Dialing up an Embryo

Are olfactory receptors digits in a developmental code?

By JOHN TRAVIS

William J. Dreyer wonders why cells don't get lost as an animal develops. He has long puzzled over how fingers and toes emerge from a growing limb, embryonic cells coalesce into a beating heart, and the billions of cells in a brain connect in just the right way.

He may have found the solution right under his nose.

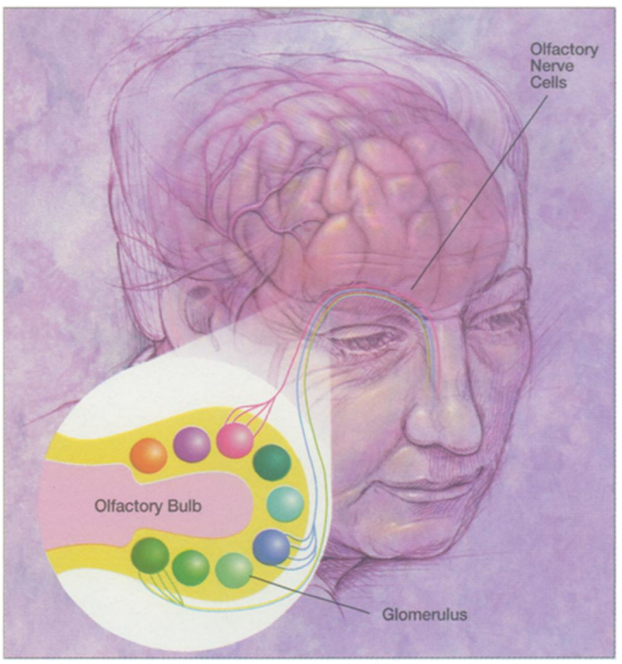
In the Aug. 4 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS), Dreyer lays out the provocative idea that the cell surface proteins in the nose that detect odors also help assemble embryos. He argues that these olfactory receptors and related proteins act as identifiers, much like the last few digits of a telephone number, that help cells to find their intended neighbors in a developing embryo.

"I've been searching for these last digits for 20 years," says Dreyer, a biologist at the California Institute of Technology in Pasadena. "No one can say for sure [the new theory] is true, but I'm up to 90 percent confident."

Dreyer's hypothesis rests on a precarious foundation: a small number of published experiments, a computer-aided analysis of genetic databases, and several unproven but plausible assumptions. Its bedrock is the 1992 discovery of the genes encoding the cell surface proteins believed to capture odorants in the nose. Mammals seem to have more than a thousand such genes. Even a simple worm has at least 550 olfactory receptor genes, comprising more than 5 percent of its genome, notes Dreyer.

Recently, investigators have made the surprising observation that these complex proteins—all of which crisscross a cell membrane seven times—play a crucial role in the development as well as the function of the olfactory system. For the nose to work, its sensory nerve cells must send out long extensions, or axons, to connect with the brain region called the olfactory bulb. This area begins the processing of odor information.

Each sensory cell appears to display copies of a single olfactory receptor. Although cells that are making a particular receptor are randomly distributed throughout areas of the nasal cavity, all their axons converge on one of two olfactory bulb regions specific to that receptor.



Though dispersed largely at random in the nose, sensory cells with identical olfactory receptors home in on the same regions of the olfactory bulb.

The olfactory receptor protein on an axon somehow determines where on the olfactory bulb it will hook up. Peter Mombaerts of Rockefeller University in New York and his colleagues have crippled genes for individual mouse olfactory receptors. The sensory cells employing those genes sent their axons toward the bulb, but the axons stopped well short of their targets. While other cues apparently guided an axon to the general vicinity of its target, the receptorless cell could not pick out its exact destination.

Dreyer now theorizes that the axon's olfactory receptor looks for copies of itself on cells in the olfactory bulb. "Maybe they're the same: the seeker and the target," he says.

