail included in the description of one or more mechanism instances. The generality of a schema is the scope (small or large) of the domain in which it can be instantiated. One can describe a single instance of a mechanism more or less abstractly. Alternatively, the schema, at whatever degree of abstraction, may have a quite general scope. The schema for the central dogma is nearly terrestrially universal, holding for most instances of protein synthesis in most species. However, the schema for protein synthesis in some RNA viruses is just

RNA→protein.

In other RNA retroviruses, it is

RNA→DNA→RNA→protein.

These schemata are just as abstract as Watson's schema of the central dogma (Figure 3) but they are much more limited in scope.

Neurobiologists and molecular biologists sometimes use the term "theory" to refer to hierarchically organized mechanism schemata of variable, though generally less than universal, scope. Mechanism schemata, as well as descriptions of particular mechanisms, play many of the roles attributed to theories. They are discovered, evaluated, and revised in cycles as science

proceeds. They are used to describe, predict, and explain phenomena, to design experiments, and to interpret experimental results.

Thinking about mechanisms as composed of entities and activities provides resources for thinking about strategies for scientific change. Known types of entities and activities in a field provide the intelligible building blocks from which to construct hypothesized mechanism schemata. If one knows what kind of activity is needed to do something, then one seeks kinds of entities that can do it, and vice versa. Scientists in the field often recognize whether there are known types of entities and activities that can possibly accomplish the hypothesized changes and whether there is empirical evidence that a possible schemata is plausible.

When instantiated, mechanism schemata yield mechanistic explanations of the phenomenon that the mechanism produces. For example, the schema for the Na^+ channel depicted in Figure 2, when instantiated, can be used to explain the depolarization of a specific nerve cell. Mechanism schemata can also be specified to yield predictions. For example, the order of the amino acids in a protein can be predicted from specification of the central dogma schema that includes a specific order of DNA bases in its coding region. Third, schemata provide "blueprints" for designing research protocols (Darden and Cook 1994). A technician can instantiate a schema in an experiment by actually choosing physical instantiations of each of the entities and the set-up conditions and letting the mechanism work. While the mechanism is operating, the experimenter may intervene to alter some part of the mechanism and observe the changes in a termination condition or what the mechanism does. Changes produced by such interventions can provide evidence for the hypothesized schema (Craver and Darden forthcoming).

When a prediction made on the basis of a hypothesized mechanism fails, then one has an anomaly and a number of responses are possible. If the experiment was conducted properly and the anomaly is reproducible, then perhaps something other than the hypothesized mechanism schema is at fault, such as hypotheses about the set-up conditions. If the anomaly cannot be resolved otherwise, then the hypothesized schema may need to be revised. One might abandon the entire mechanism schema and propose a new one. Alternatively, one can revise a portion of the failed schema. Reasoning in the light of failed predictions involves, first, a diagnostic process to isolate where the mechanism schema is failing, and, then, a redesign process to change one or more entities or activities or stages to improve the hypothesized schema (Darden 1991, 1995).

Mechanism schemata can be instantiated in biological wet-ware (as in the experimental case discussed above) or represented in the hardware of a machine. For example, a computational biologist can write an algorithm that depicts the relations between the order of DNA bases, RNA bases,

and amino acids in proteins. This algorithm represents the mechanism schema of the central dogma. Yet the algorithm itself becomes an actual mechanism of a very different kind when written in a programming language and instantiated in hardware that can run it as a simulation.

For epistemic purposes, a *mechanism sketch* may be contrasted with a schema. A sketch is an abstraction for which bottom out entities and activities cannot (yet) be supplied or which contains gaps in its stages. The productive continuity from one stage to the next has missing pieces, black boxes, which we do not yet know how to fill in. A sketch thus serves to indicate what further work needs to be done in order to have a mechanism schema. Sometimes a sketch has to be abandoned in the light of new findings. In other cases it may become a schema, serving as an abstraction that can be instantiated as needed for the tasks mentioned above, e.g., explanation, prediction, and experimental design.

6. Case Study: Discovering the Mechanism of Protein Synthesis. The discovery of the mechanism of protein synthesis illustrates piecemeal discovery of a mechanism schema, with different components discovered by different fields. It also emphasizes the importance of finding the activities, as well as the entities, during mechanism discovery.

Prior to the discovery of messenger RNA (mRNA), biochemists and molecular biologists proposed mechanisms for protein synthesis focusing on different entities and activities. The contrasting mechanism schemata are vividly illustrated in two diagrams (see Figure 4): one by Zamecnik, a biochemist, and the other by Watson, a molecular biologist.

