



Aplysia californica inking. Courtesy Genevieve Anderson.

LEARNING DEGREE ZERO

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Aplysia californica is a soft-bodied marine invertebrate that makes its living nibbling red algae in the kelp beds and rocky reefs of the Pacific coast of the United States. They are meaty, sometimes weighing more than ten pounds, and the deep hues of their food give their translucent flesh the mottled marbling of polished tortoiseshell. When scrunched up contentedly, they look a bit like rabbits, on account of two earlike tentacular horns that sit atop their faceless heads—a resemblance that long ago gave rise to the common name for the whole taxon, known as the “sea hares” since antiquity. When irritated, *A. californica* release a cloud of acrid, mucosal, purple ink from a shockingly labial cleft that runs down the length of their backs and shelters the delicate folds of a feathery, blood-rich gill. They move feelingly and with a certain dignity, like large slugs—which is exactly what they are.

Stumbling on a defunct *Aplysia* in the tide-washed flotsam of a California beach, you would be inclined to

dismiss its remains as yet another nasty gob of formless protoplasm coughed up by the deep. But in continuing your stroll, you would have walked past the creature upon which much of the modern scientific understanding of learning has been built.

For close to fifty years, *Aplysia californica* has served as the irreplaceable model organism at the center of what is arguably the most significant twentieth-century research program in the sciences of mind and behavior. In fact, on the afternoon of 8 December 2000, when the distinguished neuroscientist Eric Kandel stepped to the podium of Sweden’s Karolinska Institute to present his Nobel Prize lecture, he flashed up on the screen behind him a huge, photo-shopped image of a robust *Aplysia* sporting around its extended neck Kandel’s golden medallion—the most coveted prize in science. The mollusk, it was agreed, deserved a little bling on the occasion.

So how did a herbivorous hermaphroditic gastropod end up as a Stockholm honoree? The answer requires a quick turn through the twentieth-century science of learning and memory.

To begin with, then, ask the most basic question: What *is* “learning,” anyway? A recent handbook in the field offers the following definition:

*Learning is the process by which relatively permanent changes occur in behavior potential as a result of experience.*¹

Which is to say, learning is a little like an accelerated mechanism for evolutionary adaptation, one that works at the scale of the individual. If you can figure out how reliably to convert new experiences into revised behavior, you’ve just gotten a serious leg up on the business of being here, since you’ve effectively acquired the capacity to redeem some measure of the general unpleasantness of existence—you can now turn your bad breaks into *lessons*.

True, there is an existential price to be paid for this trick, in that now you are stuck with *memory*, against which Nietzsche (among others) railed very persuasively. But no memory, no learning, since if you can’t store information, you’ve got no way to make your past bear on your future. Learning is the process, memory is

the product. And for this reason questions about how we learn have long been entangled with the question of how we form and maintain memories.

Across the first half of the twentieth century, a variety of physiologists and experimental psychologists went after these problems in different ways. Some, like the German psychologist Hermann Ebbinghaus, worked directly with human subjects and tried to identify consistent patterns in the dynamics of information acquisition. In a series of classic experiments that involved memorizing long sequences of nonsense syllables, Ebbinghaus eventually codified what we now call “the learning curve”—a time-sequence plot of the decreasing effort needed to master a given task. Other investigators, like the Russian physiologist Ivan Pavlov and the American psychologist Edward Thorndike, left humans aside and made fundamental contributions to the understanding of learning by studying animals. Pavlov’s dogs, famously, *learned* to associate one stimulus (say, a bell) with another (say, a zap in the foot) in what has come to be known as “classical conditioning”—a behavioral phenomenon that has served ever since, for better or worse, as a basic



Forty-nine-day-old *Aplysia* juvenile, nicknamed Claire, that has just completed metamorphosis. Courtesy the National Resource for *Aplysia* at the University of Miami.

