The Educated Nervous System

Learning has a way of getting — and staying — on our nerves

By ROBERT POLLIE

Second of two articles

With its labyrinthine structure — billions of nerve cells, each with multiple interconnections — and its astonishingly sophisticated abilities, the brain has for centuries posed some of science's most vexing questions. "Thinking about the brain," writes Harvard biologist R. C. Lewontin, "has driven everyone to distraction."

One group of researchers has chosen to avoid the forbidding complexity of the mammalian brain, scanning instead the simpler neural networks of invertebrates for clues to cerebral function. From the beginning, however, invertebrate neurophysiologists have been confronted with major questions about the limits of their research: just how deep is the similarity between invertebrates and vertebrates? Can the lower organisms, for example, manage anything beyond the most rudimentary forms of learning?

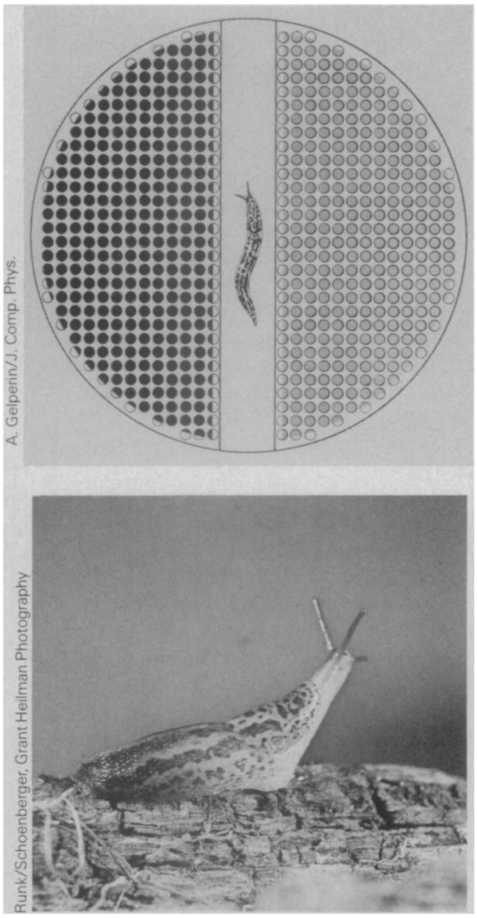
In light of recent findings, the answer to this last question now appears to be yes. Under the watchful eyes of neurophysiologists, a number of invertebrates have begun to display an unexpected degree of resourcefulness.

The garden slug *Limax,* for instance, can apparently undergo behavioral conditioning in the tradition of Pavlov's famous dogs, report Alan Gelperin of Princeton University and his co-workers. Given a choice of two foods, its customary lab diet of rat chow or a serving of instant potatoes, *Limax* will ordinarily make tracks for the potatoes. But if this potato-seeking behavior is "punished" with a drop of bitter chemicals, *Limax* learns to avoid its once-favorite meal. Next time around, the slug will steer clear of potatoes and opt for rat chow, apparently associating potatoes with an unpleasant experience. According to Gelperin, this is a clear example of *associative learning,* in which animals discover relationships between separate events.

Understanding the neural mechanisms behind this learning, says Gelperin, "is our ultimate goal." An important step has already been taken in this direction. In a modified version of the food-discrimination procedure, Gelperin and colleages have been able to "train" an isolated portion of *Limax*'s nervous system. Specifically, the slug's lips (where the taste cells are located) and brain can be surgically removed from the animal and conditioned to respond differently to two food extracts. Gelperin next hopes to identify the particular neurons involved.

