The Ricotta Eaters – ©Wikipedia

"Tell me what you eat, and I will tell you who you are."

Jean-Anthelme Brillat-Savarin

Georges M. Halpern, MD, DSc

with Yves P. Huin

Preamble

While we still suffer the worst pandemic of the century, I thought of it as an excuse to consider what is uniquely human (on the *good* side): **Pleasure**. Indeed, humans are the only species who have sex mostly to be enjoyed (and not for procreation), eat without being hungry, and drink wine or soft drinks without being thirsty.

In 2012, I published a 3-page Opinion piece in *Flavour: "***We only eat what we lik- or do we still?"** (It available on my website Dr. Georges in the Essays - Volume 2); it is still accurate, valid and current. And you can also check (again?) my essay **Down The Rabbit Hole** in the volume 6, on the same website. Indeed we -normally- eat only what we like, and nature can provide everything. But there are too many populations who are starving or malnourished; at the other end of the human societal spectrum, the food industry has managed to thrive by convincing (=buying) political leaders that it should be the main source of (flawed) education, (damaging) supply, and control of the sourcing. My Op-ed addresses these issues, but it got worse, and the future is bleak.

Pleasure

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In the **Wikipedia** entry, **Pleasure** refers to experience that feels good, that involves the enjoyment of something. It contrasts with pain or suffering, which are forms of feeling bad. It is closely related to value, desire and action: humans and other conscious animals find pleasure enjoyable, positive or worthy of seeking. A great variety of activities are experienced as pleasurable, like eating, having sex, listening to music or playing games. Pleasure is part of various other mental states such as ecstasy, euphoria and flow. Happiness and well-being are closely related to pleasure but not identical with it. There is no general agreement as to whether pleasure should be understood as a sensation, a quality of experiences, an attitude to experiences or otherwise. Pleasure plays a central role in the family of philosophical theories known as hedonism.

"*Pleasure*" refers to experience that feels good, that involves the enjoyment of something. The term is primarily used in association with *sensory pleasures* like the enjoyment of food or sex. But in its most general sense, it includes all types of positive or pleasant experiences including the enjoyment of sports, seeing a beautiful sunset or engaging in an intellectually satisfying activity. Pleasure contrasts with pain or

suffering, which are forms of feeling bad. Both pleasure and pain come in degrees and have been thought of as a dimension going from positive degrees through a neutral point to negative degrees. This assumption is important for the possibility of comparing and aggregating the degrees of pleasure of different experiences, for example, in order to perform the Utilitarian calculus.

Freud's pleasure principle ties pleasure to motivation and action by holding that there is a strong psychological tendency to seek pleasure and to avoid pain. Classical utilitarianism connects pleasure to ethics in stating that whether an action is right depends on the pleasure it produces: it should maximize the sum-total of pleasure.

Many pleasurable experiences are associated with satisfying basic biological drives, such as eating, exercise, hygiene, sleep, and sex. The appreciation of cultural artifacts and activities such as art, music, dancing, and literature is often pleasurable. Pleasure is sometimes subdivided into fundamental pleasures that are closely related to survival (food, sex, and social belonging) and higher-order pleasures (e.g., viewing art and altruism). Bentham listed 14 kinds of pleasure: sense, wealth, skill, amity, a good name, power, piety, benevolence, malevolence, memory, imagination, expectation, pleasures dependent on association, and the pleasures of relief.

The reward system contains **pleasure centers** or hedonic hotspots – i.e., brain structures that mediate pleasure or "*liking*" reactions from intrinsic rewards. Hedonic hotspots have been identified in subcompartments within the *nucleus accumbens* shell, *ventral pallidum, parabrachial nucleus*, orbitofrontal cortex (OFC), and insular cortex. The hotspot within the nucleus accumbens shell is located in the rostrodorsal quadrant of the medial shell, while the hedonic coldspot is located in a more posterior region. The posterior *ventral pallidum* also contains a hedonic hotspot, while the anterior ventral pallidum contains a hedonic coldspot. Microinjections of opioids, endocannabinoids, and orexin are capable of enhancing liking in these hotspots. The hedonic hotspots located in the anterior OFC and posterior *insula* have been demonstrated to respond to orexin and opioids, as has the overlapping hedonic coldspot in the anterior *insula* and posterior OFC. On the other hand, the parabrachial *nucleus* hotspot has only been demonstrated to respond to benzodiazepine receptor agonists.

Hedonic hotspots are functionally linked, in that activation of one hotspot results in the recruitment of the others, as indexed by the induced expression of c-Fos, an

immediate early gene. Furthermore, inhibition of one hotspot results in the blunting of the effects of activating another hotspot. Therefore, the simultaneous activation of every hedonic hotspot within the reward system is believed to be necessary for generating the sensation of an intense euphoria.

While all pleasurable stimuli can be seen as **rewards**, some rewards do not evoke pleasure. Based upon the incentive salience model of reward – the attractive and motivational property of a stimulus that induces approach behavior and consummatory behavior – an intrinsic reward has two components: a "*wanting*" or desire component that is reflected in approach behavior, and a "*liking*" or pleasure component that is reflected in consummatory behavior. Some research indicates that similar mesocorticolimbic circuitry is activated by quite diverse pleasures, suggesting a common neural currency. Some commentators opine that our current understanding of how pleasure happens within us remains poor, but that scientific advance gives optimism for future progress!

This description is a bit abstract: if pleasure is a manifestation of our brain, it is triggered -mostly- by our **senses**.

How to describe in words the **pleasure** provided by the **sight** of the major paintings of Vittorio Carpaccio, at the Gallerie Accademia, in Venice (I was in awe, and stupefied incapable of moving for [what felt like] a long time); Carpaccio's paintings also draw on a variety of figurative traditions, with references to artists such as Michelangelo

