THE RISE AND FALL OF THE NASAL EMPIRE

***Natural History*, June 2002**

Smell, above all other senses, is our link with history. It takes just a sniff of certain odors-the ozone tang of rain falling on blacktop or the crisp sting of frying onions-to instantly hurl us back decades. And our sense of smell has a history of its own, reaching back more than 500 million years. Until recently, however, scientists have had relatively little evidence on which to base a reconstruction of its evolution. They've only been able to compare the olfactory senses of living vertebrates or turn up the occasional fossil nose. But now historians of smell have been delivered a trove of new evidence, thanks to progress in deciphering the human genome and the genomes of other animals. The genes that enable us to smell reveal an epic story-the rise of an extraordinarily sophisticated sense organ and its subsequent decline in power.

It wasn't even so long ago that scientists learned how our sense of smell actually works. Air flowing into your nose carries with it a swarm of complex organic molecules that get trapped in the mucus-rich lining of the nose's inner recesses. Millions of nerve endings project into the mucus, and the molecules bump into them like driftwood floating through a kelp forest. Each neuron is studded with a dozen or so identical receptors, all made by the same gene and all bearing the same structure. Altogether there are several hundred different types of receptors. Each type is like a unique lock, and certain molecules inhaled into the nose can fit into them like a key. Once this happens, a receptor triggers a series of chemical reactions within its neuron, ultimately producing an electrical signal that hurtles along the length of the neuron and into the brain.

Each neuron bears only one type of receptor, but that same type can be found on other neurons-thousands of them-scattered across the interior of the nose. The neurons thread their way through tiny holes in the skull and attach to microscopic clumps of neurons at the front of the brain. In a remarkable feat of biological wiring, the thousands of neurons bearing the same type of receptor all converge on a single clump. The hundreds of clumps that receive signals from the different kinds of olfactory neurons act like a sort of odor map: each aroma lights up a distinct pattern of clumps, which the brain interprets to produce our perceptions of smell.

Exactly how the neurons manage to sort themselves out so precisely, no one is prepared to say. Yet these trails get blazed over and over again during our lifetime. Olfactory neurons survive only sixty days, and as they die, special cells in the nose lining mature into new olfactory neurons, which produce receptors of their own. Each of these new neurons sends out an axon that extends through a hole in the skull and somehow manages to find its correct clump in the brain.

The first scientists to discover genes for olfactory receptors were Richard Axel, of Columbia University, and Linda Buck, of Harvard, who found eighteen of them in rats in 1991. Each of the genes produces a protein that is shaped like a string folded into a distinctive series of seven loops. Axel and Buck decoded the sequences of nucleotides that make up the genes, and researchers around the world then began to search for other olfactory genes with similar sequences. They soon found many more, in rats, humans, frogs, catfish-in fact, in every other vertebrate they examined. The olfactory receptors all share a distinctive structure, but they are not identical. Their differences enable them to grab differently shaped molecules, thus allowing the perception of different odors.

The data gathered by scientists eventually pointed to a remarkable evolutionary history. The genes that make olfactory receptors in living vertebrates have all descended from a single ancient gene carried by some common ancestor. The evidence also shows that the evolution of olfactory genes has repeatedly involved two kinds of events: accidental duplication of a gene in its entirety, and subsequent mutations that introduce slight differences between the two copies. As the genes changed and multiplied, they grew into a family. And as early species of vertebrates gave rise to new ones, they passed on their olfactory genes, which continued to evolve.

The evidence for this evolution can be found in the olfactory genes carried by different vertebrates. Closely related species, such as chimpanzees and humans, always have slightly different sets of olfactory genes. Yet their sets of genes are much more similar to each other than they are to those carried by more distant relatives. By comparing the DNA sequences of olfactory genes, scientists have been able to organize them into an evolutionary tree and to trace the connection between new genes and the emergence of new lineages of vertebrates.