Zamecnik's 1953 diagram focuses upon energy production (formation of ATP) and the activation of amino acids prior to their incorporation into the protein's polypeptide chain. It depicts the microsomes (labeled 3 in the diagram) as the site of protein synthesis. (Microsomes were later shown to be ribosomes associated with other cellular components; see Zamecnik 1969, discussed in Rheinberger 1997.) This diagram clearly lacks any step for ordering the amino acids as they are incorporated into the protein. Although the nucleic acid RNA was known to be part of the microsomes, Zamecnik does not explicitly represent any nucleic acids as component entities of the mechanism. The biochemist's diagram is therefore an incomplete sketch; it lacks crucial entities and, more importantly, any reference to activities capable of ordering the amino acids.'

1. In a letter of December 8, 1999, Zamecnik recalls that they were aware of the need to include a role for DNA, beginning in 1944, because of Avery's work. Sanger's presentation in 1949 at the Cold Spring Harbor Symposium at which Zamecnik spoke showed that protein sequences did not have simple repeats. Watson and Zamecnik were discussing connections between their work, beginning with a visit in 1954 and subsequent contacts. The role of **RNA** was also being considered as an intermediary because

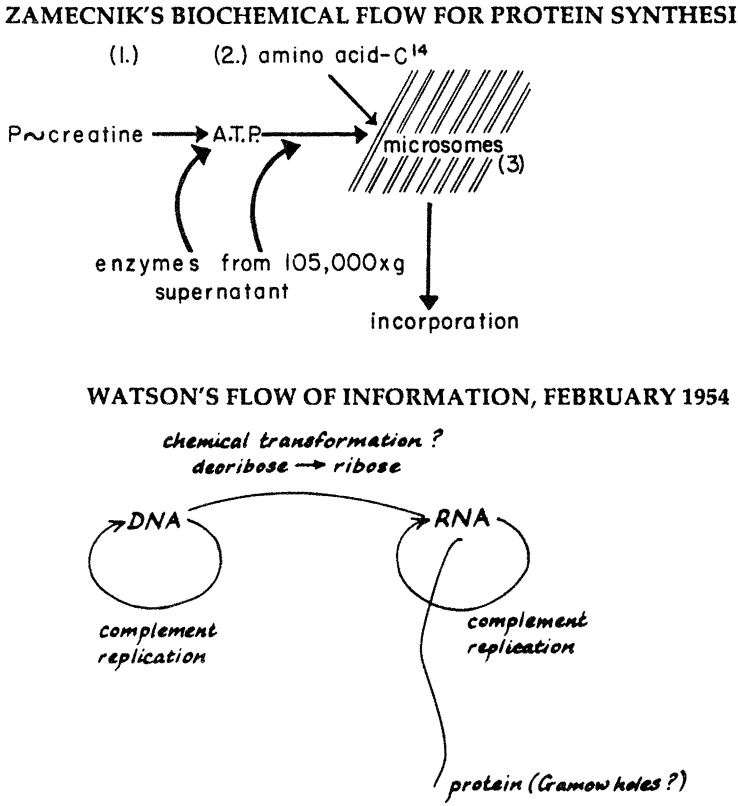

Figure 4. Biochemical and molecular biological sketches for protein synthesis. (From Horace Judson, *The Eighth Day of Creation*, expanded edition; © 1996 by Cold Spring Harbor Press. Used by permission of CSHP, James Watson, and Paul Zamecnik.)

Watson's 1954 diagram exhibits the molecular biological focus on the activities of the nucleic acids, DNA and RNA. It depicts an early, geometrico-mechanical schema for determining the order of the amino acids. George Gamow (1954), a physicist, had proposed that proteins were synthesized directly on the DNA double helix by fitting into "holes" in the helix (more technically, the major and minor grooves of the helix). Watson was aware of biochemical evidence that proteins do not form directly on DNA but instead are associated with RNA. Modifying Gamow's idea in

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of work by others. He concludes with an apt metaphor showing how the two lines of investigation were joined: "As in building a transcontinental railroad, one team starts from San Francisco, and the other from the mid-continent. They are both conscious of the way the compass is pointing, if they are to meet somewhere in the middle."

light of this evidence, Watson proposed that RNA had "Gamow holes" whose shapes were determined by the surrounding bases. Different amino acids would then fit into different holes. The ordering of the RNA bases determined the shape of the sequential holes and, therefore, the ordering of the amino acids (via a geometrico-mechanical activity). After amino acids fell into the holes, adjacent amino acids would covalently bond (an electro-chemical activity) to one another, forming the protein (discussed in Watson 1962).

