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SEX and the SECRET NERVE

Could a little-known cranial nerve be the route by which human pheromones turn us on?

By R. Douglas Fields

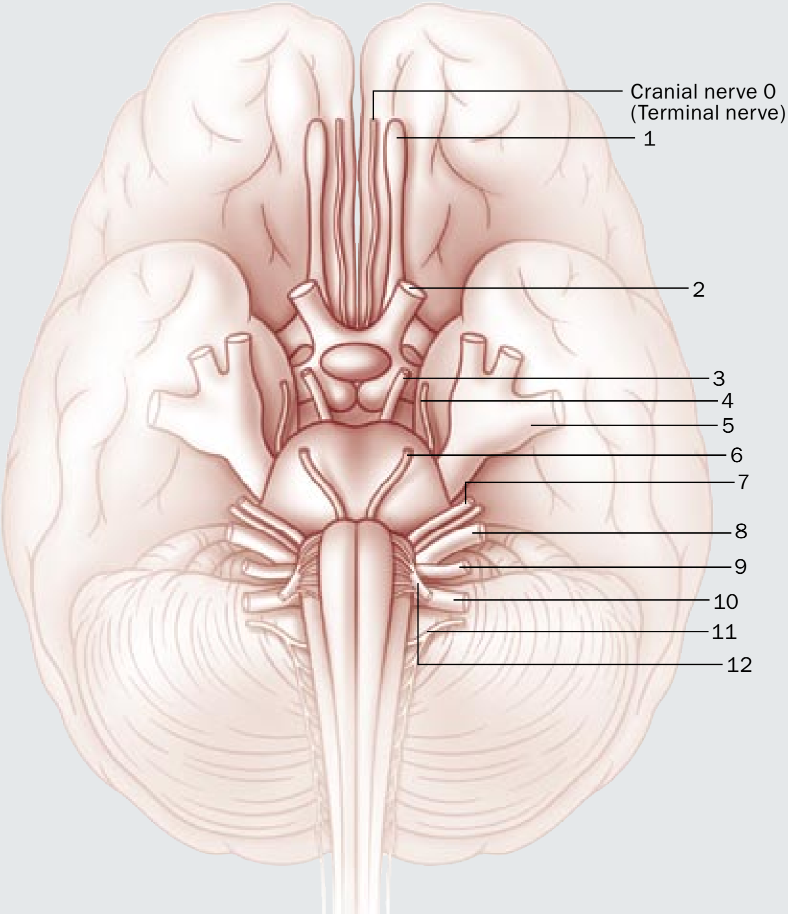
We stood around the body planning our autopsy strategy. A scalpel, we realized, was not going to be the appropriate implement for this corpse, so we made our decision. It took all three of us to muscle the slippery black bulk of the pilot whale into the screaming blur of the band-saw blade.

The whale had died of natural causes, after a distinguished military tenure conducting deep-sea operations for the U.S. Navy, which sends marine mammals to places where humans cannot safely go. In death, it was going to perform one more service—provide us with information about its magnificent brain. The navy had invited Scripps Institution of Oceanography researchers to come to its base in San Diego in the mid-1980s, and I had joined them. Dressed like fishmongers in black rubber smocks and boots, anatomist Leo S. Demski, visiting from the University of Kentucky, veterinarian Sam H. Ridgway of the Naval Oceans Systems Center and I sought to unravel a scientific mystery. It was imperative that we learn whether the whale had a certain cranial nerve—for reasons that will soon become apparent.

Every picture of the human brain you have seen is wrong. Something is missing, and the omission is not trivial. The dirty little secret is a tiny, relatively unstudied nerve sprouting from the base of the brain whose function is only now becoming clear: subliminal sexual attraction. Many scientists believe that pheromones, those silent chemical messages exchanged by members of the opposite sex in search of mates, relay subconscious signals to the brain through this obscure nerve. Others

Mysterious Nerve

Cranial nerves emerge from the floor of the brain in pairs; each pair is numbered from the front of the brain (closest to the forehead) to the back (near the spinal cord). Cranial nerve zero (also called the terminal nerve) is not in typical textbooks. Anatomists historically missed the thin nerve, perhaps because it is often inadvertently pulled off along with the tough membranes that wrap the brain.



