A Paradigm Shift from Biophysical to Neurobiological: The Fading Influence of Claude Bernard's Ideas about General Anesthesia

To the Editor:

Dr. Perouansky's insightful and provocative retrospective about Claude Bernard's influence on theories of general anesthesia[1] was a delightful read, as was the accompanying editorial.[2] The article presented an interesting mix of metaphors, at first alluding to Claude Bernard's "long shadow," and ending with a warning against only "searching where the light is bright." In addition, Dr. Perouansky discussed Bernard's influence in terms of a long-lived Kuhnian paradigm, implying that Bernard's influence persists, without concluding whether the paradigm has indeed shifted, and if so, what catalyzed this change. Here, I introduce another metaphor to illustrate the concept of "paradigm shift" and other perspectives on this question.

An illustrative metaphor for a scientific paradigm is that of an ever-expanding underground mine, where veins of knowledge are explored and illuminated by scientific mine workers. Kuhnian "normal science" expands and elaborates established veins within the mine, extracting an ever-increasing collection of knowledge, while also increasing the area to be explored (the walls bounding the mine tunnels). The material surrounding the mine walls represents nascent knowledge, mapped to varying degrees by scientific theory. The essential scientific tools are imagination and experimental methods (along with people and funding). As with real mining for valuable ore or gemstones, different veins yield at different rates and to different tools (depending on the hardness of the region). Some veins expand to reveal new side veins, attracting more scientists. In contrast, some veins stop yielding after a period of exploration, when ideas are disproven or methods fail. Kuhnian "paradigm shifts" markedly increase the extent of this scientific mine and, more importantly, change where scientists choose to explore. Paradigm shifts may be actively sought when scientific ideas are failing, indicating the need for new theoretical directions. Sometimes a new theory emerges suddenly, because a connection to another scientific discipline is made, guiding exploration in a new expansive direction. Paradigm shifts may also be triggered by new scientific methods that enable "breakthroughs" in previously impenetrable scientific barriers. In this context, I believe that a paradigm shift has indeed occurred in the science of general anesthesia and that it was multifactorial.

Karl Popper[3] defined a viable scientific hypothesis as a postulate that can be experimentally falsified. As Dr. Perouansky emphasizes, the studies of Meyer and Overton successfully elaborated on Bernard's "unitary" framework by focusing on lipids. A variety of more detailed lipid hypotheses ensued, each focused on different biophysical properties of lipids. These hypotheses were experimentally based, yet none met Popper's criteria of falsifiability. Yes, exceptions to the Meyer–Overton correlation were found, and mostly set aside without full explanation or exploration, but experimental model systems that might definitively disprove the role of lipids in anesthesia did not exist when these theories were formulated, and for the most part, they are still lacking. Thus, some lipid hypotheses remain viable (although neglected), although Popper would deem these hypotheses "unscientific" until we develop new approaches to test them. Metaphorically, this is blasting away at soft parts of the wall, although critical knowledge is only in the hard parts, for which we have few tools to excavate.

Conceptual and experimental advances in the broader scientific fields of biophysics, molecular biology, and neurobiology also influenced theories of general anesthesia. Franks and Lieb[4] launched their assault on lipid theories using then new biophysical tools (neutron diffraction) that accurately measured effects of clinical anesthetic concentrations on the structure of lipid bilayers. Although Franks and Lieb[4] may not have fully envisioned the paradigm shift to come, they deserve credit for leading the field away from a barren area (lipids) toward richer scientific territory (protein). This shift was facilitated by concurrent developments in molecular biology. Molecular tools enabled scientists to insert mutations into suspected anesthetic binding sites on potential target proteins ("reverse pharmacology"), including neuronal ion channels, and eventually to alter anesthetic target proteins in transgenic animals ("knock-ins"). These were hard experiments but provided definitive advances in understanding anesthetic mechanisms and helped further undermine unitary concepts.