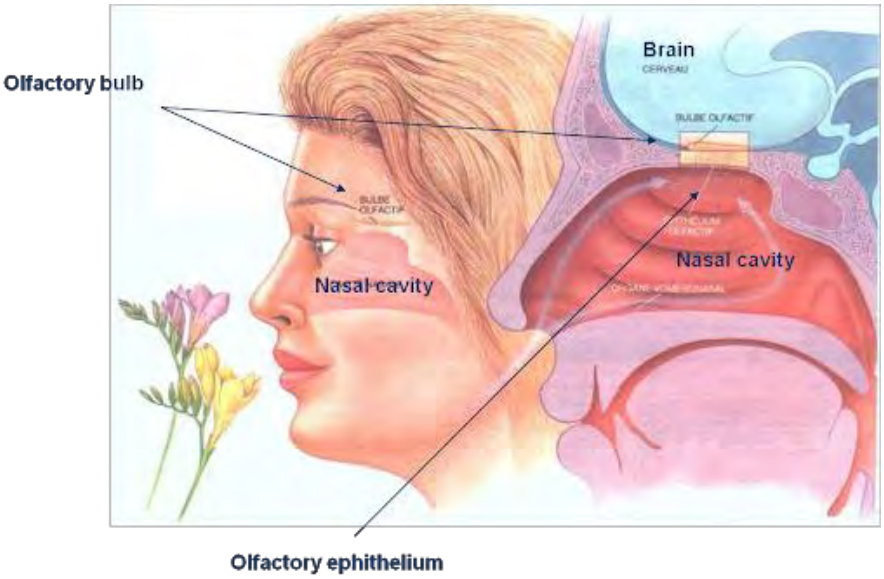
and Dürer, but with his own, unrivaled genius ; or **listening** to what happened on Christmas Day 1989, when Berlin (and soon the world) experienced something like a celestial gift: the "*Ode to Freedom*," a composite event, spread out over the centuries so to speak, by Schiller, Beethoven - and Leonard Bernstein. The occasion was to celebrate the fall of the Berlin Wall in a manner which would impress itself once and for all on people's minds. The Ode "*To Freedom*" - as Bernstein had the soloists and chorus sing in the final movement of Beethoven's Ninth Symphony - indeed symbolized for many Germans a depth of joy they had hitherto hardly known: freedom, a gift from the gods; or **touching**, caressing the skin of a lover, warm and slightly moist, after multiple orgasms; or **smelling** the indestructible, well alive, and still favorite perfume Chanel N°5; or **tasting** a slice from a D'Artagnan® *terrine* of duck *foie gras*, baked in the oven according to the instructions of Ariane Daguin… And the list can go on, and on, and on!

Pleasures are often difficult, impossible to be shared because they escape our attempts to translate them in words. Some languages offer opportunities, but most remain closed. But enjoying food (and some beverages) are universal and form a stable pedestal for family and social life; currently, because of the COVID-19 pandemic, their absence is strongly resented, and complaints are growing daily.

Hence let us explore **olfaction** (smell), **taste**, and then some.

Wikipedia offers a comprehensive, updated entry: **Olfaction**, or the **sense of smell**, is the special sense through which smells (or odors) are perceived. It occurs when an odor binds to a receptor within the nasal cavity, transmitting a signal through the olfactory system. Olfaction has many functions, including detecting hazards, and pheromones, and plays a role in taste.

Olfaction in Pleasure



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Glomeruli aggregate signals from these receptors and transmit them to the olfactory bulb, where the sensory input will start to interact with parts of the brain responsible for smell identification, memory, and emotion.

There are many different causes for alteration, lack, or disturbance to normal olfaction, and can include damage to the peripheral nose or smell receptors, or central problems affecting the brain. Some causes include upper respiratory infections, traumatic brain injury, and neurodegenerative disease.

Early scientific study of olfaction includes the extensive doctoral dissertation of Eleanor Gamble, published in 1898, which compared olfactory to other stimulus modalities, and implied that smell had a lower intensity discrimination.

But centuries earlier, as the Epicurean and atomistic Roman philosopher Lucretius (1st century BCE) speculated, different odors are attributed to different shapes and sizes of "atoms" (odor molecules in the modern understanding) that stimulate the olfactory organ. A modern demonstration of that theory was the cloning of olfactory receptor proteins by Linda B. Buck and Richard Axel (who were awarded the Nobel Prize in 2004), and subsequent pairing of odor molecules to specific receptor

proteins. Each odor receptor molecule recognizes only a particular molecular feature or class of odor molecules. Mammals have about a thousand genes that code for odor reception. Of the genes that code for odor receptors, only a portion are functional. Humans have far fewer active odor receptor genes than other primates and other mammals.

In mammals, each olfactory receptor neuron expresses only one functional odor receptor. Odor receptor nerve cells function like a key–lock system: if the airborne molecules of a certain chemical can fit into the lock, the nerve cell will respond.

The Lady and the Unicorn, a Flemish tapestry depicting the sense of smell, 1484–1500.
© *Musée National du Moyen Âge*, Paris.

There are, at present, a number of competing theories regarding the mechanism of odor coding and perception. According to the shape theory, each receptor detects a feature of the odor molecule. The weak-shape theory, known as the odotope theory, suggests that different receptors detect only small pieces of molecules, and these minimal inputs are combined to form a larger olfactory perception (similar to the way visual perception is built up of smaller, information-poor sensations, combined and refined to create a detailed overall perception).

According to a new study, researchers have found that a functional relationship exists between molecular volume of odorants and the olfactory neural response. An alternative theory, the vibration theory proposed by Luca Turin, posits that odor receptors detect the frequencies of vibrations of odor molecules in the infrared range by quantum tunnelling. However, the behavioral predictions of this theory have been called into question. There is no theory yet that explains olfactory perception completely.

The state of the field as of 2020 —its history and current laboratory routines and practice— has been surveyed and studied in a new book *Smellosophy: What the Nose tells the Mind*, authored by historian, philosopher, and cognitive scientist Ann-Sophie Barwich.

In **humans** and other vertebrates, smells are sensed by olfactory sensory neurons in the olfactory epithelium. The olfactory epithelium is made up of at least six morphologically and biochemically different cell types. The proportion of olfactory epithelium compared to respiratory epithelium (not innervated or supplied with nerves) gives an indication of the animal's olfactory sensitivity. Humans have about 10 cm^2 (1.6 sq in) of olfactory epithelium, whereas some dogs have 170 cm^2 (26 sq in). A dog's olfactory epithelium is also considerably more densely innervated, with a hundred times more receptors per square centimeter. The sensory olfactory system integrates with other senses to form the perception of flavor. Often, land organisms will have separate olfaction systems for smell and taste (orthonasal smell and retronasal smell), but water-dwelling organisms usually have only one system.

Molecules of odorants passing through the superior nasal concha of the nasal passages dissolve in the mucus that lines the superior portion of the cavity and are detected by olfactory receptors on the dendrites of the olfactory sensory neurons. This may occur by diffusion or by the binding of the odorant to odorant-binding proteins. The mucus overlying the epithelium contains mucopolysaccharides, salts, enzymes, and antibodies (these are highly important, as the olfactory neurons provide a direct passage for infection to pass to the brain). This mucus acts as a solvent for odor molecules, flows constantly, and is replaced approximately every ten minutes.