TAMI TOLPA; SOURCE: "NERVUS TERMINALIS (CRANIAL NERVE ZERO) IN THE ADULT HUMAN," BY G. N. FULLER AND P. C. BURGER, IN *CLINICAL NEUROPATHOLOGY*, VOL. 9, NO. 6; NOVEMBER 1990

are skeptical. How can a little-studied nerve be involved in activities with such important implications for human behavior—especially when anatomists have scrutinized every minute detail of the human body for centuries? Could there be more to choosing a mate than we consciously realize? Researchers like us have been working to find out.

Tracking this mysterious cranial nerve brought me to the pilot whale, as a model for understanding our fellow mammals. For reasons that I will explain, it was particularly important to find out if this nerve exists in whales.

Most nerves enter the brain through the spinal cord, but some—the cranial nerves—enter the brain directly. The existence of some of the cranial nerves, if not their precise function, has been known since the time of Greek philosopher and physician Galen (who lived circa A.D. 129 to 210). Today we understand that they provide the vital senses of smell, sight, hearing, taste and touch; they are also involved in the movement of the eyes, jaw, tongue and face. Cranial nerves emerge from the floor of the brain in pairs, like a multilegged centipede. As every medical student knows, each nerve pair is numbered in sequence from the front of the brain (closest to the forehead) to the back (near the spinal cord).

Cranial nerve one is the olfactory nerve. All the scents of the world enter our brain through this nerve. Next, immediately behind the olfactory nerve, is cranial nerve two, the optic nerve. The optic nerve connects the eyes to the brain. The pairs continue in sequence to the 12th cranial nerve, which extends from the tongue and enters the brain near the spinal cord. Each pair was carefully identified, numbered and studied in detail. Then, in the late 1800s, neuroanatomists had their tidy understanding of cranial nerves attacked, so to speak, by a shark.

In 1878 German scientist Gustav Fritsch noticed a slender cranial nerve entering the brain of a shark just ahead of all the known nerves. No one else had noticed it before. Even today countless students in anatomy classes dissect dogfish sharks, but few detect the nerve because it is still not in the textbooks.

The discovery put anatomists in a predicament. Because it was located in front of the olfactory nerve, the new nerve should have been named cranial nerve one. But renumbering all the cranial nerves at this point was impossible, because their identities were deeply entrenched in the medical vocabulary. The solution was to christen this new find "nerve zero," the "terminal nerve." Most people forgot about it altogether. It just did not fit within the 12-nerve curriculum. And anyway, all five senses were accounted for by the other cranial nerves. How important could this little nerve be?

It would have been easier to overlook this inconvenient discovery if nerve zero were present only in sharks. But over the next century anatomists found the wispy nerve springing from the brain just in front of the olfactory nerve in almost all vertebrates (animals with backbones). To their chagrin, they found the nerve in humans, too, in 1913. Usually it is ripped away during dissection when the tough membranes that wrap the brain are peeled off, but if one knows where to look and is especially careful, the little nerve is always there. What is its purpose?

One clue comes from how it is connected in the brain. Like the olfactory nerve, nerve zero sends its endings to the nose. Perhaps, some researchers argue, this nerve is simply a frayed strand of the olfactory nerve and not a separate cranial nerve at all. The dead pilot whale, my colleagues and I realized, was a perfect opportunity to examine that notion by looking directly to an example from nature.

Whales and dolphins are unique in having a blowhole on the top of their head. Whales evolved from aquatic mammals that breathed through nostrils in the front of the face. Over the course of millions of years of evolution the nostrils gradually migrated to the top of their head. In the process, whales and dolphins gave up the sense of smell, and they lost their olfactory nerve. We realized that if nerve zero were also involved in the sense of smell—as just a twig branching off of the olfactory nerve—it, too, would have been abandoned in the evolutionary exchange of nostrils for blowhole. But if, as we suspected, nerve zero did something else, it might still be present in whales.

Before I relate the results of our autopsy, you must have a look at some of the evidence that raised our suspicions that nerve zero connects the sense of smell to sex.