From this speculation, Dreyer developed the idea that an axon migrates to its target along a gradient of different olfactory receptors to which it binds more and more tightly. Only when the axon meets a bulb cell bearing its own receptor, the one to which it binds most strongly, is its journey completed.

If the olfactory system resorts to such receptor gradients, perhaps so does the whole developing embryo. "If you have such an elegant system for building one part of the brain, are you really going to invent something totally different for the next piece of the brain, or for building a finger or heart?" says Dreyer.

Last year, Dreyer plunged into genomics, a fledgling field that employs computers to survey the flood of data on newly isolated genes. He began to examine databases of expressed sequence tags (ESTs), which represent fragments of genes that are active in cells. Searching through large EST databases, Dreyer found that ESTs from the liver, lung, prostate, eye, kidney, heart, testes, and other tissues match olfactory receptor genes. His survey, supported by several studies from other research groups, suggests that all tissues make at least a few olfactory receptors.

"What are they there for? They're not there to smell the roses," contends Dreyer. "They're there for the receptor gradients that pull all types of cells together."

The biologist emphasizes that other cell surface proteins, as well as proteins secreted by cells, would also help olfactory receptors assemble embryos. "These molecules fulfill many of the addressing functions . . . by providing the equivalent

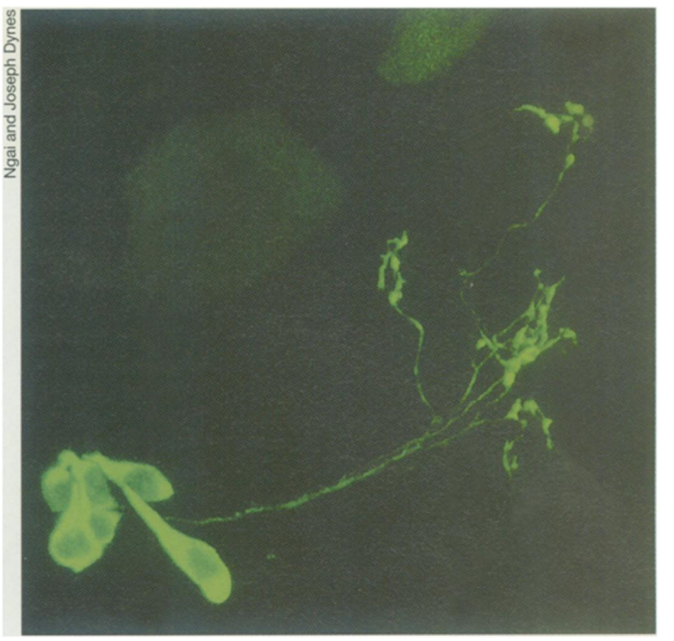
of country codes, area codes, and regional codes, etc.," he proposes in PNAS.

Dreyer acknowledges that his picture of olfactory receptors offering embryonic targets rests on the contention that, in addition to recognizing odors, these proteins can bind to copies of themselves and to similar receptors. "These things are built to recognize molecules," he says. "It's perfectly reasonable, [but] there's no evidence. It's pure hypothesis."

Dreyer has outlined several experiments to test his theory. For example, he encourages researchers to mark when and where in an embryo the individual olfactory receptor genes are active. Those experiments would have to be analyzed carefully, he notes, because an embryo may show only a speckled pattern of cells expressing a particular receptor, much as only a small number of people in a specific area code would have the same last four digits in their phone number.

Mombaerts suggests another test: Scientists could create mice in which a large number of olfactory receptor genes have been disabled.

While a few biologists have already dismissed Dreyer's hypothesis as far-fetched, others are keeping an open mind. "The notion that olfactory receptor genes may be expressed in other cell types than olfactory sensory neurons deserves our full attention. I am afraid that this issue has never been seriously addressed," says Mombaerts.



Ngai and Joseph Dynes

Sensory cells (labeled in green) in the nose (left) extend their axons to targets in the initial odor-processing region of the brain (right).

