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Perfume

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In Search of an Olfactory Mozart

Jean-Baptiste Grenouille, the "hero" of the novel *Perfume,*[1] was born unwanted under the gutting table of a fishmonger's stall in "the most putrid spot" in Paris in 1738, and was immediately abandoned by his disgusted mother, who was "still quite pretty and had almost all her teeth and—except for gout and syphilis and a touch of consumption—suffered from no serious disease" (Figure 1). In this strange and perverse tale, the foundling Grenouille ("frog" in French) bounced (leapt?) among priests and wet–nurses who undertook his care for charity, but each only briefly, because they found him too eerie to keep around: he produced no odors—he did not have a baby's captivating smell. Yet while producing no odors of his own, Grenouille grew to have an uncanny ability to detect the odors around him. He could smell what was unseen behind walls or within containers, and had no fear of night because he could navigate in the dark by smell alone.

AN OLFACTORY MISSION

On one defining nasal sojourn, Grenouille sniffed a trace of the perfect, irresistible smell. Following the scent through the back alley-ways of nocturnal Paris, he easily located its source. Not surprisingly—this is a novel, after all—the source was a nubile virgin from whose every pore and orifice emanated the irresistible aroma of "pure beauty" without which "his life would have no meaning." Unfortunately, Grenouille had to terminate this particular damsel's life to obtain an adequate sampling of the essential essence, but this gave his life a purpose: "to revolutionize the odoriferous world . . . [to become] . . . the greatest perfumer of all time." A Mozart of smells.

But his calling had to wait. Grenouille was farmed out for child labor in the noxious vats of a tanner, where he grew into a surly but reclusive misanthrope. But one day, while delivering an order of leather to a perfumery, he fell upon his opportunity. The House of Baldini had been one of the leading perfumeries in Paris, but its aging owner had lost his "nose," and had been forced to rely on his wholly imitative assistant. The firm was failing, but Grenouille persuaded them to take him on as the sorcerer's apprentice. Finally, his mission was under way!

It has been estimated that a normal human can resolve about 10,000 different odors, but Grenouille could detect "hundreds of thousands of specific smells and kept them so clearly, so randomly, at his disposal, that he could not only recall them . . . but could also actually smell them simply upon recollection . . . and knew how to arrange new combinations of them, to the point where he created odors that did not exist in the real world." He spent years at Baldini's on subsistence wages and rude living conditions slaving away to learn "fractionary" smelling and every detail of the extraction of essences. He learned to purify odors that could induce any specified type of behavior from people, allowing him silently to manipulate his world.

Grenouille moved to Grasse, the perfume capital of France, and began systematically collecting the material required for his ultimate objective. Unlike normal essences that only required sacrificing many flowers, *the* Essence required sacrifices more violent than violet. Grenouille's subjects could be shorn and blots taken of their entire bodies' unutterably ecstatic mix of exudations . . . only if they would lie perfectly, endlessly still.

WHAT DO WE KNOW ABOUT WHAT WE SMELL?

The past decade has seen rapid advances in our understanding of the genetic basis of the *detection* side of olfaction, as well as some aspects of its *perception.* The olfactory epithelium is the most externally accessible direct part of the brain and central nervous system (CNS). As shown in Figure 2, the olfactory epithelium essentially dangles olfactory neurons (ONs) into the nasal airways, where olfactory receptor molecules (ORs) can bind to inhaled odorant molecules wafting by. OR molecules are encoded by members of a large and ancient gene family called "serpentine" or seven-transmembrane cell surface receptors because, as shown in Figure 3, the OR protein passes seven times through the ON cell membrane. An odorant molecule sticks to a receptor it encounters if the receptor's binding regions chemically "fit" the odorant. This event alters the intracellular part of the receptor molecule, triggering a chain of response that sends a neural

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Figure 1. Fishmonger.

signal along that neuron, through the cribiform plate, to the CNS.

The discrimination of smells begins in the olfactory epithelium, where humans have a crudely guesstimated 5–10 million ONs—crudely, because estimates for rodents, which are much smaller, are around 15–20 million; dogs have an estimated 200 million. But the number of ONs does not tell the whole story. An odorant, say a molecule of apple aroma, will only bind to a small subset of the different ORs with which it comes into contact (different parts of the odorant may fit the binding pocket of different ORs).