Dr. Perouansky touched briefly on a foundational issue that, in my opinion, truly heralds the occurrence of a paradigm shift in our field: redefining general anesthesia. Embedded within the unitary hypothesis was the idea that general anesthesia is a singular state transition, from irritable to unresponsive, even to noxious stimuli (minimum alveolar concentration-immobility). The distinct concept of minimum alveolar concentration-awake,[5] together with clinical evidence that perceptive awareness and memory formation can occur in anesthetized immobile patients, led both clinicians and researchers to a more nuanced and neurobiological framework for understanding and studying general anesthesia. It is now widely accepted that anesthetics produce distinct neurobehavioral (and clinically relevant) endpoints *via* actions on separate neural circuits and networks. Furthermore, distinct classes of anesthetics can be recognized based on relative potencies for clinical endpoints, correlating with activity at distinct sets of molecular targets.[6,7] These observations defy unitary concepts at multiple system levels.

In summary, the last few decades have been a period of maturation and diversification in research on general anesthesia, and there is little room now for 19th century

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thinking, despite the seductive elegance of Claude Bernard's ideas. Although the Meyer–Overton correlation has not been expunged from textbooks, and the biophysical concept of hydrophobicity remains important to anesthetic pharmacology, these ideas have been subsumed into a broader neurobiological framework. Research investigating unitary mechanisms or even alluding to these mechanisms in discussions of new experiments is diminishing. Are unitary hypotheses dead? Not quite. Many ideas central to unitary hypotheses have collapsed, and few scientists dig there, but some tunnels of knowledge in that area remain surrounded by hard material that resists excavation. Instead, research on mechanisms of anesthesia is emerging as a field of systems neurobiology, linked closely to research on mechanisms of consciousness.[8–10] Moreover, advances in our scientific understanding of general anesthesia are starting to translate into promising efforts to develop better general anesthetic drugs[11] and improved monitors for assessing depth of anesthesia.[12]

Stuart A. Forman, M.D., Ph.D., Harvard Medical School, Boston, Massachusetts and Massachusetts General Hospital, Boston, Massachusetts. saforman@partners.org

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In Reply:

We were interested to read the letter from Sette *et al.*[1] regarding our editorial. We agree that the "Shoulders of Giants" analogy extends back into antiquity. Interestingly, one use of this aphorism in the history of the accumulation of knowledge is that it has been used throughout the ages to enable the opinions of early intellectual giants to be amended by subsequent generations, despite their perceived diminished stature.

A classic example is cited here from ancient Jewish rabbinic tradition. There is an accepted step-wise regression in rabbinic legal stature and authority with the passage of generations, but this may impair the forces of progression and innovation. In an elegant attempt to justify his departure from the legal opinions of his forebears, R. Isaiah di Trani (c. 1180–1250), the leading Italian Talmudist of his generation, wrote as follows[2]:

> I applied to myself the parable of the philosophers … The wisest of the philosophers was asked: "We admit that our predecessors were wiser than we. At the same time, we criticize their comments, often rejecting them and claiming that the truth rests with us. How is this possible?" The wise philosopher responded. "Who sees farther, a dwarf or a giant? Surely a giant for his eyes are situated at a higher level than those of a dwarf. But if the dwarf is placed on the shoulders of the giant, who sees further? Surely the dwarf, for now the eyes of the dwarf are situated at a higher level than those of the giant. So too, we are dwarfs, astride the shoulders of giants. We master their wisdom and move beyond it. Due to their wisdom we grow wise and are able to say all that we say, but not because we are greater than they. …. Wisdom is greater than the wise".

This passage was cited by Leiman[3], in an encyclopedic review of the aphorism "Shoulders of Giants" in rabbinic literature. He reported that R. Isaiah di Trani "openly acknowledged his literary debt to contemporary non-Jewish philosophers" (in this case to Bernard of Chartres), and went on to state that in the Talmudic context, "the aphorism was particularly ingenious and apt, for it paid tribute simultaneously to progression and regression… On the one hand, the earlier generations are depicted as giants and the later generations as dwarfs – a clear case of regression. On the other hand, the dwarfs see farther than the giants – clearly evidence for progression."[3] We believe that the art and science of medicine rightly share some elements of this duality.

Yehuda Ginosar, B.Sc., M.B.B.S.,* Alexander M. Binshtok, Ph.D. *Hadassah Hebrew University Medical Center, Jerusalem, Israel. yginosar@netvision.net.il

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