John Ngai, who studies development of the vertebrate olfactory system at the University of California, Berkeley, admits he was ready to reject Dreyer's theory but found he couldn't.

"One experiment could tell us that the theory is totally impossible or implausible, but I haven't found that experiment yet. I don't know of any one thing that unequivocally says it's wrong," he says.

As for Dreyer, he has faced skepticism before and had the last laugh. In 1965, he and a colleague put forth the radical notion that immune cells shuffle DNA sequences to create the genes encoding the many antibodies and cell surface proteins that recognize infectious organisms. The idea was ridiculed initially but later proven correct. Dreyer is now hoping that history will repeat itself. □

Biology

Oh, not those jet-ski things again!

If motorboats were bad for nesting birds, jet skis promise to be worse.

Personal watercraft, both the stand-up and sit-down styles, disrupt breeding colonies even more than boats chugging by, says Joanna Burger of Rutgers University in Piscataway, N.J. She watched common terns nesting on an island in Barnegat Bay, N.J. As watercraft roared past, she kept track of how many birds became alarmed and soared into the air. Other studies have linked frequent alarms to declines in breeding.

The New Jersey channel was posted for "no wake," but Burger recorded plenty of fast, noisy traffic. She found that the birds reacted most dramatically early in the breeding season.

In these periods, a personal watercraft zipping by would send some 200 birds flapping into the air, more than six times as many as a motorboat passing. In the August CONDOR, Burger recommends that personal watercraft not be allowed within 100 meters of nesting colonies. —*S.M.*

New hunting trick explains bird luck

A hunting method that ornithologists had never recognized may explain why the red knot is such a lucky bird.

A kind of sandpiper, the knot stalks wet shores, hunting for buried mollusks and hard-shelled crustaceans. Finding bivalves can be tough, since they just clam up and give no clues to their location.

Yet red knots detected these buried treasures seven to eight times more often than predicted by models of random searching, according to a team led by Theunis Piersma from the University of Groningen in the Netherlands. The knots also beat the odds for hunting by touch, which is how some other shorebirds including oystercatchers find their prey.

The secret is right on the tip of the bill, the team reports. Microscopic examination revealed pits containing stacks of cells called Herbst corpuscles, similar to the organs used by other shorebirds to detect vibrations from wriggling prey.

The researchers propose that the red knots, however, use the system in a different way. As the knots drive their bills into the sand, causing water movement, the Herbst corpuscles sense pressure variations that occur when an immobile object, like a hidden bivalve, obstructs the flow.

In tests in captivity, birds were trained to indicate whether sand pails hold hidden mollusks. They could manage their task only when the sand was wet. Sounds of life did not seem relevant since the birds responded to rocks as well as to living prey.

The observation that the birds prefer to feed in sand so wet that there are puddles "suddenly makes sense," the researchers say in the August 7 PROCEEDINGS OF THE ROYAL SOCIETY OF LONDON B. —*S.M.*

Aspirin works on plants, too

Pain in the lower bark? Ralph A. Backhaus tells a plant to take two aspirin and call him in the morning.

Backhaus of Arizona State University in Tempe and his colleagues have unraveled a key mystery in the way aspirin shuts down a plant's response to injury. Although plants may not feel pain as people do, they do respond to injuries by pumping out a chemical called jasmonic acid. They even produce vapors, chemicals related to the jasmine in commercial perfumes, that waft from the injured plant and cause responses in neighbors.

For years, researchers have known that aspirin somehow shuts down plants' jasmonic acid output, which requires the enzyme allene oxide synthase. The synthase has "virtually nothing in common" with the enzyme that aspirin disables in humans, yet the researchers found that the painkiller knocks out both substances with the same kind of chemical reaction. Details appeared in the July 17 JOURNAL OF BIOLOGICAL CHEMISTRY. —*S.M.*