Mammals have around 1–2 *thousand* different OR genes, our largest gene family. A history of repeated gene duplication events has littered our genome with clusters of OR genes on almost every chromosome (Figure 4). After duplication, these OR genes evolved differences in their binding domains Figure 3 (and see[3]) with the result that each receptor type can attach to particular chemical properties an odorant may have.

This provides a large repertoire of potential odorant recognition, but a given OR gene also varies among individuals, probably because selection has favored variety *per se* so individuals can respond to an open-ended array of molecules they might encounter. Most odorants will be recognized by at least some of this large repertoire, an efficient evolutionary strategy compared to the amount of natural selection it would take to evolve a specific receptor for each odorant an individual might be exposed to in ever-changing and unpredictable environments. Consistent with this, many substance-specific anosmias (smell deficiencies) have been reported that have not been related to specific receptor variation. A random combinatorial detection system also can explain why we can all smell gasoline, and Eurasians and Africans can smell New World fruits like corn and tomatoes—things they certainly did not evolve to smell.

Primates, and humans in particular, are thought not to follow their noses as much as other mammals do, and this is reflected in the OR genes. Repeated OR gene duplication events provide opportunity for mutations to arise in the many different ORs, and selection is likely to be weak in relation to most individual ORs nestled within the family of a thousand. One result is that a fraction of these genes are *pseudogenes,* that is, have experienced mutations that make them no longer functional (Figure 4). In rodents, who rely heavily on olfaction, 20% of the OR genes are pseudogenes, but the fraction is much higher in primates, and about 60% of human OR genes are pseudogenes. Both functional ORs and pseudogenes are scattered across our chromosomes, showing that the loss of functional OR genes is not restricted to some subclasses of ORs. The loss process is on-