This geometrical "holes" schema was plausible: It provided entities and activities that could produce the end product (the ordered amino acids in the protein), and it was consistent with available evidence that RNA was involved in the mechanism. However, evidence soon disproved this plausible schema. Although the DNA base sequences in different species were very different, the base sequences of ribosomal RNA (where most RNA was concentrated) were very similar across species (Belozersky and Spirin 1958, discussed in Crick 1959). If ribosomes were similar from species to species, then it was unlikely that they had sufficiently differently shaped holes to produce the different orderings of amino acids in different proteins.

Thus, both the biochemical and molecular biological schemata proved problematic. Although the biochemical schema clearly indicated the source of energy for the formation of covalent bonds (ATP) and identified microsomes as the site of protein synthesis, it had no activity to order the amino acids. The hypothesized molecular biological mechanism proved to be wrong because the ordering of amino acids is not accomplished by geometrically arranging them in holes in RNA. Additional theoretical and empirical work was required to discover the additional entities and activities necessary for protein synthesis. These include transfer RNAs (Crick 1958), which deliver each of the 20 amino acids to the ribosome, and messenger RNA. Messenger RNA is the linear copy of DNA that provides the ordering of the amino acids via the activity of hydrogen bonding between its bases and the complementary ones in the transfer RNAs. The ribosome turned out to be the non-specific site where mRNA and transfer RNAs come together to properly orient the amino acids in space for covalent bonding in the proper order. (For more on the discovery of transfer and messenger RNA, see Judson 1996, Morange 1998, Olby 1970, Rheinberger 1997). The discovery of the mechanism of protein synthesis required entities and activities from both fields to correct and elaborate hypotheses about the RNA stage of the mechanism and to find the appropriate activity, hydrogen bonding, for ordering amino acids during protein synthesis.

The theories in the field of molecular biology can be viewed as sets of mechanism schemata. The primary ones are DNA replication, the mech-

anism of protein synthesis, and the many mechanisms of gene regulation. A complete history of their development would emphasize the importance of the discovery of weak chemical bonding by Linus Pauling and the critical role of this activity in these discoveries by Francis Crick (1988, 1996) and others. Thus, descriptively adequate historical accounts need to discuss the discovery of new kinds of activities, such as hydrogen bonding, as well as the discovery of new entities (which is where the focus usually lies). This example also illustrates how thinking about a kind of activity can guide the construction of a mechanism, when Crick reasoned that nucleic acid bases were particularly suited to hydrogen bonding and used that activity to postulate transfer RNAs and their action. Further, the example shows how incomplete sketches point to black boxes that need to be filled and how incorrect schemata can be changed by substituting another kind of activity. Explicit knowledge of kinds of activities is thus crucial when resolving anomalies and constructing new mechanisms.

7. Activities, Intelligibility, and Explanation (Epistemic Adequacy). Yet another justification (our third, along with the ontic and descriptive) for thinking about mechanisms in terms of activities and entities is epistemic: as we have illustrated, both are integral to giving mechanistic explanations. The contemporary mechanical world view, among other things, is a conviction about how phenomena are to be understood. Activities are essential for rendering phenomena intelligible (Machamer forthcoming). The intelligibility consists in the mechanisms being portrayed in terms of a field's bottom out entities and activities.

Let us briefly, and incompletely, sketch some of the implications of this claim. The understanding provided by a mechanistic explanation may be correct or incorrect. Either way, the explanation renders a phenomenon intelligible. Mechanism descriptions show *how possibly*, *how plausibly*, or *how actually* things work. Intelligibility arises not from an explanation's correctness, but rather from an elucidative relation between the explanans (the set-up conditions and intermediate entities and activities) and the explanandum (the termination condition or the phenomenon to be explained). Protein synthesis can be elucidated by reference to Gamow holes. The ability of nerves to conduct signals can be rendered intelligible by reference to their internal vibrations. Neither of these explanations is correct; yet each provides intelligibility by showing how the phenomena might possibly be produced.

We should not be tempted to follow Hume and later logical empiricists into thinking that the intelligibility of activities (or mechanisms) is reducible to their regularity. Descriptions of mechanisms render the end stage intelligible by showing how it is produced by bottom out entities and activities. To explain is not merely to redescribe one regularity as a series

of several. Rather, explanation involves revealing the *productive* relation. It is the unwinding, bonding, and breaking that explain protein synthesis; it is the binding, bending, and opening that explain the activity of Na^+ channels. It is not the regularities that explain but the activities that sustain the regularities.