Smell and Pheromones

Smell is the most ancient of all the senses—even the lowly bacterium must discern the difference between nutritious and noxious substances by sniffing (detecting chemicals in) its environs. Humans, who have a weak sense of smell compared with most mammals, nonetheless have 347 different types of sensory neurons in the olfactory epithelium, where cells for smell reside in the nose. Each one detects a different type of odor, and all the varied aromas and stenches we know result from mixtures of responses of these 347 types of receptor cells. In comparison, every color we see results from signal combinations of only three types of sensory neurons in the retina (red-, green- or blue-sensitive cones), vision's sensing layer at the back of the eyes.

> (Indications are that people do exchange such **secret pheromone** messages.)

Animals rely heavily on the sense of smell and other nonverbal cues for communication. From frenzied June beetles to tomcats pursuing a queen in heat, pheromones are important for selecting mates and stimulating reproduction throughout the animal kingdom. A stallion curls its upper lip and inhales deeply to snuffle pheromones from a mare in heat, a behavior called flehmen. Many animals also rely on the sense of smell to determine sex, social rank, territories, reproductive status and even identity of specific individuals, such as their own mates or offspring.

In humans, mate selection and sexual reproduction are far more complex, but there are indications that people do exchange such secret pheromone messages. We will examine the evidence—some of it reported only in the past few months—but for now it is sufficient to appreciate that pheromones differ in two important ways from the chemicals that excite our sense of smell. For a smell to waft a distance from its source, the odor-producing molecules must be very small and volatile (able to float great distances in the air). Not so for pheromones, which can be large molecules passed between the noses of individuals during intimate contact, such as kissing.

Second, not all pheromones have an odor. If pheromones were to excite nerve endings that convey their signals directly to brain regions controlling sexual reproduction, bypassing the cerebral cortex where consciousness arises, they could act like an unseen olfactory cupid—putting a romantic twinkle in the eye of a certain member of the opposite sex—and we would never know it.

sal cavity known as the vomeronasal organ. This organ, in turn, is connected to a tiny "accessory" olfactory bulb, next to the main olfactory bulb involved in the sense of smell. From there, nerves connect to areas of the brain involved in sexual arousal (such as the amygdala) rather than to the olfactory cortex. In rodents, for example, stimulating the vomeronasal organ with pheromones can release a flood of sex hormones into the blood.

Acting through the vomeronasal organ, pheromones influence the frequency of estrus and

(Pheromones could act like an unseen olfactory cupid—putting a **romantic twinkle** in the eye of a mate.)

As it turns out, nerve zero's connections in the brain leave open that very possibility. To explain how requires a more detailed look at the circuitry for the sense of smell and for a special structure in the nose of many animals that detects pheromones, called the vomeronasal organ.

The olfactory nerve connects sense cells in our nose to the olfactory bulb inside our skull. This neural bulb is a massive relay point containing a nest of synapses. Raw incoming sensory information from the 347 kinds of odor receptors is first sorted here, then processed to analyze and discriminate among the universe of odors. The signals next pass to the olfactory cortex for finer discrimination and conscious perception of the odor.

For many animals that rely on pheromones for sexual communication, the key place for sensing these chemicals is a specialized area inside the na-

stimulate sexual behavior and ovulation in animals. The wrong pheromones can even terminate a pregnancy. In 1959 Hilda M. Bruce of the National Institute for Medical Research in London reported that an embryo will not implant in the uterus of a recently mated female mouse if she is exposed to the smell of urine from an unfamiliar male. Instead the embryo will be aborted, and the female will return to estrus. In contrast, the smell of urine from her mate does not prevent implantation and pregnancy.

In research published in 2006, Nobel laureate Linda Buck and her colleague Stephen Liberles of the Fred Hutchinson Cancer Research Center in Seattle identified 15 members of a new family of receptor proteins. These receptors, found in the mouse nose, exist on the surface of sense cells that detect pheromones, lending credence to the

Pilot whale brains lost the olfactory nerve during evolution but retained nerve zero—an important clue to its function.