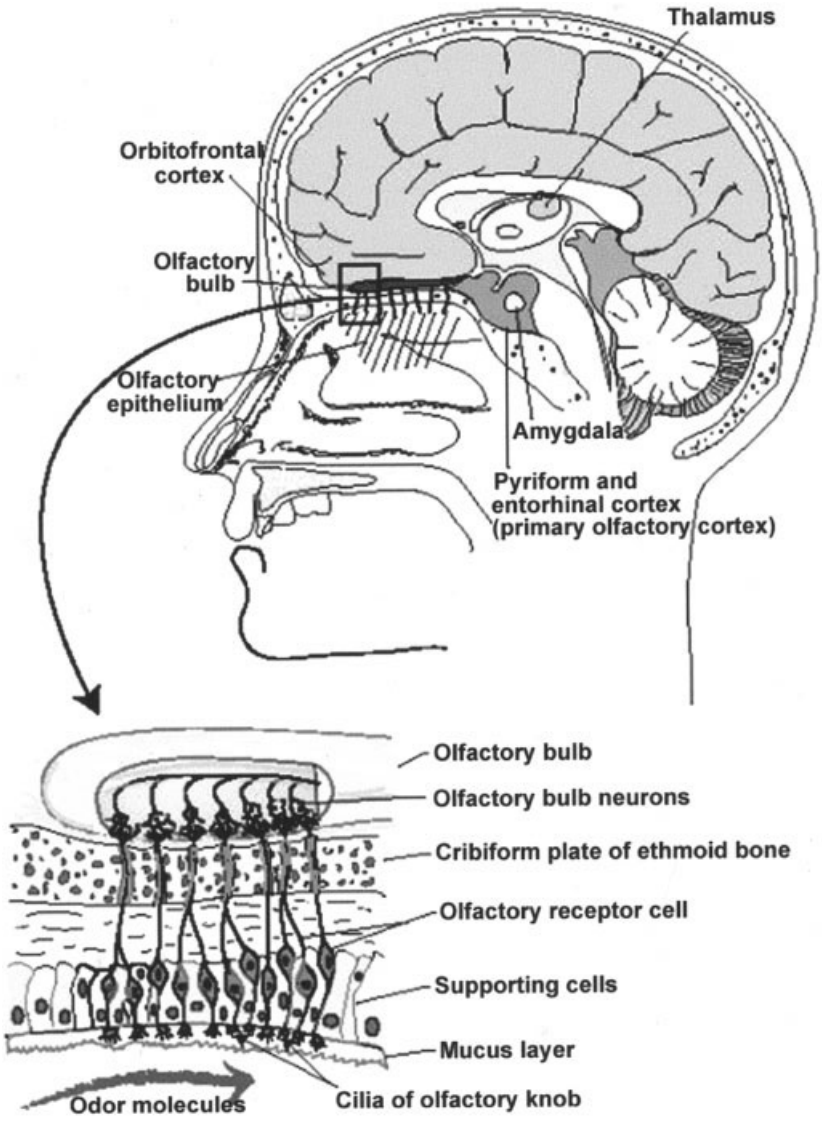

Figure 2. The olfactory detection apparatus. From Weiss and Buchanan.[2]

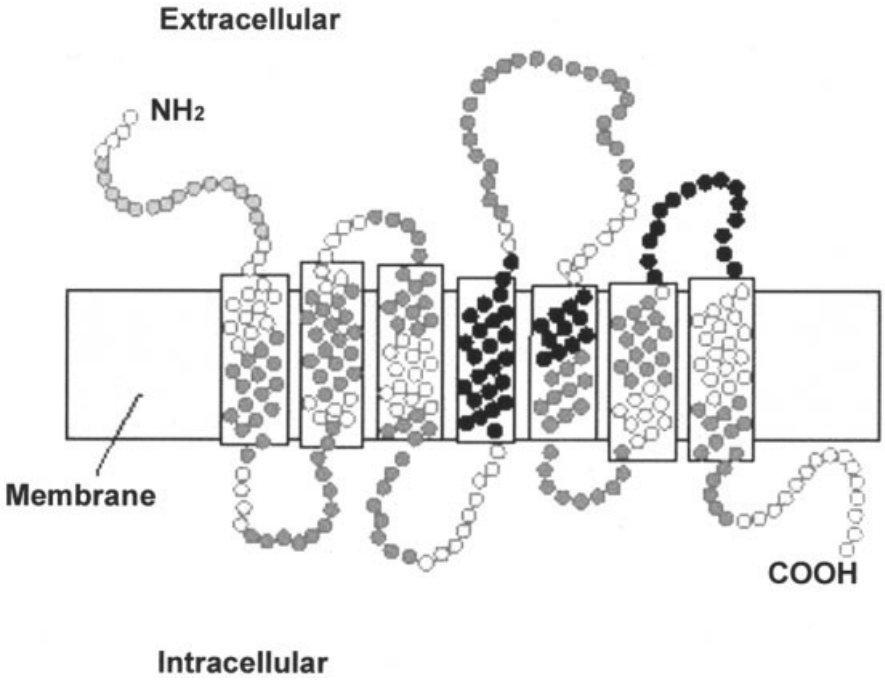

Figure 3. Structure of olfactory cell-surface receptor molecules. Greyshade relates to degree of variability among OR genes, probably related to odorant binding properties. From Weiss and Buchanan.[2]

going, because at least 10% of our pseudogenes are polymorphic, that is, there are both functional and nonfunctional alleles within the population.[4]

Olfactory degeneration seems particularly common in the human lineage compared to our chimpanzee relatives.[5,6] But our knowledge is still tentative and not entirely consistent with the theory that a general rather than odorant-specific receptor repertoire is evolving: despite an overall loss of functionality, there is evidence in chimpanzees for conservative selection keeping some OR genes from varying, and in humans for directional selection favoring a specific new variant in some OR genes, as if some substances have been specifically important for us to smell. However, it's not obvious what those substances were, and since the genetic variants are shared among humans, the selection must either have occurred in Africa before the expansion of modern human ancestors or else have been consistently found across the diverse global environments into which we expanded. The idea of odorant-specific selection is also somewhat at odds with the idea that olfaction is a combinatorial rather than specific phenomenon. So at this stage we reconstruct scenarios for olfactory adaptation at our peril. Indeed, our general olfactory degeneration could be unrelated to olfaction but instead an affordable price for something else related to our head shape, like facial shortening related to diet, upright posture, or language.

