# WHO SMELLS BEST?

## AT GRANNY'S HOUSE

My grandmother's home had a very particular smell. I recall it as a blend of dried flowers, fresh soap and old furniture which, although subtle and clean, made an unmistakable and intense sensory impression whenever I stepped into her dark, narrow hallway. To this day, when my nose detects elements of this smell in a shop or someone's home, the memories come rushing back. Smells affect us in fascinating ways, from elusive subconscious nudges to freight trains of flavour, and as part of our sensory apparatus smell is unparalleled in evoking memories, emotions and enjoyment.

While studying medicine, I worked as a bartender at St Paul's Apothek in the Danish city of Aarhus. Housed in an old apothecary building, the restaurant was and is based on the concept of pairing sophisticated cocktails with well-cooked meals. No wine, but an endless combination of aromatic and flavoursome cocktails that complement the food and raise it to an even higher level.

I was fascinated by this principle of playing with the senses, particularly smell. Looking forward to pursuing my studies, I assumed that neurology and ENT – ear, nose and throat – would bring insights into the intriguing world of smell. I was sorely disappointed.

I bought the thickest textbook I could find about the cranial nerves, which notably provide the head with the special neural network that enables us to smell, see, hear, taste, use facial expressions, feel facial touches and keep our balance. This tome had a trifling three lines about testing olfaction – the sense of smell – a function deemed unworthy of in-depth investigation.

I spent the summer of 2012 volunteering at the ENT clinic at Aarhus University Hospital, which had a kit with 12 scent pens, enough to perform a simple olfactory test. The unit also had flexible scopes with lit tips, used to examine the upper nasal cavity. Here lie the mucous membranes, whose smell receptors capture scented particles and trigger an olfactory firework extravaganza each time we eat or perceive a smell. Sadly, I found that olfactory mucous membranes looked just like the rest of the inner nasal cavity surface.

The smell test kit had several exotic options for the average Dane, including German sauerkraut, a smell rarely recognisable to a Danish nose. And unless the mucous membrane was visibly diseased and a candidate for surgical or medical treatment, we literally had no therapeutic option to offer our patients.

In short, this stint was not the medical revelation I had expected, yet it came to define my career. The path that led me to become an ENT specialist was closely tied to smell research – delving into chemical scent molecules, known as odorants, the nasal sensory apparatus and the brain's perception of smell. Everywhere I looked, I found new questions about olfaction. One defining element was the numerous interviews I conducted with patients who had lost their sense of smell, whom I saw and treated at the Clinic for Smell and Taste Disorders at Gødstrup Regional Hospital. I discovered just how underrated our remarkable sense of smell is, and that this lack of appreciation is by no means a new phenomenon.

## COMING LATE TO SCIENCE

As early as 300 BCE, the Greek philosopher Aristotle wrote that, unlike the qualities of sounds and colours, the quality of a smell is unclear, the human sense of smell being imprecise and generally very poor. Indeed, sounds and colours consist of waves with frequencies we can systematically examine. Not so with smells. Anatomical drawings of the human eye and ear have changed little over the past 500 years, whereas olfactory encoding has been a well-kept secret until quite recently.

In 1838, the German scientists Matthias Schleiden and Theodor Schwann, benefiting from advances in microscope design, observed that cells are the fundamental building blocks of both plants and animals. Microscopy quickly became a pillar in medical research, enabling scientists to delve ever deeper into the senses.

The Italian anatomist Alfonso Corti discovered the sound-sensing hair cells of the inner ear in 1851. In 1854, the German anatomist Carl Bergmann described how cone- and rod-shaped cells at the back of the eye register incoming light. This paved the way for further research into sight and hearing. Meanwhile, throughout the twentieth century, smell scientists continued to fumble in the dark, debating whether molecular vibrations or chemical bonds evoked smells. Quite simply, no one knew how olfaction worked.

Then, in 1991, the American biologists Linda Buck and Richard Axel finally identified the receptors that detect chemical odorants. After a decade of little recognition beyond that of their own peers, Buck and Axel received the Nobel Prize in medicine in 2004. At last, olfaction research was on the academic map, moving beyond its original few dozen university basement laboratories and desks. Researchers could finally test and seek to verify centuries of speculation and theory in a new light.