The binding of the ligand (odor molecule or odorant) to the receptor leads to an action potential in the **receptor neuron**, via a second messenger pathway,

depending on the organism. In mammals, the odorants stimulate adenylate cyclase to synthesize cAMP via a G protein called G_{olf}. cAMP, which is the second messenger here, opens a cyclic nucleotide-gated ion channel (CNG), producing an influx of cations (largely Ca^{2+} with some Na^{+}) into the cell, slightly depolarizing it. The Ca^{2+} in turn opens a Ca^{2+}- activated chloride channel, leading to efflux of Cl^{-}, further depolarizing the cell and triggering an action potential. Ca^{2+} is then extruded through a sodium-calcium exchanger. A calcium-calmodulin complex also acts to inhibit the binding of cAMP to the cAMP-dependent channel, thus contributing to olfactory adaptation.

Averaged activity of the receptor neurons can be measured in several ways. In vertebrates, responses to an odor can be measured by an electro-olfactogram or through calcium imaging of receptor neuron terminals in the olfactory bulb. In insects, one can perform electroantennography or calcium imaging within the olfactory bulb.

Olfactory sensory neurons project axons to the brain within the olfactory nerve, (cranial nerve I). These nerve fibers, lacking myelin sheaths, pass to the olfactory bulb of the brain through perforations in the cribriform plate, which in turn projects olfactory information to the olfactory cortex and other areas. The axons from the olfactory receptors converge in the outer layer of the olfactory bulb within small (≈50 micrometers in diameter) structures called glomeruli. Mitral cells, located in the inner layer of the olfactory bulb, form synapses with the axons of the sensory neurons within glomeruli and send the information about the odor to other parts of the olfactory system, where multiple signals may be processed to form a synthesized olfactory perception. A large degree of convergence occurs, with 25,000 axons synapsing on 25 or so mitral cells, and with each of these mitral cells projecting to multiple glomeruli. Mitral cells also project to periglomerular cells and granular cells that inhibit the mitral cells surrounding it (lateral inhibition). Granular cells also mediate inhibition and excitation of mitral cells through pathways from centrifugal fibers and the anterior olfactory nuclei. Neuromodulators like acetylcholine, serotonin and norepinephrine all send axons to the olfactory bulb and have been implicated in gain modulation, pattern separation, and memory functions, respectively.

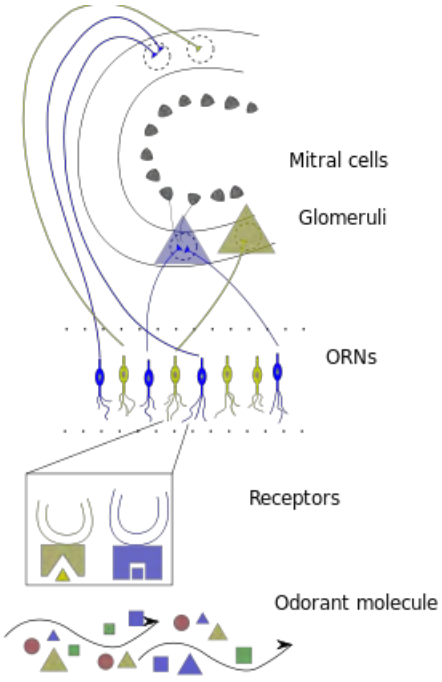
The **mitral cells leave the olfactory bulb** in the lateral olfactory tract, which synapses on five major regions of the cerebrum: the anterior olfactory nucleus, the olfactory tubercle, the amygdala, the piriform cortex, and the entorhinal cortex. The anterior olfactory nucleus projects, via the anterior commissure, to the contralateral olfactory bulb, inhibiting it. The piriform cortex has two major divisions with anatomically distinct organizations and functions. The anterior piriform cortex (APC) appears to be better at determining the chemical structure of the odorant molecules, and the posterior piriform cortex (PPC) has a strong role in categorizing odors and assessing similarities between odors (e.g., minty, woody, and citrus are odors that can, despite being highly variant chemicals, be distinguished via the PPC in a concentration-independent manner). The piriform cortex projects to the medial dorsal nucleus of the thalamus, which then projects to the orbitofrontal cortex. The orbitofrontal cortex mediates conscious perception of the odor (citation needed). The three-layered piriform cortex projects to a number of thalamic and hypothalamic nuclei, the hippocampus and amygdala and the orbitofrontal cortex, but its function is largely unknown. The entorhinal cortex projects to the amygdala and is involved in emotional and autonomic responses to odor. It also projects to the hippocampus and is involved in motivation and memory. Odor information is stored in long-term memory and has strong connections to emotional memory. This is possibly due to the olfactory system's close anatomical ties to the limbic system and hippocampus, areas of the brain that have long been known to be involved in emotion and place memory, respectively.

Since any one receptor is responsive to various odorants, and there is a great deal of convergence at the level of the olfactory bulb, it may seem strange that human beings are able to distinguish so many different odors. It seems that a highly complex form of processing must be occurring; however, as it can be shown that, while many neurons in the olfactory bulb (and even the pyriform cortex and amygdala) are responsive to many different odors, half the neurons in the orbitofrontal cortex are responsive to only one odor, and the rest to only a few. It has been shown through microelectrode studies that each individual odor gives a particular spatial map of excitation in the olfactory bulb. It is possible that the brain is able to distinguish specific odors through spatial encoding, but temporal coding must also be taken into account. Over time, the spatial maps change, even for one particular odor, and the brain must be able to process these details as well.

Inputs from the two nostrils have separate inputs to the brain, with the result that, when each nostril takes up a different odorant, a person may experience perceptual rivalry in the olfactory sense akin to that of binocular rivalry.

The process by which olfactory information is **coded in the brain to allow for proper perception** is still being researched and is not completely understood. When an odorant is detected by receptors, they in a sense break the odorant down, and then the brain puts the odorant back together for identification and perception. The odorant binds to receptors that recognize only a specific functional group, or feature, of the odorant, which is why the chemical nature of the odorant is important.

After binding the odorant, the receptor is activated and will send a signal to the glomeruli. Each glomerulus receives signals from multiple receptors that detect similar odorant features. Because several receptor types are activated due to the different chemical features of the odorant, several glomeruli are activated as well. All of the signals from the glomeruli are then sent to the brain, where the combination of glomeruli activation encodes the different chemical features of the odorant. The brain then essentially puts the pieces of the activation pattern back together in order to identify and perceive the odorant. This distributed code allows the brain to detect specific odors in mixtures of many bad odors.