A battery of variable odorant receptors would seem to be a remarkably simple, if crude, way to detect the unpredictable chemical aspects of one's environment, but that is somewhat misleading. Having a large number of OR genes does not by itself enable the brain to identify what's being sniffed. If each ON expressed all OR genes, every smell would activate every ON and the brain would be awash in olfactory confusion: everything would smell the same (evidence suggests this may be how the world seems to a nematode). Instead, each mature ON expresses only a single OR gene, repressing expression of the thousand other OR genes in the genome.[7] This is a remarkable control system that bears some resemblance to the production of antibodies, the expression of X-linked color-vision genes, or the switching of hemoglobin genes during development. But none of these mech-

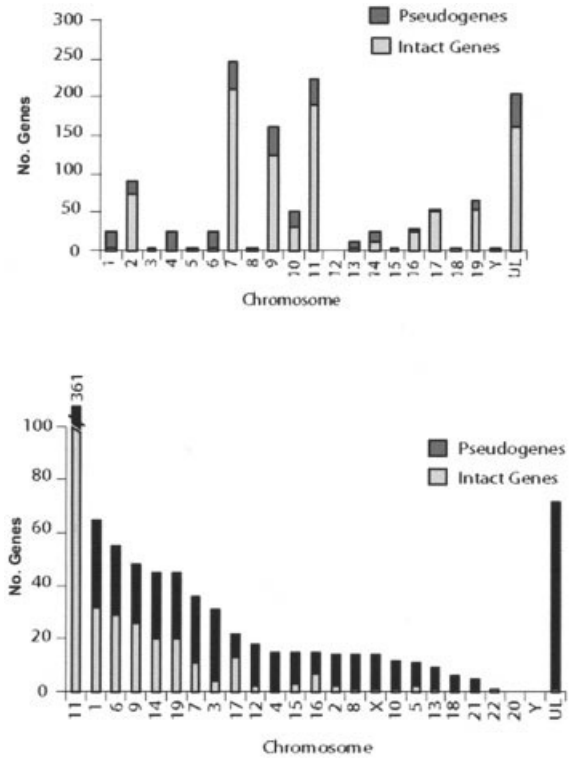

Figure 4. Distribution of olfactory receptor genes and the fraction of these that are pseudogenes, in the mouse (top) and human (bottom) genomes. From Weiss and Buchanan.[2]

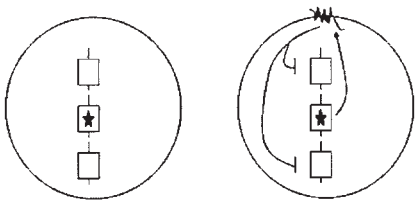

Figure 5. Hypothetical means to achieve single olfactory receptor gene expression in an olfactory neuron. The OR protein coded by lucky first gene to be expressed in a given ON (star) makes its way to the cell surface (arrow) but somehow also back to the nucleus where it inhibits expression of other ORs (feedback lines).[8]

anisms can account for the one gene on one chromosome shutting down thousands of others across the genome, as happens with the OR genes.

We don't yet know the mechanism, but there are clever guesses and experimental hints.[9] One is that OR expression is a statistical race, and the OR protein coded by the lucky first OR gene to be expressed somehow returns to the nucleus and directly shuts down all the other ORs in that cell (Figure 5).[8,9] This is at best incomplete, but one can predict that because the mechanism seems so refined and specific, there must be related mechanisms at work in the genome—yet because of its widespread effects, the mechanism is likely to be rather simple.

That a given ON only expresses one of its thousands of OR genes might seem to be rather constraining, but there are millions of ONs in the nose, so each receptor gene will still be expressed in thousands, or tens of thousands, of different neurons. The more ONs expressing a given gene, the greater the chance an odorant will activate enough of them so the smell can be detected (hence, the incredible sniffativity of dogs!).