laboratory proxy for learning writ large. Thorndike, working at Columbia University, studied cats as they tried to figure out how to escape from a locked box. Whereas in Pavlovian classical conditioning there is an arbitrary relationship between the stimuli to be associated (Bell? Electrocutation? No logical connection), in Thorndike's experiments the cats were learning to make associations that weren't arbitrary at all (pull latch, *get out of box*). This kind of learning—learning, via payoffs, about the world of causes and effects—came to be called “operant conditioning.” Philosophically oriented wags have tended to wonder just how different these two kinds of conditioning really are (isn't classical conditioning simply the operant conditioning of animals forced to live in the “environment” of a laboratory?), but put this knotty matter aside. What was significant was that all of these learning situations were shown to share many consistent features: practice makes perfect; time off tends to reduce competency; reacquisition of capacities is faster than at the first go. And these sorts of generalities could be quantified, parameterized, and shown to possess reliable statistical signatures that were conserved across experimental animals and scenarios.

By mid-century, then, there was broad consensus among researchers about the descriptive features of the basic behavioral dynamics of learning. But there was nothing even remotely consistent about the various theories proposed to explain the underlying physiology of the process. How did learning *actually happen*? What was going on in the brain that accounted for these observable changes in the doings of dogs, cats, monkeys, mice, and army recruits? (The latter were great experimental subjects—a perfectly captive audience.) No one could say with any satisfaction. Yes, people knew a fair bit about nerves and how they transmitted signals around the body. Yes, there was some evidence that regions of the mammalian brain were specialized to manage particular cognitive, sensory, and motor activities. And yes, there were even some ideas about how to tie brain activity to behavior (one thinks here of the work of both Donald Hebb and Karl Pribram).

Nevertheless, exactly how the nervous system acquired and stored new information was hotly disputed, and even the best arguments remained largely speculative. Among other difficulties, the available experimental data were exceedingly hard to interpret. For instance, in a fascinating and discouraging set of investigations in this area, the most important American learning researcher in the period, Karl Lashley, demonstrated that you could take rats that had learned

how to run a given maze, and then *surgically remove various bits of their brains*, and they still generally managed to find their way to the cheese. In the end, their performance appeared to have more to do with *how much* of their brains you removed—not *what part*. But how could one investigate the basic biology of learning and memory if it was so difficult to specify *where to look*? This sort of thing depressed physiologists, who like to find organs for different functions. Meanwhile, the psychologists largely took up versions of what is called “behaviorism,” a paradigm of mind science that black-boxed cognitive activity, and treated organisms like input/output systems—which did not make for much progress on the internal biology of learning. Surveying the field in the early 1950s, Lashley, old and resigned, summed up the situation on a paradoxical note: “I sometimes feel, in reviewing the evidence... that the necessary conclusion is that learning is *just not possible*.”²

And yet, of course, it was. The question was: How to learn about learning?

In an important book published in 2007, *Science without Laws*, Angela Creager and a number of other historians of science drew attention to the importance of “model organisms” in the history of twentieth-century biology. There are whole fields of investigation that seem inextricable from particular creatures, which for various reasons (rational foresight, historical contingency) end up functioning as obligatory passage points for disciplinary development. What would the twentieth-century study of genetics have been without *Drosophila* (the fruit fly)? Inconceivable. What about virology absent TMV (the Tobacco Mosaic Virus)? Similarly difficult to imagine. So profound is this linkage between certain kinds of science and certain specific beasts that it has been dignified with a name, the Kuffler-Grundfest principle: “For every biological problem there is a suitable organism in which to study it.”³

When, in the early 1960s, Kandel—then an ambitious young medical doctor—decided to turn his research attentions to the neurophysiology of learning and memory, he took this principle to heart. Cats? Dogs? Rats? Too complicated. The learned behaviors in question? Too intricate. Despite his Viennese origins and expansive interest in the nuance and complexity of Freudian psychoanalysis, Kandel had a biophysicist's appetite for radical reduction. He wanted to study learning in an animal built for the very simplest kinds of information acquisition and storage. An animal that could be understood as a little laboratory learning-machine: limited behavioral repertoire; large, simple

wiring; a resilient metabolism; and, ideally, small teeth (no one likes getting chomped by lab animals).

Hello, *Aplysia californica*.