DAVID A. NORTHCOTT *Corbis*

idea of a separate pathway for pheromones in mammals. These cells are different from the receptors that detect odors. Each of the newly discovered TAARs (trace amine-associated receptors) responds selectively to specific nitrogen-containing molecules in mouse urine. The concentration of one of these chemicals increases in mouse—and human—urine under the stresses associated with mating behavior, such as those involving dominance and submission. Two of the TAARs are excited by compounds found exclusively in the urine of male mice, but only after puberty, also suggesting a sex link. Incidentally, behavioral researchers had previously identified one of these compounds and found that it accelerated the onset of puberty in female mice.

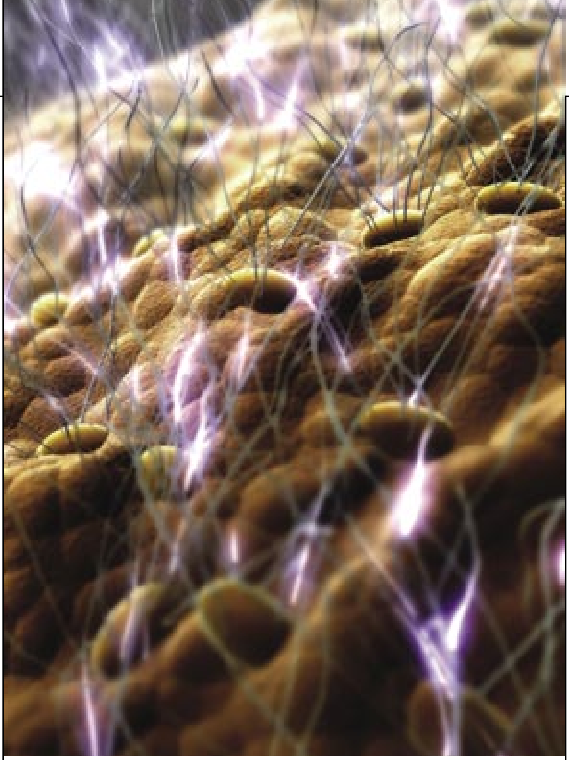
We now have an understanding of pheromones in mice that extends from molecules to sexual behavior, but what about pheromones in humans? Intriguingly, Buck found that humans have the genes to make at least six of the same pheromone receptors present in mice.

Nerve Zero's Role

Although some scientists claim to have detected an operational vomeronasal organ in humans as well, most believe that it appears to be vestigial. As is the case with gill slits, we possess vomeronasal organs only during our fetal lives, after which they atrophy. So if pheromones are sending sexual signals to human brains, they are not relying on the vomeronasal organ to relay them. Instead nerve zero might be stepping into the breach.

Consider the following anatomical features of nerve zero. Like its olfactory cousin, nerve zero has its endings in the nasal cavity, but remember that it sends its nerve fibers to the hot-button sex regions of the brain: the medial and lateral septal nuclei and preoptic areas. These regions of the brain are concerned with the "nuts and bolts" of reproduction. They control release of sex hormones and other irresistible urges such as thirst and hunger. The septal nucleus can act on and be influenced by the amygdala, hippocampus and hypothalamus. Damage to the septal nuclei causes behavioral changes in sexual behavior, feeding, drinking and rage reactions. Thus, in connecting the nose to the reproductive centers of the brain, nerve zero completely bypasses the olfactory bulb.

Cutting the olfactory nerve or removing the vomeronasal organ will disrupt normal mating behavior in rodents, suggesting that the olfactory nerve transmits pheromone messages from the vomeronasal organ. But in the past few years, researchers have come to understand that nerve



Vomeronasal organ in a mouse transmits sexual signals to the brain. In humans the organ is vestigial. Could nerve zero provide a similar function?

EURELIOS/PHOTOTAKE

zero *also* sends fibers to the vomeronasal organ—and that nerve zero's fibers run extremely close to the fibers of the olfactory nerve. As a result, in experiments in which the olfactory nerve was deliberately severed, investigators may have inadvertently cut through nerve zero as well.

In 1987 neuroscientist Celeste Wirsig, then at Baylor College, carefully severed the nerve zero of male hamsters, leaving the olfactory nerve unscathed (as shown by the fact that hamsters with a severed nerve zero could find a hidden cookie just as fast as control animals could). The hamsters with a severed nerve zero failed to mate.