Schematic of the early olfactory system including the olfactory epithelium and bulb. Each ORN expresses one OR that responds to different odorants. Odorant molecules bind to ORs on cilia. ORs activate ORNs that transduce the input signal into action potentials. In general, glomeruli receive input from ORs of one specific type and connect to the principal neurons of the OB, mitral and tufted cells (MT cells). - © Wikipedia

It is a general idea that the layout of brain structures corresponds to physical features of stimuli (called topographic coding), and similar analogies have been made in olfaction with concepts such as a layout corresponding to chemical features (called chemotopy) or perceptual features. While chemotopy remains a highly controversial concept, evidence exists for perceptual information implemented in the spatial dimensions of olfactory networks.

Although conventional wisdom and lay literature, based on impressionistic findings in the 1920s, have long presented human olfaction as capable of distinguishing between roughly 10,000 unique odors, recent research has suggested that the average individual is capable of distinguishing over one trillion unique odors. Researchers in the most recent study, which tested the psychophysical responses to combinations of over 128 unique odor molecules with combinations composed of up to 30 different component molecules, noted that this estimate is "*conservative*" and that some subjects of their research might be capable of deciphering between **a thousand trillion odorants**, adding that their **worst performer could probably still distinguish between 80 million scents**.

Authors of the study concluded, "*This is far more than previous estimates of distinguishable olfactory stimuli. It demonstrates that the human olfactory system, with its hundreds of different olfactory receptors, far outperforms the other senses in the number of physically different stimuli it can discriminate*." However, it was also noted by the authors that the ability to distinguish between smells is not analogous to being able to consistently identify them, and that subjects were not typically capable of identifying individual odor stimulants from within the odors the researchers had prepared from multiple odor molecules. In November 2014 the study was strongly criticized by Caltech scientist Markus Meister, who wrote that the study's "*extravagant claims are based on errors of mathematical logic*". The logic of his paper has in turn been criticized by the authors of the original paper!

Different people smell different odors, and most of these differences are caused by genetic differences. Although odorant receptor genes make up one of the largest gene families in the human genome, only a handful of genes have been linked conclusively to particular smells. For instance, the odorant receptor OR5A1 and its genetic variants (alleles) are responsible for our ability (or failure) to smell β-ionone, a key aroma in foods and beverages. Similarly, the odorant receptor OR2J3 is associated

with the ability to detect the "grassy" odor, cis-3-hexen-1-ol. The preference (or dislike) of cilantro (coriander) has been linked to the olfactory receptor OR6A2.

Ever since scientists began studying olfaction at the turn of the 20th century, they have been interested in how the **sense of smell differs between the two sexes.** Between 1997 and 2017, the publication of scientific studies on the olfactory system has increased by more than threefold. An important discovery that has increased the attention on the olfactory system is the finding that sex effects on the olfactory system can determine the heterogeneity of certain psychotic disorders.

Some of the earliest studies that investigated sex differences and the human sense of olfaction determined that the odor detection, identification and discrimination abilities of women were superior to those of men. The **female superiority** in olfactory abilities, which is most evident in odor identification assessments, appears to be consistent across virtually all tested age groups and cultures. This phenomenon remained supported during the 1990s after the "*Smell Survey*," which was one of the largest olfactory endeavors to ever be conducted, as it involved over 1.5 million people.

La Transmission. © Vincent Desailly

In Champagne, France, some of the best winemakers are female; they organized as *La Transmission*, and run small, tiny estates, as well as the most famous, blue-chip

maisons like Krug or Taittinger.

Many different factors have been used to support the notion that **females**, on average, **have superior olfactory skills**, which include neuroendocrine agents, social and cognitive factors, as well as structural differences that have been assessed by functional magnetic resonance imaging (fMRI). One of the primary factors that has been proposed to be responsible for the female superiority in olfaction capabilities is neuroendocrine agents and their interaction with the olfactory system.

While circulating levels of gonadal hormones do not appear to have a direct effect on olfaction, direct links between these agents and the sense of smell have been recorded. More specifically, females appear to have the highest odor sensitivity to androstenone, which is an odorous steroid structure pheromone that is secreted from the axillary region, and other similar musk odorants. Many of the observed fluctuations in the olfactory sensitivity of women have been observed during their normal cycling events; however, these same fluctuations appear to remain consistent in women who are taking oral contraceptives. This observation thus points to the possibility that ovarian hormones may not be the primary neuroendocrine factor responsible for this difference in olfaction capabilities. While this may be true, other studies have found that women who are in their late stages of pregnancy or those who have just received estrogen injections exhibit changes in their threshold level of olfactory sensitivity to certain stimuli. The wide range of potential conclusions for how sex hormones play a role in olfactory function are complex and therefore require further analysis to determine the potential endocrine-related influences on smell perception.

Differences in the olfactory performance of both sexes have been observed at every stage of life, beginning with newborn female babies who show more interest in olfactory cues as compared to their male counterparts. Increased odor awareness has also been found to vary between male and female children at an early age. Many researchers believe that since many female stereotyped activities such as cooking, cleaning and the use of cosmetic products are often encouraged from a very early age, female children have a greater long-term exposure to a wider variety of odors. This greater amount of exposure to odors has subsequently led many women to also exhibit an increased sensitivity to certain odorants as well.

Many of the olfactory assessment tasks that have been used to determine the

superiority of the olfactory capabilities of females often involve the use of various verbal components. Since men are generally associated with having lower verbal skills than women, it has been postulated that these **higher verbal skills** might make it easier for women to determine the correct descriptions for odors during these assessments.

Throughout the world, industrial jobs remain dominated by men. Since many of these industrial jobs either require workers to handle or indirectly expose them to a wide range of potentially harmful chemicals like soot and cadmium, olfactory impairment is often inevitable. However, this type of occupational exposure will typically only affect olfactory threshold tasks, as compared to olfactory identification or discrimination tests. Another factor that might be responsible for the sex differences in olfactory capabilities is the fact that **men generally age faster** than females; therefore, olfactory abilities will deteriorate more rapidly in men.

To determine structural differences that might exist between men and women following odor-induced activation tests fMRI has been widely used. In a 2018 study, fMRI imaging was taken of thirty healthy subjects, of which included 17 women, who were stimulated with mint and butanol. This study found that the most prominent sex differences appear in the right middle/superior temporal lobe, which is particularly active in olfactory processes. Aside from studies utilizing fMRI results, researchers have also analyzed the microcircuitry of the olfactory bulbs of men and women and determined that while the male olfactory bulb is typically less dense than those of women, women tend to have smaller olfactory bulbs. In terms of the total inhaled volume capacity through the nose, it appears that while women tend to have smaller nose openings, the intranasal volume of women does not appear to be any different than that of men. While some small differences between men and women have been observed, the results have not been uniform and must therefore be studied further in order to make a definitive conclusion.