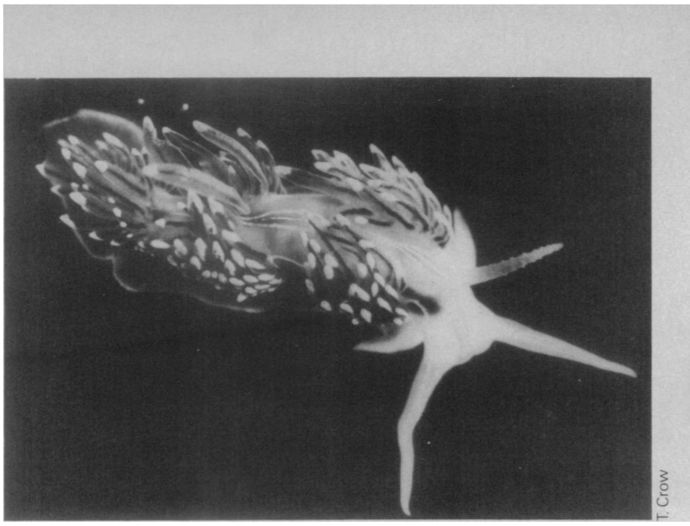
The sea slug *Hermissenda* displays an aptitude for another form of associative learning, in a training procedure developed by Daniel Alkon of the Marine Biological Laboratory at Woods Hole, Mass. First, *Hermissenda* is positioned in one end of a glass tube, and a light is flipped on at the other end. Following the light burst, the slug is subjected to a spin on a phonograph-style turntable. Though normal, unconditioned slugs will head straightaway for illuminated areas, animals that have been put through the training routine a number of times hesitate when the light flashes on, as though bracing for another bout on the turntable. "The animals learn that light predicts rotation," Alkon says. "This is in very many respects identical to conditioning in vertebrates."

Moreover, Alkon and his co-workers have uncovered much of the cellular and chemical machinery behind *Hermissenda*'s conditioning, sketching perhaps the most comprehensive portrait of any learning mechanism, associative or nonassociative, to date. The anatomical site of learning, it turns out, is in the slug's eyes. Alkon has found that during training six of the slug's light receptor cells, called type B cells, acquire new electrical properties. Specifically, potassium channels in the cell membranes are blocked in such a way that the cells become more responsive to light. This may seem paradoxical, since conditioned animals are actually slower to approach illuminated areas. But several researchers, including Terry Crow of the University of Pittsburgh, have found evidence that the light-induced activity of type B receptors inhibits muscles that would normally propel the slugs toward



The garden slug Limax *can be taught to avoid foods it once found appealing. The slug is pictured between meals on the test apparatus (top) and in a more natural setting (bottom).*

Facing page: the sea slug Hermissenda *(left). Slugs-in-training (right). The animals are positioned in glass tubes (closeup, inset), around the rim of a turntable. Slugs are drawn toward the center by a light, whereupon the turntable begins spinning.*



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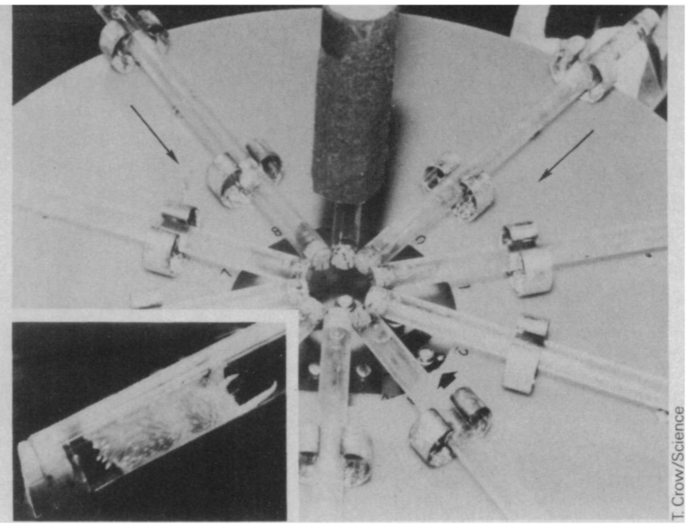

T. Crow/Science

light. The more active the type B cells, says Crow, the greater the tendency of the slugs to stay put.

The way in which this learning change comes about is quite complex. Apparently, rotation stimulates a small balance organ called the statocyst, which then sends impulses to the type B cells in the eyes. Under most circumstances, these impulses have only a mild, short-lived effect on the cells; no learning takes place. If, however, the impulse arrives soon after the receptors have been stimulated by the blinking on of a light, there is a "profound, long-lasting" impact on the cells, according to Alkon. Receptors stimulated by light are, in a sense, more vulnerable to the effects of the impulses, and a sequence of chemical events is triggered. This leads eventually to the activation of a protein kinase enzyme, which alters the cell membrane. Hence, *Hermissenda's* cellular apparatus detects and remembers a specific temporal relationship between two events: light precedes rotation.