Aplysia sifted to the top of the heap of possible creatures (Crayfish? Squid? Pillbugs?) on account of having huge, fat neurons—and relatively few of them. We are talking 20,000 or so nerve cells in the whole central nervous system, as against 100 million or more in your standard mammal. Also, conveniently, *Aplysia* have organized their “brain” into half a dozen little brainlets called “ganglia” which are located in some proximity to the parts of the body they control. This makes for handy dissection. They are also pretty mellow and hardy, so you can decapitate them or clamp their heads in a thumb-screw and they basically just carry on with their very limited business.

But was that business so limited that they actually *couldn't learn*? This was the first problem that Kandel and his collaborators had to work out, and they did so successfully in a series of publications in the 1960s and early 1970s, showing conclusively that if you were patient and you had a Waterpik and a small cattle-prod (both used for poking them), you could train an *Aplysia* to carry out most of the behavioral repertoire of traditional learning research. They could be “sensitized” (i.e., they learned to get jumpy after bad experiences), they could get “habituated” (i.e., learn to disregard stuff that initially made them nervous), and—impressively—they could even be *classically conditioned*, learning to associate one stimulus with another.⁴ They would also do most of this stuff with their intact brainlets carefully removed from their bodies and laid on a sheet of glass to their left or right, provided one didn't sever the various nerves that wired them up.

With one or another version of this arrangement, Kandel and his labmates had to hand the most powerful experimental setup ever devised for studying learning at the level of individual neurons. They had found a system simple enough to study at the cellular, and eventually at the molecular, level, but complex enough to show responses one could comfortably call behavioral. By tapping specific cells with tiny electrodes, it was possible to monitor the actual signaling that triggered specific behaviors, and using chemical baths one could mess about with the crucial juice that lies between the ends of “connecting” nerve cells—the synapses. You could even draw up a straightforward wiring diagram of several *Aplysia* activities, including the main behavior the group investigated: a reflexive retraction of the gill, a self-protecting response driven by a very simple circuit—a few dozen neurons. These

scientists were down at the level where a living creature looks a lot like a doorbell. An oozy, messy doorbell, yes. A doorbell with the capacity to learn and remember, yes. But a doorbell nevertheless.

So what's the answer? Simple learning turns out to be largely a product of “synaptic plasticity”—adjustments in the connectivity of different bits of the circuitry. As stuff happens to us and we respond, those synapses change. The durability of those changes amounts to our short-term memory.

But that's just the beginning. It would be only a slight exaggeration to say that unfolding the ramifying results and implications of this early *Aplysia* work would require a textbook of modern neuroscience. Something like, say, Kandel's 1414-page *Principles of Neural Science*. The core papers of that work from the 1960s and 1970s have now been cited tens of thousands of times and spawned major research initiatives into every imaginable aspect of the biochemistry, genetics, development, and evolution of the central nervous system and its functions.

And though there is basically no animal into which neuroscientists have not stuck a few electrodes, *Aplysia* still retains a privileged place in the world of brain science, and many of them go under the knife each year in laboratories around the world. In fact, back in 1995, the National Institutes of Health dug deep into the public purse to fund the creation of the National Resource for *Aplysia* in south Florida, right near Miami. This very considerable facility breeds, raises, and ships tens of thousands of *Aplysia* each year, to feed the maw of science.

I have the clearest memory of my own *Aplysia* lab in an invertebrate seminar in college. We received, in pairs, small white coolers each containing one grapefruit-sized sea slug hunched forlornly in the corner. I put my hand in the water and ran a consoling stroke down its slippery flank. In reply, the very finest and thready tendril of mauve slime oozed slowly from its openness.

I was a student, there to learn. The strange thing was, we both were. But only one of us would get out of the class alive.

1 John R. Anderson, *Learning and Memory: An Integrated Approach* (New York: Wiley, 1995), p. 4.

2 Karl Lashley, “In Search of the Engram,” *Society of Experimental Biology Symposium*, no. 4 (1950), pp. 454–482.

3 The coinage, somewhat playful, is Eric Kandel's, in his *In Search of Memory* (New York: Norton, 2006).

4 It has subsequently been shown that they are capable of operant conditioning as well. For a discussion, see Björn Brembs et al., “Operant Reward Learning in *Aplysia*: Neuronal Correlates and Mechanisms,” *Science*, no. 296 (May 2002), pp. 1706–1709.