Flavor perception is an aggregation of **auditory, taste, haptic, and smell sensory information**. **Retronasal smell** plays the biggest role in the sensation of flavor. During the process of mastication, the tongue manipulates food to release odorants. These odorants enter the nasal cavity during exhalation. The olfaction of food has the sensation of being in the mouth because of co-activation of the motor cortex and olfactory epithelium during mastication.

Olfaction, taste, and trigeminal receptors (also called chemesthesis) together contribute to flavor. The human tongue can distinguish only among five distinct qualities of taste, while the nose can distinguish among hundreds of substances, even in minute quantities. It is during exhalation that the olfaction contribution to flavor occurs, in contrast to that of proper smell, which occurs during the inhalation phase of breathing. **The olfactory system is the only human sense that bypasses the thalamus and connects directly to the forebrain.**

The MHC genes (known as HLA in humans) are a group of genes present in many animals and important for the immune system; in general, offspring from parents with differing MHC genes have a stronger immune system. Fish, mice, and female humans are able to smell some aspect of the MHC genes of potential sex partners and prefer partners with MHC genes different from their own. **Humans can detect blood relatives from olfaction**. Mothers can identify by body odor their biological children but not their stepchildren. Pre-adolescent children can olfactorily detect their full siblings but not half-siblings or step siblings, and this might explain incest avoidance and the Westermarck effect. Functional imaging shows that this olfactory kinship detection process involves the frontal-temporal junction, the insula, and the dorsomedial prefrontal cortex, but not the primary or secondary olfactory cortices, or the related piriform cortex or orbitofrontal cortex. Since inbreeding is detrimental, it tends to be avoided.

Specific terms are used to describe disorders associated with smelling:

Anosmia – inability to smell
Hyperosmia – an abnormally acute sense of smell
Hyposmia – decreased ability to smell
Presbyosmia – the natural decline in the sense of smell in old age
Dysosmia – distortion in the sense of smell
Parosmia – distortion in the perception of an odor
Phantosmia – distortion in the absence of an odor, "hallucinated smell"
Heterosmia – inability to distinguish odors
Olfactory reference syndrome – psychological disorder that causes the patient to imagine he or she has strong body odor
Osmophobia – aversion or psychological hypersensitivity to odors.

Among these disorders, the most frequent is **Anosmia**. It is the inability to smell. It may be partial or total and can be specific to certain smells. Reduced sensitivity to some or all smells is hyposmia.

In the United States 3% of people age over 40 are affected by anosmia. In 2012 smell was assessed in persons aged 40 years and older with rates of anosmia/severe hyposmia was 0.3% at age 40–49 rising to 14.1% at age 80+. Rates of hyposmia was much higher: 3.7% at age 40– 49 and 25.9% at 80+.

Anosmia can have a number of harmful effects. People with sudden onset anosmia may find food less appetizing, though congenital anosmics rarely complain about this, and none report a loss in weight. Loss of smell can also be dangerous because it hinders the detection of gas leaks, fire, and spoiled food. The common view of anosmia as trivial can make it more difficult for a patient to receive the same types of medical aid as someone who has lost other senses, such as hearing or sight.

Many experience one sided loss of smell, often as a result of minor head trauma. This type of anosmia is normally only detected if both of the nostrils are tested separately. Using this method of testing each nostril separately will often show a reduced or even completely absent sense of smell in either one nostril or both, something which is often not revealed if both nostrils are simultaneously tested. Losing an established and sentimental smell memory (e.g., the smell of grass, of the grandparents' attic, of a particular book, of loved ones, or of oneself) has been known to cause feelings of depression. Loss of the ability to smell may lead to the loss of libido, though this usually does not apply to loss of smell present at birth.

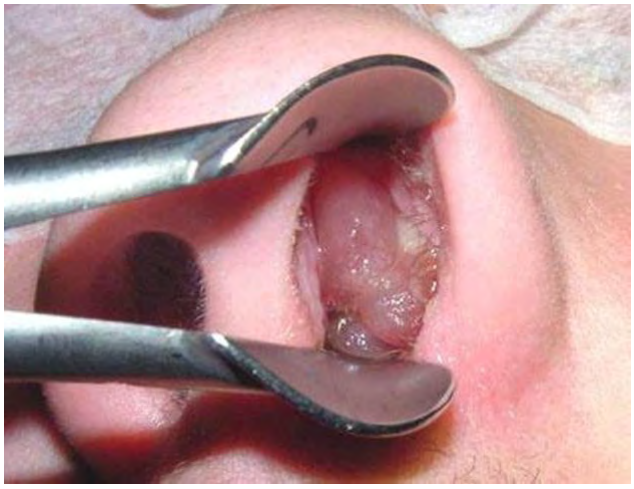
Often people who have loss of smell at birth report that they pretended to be able to smell as children because they thought that smelling was something that older/mature people could do or did not understand the concept of smelling but did not want to appear different from others. When children get older, they often realize and report to their parents that they do not actually possess a sense of smell, often to the surprise of their parents.

A study done on patients suffering from anosmia found that when testing both nostrils, there was no anosmia revealed; however, when testing each nostril individually, tests showed that the sense of smell was usually affected in only one of the nostrils as opposed to both. This demonstrated that unilateral anosmia is not

uncommon in anosmia patients.

A temporary loss of smell can be caused by a blocked nose or infection. In contrast, a permanent loss of smell may be caused by death of olfactory receptor neurons in the nose or by brain injury in which there is damage to the olfactory nerve or damage to brain areas that process smell (see olfactory system). The lack of the sense of smell at birth, usually due to genetic factors, is referred to as *congenital anosmia.* Family members of the patient suffering from congenital anosmia are often found with similar histories; this suggests that the anosmia may follow an autosomal dominant pattern. Anosmia may very occasionally be an early sign of a degenerative brain disease such as Parkinson's disease and Alzheimer's disease.

Another specific cause of permanent loss could be from damage to olfactory receptor neurons because of use of certain types of nasal spray, i.e., those that cause vasoconstriction of the nasal microcirculation. To avoid such damage and the subsequent risk of loss of smell, vasoconstricting nasal sprays should be used only when absolutely necessary and then for only a short amount of time. Non-vasoconstricting sprays, such as those used to treat allergy-related congestion, are safe to use for prescribed periods of time. Anosmia can also be caused by **nasal polyps**. These polyps are found in people with allergies, histories of sinusitis, and family history. Individuals with cystic fibrosis often develop nasal polyps.