In support of this mechanism, Alkon's group has not only found specific changes in the receptor cell membranes of trained animals, but has also demonstrated that these changes can account for the learning *Hermissenda* displays. One of Alkon's co-workers, Joseph Farley of Princeton University, has operated on untrained slugs and electrically induced the membrane changes supposed to be responsible for learning. "When we sew the animals back up and put them on the testing apparatus, they act just like trained animals," Alkon says. "This is the first demonstration that membrane changes can cause learning changes."

Hermissenda and *Limax* have been recently joined on the list of educable invertebrates by the marine snail *Aplysia californica*. A team of Columbia University researchers discovered an apparently associative capacity in the snail's gill withdrawal reflex, and a similar capacity has been postulated in its tail withdrawal reflex by Terry Walters and John Byrne at the University of Texas Medical School at Houston. Both groups propose a biochemical mechanism different from *Hermissenda's*, but the general neural framework is the same in one important respect: an initial stimulus primes a nerve cell for changes induced by a second stimulus. In this way, the animal learns about sequences of events.

How much light do such findings shed on the dark corners of the vertebrate brain? "It would be jumping the gun to say the invertebrate work has much to do with vertebrates, but the ingredients are there," says Alkon. "The membrane channels we've discovered as storage mechanisms are not at all unique to *Hermissenda* — they're present in many vertebrate systems."

Some new evidence on this issue comes from the lab of vertebrate neurobiologist Charles Woody at the University of California at Los Angeles. Woody, who is studying conditioning in cats, says he has begun to find "some really exciting parallels" with Alkon's model. Recent experiments performed by Woody and Alkon indicate that conditioning mechanisms in the cat's motor cortex may involve a protein kinase and other chemical steps found in *Hermissenda*.

The clear hope of many invertebrate researchers is that the mechanisms they have uncovered are letters in a universal alphabet of animal learning. Columbia researcher Eric Kandel is certainly optimistic. It is likely, he recently told a gathering of neuroscientists, "that more complex learning processes use the building blocks available for simpler forms." Kandel also believes that the information vacuum separating the higher-order analyses of psychology and the microscopic particulars of neurobiology might soon be filled. "Questions posed by both fields are beginning to merge on a common ground," he says.

But there are still vast distances to be crossed before psychological descriptions of behavior and cognition can be replaced by what Kandel calls a "biological grammar of mentation." "It's very hard to say whether the underlying processes being looked at in invertebrates are going to be relevant to vertebrates," says Stanford University neuropsychologist Richard Thompson. "The invertebrate work shows how the nervous system can form plasticity, but it's a very simple sort of plasticity." Robert Rescorla, a learning theorist at the University of Pennsylvania, agrees: "They're looking at how organisms relate two events. But how a creature might use these mechanisms in making complex, creative deductions is something that behavioral theories, even at the mammalian level, are not prepared to deal with."

Nevertheless, the impact of the invertebrate research is already being widely felt. For one thing, the findings lend strong support to the increasingly popular notion that learning results from changes in nerve transmission, not from new configurations in the neuronal wiring itself. Connections may get stronger or weaker, according to this view, but all the hardware necessary for learning is in the brain, waiting to be activated. As Rescorla explains, "New associations might be built on preexisting connections."

Most important, says Walters, the invertebrate work has given scientists a few concrete examples of ways learning can be accomplished: "This represents at the very least a major advance in the kinds of mechanisms people can begin to look for in the mammalian nervous system."

And, owing to a recent innovation in research methods, the looking may begin soon, according to Walters. Whereas in the past the complexity of the mammalian brain prevented neurophysiologists from observing many cellular processes, researchers can now remove small slabs of brain tissue, keep them alive for long periods, and monitor the activity of individual cells. "You can do with those cells virtually everything you can do with invertebrate neurons," Walters says.

"This is really one of the most exciting periods in neurobiology," says Crow. "I think there's hope, whereas a few years ago people thought the learning process was so complicated it defied analysis." Walters is more emphatic: "A lot of us feel that the field's about to explode." □