However, something more is required if odor *perception* is to be specific. This, too, turns out to be very orderly. As shown in Figure 5, all the ONs that express a given OR gene—regardless of where those neurons lie in the olfactory epithelium—send their projections through the cribiform plate to the same subset of centers, or *glomeruli,* in the olfactory bulb. A glomerulus serves as a collection point for identical signals, and like an amplifying electrical relay distributes that signal to parts of the brain involved in processing odor information (Figure 6). Each part thus "knows" which bulb sent the signal and hence which OR genes initiated it. Within a person's lifetime, signals from the same odorant will be sent via the same route, so the brain can keep the books straight—a catalog of smells. Because of the way the olfactory epithelium develops in the embryo, this tracking will be similar—but by no means identical—among people.

THE MATING AURA

Most of what we have been discussing is "optional" in a sense. But if smelling bananas is nice, some things are nice *and* necessary. In particular, no species can afford to leave finding mates to chance, and many do this by smell. Grenouille's trick was to identify the essence of human mating scents. In the animal world, mate detection is brought about largely by pheromones, emitted by one sex and *specifically* detected by the other in whom species-specific response is triggered.

Mammalian pheromones comprise a variety of substances, including urinary proteins and vaginal secretions that become aromatic and travel to be received by the object of the emitter's affections. Pheromone reception occurs in the vomeronasal organ (VNO), located near the olfactory epithelium, tipward within the nose. VN neurons go to a distinct part of the olfactory bulb but unlike the ORs, project to several glomeruli.

Pheromone detection involves several hundred vomeronasal receptor (VR) genes, evolutionarily related to OR genes but expressed in the VNO. The VR genes are similar in many respects to the OR genes.[3] Their history of duplication has left many VR pseudogenes, even in rodents that rely on pheromones, and the functional VRs

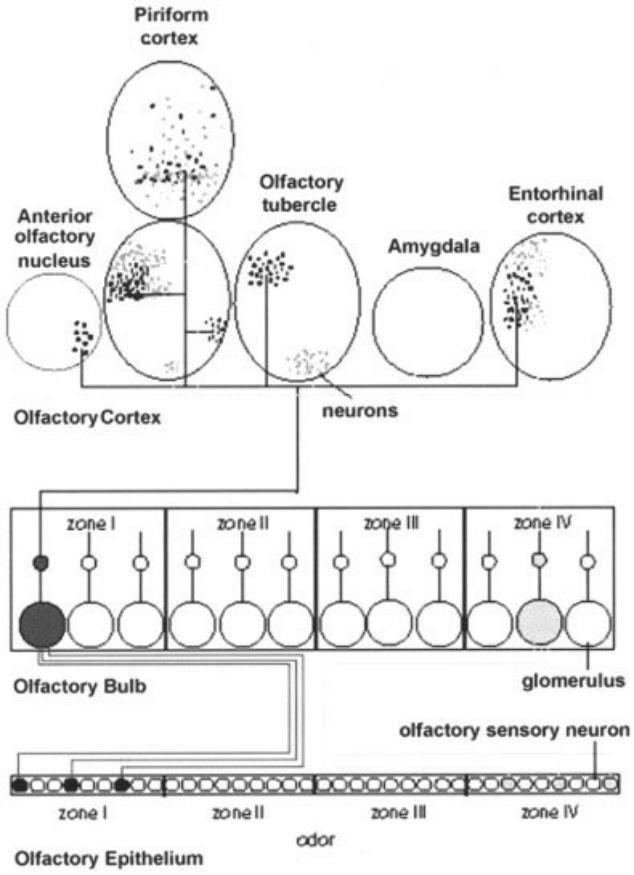

Figure 6. Orderly olfactory wiring from the OR in the olfactory epithelium, to glomeruli in the olfactory bulb to various regions in the brain. From Weiss and Buchanan.[2]

are about as variable as ORs, a rather remarkable fact if it is true that pheromone detection has evolved to be highly specific and programmed. VRs may respond to different classes of proteins, such as found in urine, and some are highly sensitive to such compounds. But mouse urinary pheromones are a complex mix coded by a diverse and variable pheromone gene family.[10] What this means is that the idea that strongly selected stereotypical behavior may not depend on highly specific one-for-one signal-reception mechanisms as had been thought. But how the system works is not clear.