Massive Nasal Polyposis © Merck Manual

When I was in practice, in Paris, France (1964-1985), I saw a lot of these patients

with massive masses of polyps, completely obstructing the passage of air. Their complaint was '*Doctor, whatever I eat tastes like cardboard. It is impossible to bear! And I cannot smell the food burning if I forget to switch off the burner; it's very dangerous. And I don't even want to mention my social and sex lives: they are dead. PLEASE HELP!'*

Amiodarone is a drug used in the treatment of arrhythmias of the heart. A clinical study demonstrated that the use of this drug induced anosmia in some patients. Although rare, there was a case in which a 66-year-old male was treated with amiodarone for ventricular tachycardia. After the use of the drug, he began experiencing olfactory disturbance, however after decreasing the dosage of amiodarone, the severity of the anosmia decreased accordingly hence correlating the use of amiodarone to the development of anosmia.

Chemosensory disturbances, including loss of smell or taste, are the predominant neurological symptom of COVID-19. As many as 80% of COVID-19 patients exhibit some change in chemesthesis, including smell. Loss of smell has also been found to be more predictive of COVID-19 than all other symptoms, including fever, cough or fatigue, based on a survey of 2 million participants in the UK and US. Google searches for "*smell", "loss of smell", "anosmi*a", and other similar terms increased since the early months of the pandemic, and strongly correlated with increases in daily cases and deaths.

Many countries list anosmia as an official COVID-19 symptom, and some have developed "*smell tests*" as potential screening tools.

In 2020, the Global Consortium for Chemosensory Research, a collaborative research organization of international smell and taste researchers, formed to investigate loss of smell and related chemosensory symptoms.

The List of Causes in the Wikipedia entry is 2-page long!

Anosmia can be diagnosed by doctors by using acetylcysteine tests. Doctors will begin with a detailed elicitation of history. Then the doctor will ask for any related injuries in relation to anosmia which could include upper respiratory infections or head injury. Psychophysical Assessment of order and taste identification can be used to identify anosmia. A nervous system examination is performed to see if the cranial nerves are damaged. The diagnosis, as well as the degree of impairment, can now be

tested much more efficiently and effectively than ever before thanks to "*smell testing kits*" that have been made available as well as screening tests which use materials that most clinics would readily have. Occasionally, after accidents, there is a change in a patient's sense of smell. Particular smells that were present before are no longer present. On occasion, after head traumas, there are patients who have unilateral anosmia. The sense of smell should be tested individually in each nostril.

Many cases of **congenital anosmia** remain unreported and undiagnosed. Since the disorder is present from birth the individual may have little or no understanding of the sense of smell, hence is unaware of the deficit. It may also lead to reduction of appetite.

Though anosmia caused by brain damage cannot be treated, anosmia caused by inflammatory changes in the mucosa may be treated with **glucocorticoids**. Reduction of inflammation through the use of oral glucocorticoids such as prednisone, followed by long term topical glucocorticoid nasal spray, would easily and safely treat the anosmia. A prednisone regimen is adjusted based on the degree of the thickness of mucosa, the discharge of oedema and the presence or absence of nasal polyps. However, the treatment is not permanent and may have to be repeated after a short while. Together with medication, pressure of the upper area of the nose must be mitigated through aeration and drainage.

Anosmia caused by a nasal polyp may be treated by steroidal treatment or removal of the polyp.

Although very early in development, **gene therapy** has restored a sense of smell in mice with congenital anosmia when caused by ciliopathy. In this case, a genetic condition had affected cilia in their bodies which normally enabled them to detect air-borne chemicals, and an adenovirus was used to implant a working version of the IFT88 gene into defective cells in the nose, which restored the cilia and allowed a sense of smell.

Taste in Pleasure

After -and with smell- **taste** is one of our major five senses.

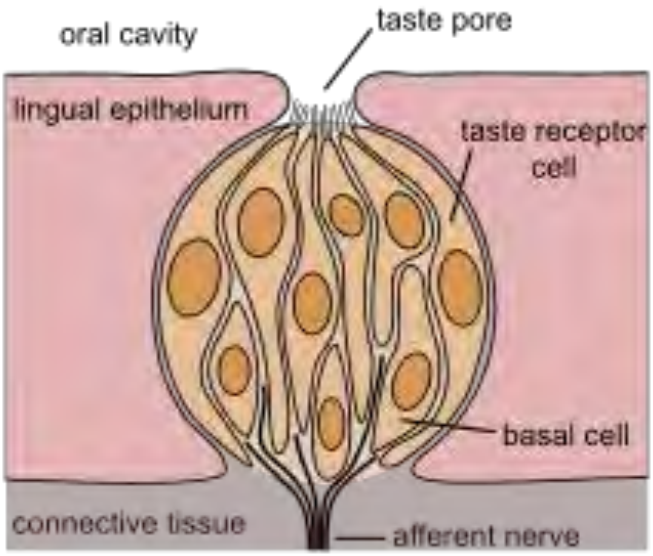
Ayurveda, an ancient Indian healing science, has its own tradition of basic tastes, comprising **sweet, salty, sour, pungent, bitter & astringent.** In the West, Aristotle postulated in c. 350 BCE that the two most basic tastes were **sweet and bitter**. He was one of the first identified persons to develop a list of basic tastes. And the Ancient Chinese regarded **spiciness** as a basic taste.

The **gustatory system** or **sense of taste** is the sensory system that is partially responsible for the perception of taste (flavor). Taste is the perception produced or stimulated when a substance in the mouth reacts chemically with taste receptor cells located on taste buds in the oral cavity, mostly on the tongue. Taste, along with olfaction and trigeminal nerve stimulation (registering texture, pain, and temperature), determines flavors of food and other substances. Humans have taste receptors on taste buds and other areas including the upper surface of the tongue and the epiglottis. The gustatory cortex is responsible for the perception of taste.

The tongue is covered with thousands of small bumps called papillae, which are

visible to the naked eye. Within each papilla are hundreds of taste buds. The exception to this is the filiform papillae that do not contain taste buds. There are between 2000 and 5000 taste buds that are located on the back and front of the tongue. Others are located on the roof, sides and back of the mouth, and in the throat. Each taste bud contains 50 to 100 taste receptor cells.

Taste receptors in the mouth sense the five taste modalities: sweetness, sourness, saltiness, bitterness, and savoriness (also known as *savory* or *umami*). Scientific experiments have demonstrated that these five tastes exist and are distinct from one another. Taste buds are able to distinguish between different tastes through detecting interaction with different molecules or ions. Sweet, savoriness, and bitter tastes are triggered by the binding of molecules to G protein-coupled receptors on the cell membranes of taste buds. Saltiness and sourness are perceived when alkali metal or hydrogen ions enter taste buds, respectively.



