INFECTION AND IMMUNITY, Sept. 2009, p. 3517–3519 Vol. 77, No. 9
0019-9567/09/$08.00+0 doi:10.1128/IAI.00623-09

EDITORIAL

Mechanistic Science[▽]

"Science is the knowledge of consequences, and dependence of one fact upon another."

—Thomas Hobbes (7)

In reviews of manuscripts and grants, the words "mechanistic" and "descriptive" are often misused as synonyms for "good" and "bad," respectively (6, 9). The extraordinary power of these words requires us to wield them carefully when critiquing science. In an earlier essay, we considered the epithet "descriptive" as applied to science and argued for an important role of descriptive studies in biology, while also acknowledging a general preference for studies that go further by including experimental work (3). Here we consider the more favored adjective "mechanistic" and explore its usage, meanings, implications, and limitations. Recognizing the centrality of mechanistic research to the history of science (1), we seek to explore what biological scientists mean when they use this term.

Definitions. At first glance, one is struck by the fact that the terms "descriptive" and "mechanistic" are often used antagonistically as descriptors of scientific quality, yet they are not antonyms. "Descriptive" is defined as "referring to, constituting, or grounded in matters of observation or experience," while "mechanism" is defined as "the fundamental processes involved in or responsible for an action, reaction or other natural phenomenon" (http://www.merriam-webster.com/dictionary/). From these definitions, "descriptive" can be seen as analogous to the interrogatives "who," "what," "where," and "when," whereas "mechanistic" in turn asks "how" and "why." Hence, these terms collectively encompass the spectrum of inquiry. But if "descriptive" and "mechanistic" are not antonyms, what accounts for the general preference for mechanistic over descriptive work?

As "descriptive" and "mechanistic" denote different qualities, at least in the minds of reviewers, we must probe further to ascertain what these terms mean in the scientific vernacular. We suggest that these words mean different things to different people. Since practically all laboratory-based biological science is based on recording evidence from experimentation, an argument can be made that all science is in some form descriptive. However, this is unsatisfactory because every scientist intuitively knows that there are qualitative differences in scientific studies. Hence, the first problem we encounter is in the precision of language, as we try to understand and convey meaning in words. The word "mechanistic" is used to refer to both complex natural phenomena and man-made mechanical devices. The machine as an analogy for the natural world owes much to the writings of Hobbes and Descartes (even though the latter could not bring himself to ascribe the human soul to a mechanical process). Like Hobbes, the modern scientist makes the implicit assumptions that phenomena have rational explanations and that events may be connected as cause and effect. Scientists seeking mechanisms to explain the workings of the natural world are only the latest practitioners in a philosophical continuum extending back to the 17th century (1, 4).

The explanation for many biological phenomena requires a basic understanding of causal mechanisms (4). However, "mechanism" can mean different things in different fields. For example, in the late 1950s the problem of protein synthesis was central to biology, and "mechanism" to biochemists meant the formation of covalent bonds in polypeptides, whereas to molecular biologists "mechanism" was the means by which the genetic code is translated into proteins (5). Although these approaches were eventually reconciled during the great synthesis of the mid-1960s (5), it is noteworthy for our discussion that the word "mechanism" can hold different meanings even in closely related fields like biochemistry and molecular biology. Furthermore, the meaning of the term "mechanism" with respect to science has changed over time, from a version of philosophical materialism in opposition to vitalism to a stepwise explanation of how system components interact to produce an outcome (1).