Human mate choice certainly involves cognition, but it has long been wondered whether lurking behind all of that is a subliminal pheromone sense. Primates have the opportunity, provided by regular ovulation cycles, sexual swellings, and the like. However, the VNO in monkeys and apes is more rudimentary, and seems completely degenerate in humans. Recent genetic research has found that with one possible exception all our known VR genes are nonfunctional remnants. In addition, humans and other Old World monkeys and apes have lost a necessary VNO signal-transmission gene. Probably, selection on the VN system relaxed *after* something was lost or changed in the perceptive side in the brain itself. Today, we work our way through the sexual maze with software, not hardware.

One might thus conclude that Grenouille's trick is a total fiction. But there is another route that may have a pheromone-like effect. The genes in the HLA system, best known for immune reactions and tissue-transplant rejection, are numerous and highly variable. There have been persistent reports in humans, and experimental results in mice, suggesting an HLA role in sexual conduct. Armpit and genital odors are at least generally recognizable (both were important to Grenouille!) and have erotic properties. Humans and mice can scent specific individuals in a way that may affect mating and may involve airborne transport of HLA proteins, perhaps transported by the urinary pheromones.[2,11] This has been suggested as a pheromonal mechanism for comparing one's own HLA types to those of others. Mice prefer mating with mice genetically different from themselves, which could be an inbreeding-avoidance mechanism as well as providing greater HLA variation that could help offspring in facing diverse infectious agents. However, in aspects of social behavior mice prefer nesting with others like themselves—staying close to their relatives.

The human evidence is generally similar, though still equivocal. Some studies suggest that women prefer men who are like their fathers and/or unlike themselves, but when taking oral contraceptives (that mimic pregnancy) their preference is for HLA-similarity (e.g., seeking the supportive environment of kin?). Interestingly, in a large OR cluster in the HLA region, a substantially higher than average fraction of the genes are functional[12]; perhaps pheromonal effects, whatever their nature, are mediated by olfaction instead of or as well as HLA genes. The poet John Donne mused that venereal disease (especially syphilis, the "Indian Vermine") so conspicuously manifested itself in destruction of the nose so the offending person could not smell his own stink.[13] No matter what the complex truth turns out to be, it seems bad news for Grenouille, because the HLA system works to identify individual uniqueness, the opposite of a universal attractant that would be profitable to perfumers.

CAN THERE BE AN OLFACTORY PRODIGY?

Any of us can detect some specific scents in mixtures, such as when we may ask a friend "does this have cilantro in it?" But none of us can walk into a kitchen and smell cilantro in the closed refrigerator! Grenouille had direct cognitive access to all his individual ONs (since each is specific to a receptor). More remarkably, since a given odorant triggers multiple receptors, Grenouille had cognitive access to all the specific combinations.

Mozart's musical genius was probably inborn and both highly specific and uniquely complex, never to be repeated. However, even an average person can smell thousands of substances and has inherited just as unique a combination of olfactory detecting alleles, as Mozart did of musical-composing ones (whatever that may mean), never to be repeated. Someone might by chance inherit few pseudogenes and a lucky combination of receptor variants, and hence a larger functional repertoire—an olfactory Salieri perhaps. But the chance of getting the best of the alleles segregating all 400 OR genes in a given population has to be miniscule—no more than one in billions. Of course there's only been one Mozart (and one fictional Grenouille!) among many billions of people. However, if inherited OR variation does matter, then a human olfactory genius would probably not be sniffing his way around Austria, but in Africa where human OR genes vary more than they do in other populations. However, if there is any evidence that Africans have keener senses of smell than others, I'm unaware of it.

Perhaps a more plausible way to be an olfactory prodigy would be to inherit fortunate allele(s) in the *perception* mechanism—the way the brain processes the signal. We can only speculate at present, but variation in general olfactory information processing speed, neural connectivity, or memory might enable greatly enhanced awareness of things that most of us can smell but can't parse or never notice. A recent precedent is a mouse that because of a deleted ion-channel gene transmits olfactory messages many times faster than in normal mice.[14] This mouse is superior in sensitivity, not specificity, but shows how a simple variant could have major effects. It will be interesting to see if the perfume industry will start using these mice.