Similarly, in 1980, neuroscientists observed that electrically stimulating the olfactory nerve could trigger sexual responses in fish and other animals. But could this sexual behavior actually result from a stimulated nerve zero, which runs close to the olfactory nerve for most of its length? Neuroanatomists R. Glenn Northcutt of the University of Michigan at Ann Arbor (now at the University of California, San Diego) and Demski of Kentucky (now at the New College of Florida) suspected as much. They also knew that on their way to the brain, some fibers in nerve zero took an unexpected side trip and sent branches to the retinas of the eyes. This may seem odd until you realize that for most plants and animals, reproduction is seasonal—and day length is the most

(The Author)

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Chemical Messages

What is it about sexual attraction that can instantly draw two people together? Could pheromones be a factor for human couples, as they are for other animals? Research on molecules that protect us from infections offers intriguing clues.

In many animals, the nose can determine sex and reproductive status by sensing trace hormones and other compounds in urine and sweat. A different class of molecules provides information about the individual identity of a mate. Such macromolecules, called major histocompatibility complex (MHC) proteins, sit on the surface of cells to allow the immune system to distinguish the body's own cells from foreign ones.

Here is how it works. MHC molecules are huge proteins equipped with bird-beak-like appendages that snatch small protein fragments inside cells and poke them through the cell membrane for guard patrols called T cells to inspect. If the protein fragments are foreign, the immune system attacks.

Some studies suggest that people can discern whether someone has different MHC genes. Biologist Claus Wedekind of the University of Edinburgh reported in the mid-1990s that in one study women preferred the odor of T-shirts worn two nights by men who had different MHC genes from their own; men had the same ability to distinguish MHC genes by smell. In a 1997 study geneticist Carole Ober of the University of Chicago and her colleagues reported that people avoid mating with individuals carrying the type of MHC genes most similar to those of their own mothers.

It makes good evolutionary sense to mate with someone who has a different set of MHC genes, because doing so increases the arsenal of immune system genes in your children and thus allows them to better resist infection. It is also biologically important to diminish sexual arousal toward one's own family members, who are most likely to share your variety of MHC genes. The Wedekind and Ober studies suggest that an individual's odor is affected by the particular variety of MHC genes he or she has. This effect may come about because differences in an individual's immune system alter the body's bacterial flora and, in turn, the resulting odors created by the breakdown of sweat and apocrine gland secretions by these bacteria. But would nature leave such a vital process as mate selection under the control of microbes, which can change with infections and other environmental influences?

As it turns out, it is not the MHC protein itself that is the pheromone. Recent research indicates that it is the small protein fragment clutched in the jaws of the MHC molecule. In 2004 neurobiologist Trese Leinders-Zufall of the University of Maryland School of Medicine and her colleagues found that when synthetic protein fragments that are more readily picked up by classes of MHC proteins in unfamiliar mice were added to the urine of the female mouse's mate, pregnancy was blocked just as if she had been exposed to urine from an unfamiliar male mouse. *—R.D.F.*

Stallion snuffles pheromones from a mare in heat.

KIT HOUGHTON *Corbis*

accurate way to gauge time of year. Many scientists suspect that a nerve involved in mating and reproduction might also connect to the retina to keep a constant check on the calendar. Regardless of function, this place was where nerve zero and the olfactory nerve parted company, so Northcutt and Demski were able to apply a mild electric shock to goldfish nerve zero fibers in this site without stimulating the olfactory nerve at the same time. When they did, the male goldfish responded instantly by releasing sperm.

So in addition to the anatomical evidence that nerve zero connected the nose to parts of the brain controlling sexual reproduction, strong physiological evidence now existed that—in fish at least—nerve zero might be a sensory system for responding to sex pheromones and regulating reproductive behavior. Another lead pointing to a sexual role for nerve zero would come from my own research, again on a creature from the sea.