These comparisons suggest that the common ancestor of living vertebrates-a primitive fish that lived about 530 million years ago-used a tiny collection of olfactory receptors for smelling. Lampreys, which are jawless fish that belong to the oldest living lineage of vertebrates, use only a handful of olfactory receptor genes. What's more, those genes belong to the oldest lineages of olfactory receptor genes. Apparently, by the time jawed fishes evolved, the repertoire of olfactory receptor genes had become much more complex. All living jawed fishes studied so far have about a hundred genes for smelling.

Instead of pulling air through a nose, as we do, fish let water circulate through a nasal cavity above their mouth. And living underwater, they are most sensitive to molecules that dissolve easily in water and can thus be swept into their nasal cavities. When a branch of vertebrates came on land 360 million years ago, they encountered a new environment of scents, and their old olfactory receptors were not well adapted to perceiving insoluble molecules wafting through the air. Through mutation and natural selection, one branch of olfactory genes in these vertebrates diversified into a giant new family that may well have been more effective at detecting the airborne chemicals.

Living frogs may preserve something of this ancient transition. On land, a frog sucks in air and detects odors with the receptors at the rear of its nose. But when a frog dives, a flap seals off the back half of the nose from the water, while a special set of olfactory sensory neurons housed in the front of the nose allows the animal to smell underwater. It turns out that the receptors in the front are all made by the most primitive, fishlike genes in the frog's olfactory collection; those in the rear are formed by the new class of genes shared by every land vertebrate.

Though all living land vertebrates come equipped with a big battery of olfactory receptor genes, mammals have become exquisitely adept at smelling. Predatory mammals such as dogs and wolves use their noses to track prey for miles, while deer, rats, and other mammalian prey can sniff danger in a millionth of a gram of urine. Smell guides our appetite: the smell of ripe fruit appeals to us, while the smell of rotting meat drives us away. Males and females judge one another on the basis of their scents, and smell is also crucial in the bonding between mother and infant.

In the past few years, as scientists have worked on sequencing entire genomes, the search for olfactory receptors has shifted into overdrive. Instead of using molecular probes to grope for actual fragments of DNA, scientists can now search for patterns in online databases and find dozens of olfactory genes at a time. Researchers have published drafts of genomes not only for humans but also for many laboratory favorites, such as fruit flies and yeast. For scientists who study smell, the most valuable genome has been that of the mouse, which shares with humans a common ancestor that lived about 100 million years ago. A comparison of the mouse's olfactory genes with ours shows we've taken very different paths since we parted ways.

Researchers now estimate that a mouse has 1,500 genes for olfactory receptors. That means a tremendous portion of the mouse genome-about one in every twenty of its 30,000 genes-is connected to smell. But only about 1,200 of these genes actually seem to work. The remaining 300 are marred by mutations that have most likely rendered them useless. These mutations act like bugs in software, causing the neuron's protein-building machinery to come to a screeching halt when it tries to read the damaged genes. Known as pseudogenes, these ruined stretches of DNA are an inevitable by-product of the fast-paced evolution of smell in mammals. And unless other mutations delete these pseudogenes from the genome, they simply linger, passed down from parent to offspring.

Mice and their fellow rodents have been pushing the boundaries of olfaction for millions of years. Meanwhile, our own olfactory universe has been shrinking. Researchers have carried out preliminary surveys of olfactory receptor genes in apes, and they've found that 40 percent of the known olfactory receptor genes in gibbons and orangutans are pseudogenes. In gorillas and chimpanzees, our closest living relatives, the proportion climbs to 50 percent. And among humans, the numbers become even more embarrassing. Current estimates put the total number of our olfactory receptor genes at 900, and of those genes, only 320 or so work. In other words, almost two-thirds of our olfactory genes are broken.

When it comes to smell, our primate ancestors have been getting by with less for millions of years. Apes, which emerged about 20 million years ago, apparently came to rely more on vision and less on smell. The shift may have had something to do with changes in diet and perhaps even in social structure. Whatever the reason, as noses became less crucial to ape survival, the evolution of olfactory receptor genes into pseudogenes became less harmful. The decay accelerated with the rise of hominids 5 million years ago. It's possible that as ancestral humans began hunting and digging up tubers, they relied more on sharp eyes than on sharp noses. Perhaps even the rise of language helped reduce their need to use a vocabulary of scents.