Where is the line of demarcation between "descriptive" and "mechanistic?" Starting with the assumption that there is a difference between "descriptive" and "mechanistic" science and seeking a clear line of demarcation that can be expressed in words, one immediately runs into the problem that the description of a process can be considered the mechanism for another process. To further illustrate this point, let us consider a hypothetical situation. A scientist walks into a dark room and encounters impenetrable darkness. A candle is lit and the scientist now perceives the outline of the room. The scientist decides to investigate the phenomenon of light. The mechanism responsible for the light is the candle. However, the scientist notes that only part of the candle emits light and determines that the mechanism for light is the flame. In describing the flame, the investigator establishes that the mechanism for the flame is combustion. Describing combustion, the scientist determines that the mechanism is a series of oxidation-reduction reactions that in turn are explained by electron transfer and, ultimately, quantum mechanics. At each step, the description of a process provides only a partial explanation in search of a deeper mechanism that must in turn be described (Table 1). What is striking in this hypothetical situation is that the difference between description and mechanism is one of proximate causation. Hence, the epithets "descriptive" and "mechanistic" are epistemologically related and differ quantitatively rather than qualitatively. In other words, observations become regarded as progressively less descriptive and more mechanistic as one probes more deeply into a phenomenon. In fact, one might argue that there is no real line of demarcation between descriptive and mechanistic science but that the difference is rather a matter of depth and one's preferences.

The scientist in the dark room also gives us a model with which to explore the difference between descriptive and experimental science, a point that we emphasized in our earlier essay

▽ Published ahead of print on 13 July 2009.

TABLE 1. A scientist considers the illumination of a dark room

Description	Mechanism
Light	Candle
Candle	Flame
Flame	Combustion
Combustion	Chemical reaction
Chemical reaction	Oxidation-reduction
Oxidation-reduction	Electron loss and gain
Electron loss and gain	Quantum mechanics
Quantum mechanics	Metaphysics

TABLE 2. A scientist considers the cause of a skin lesion

Description	Mechanism
Pain, redness, swelling, and heat	Inflammation
Inflammation	Cellular infiltration and vascular leakage
Cellular infiltration and vascular leakage	Chemokines, cytokines, and arachidonic acid derivatives
Chemokines, cytokines, and arachidonic acid derivatives	Signaling cascade activation
Signaling cascade activation	Agonist-receptor interactions
Agonist-receptor interactions	Microbe-associated molecular patterns
Microbe-associated molecular patterns	*Staphylococcus aureus*

(3). Note that the scientist can assign causality to the association between a lit candle and an illuminated room by extinguishing the candle, noting the return of darkness, and subsequently validating that the candle is responsible for light by reigniting the flame. Furthermore, our thought experiment illustrates the issue of "significance" of a scientific observation. The assessment of significance is a major criterion in grant or manuscript review, yet we have few tools for judging the significance of a finding in real time other than judgment and experience. One might argue that since the scientist needs light in order to see, the most significant finding is the association of the candle with light. The mechanistic details following subsequent questions may be important for understanding the related phenomena but are not essential in the context of a dark room unless the scientist decides to use the information to design a better candle or kindle a brighter fire. Hence, the significance of a finding is often related to the subsequent development and application of the revealed information and may become apparent only over time. Our hypothetical scenario also provides insight into the line of demarcation between science and nonscience. As when one peels away the successive layers of an onion or opens a series of nested Russian dolls, each revealed mechanism becomes a new description leading to a new mechanistic question, until the investigator arrives at a point where scientific inquiry cannot proceed without entering the realm of metaphysics.

Moving from the dark room into the world of *Infection and Immunity*, it is possible to envisage similar scenarios in which it is difficult to identify a clear demarcation between descriptive and mechanistic science. For example, consider a disease characterized by a red, hot, painful, and swollen skin lesion. The investigator would note that this collection of signs and symptoms corresponds precisely to rubor, calor, dolor, and tumor, the Latin terms used to describe inflammation. These terms in aggregate represent descriptors that denote "inflammation," a process that provides a mechanism for the disease (Table 2). To investigate the mechanism of inflammation, the investigator employs a microscope and determines that the lesion is a result of an influx of neutrophils. While investigating the presence of neutrophils, the investigator discovers chemotaxis, alterations in chemokine expression, activation of signaling pathways, and perhaps the presence of microbe-associated molecular patterns responsible for chemokine elicitation. In essence, the boundary between descriptive and mechanistic science is moving and subjective and depends on both the depth of the experimental question and the technological sophistication of the investigator. In other words, one scientist's mechanism may become another's descriptive starting point.