A SYMPHONY OF MOZARTS

Jean-Baptiste Grenouille dreamed of being a compositional as well as detection genius, who would match the glory of the legendary Parisian scent-maestro Muzio Frangipani, who in 1500 introduced a famous Central American fragrance that bears his name (Figure 7). But before he could achieve this status, Grenouille was caught and convicted of murdering the young women whose scents he

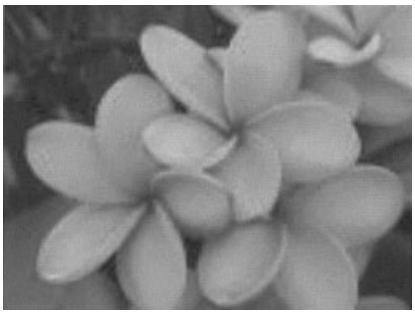

Figure 7. Scratch 'n sniff Frangipani flowers. Photo taken by the author at Lamanai Maya ruins, Belize (if this patch doesn't work, please complain to the Editor).

had extracted. However, the police did not know about the scents nor the reason for his crimes, and at the site of his public execution he released a drop of his special Essence, and "the result was that the scheduled execution of one of the most abominable criminals of the age degenerated into the largest orgy the world had seen since the second century before Christ." He from the most stinking spot in the world, made the entire world love him!

So Grenouille lived, but in sorrow. He could make the whole world love him, but in producing no odors of his own he faced the bleak prospect of remaining evermore a stranger to himself. So one midnight dark and dreary, Grenouille wandered weak and weary upon a graveyard campfire, peopled by the lowest life in Paris. He sprinkled himself liberally with Essence, and in the overpowering affection this generated he was devoured by the rabble, down to the last morsel. "Jean-Baptiste Grenouille had disappeared utterly from the earth."

Commercial perfume was perhaps originally designed to cover the fetid stenches of urban life so its attractions could be enjoyed, but for a long time the perfume industry has striven to produce the definitive *Eau de Oh!* Even if we don't have a chemically specified mating system, that doesn't mean one cannot manipulate whatever sex-related olfactory lures *might* be present. The degree to which scents are learned to be sexual as opposed to having been designed by nature that way is not clear, and our lack of pheromones would suggest the former. But then what about repeated suggestions that musk and androstenone have that magic whiff for us as they do for other mammals? Are they learned attractants? Are they detected by those ORs that do seem to have undergone specific selection? But why *musk?*

The Monell Chemical Senses Center (http://www.monell.org/index.htm) and other companies that exist in reality rather than fiction aim to identify and manufacture individual preferences for aromas. This is to enable food and cosmetic houses to manipulate our tastes for their interests, or so we might manipulate potential mates for *our* interests. While the major thrust of current science is to find inherited variation, these companies would eagerly employ a somewhat less criminal (or not-yet-caught) empirical alchemist like Grenouille. But as he discovered, social chaos will follow if science ever identifies a universal Essence that can, so to speak, be disembodied and put in a bottle.

Whether exceptional olfaction is in the nose, or in the mind, is perhaps the most interesting unanswered question. And it is a much more general evolutionary question at that, because olfaction is only one of several ways in which we've evolved to deal with aspects of the environment that cannot be specified in advance and hence are hard to encode in genes, but that must be detected and interpreted for survival. These include combinatorial molecular detection in the immune system, a two-dimensional sensory matrix of frequency-sensitive receptors to detect electromagnetic radiation (vision), a linear array of mechanoreceptors to detect frequency-specific air vibration (hearing), and a body-map of touch receptors. Each uses different mechanisms but they are logically and in some ways genetically similar and conceptually straightforward.[2] Each sends orderly and hence interpretable signals to the brain. What happens there is still largely unknown, but we do know that each system has genetic variation. In that respect, each of us is just as unique as Mozart—we live in a world of sensory genius.

NOTES

I welcome comments on this column: kenweiss@psu.edu. I have a feedback and supplemental material page at http://www.anthro.psu.edu/weiss_lab/index.html. I thank Anne Buchanan and John Fleagle for critically reading this manuscript, Peter Mombaerts for helpful discussion, and Ela and Janusz Sikora for the aromatic gift of *Perfume*.

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