In 1985, while studying nerve zero of a stingray using the electron microscope, I saw something peculiar: many of its axons (nerve fibers) were stuffed with what looked like minuscule black spheres. They turned out to be peptide hormones packed tightly together like pellets in a

(Nerve impulses travel out from the brain **through nerve zero**, but their purpose is unknown.)

shotgun shell. And at the tips of some of these nerves I observed the release of these hormones and their uptake by tiny blood vessels—suggesting that nerve zero may in fact be a neurosecretory organ, meaning that it regulates reproduction by releasing hormones in much the same way as the pituitary gland does. This new clue that the terminal nerve released sex hormones, together with the knowledge that it connected the nose to parts of the brain controlling sexual reproduction, triangulated on one conclusion: pheromones.

Yet skeptical scientists have credited arousal exclusively to the olfactory nerve, still arguing that nerve zero is not a separate cranial nerve at all but simply a frayed strand of the olfactory nerve. So when Demski and I heard that a pilot whale had just died at the San Diego Naval Base, we jumped at the chance to examine it. This animal could show us whether nerve zero was truly autonomous and might even help to illuminate its function.

Whale of a Find

Back in the lab at Scripps, Demski reached into a plastic bucket with gloved hands and withdrew the pilot whale's brain that we had removed from the immense carcass. It was about the size of a soccer ball and resembled a human brain, except that its cerebral cortex had tighter and more numerous convolutions—almost kinky in comparison to the wavy folds of a human cortex.

After turning over the whale brain for a look at its underside, we were struck by the strangeness of seeing a mammalian brain devoid of its olfactory nerves. (Remember that whales lost their sense of smell in exchange for blowholes.) Demski carefully peeled away the membranes from the area in which we expected to find a pair of nerve zeros, assuming they had not been lost along with the olfactory nerves. With the surprise of unwrapping a present, we found them: two slender white nerves headed toward the whale's blowhole.

Our postmortem on the pilot whale had proved that nerve zero was a distinct neural entity, not just a fragment of the olfactory nerve. And for whales and dolphins, which had sacrificed their sense of smell and the olfactory nerves that made it possible, whatever nerve zero did was too precious to survival for evolution to abandon.

Despite the intriguing findings, nerve zero's role in the sexual behavior of humans remains unclear. Recent research in mice has revealed the presence of certain sensory neurons that are *not* associated with the vomeronasal organ but that respond to pheromone stimulation. So even without a functioning vomeronasal organ, our noses may nonetheless contain sensory neurons capable of responding to pheromones.

How much of this labor is split between the olfactory nerve and nerve zero is not yet worked out. Obviously, nerve zero is doing something different with the information it is receiving from the nose, because it does not connect to the olfactory bulb where smells are analyzed. Moreover, it connects to parts of the brain controlling reproduction, and it releases a powerful sex hormone (GnRH) into the blood. Nerve zero develops very early in embryos, and studies show that all the neurons in the forebrain that produce GnRH use the fetal nerve zero as a pathway to migrate along to find their proper place in the brain. When this embryonic pathway is disrupted, Kallmann's syndrome is the result. This disorder not only impairs people's sense of smell, it leaves them unable to mature sexually beyond puberty. Undoubtedly, nerve zero has other functions in addition to reproduction—most cranial nerves transmit both sensory and motor (related to body movement) traffic. Electrical impulses have been detected traveling out from the brain through nerve zero, but what the outgoing messages do is unknown.

Ultimately, more research will be needed to fully detail nerve zero's role in the brain. But at least now you understand that nature provides a hidden channel of communication between the sexes to sustain the cycle of life, and scientists know where to begin to solve this intriguing puzzle. This secret nerve, missing from textbooks but shared by creatures from sharks to people, remains, like the intimate function it serves, still wrapped in secrecy. **M**

(Further Reading)

- **The Terminal Nerve (Nervus Terminalis) Structure, Function and Evolution.** Special issue of *Annals of the New York Academy of Sciences,* Vol. 519; January 1987.
- **Pheromones and Animal Behavior.** Tristram D. Wyatt. Cambridge University Press, 2003.
- **Terminal Nerve.** Leo S. Demski in *Encyclopedia of Neuroscience.* Third edition. Edited by George Adelman and Barry H. Smith. Elsevier, 2004.

- Pheromone facts are available at **www.sciammind.com**