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The basic taste modalities contribute only partially to the sensation and flavor of food in the mouth—other factors include smell, detected by the olfactory epithelium of the nose; texture, detected through a variety of mechanoreceptors, muscle nerves, etc.; temperature, detected by thermoreceptors; and *"coolness*" (such as of menthol) and "*hotness*" (pungency), through chemesthesis.

As the gustatory system senses both harmful and beneficial things, all basic taste

modalities are classified as either aversive or appetitive, depending upon the effect the things they sense have on our bodies. Sweetness helps to identify energy-rich foods, while bitterness serves as a warning sign of poisons.

Among humans, taste perception begins to fade around 50 years of age because of loss of tongue papillae and a general decrease in saliva production. Humans can also have distortion of tastes through dysgeusia.

The gustatory system allows animals to distinguish between safe and harmful food, and to gauge foods' nutritional value. Digestive enzymes in saliva begin to dissolve food into base chemicals that are washed over the papillae and detected as tastes by the taste buds. The tongue is covered with thousands of small bumps called papillae, which are visible to the naked eye. Within each papilla are hundreds of taste buds. The exception to this are the filiform papillae that do not contain taste buds. There are between 2000 and 5000 taste buds that are located on the back and front of the tongue. Others are located on the roof, sides and back of the mouth, and in the throat. Each taste bud contains 50 to 100 taste receptor cells.

Bitter foods are generally found unpleasant, while sour, salty, sweet, and umami tasting foods generally provide a pleasurable sensation. The five specific tastes received by taste receptors are saltiness, sweetness, bitterness, sourness, and *savoriness*, often known by its Japanese term "*umami*" which translates to 'deliciousness'. As of the early twentieth century, Western physiologists and psychologists believed there were four basic tastes: sweetness, sourness, saltiness, and bitterness. At that time, savoriness was not identified, but now a large number of authorities recognize it as the fifth taste.

One study found that both salt and sour taste mechanisms detect, in different ways, the presence of sodium chloride (salt) in the mouth. However, acids are also detected and perceived as sour. The detection of salt is important to many organisms, but specifically mammals, as it serves a critical role in ion and water homeostasis in the body. It is specifically needed in the mammalian kidney as an osmotically active compound which facilitates passive re-uptake of water into the blood. Because of this, salt elicits a pleasant taste in most humans.

Sour and salt tastes can be pleasant in small quantities, but in larger quantities become more and more unpleasant to taste. For sour taste this is presumably

because the sour taste can signal under-ripe fruit, rotten meat, and other spoiled foods, which can be dangerous to the body because of bacteria which grow in such media. Additionally, sour taste signals acids, which can cause serious tissue damage.

Sweet taste signals the presence of carbohydrates in solution. Since carbohydrates have a very high calorie count (saccharides have many bonds, therefore much energy), they are desirable to the human body, which evolved to seek out the highest calorie intake foods. They are used as direct energy (sugars) and storage of energy (glycogen). However, there are many non- carbohydrate molecules that trigger a sweet response, leading to the development of many artificial sweeteners, including saccharin, sucralose, and aspartame. It is still unclear how these substances activate the sweet receptors and what adaptational significance this has had.

The **Savory** taste (known in Japanese as "umami") was identified by Japanese chemist Kikunae Ikeda, which signals the presence of the amino acid L-glutamate, triggers a pleasurable response and thus encourages the intake of peptides and proteins. The amino acids in proteins are used in the body to build muscles and organs, transport molecules (hemoglobin), antibodies, and the organic catalysts

known as enzymes. These are all critical molecules, and as such it is important to have a steady supply of amino acids, hence the pleasurable response to their presence in the mouth.

Pungency (piquancy or hotness) had traditionally been considered a sixth basic taste. In 2015, researchers suggested a new basic taste of fatty acids called fat taste, although *oleogustus* and *pinguis* have both been proposed as alternate terms.

Sweetness, usually regarded as a pleasurable sensation, is produced by the presence of sugars and substances that mimic sugar. Sweetness may be connected to aldehydes and ketones, which contain a carbonyl group. Sweetness is detected by a variety of G protein coupled receptors (GPCR) coupled to the G protein gustducin found on the taste buds. At least two different variants of the "*sweetness receptors*" must be activated for the brain to register sweetness. Compounds the brain senses as sweet are compounds that can bind with varying bond strength to two different sweetness receptors. These receptors are T1R2+3 (heterodimer) and T1R3 (homodimer), which account for all sweet sensing in humans and animals. Taste detection thresholds for sweet substances are rated relative to sucrose, which has an index of 1. The average human detection threshold for sucrose is 10 millimoles per liter. For lactose it is 30 millimoles per liter, with a sweetness index of 0.3, and 5-nitro-2-propoxyaniline 0.002 millimoles per liter. "*Natural*" sweeteners such as saccharides activate the GPCR, which releases gustducin. The gustducin then activates the molecule adenylate cyclase, which catalyzes the production of the molecule cAMP, or adenosine 3', 5'-cyclic monophosphate. This molecule closes potassium ion channels, leading to depolarization and neurotransmitter release. Synthetic sweeteners such as saccharin activate different GPCRs and induce taste receptor cell depolarization by an alternate pathway.

Sourness is the taste that detects acidity. The sourness of substances is rated relative to dilute hydrochloric acid, which has a sourness index of 1. By comparison, tartaric acid has a sourness index of 0.7, citric acid an index of 0.46, and carbonic acid an index of 0.06.

Sour taste is detected by a small subset of cells that are distributed across all taste buds called Type III taste receptor cells. H+ ions (protons) that are abundant in sour substances can directly enter the Type III taste cells through a proton channel. This channel was identified in 2018 as otopetrin 1 (OTOP1). The transfer of positive

charge into the cell can itself trigger an electrical response. Some weak acids such as acetic acid, can also penetrate taste cells; intracellular hydrogen ions inhibit potassium channels, which normally function to hyperpolarize the cell. By a combination of direct intake of hydrogen ions through OTOP1 ion channels (which itself depolarizes the cell) and the inhibition of the hyperpolarizing channel, sourness causes the taste cell to fire action potentials and release neurotransmitter.

The most common foods with natural sourness are fruits, such as lemon, grape, orange, tamarind, and bitter melon. Fermented foods, such as wine, vinegar or yogurt, may have sour taste. Children in the US and UK show a greater enjoyment of sour flavors than adults, and sour candy containing citric acid or malic acid is common.

