

PERSPECTIVES & OPINIONS

■ Jeff Lichtman

CLOSELY WATCHED ORGANISMS

Sean Kerran

JEFF LICHTMAN LIKES TO invoke baseball legend Yogi Berra's famous line "You can observe a lot by watching" to describe his own work. Lichtman, who is a professor of molecular and cellular biology at Harvard University and has participated in planning for HHMI's Janelia Farm Research Campus, is a self-described "neuronal ethologist." He watches nerve cells in their native habitat—the animal. Powerful new microscopes are facilitating a trend toward observational biology, which Lichtman contends has some key advantages over experimental biology.

For me, an observational approach to biology is very natural, but it's not that common in my field. Most of modern biology, and indeed science education from elementary school on up, is actually rooted in deduction: You start with an idea and use experimental tools to manipulate variables to test that hypothesis.

The aim of the deductive scientific method is to try your hardest to prove the idea wrong. If you keep failing at these attempts, the hypothesis stays alive, even though you haven't actually proved it. But where have you gotten? Given that the idea was already out there, all you've done is maintain the status quo. Refuting a hypothesis, on the other hand, leads to paradigm shifts. But it requires compelling data against the hypothesis, which is difficult to obtain, and when it is negative data, it is even more difficult to publish.

So with deduction, hypotheses tend to become entrenched as the weight of the published record becomes progressively lopsided. You could provide a virtually limitless amount of evidence consistent with the hypothesis that Earth is flat, but that doesn't make it so.

Observational, or inductive, science proceeds in a different way. The researcher simply observes a biological system, and hypotheses emerge as a consequence of, rather than as the motivation for, the observation. Nobel laureate Sydney Brenner said, "Progress in science depends on new techniques, new discoveries, and new ideas, probably in that order," which is a good way to sum up how inductive science works. This approach, however, has its own pitfalls. First, your hypotheses are only as good as the observational tools at your disposal. Second, your life experience molds your worldview and therefore your observational abilities. You see things that resonate in your mind as real and interesting, and you ignore those things that don't.

The strength of inductive science, however, is that new observational tools often reveal unexpected things that force you to confront the disconnect between the current worldview and the revealed world—especially

when you have young colleagues, who bring fewer biases to biological phenomena. Microscopes are particularly valuable tools for this endeavor in neurobiology because they are a direct link between cell-biological phenomena and the visual system, our most sophisticated sensory mechanism.

In the 1990s, neuroscience turned sharply toward molecular genetics. Many remarkable technological advances have resulted, including the ability to make mice that express fluorescent proteins from jellyfish. In our lab and others', these animals have dramatically improved the ability to visualize neurons over time in living animals (so-called intravital microscopy). Automated microscopes and computational tools also allow assessment of the structure of many individual nerve cells in one preparation. Together, these innovations may enable us to describe all the synaptic linkages in neuronal circuits, what I like to call "connectomics." By providing a complete description of the wiring of the brain, these maps may give us a window into the inner workings of the mind and may even yield insights into "connectopathies," where the wiring has gone awry.

Some optimists believed that knowing the complete genome sequences of animals meant it was just a matter of time before we would understand essentially all biological phenomena as molecular cascades. My sense is that this optimistic view now holds less sway. So many concurrent and interacting molecular reactions occur within cells that scientists simply cannot reduce a living cell, much less a multicellular organism, to just so many bags of molecules, hoping to extrapolate the organism's full repertoire of behaviors. Observational approaches of neuronal behavior may provide a much-needed bridge between molecules and brains. Just as nature videographers working in the wild show us a far better view of behavior than we could obtain by observing specimens in a museum case or even a zoo, intravital imaging helps us move out of the culture dish and into the real jungle of the brain. —Interview by Julie Corliss ■