This discussion brings us back to our four bottom out kinds of activities: geometrico-mechanical, electro-chemical, electro-magnetic and energetic. These bottom out activities are quite general kinds of abstract means of production that can fruitfully be applied in particular cases to explain phenomena. (For a discussion of how this works in the case of balancing, a geometrico-mechanical kind of activity, see Machamer and Woody 1994.) Mechanistic explanation in neurobiology and molecular biology involves showing or demonstrating that the phenomenon to be explained is a product of one or more of these abstract and recurring types of activity or the result of higher-level productive activities.

There is no logical story to be told about how these bottom out activities, these kinds of production, come to inhabit a privileged explanatory position. What is taken to be intelligible (and the different ways of making things intelligible) changes over time as different fields within science bottom out their descriptions of mechanisms in different entities and activities that are taken as, or have come to be, unproblematic. This suggests quite plausibly that intelligibility is historically constituted and disciplinarily relative (which is nonetheless consistent with there being universal general characteristics of intelligibility).

We also believe it to be likely, although we cannot argue for it here, that what we take to be intelligible is a product of the ontogenic and phylogenetic development of human beings in a world such as ours. Briefly, sight is an important source for what we take to be intelligible; we directly see many activities, such as movement and collision (Cutting 1986, Schaffner 1993). But seeing is not our only means of access to activities. Importantly, our kinesthetic and proprioceptive senses also provide us with experience of activities, e.g., pushing, pulling, and rotating. Emotional experiences also are likely experiential grounds of intelligibility for activities of attraction, repulsion, hydrophobicity, and hydrophilicity. These activities give meanings that are then extended to areas beyond primitive sense perception. The use of basic perceptual verbs, such as "see" or "show," are extended to wider forms of intelligibility, such as proof or demonstration.

Intelligibility, at least in molecular biology and neurobiology, is provided by descriptions of mechanisms, that is, through the elaboration of constituent entities and activities that, by an extension of sensory experience with ways of working, provide an understanding of how some phenomenon is produced.

8. Reduction. Philosophical discussions of reduction have attempted to shed light on issues in ontology, scientific change, and explanation. Because we have introduced the notion of relative bottoming out, we do not address issues about ultimate ontology. Instead, our focus, vis-a-vis reduction, is on scientific change and explanation.

Models of reduction, including deductive models (e.g., Nagel 1961, Schaffner 1993), have been claimed to be ways to characterize scientific change and scientific explanation. These models do not fit neuroscience and molecular biology. Instead, we suggest the language of mechanisms.

Theory change in neuroscience and molecular biology is most accurately characterized in terms of the gradual and piecemeal construction, evaluation and revision of multi-level mechanism schemata (Craver 1998, Craver and Darden forthcoming). Elimination or replacement should be understood in terms of the reconceptualization or abandonment of the phenomenon to be explained, of a proposed mechanism schema, or of its purported components. This contrasts with the static two-place relations between different theories (or levels) and with the case of logical deduction.

Deductive models have also been taken to provide an analysis of explanation, with lower levels explaining higher levels through the identification of terms and the derivation of the higher-level laws from the lower-level (for the details, see Schaffner 1993). Aside from the fact that identification and derivation are peripheral to the examples we have discussed (as Schaffner admits), this model cannot accommodate the prevalent multi-level character of explanations in our sciences. In these cases, entities and activities at multiple levels are required to make the explanation intelligible. The entities and activities in the mechanism must be understood in their important, vital, or otherwise significant context, and this requires an understanding of the working of the mechanism at multiple levels. The activity of the Na^+ channel cannot be properly understood in isolation from its role in the generation of action potentials, the release of neurotransmitters, and the transmission of signals from neuron to neuron. Higher-level entities and activities are thus essential to the intelligibility of those at lower levels, just as much as those at lower levels are essential for understanding those at higher levels. It is the integration of different levels into productive relations that renders the phenomenon intelligible and thereby explains it.

9. Conclusion. Thinking about mechanisms gives a better way to think about one's ontic commitments. Thinking about mechanisms offers an interesting and good way to look at the history of science. Thinking about mechanisms provides a descriptively adequate way of talking about science and scientific discovery. Thinking about mechanisms presages new ways to handle some important philosophical concepts and problems. In

fact, if one does not think about mechanisms, one cannot understand neurobiology and molecular biology.

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