Published in final edited form as:
Anesthesiology. 2013 April ; 118(4): 984–985. doi:10.1097/ALN.0b013e3182860777.

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

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To the Editor

Professor 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 paper 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." Also, Prof. 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" dramatically 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 multi-factorial.

Karl Popper defined a viable scientific hypothesis as a postulate that can be experimentally *falsified.*[3] As Prof. Perouansky emphasizes, the studies of Meyer and Overton successfully elaborated on Bernard's "unitary" framework by focusing on lipids. A variety of more

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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), while 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 while 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 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.[4] While Franks and Lieb 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.

Prof. Perouansky touched briefly upon a foundational issue that, in my opinion, truly heralds the occurrence of a paradigm shift in our field: re-defining 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 (MAC-immobility). The distinct concept of MAC-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 neuro-behavioral (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 thinking, despite the seductive elegance of Claude Bernard's ideas. While 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]

Acknowledgments

Support: Dr. Forman conducts basic research on molecular mechanisms of general anesthesia and is the recipient of support from NIH grants (R01GM089745 and P01GM58448) and the MGH Dept of Anesthesia Critical Care & Pain Medicine.

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