In hindsight, it is remarkable that smell receptors remained undetected for so long. Analyses of the human genome reveal that about three percent of our genes code for smell receptors, making this the largest group of genes identified. It takes an awful lot of DNA to code all our active and inactive smell receptors.

## FROM CHEMISTRY TO THE BRAIN

Our upper nasal cavity has 400 types of smell receptors. We have roughly 6 to 10 million olfactory receptor neurons – ORNs – which are prepared at every breath to capture tiny chemical molecules and send a signal to our brain. All the chemical molecules our olfactory receptors can register are called odorants. The smell of coffee contains more than 400 odorants, each capable of binding to a variety of our ORN array, which then sends a single aggregated signal to the brain.

That signal is not merely "Coffee's ready!" It is far more complex, containing a mass of nuances which, to a well-trained nose, can reveal the beans' roasting time, origin and brewing method. I often compare this olfactory image to a retailer's barcode. Imagine the scanner at the checkout, which rapidly recognises the combination of thick, thin and absent lines, thereby decoding the identity of the specific item.

Smell is wired to directly signal the brain areas that control emotional reactions such as enjoyment and disdain. We do not simply register a smell. The signal also changes depending on whether we inhale or exhale. Inhaled air reveals the smells in our vicinity; exhaled air reflects the odorants in our mouths and throats.

This equips us to react differently, and appropriately, depending on whether, say, we are driving on a hot day past a field with freshly spread manure, or breathing out and detecting faecal-type odorants in our mouths. In the first case, we discreetly hold our noses. In the second, we spit out the food or perhaps even reflexively vomit.

Likewise, a fresh strawberry dangled in front of the nose will trigger cravings in many people, and biting into the sweet, juicy berry will be pure enjoyment as the aroma spreads from the mouth to the throat and nose. The brain also changes its interpretation of sensory perceptions to reward appropriate behaviour that increases our chance of survival. To a hungry person whose brain is begging for sugar, even a dry biscuit can be a source of extreme pleasure.

I vividly recall an exercise from my army days. As a young cadet I had spent several days outdoors with my unit undergoing rigorous physical training, largely without food or sleep. We chanced upon a tube of old margarine dropped from a field ration, and two of us shared the treasure, relishing the synthetic-tasting but energy-rich gobs. The greasy mass lodged between our teeth, but quite literally did us a fat lot of good.

I have never felt the urge to repeat this one-course banquet, but the underlying mechanism – the way the brain's reward centre lights up like a Christmas tree when we feed our bodies – has been essential to human survival for millennia. Even so, only in the last century have we begun to really understand how many smells in our surroundings can actually stimulate this vital brain function.

## 10,000 OR A TRILLION?

Back in 1927, two American chemists, Ernest Crocker and Lloyd Henderson, were searching for an objective way to classify smells, aiming to create a system that would enable the study of smell in line with the study of sight and hearing. The result was a numeric coding system with four-digit identifiers to cover every conceivable smell. The Crocker–Henderson mathematical system made it theoretically possible to identify 6,561 distinct smells, which Crocker generously rounded up several years later to 10,000, a figure cited in textbooks and academic articles for nearly a century.

After Buck and Axel discovered hundreds of types of ORNs, in 2014 the German smell researcher Andreas Keller and his colleagues adjusted the old mathematical formula. Increasing the potential number of smells humans can distinguish among to upwards of a trillion. This is admittedly a very theoretical estimate. Still, today's knowledge of our olfactory capabilities would probably have shocked Aristotle.

Not everyone has the same ability, however, and the difference between two randomly chosen individuals shows some 30% of variation in the genes coding for the 400 types of ORN. Imagine people smelling an orange. Genetic differences mean the barcodes these people's ORNs send to the brain for the very same orange will be very different. Most smells consist of multiple odorants and generally stimulate people in a similar way. But there are exceptions, such as the coriander plant and its dried seeds, widely known as a love-it-or-hate-it ingredient, not least in Thai cuisine.

A single sub-type of the ORN called OR6A2 can change the way a person perceives coriander: not as a pleasant, fresh, aromatic scent, but as a pungent, soapy flavour. This receptor creates an overlap between soap and coriander in the barcode, meaning a person will find it only slightly better than having their mouth washed out with soap. They find it harder to swallow food containing coriander because their brain interprets the soapy scent as a strong warning signal: "Spit out!"