"Descriptive" and "mechanistic" in the scientific vernacular. The scientist in a dark room and the example of inflammation suggest that there is no bright line of demarcation separating the terms "descriptive" and "mechanistic" as applied to science. Given the inexactitude of "descriptive" and "mechanistic" and the vagaries associated with their meaning, labeling research as "descriptive" or "mechanistic" is often not a productive exercise. Although we may agree with the statement that many of the most important discoveries in the sciences relate to novel mechanisms (5), "descriptive" should not be used as a derogatory term, since description is a critical element of the scientific process and elucidation of a "mechanism" always requires some form of description. Since "mechanistic" is not an antonym for "descriptive" and description can provide a mechanism in certain contexts, we are still left with the question of exactly what scientists mean when they use such terms in reviews. Probably the most honest answer to this question is that we do not always know, since the definitional boundaries are sufficiently fuzzy that these terms probably mean different things to different people.

The problem in demarcating "descriptive" and "mechanistic" is nicely illustrated by crystallography. Solving the structure of a protein or nucleic acid may be considered a strictly descriptive exercise, since the output is often a series of atomic coordinates. However, describing a structure frequently provides key insights into function and mechanisms. In this regard, we are reminded that the description of DNA structure provided the critical insight for the mechanism of genetic replication, the conservation of information, and the deciphering of the genetic code. Hence, crystallographic studies that yield functional insights may be considered "mechanistic" despite the essentially descriptive nature of diffraction data.

"Descriptive" is closely related to "empirical," or that which is observed without regard to theory. However, the root of "empirical" is "experimental," which expands upon mere description by introducing perturbations into a system. This in turn may lead to novel hypotheses and predictions that can be tested, thereby completing the transition to "mechanistic" theory-driven models. The preference for "mechanistic" as a descriptor may be a result of the historical importance of elucidating mechanisms in science. Bechtel and Abrahamsen have noted that explanations based on mechanism are inherently attractive because they are able to avoid the limitations of linguistics by using diagrams and introduce directionality to the process of discovery and hypothesis testing (2). However, there are problems with attempting to reduce all biological sciences to a search for mechanisms. A description of a novel discovery or hypothesis can be of greater interest than the elucidation of a highly predictable or conventional mechanism (10).

Implications for reviewers. When reviewers ask for more-"mechanistic" studies, some are probably asking for experimental work that establishes causality between the observations being reported. For example, a paper that reports a simple correlation between two phenomena might be criticized as insufficiently "mechanistic" because correlation does not necessarily imply causation (i.e., what happens if you blow out the candle?). In such instances, the reviewer can be most helpful by suggesting specific experiments to allow the inference of causation. In other cases, reviewers requesting mechanistic studies may desire more depth in ascertaining the explanation for a reported observation. One of the most frequent reasons for a paper to be labeled "descriptive" is that it fails to interpret its observations and tell a coherent story. As Peter Medawar observed, scientists tell "stories which are scrupulously tested to see if they are stories about real life" (8). A description followed by a hypothesis can still tell a story, albeit a tentative one, but a paper that reports disconnected phenomena without a narrative to bind them together is likely to be poorly received and labeled as "merely descriptive."

It would be best if the terms "descriptive" and "mechanistic" were not employed in scientific critiques unless accompanied by more-specific language to explain precisely what reviewers mean. Ideally, reviewers should state specifically what is required to make the manuscript suitable for publication. We suspect that for many scientists, the meanings of these terms are like Supreme Court Justice Potter Stewart's famous comment, "I know it when I see it," in reference to pornography. However, we argue that science, despite its potential to thrill, is not pornography and that thoughtful and carefully chosen words can greatly facilitate communication between reviewers and authors. Science must describe what, when, and where events are occurring, as well as explain the mechanisms of how and why they are linked together, in order to illuminate the darkness.

A.C. thanks L. Pirofski for many discussions on this topic over the years.

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