The decay of our genome hasn't been random, however. The common ancestor of mice and humans bequeathed to both our lineages the same major families of olfactory receptor genes. In humans, most of these genes no longer work, but we still have a few functioning survivors in each gene family. Evolution has pruned back our olfactory tree, it seems, rather than ripping it out. The evidence from our genome hints that, like mice, we can still perceive a broad range of smells. We just do a much worse job at making fine distinctions between them.

Humans are not the only mammals that have let their genetic machinery for smelling fall apart. Dolphins, for example, descend from a hoofed mammal that adapted to life in the ocean about 50 million years ago. Along the way, the dolphin nose was modified into a blowhole. In addition, a dolphin can create vibrations by pushing air back and forth through flaps in the nasal cavity. These vibrations pass out of the animal's head and into the surrounding water, where they bounce off fish and other nearby objects. With exquisitely sensitive ears, the dolphin can hear these echoes and turn them into three-dimensional images in its brain.

Given that dolphins keep their blowholes sealed underwater and that their nasal cavities have turned into sound generators, anatomists have long speculated that these animals lost their original sense of smell. (Dolphins can detect chemicals in water, but the evidence suggests that they use their tongue rather than their nose.) Recently, a team of German researchers decided to carry out a preliminary survey of the genes for olfactory receptors in the striped dolphin. They discovered thirteen, but among those genes they could not find a single one that actually worked. For dolphins, the sense of smellappears to live on only as a genetic ghost.

Our own species probably won't go quite so far, but the future of our nose looks dim. In an increasingly industrialized world, smell is probably even less important than it was in the past, so olfactory pseudogenes may become even more common. We may be on our way to living with the bare minimum number of genes for smelling.

The fact that we lug around 580 defunct genes may seem bizarre, particularly when you consider that their close cousins continue to work in other mammals. But neither our DNA nor our bodies are perfectly designed. In the early 1800s, when Charles Darwin was learning his biology, most English naturalists believed that God created every species of animal and plant individually to perfectly fit its particular habitat. Darwin considered this absurd. Who would intentionally give ostriches tiny useless wings? Why should eyes begin to grow on fish living in caves and then degenerate into useless tissue? Why do we humans carry vestigial tailbones inside our bodies?

Darwin watched naturalists struggling to find explanations that could reconcile perfect design and imperfect anatomy. British anatomist Richard Owen, for example, abandoned the idea that vestigial organs were perfectly designed. Instead, he claimed that God produced a series of new designs over time, each of which was based on an "archetype"-a kind of transcendental blueprint. Ostriches had wings because God based them on the body plan for birds. Similarly, geologist John MacCulloch suggested that God pursued each plan until its potential was exhausted. "What bosch!!" Darwin wrote in a notebook. "The designs of an omnipotent creator, exhausted and abandoned. Such is Man's philosophy, when he argues about his Creator!"

In vestigial structures, Darwin saw compelling evidence that species had evolved. Blind cave fish, for example, descended from sighted fish that lived in neighboring rivers. "On the view of descent with modification," he wrote in the *Origin of Species*, "we may conclude that the existence of organs in a rudimentary, imperfect, and useless condition, or quite aborted, far from presenting a strange difficulty, as they assuredly do on the ordinary doctrine of creation, might even have been anticipated, and can be accounted for by the laws of inheritance."

Darwin didn't need to put his theories through contortions to account for flightless birds and cave fish. Vestigial organs were exactly the sort of thing you'd expect to emerge as lifeforms adapted gradually to their surroundings. And today, as scientists discover hundreds of vestigial genes that have lurked in our genome for millions of years, the reality of evolution is now, more than ever, as plain as the nose on Darwin's face.