The simplest receptor found in the mouth is the sodium chloride (salt) receptor. **Saltiness** is a taste produced primarily by the presence of sodium ions. Other ions of the alkali metals group also taste salty, but the further from sodium, the less salty the sensation is. A sodium channel in the taste cell wall allows sodium cations to enter the cell. This on its own depolarizes the cell, and opens voltage-dependent calcium channels, flooding the cell with positive calcium ions and leading to neurotransmitter release. This sodium channel is known as an epithelial sodium channel (ENaC) and is composed of three subunits. An ENaC can be blocked by the drug amiloride in many mammals, especially rats. The sensitivity of the salt taste to amiloride in humans, however, is much less pronounced, leading to conjecture that there may be additional receptor proteins besides ENaC to be discovered.

The size of lithium and potassium ions most closely resemble those of sodium, and thus the saltiness is most similar. In contrast, rubidium and caesium ions are far larger, so their salty taste differs accordingly. The saltiness of substances is rated relative to sodium chloride (NaCl), which has an index of 1. Potassium, as potassium chloride (KCl), is the principal ingredient in salt substitutes and has a saltiness index of 0.6.

Other monovalent cations, e.g., ammonium (NH_4^+), and divalent cations of the alkali earth metal group of the periodic table, e.g., calcium (Ca^{2+}), ions generally elicit a bitter rather than a salty taste even though they, too, can pass directly through ion channels in the tongue, generating an action potential. But the chloride of calcium is saltier and less bitter than potassium chloride and is commonly used in pickle brine

instead of KCl.

Bitterness is one of the most sensitive of the tastes, and many perceive it as unpleasant, sharp, or disagreeable, but it is sometimes desirable and intentionally added via various bittering agents. Common bitter foods and beverages include coffee, unsweetened cocoa, South American mate, coca tea, bitter gourd, uncured olives, citrus peel, many plants in the family Brassicaceae, dandelion greens, horehound, wild chicory, and escarole. The ethanol in alcoholic beverages tastes bitter, as do the additional bitter ingredients found in some alcoholic beverages including hops in beer and gentian in bitters. Quinine is also known for its bitter taste and is found in tonic water.

Bitterness is of interest to those who study evolution, as well as various health researchers since a large number of natural bitter compounds are known to be toxic. The ability to detect bitter-tasting, toxic compounds at low thresholds is considered to provide an important protective function. Plant leaves often contain toxic compounds, and among leaf-eating primates there is a tendency to prefer immature leaves, which tend to be higher in protein and lower in fiber and poisons than mature leaves. Amongst humans, various food processing techniques are used worldwide to detoxify otherwise inedible foods and make them palatable. Furthermore, the use of fire, changes in diet, and avoidance of toxins has led to neutral evolution in human bitter sensitivity. This has allowed several loss of function mutations that has led to a reduced sensory capacity towards bitterness in humans when compared to other species.

The threshold for stimulation of bitter taste by quinine averages a concentration of 8 μM (8 micromolar). The taste thresholds of other bitter substances are rated relative to quinine, which is thus given a reference index of 1. For example, brucine has an index of 11, is thus perceived as intensely more bitter than quinine, and is detected at a much lower solution threshold. The most bitter natural substance is amarogentin a compound present in the roots of the plant *Gentiana lutea* and the most bitter substance known is the synthetic chemical denatonium, which has an index of 1,000. It is used as an aversive agent (a bitterant) that is added to toxic substances to prevent accidental ingestion. It was discovered accidentally in 1958 during research on a local anesthetic, by MacFarlan Smith of Gorgie, Edinburgh, Scotland.

Research has shown that TAS2Rs (taste receptors, type 2, also known as T2Rs) such as TAS2R38 coupled to the G protein gustducin are responsible for the human ability to taste bitter substances. They are identified not only by their ability to taste for certain "*bitter*" ligands, but also by the morphology of the receptor itself (surface bound, monomeric). The TAS2R family in humans is thought to comprise about 25 different taste receptors, some of which can recognize a wide variety of bitter-tasting compounds. Over 670 bitter-tasting compounds have been identified, on a bitter database, of which over 200 have been assigned to one or more specific receptors. Recently it is speculated that the selective constraints on the TAS2R family have been weakened due to the relatively high rate of mutation and pseudogenization. Researchers use two synthetic substances, phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) to study the genetics of bitter perception. These two substances taste bitter to some people but are virtually tasteless to others. Among the tasters, some are so-called "*supertasters*" to whom PTC and PROP are extremely bitter. The variation in sensitivity is determined by two common alleles at the TAS2R38 locus. This genetic variation in the ability to taste a substance has been a source of great interest to those who study genetics.

Gustducin is made of three subunits. When it is activated by the GPCR, its subunits break apart and activate phosphodiesterase, a nearby enzyme, which in turn converts a precursor within the cell into a secondary messenger, which closes potassium ion channels. Also, this secondary messenger can stimulate the endoplasmic reticulum to release Ca2+ which contributes to depolarization. This leads to a build-up of potassium ions in the cell, depolarization, and neurotransmitter release. It is also possible for some bitter tastants to interact directly with the G protein, because of a structural similarity to the relevant GPCR.

Savory, or umami is an appetitive taste. It can be tasted in cheese and soy sauce. A loanword from Japanese meaning "good flavor" or "good taste", *umami* is considered fundamental to many East Asian cuisines and dates back to the Romans' deliberate use of fermented fish sauce (also called *garum*).

Umami was first studied in 1907 by Ikeda isolating dashi taste, which he identified as the chemical monosodium glutamate (MSG). MSG is a sodium salt that produces a strong savory taste, especially combined with foods rich in nucleotides such as

meats, fish, nuts, and mushrooms.

Some savory taste buds respond specifically to glutamate in the same way that "sweet" ones respond to sugar. Glutamate binds to a variant of G protein coupled glutamate receptors. L-glutamate may bond to a type of GPCR known as a metabotropic glutamate receptor (mGluR4) which causes the G-protein complex to activate the sensation of umami.

Measuring the degree to which a substance presents one basic taste can be achieved in a subjective way by comparing its taste to a reference substance.

Sweetness is subjectively measured by comparing the threshold values, or level at which the presence of a dilute substance can be detected by a human taster, of different sweet substances. Substances are usually measured relative to sucrose, which is usually given an arbitrary index of 1 or 100. Rebaudioside A is 100 times sweeter than sucrose; fructose is about 1.4 times sweeter; glucose, a sugar found in

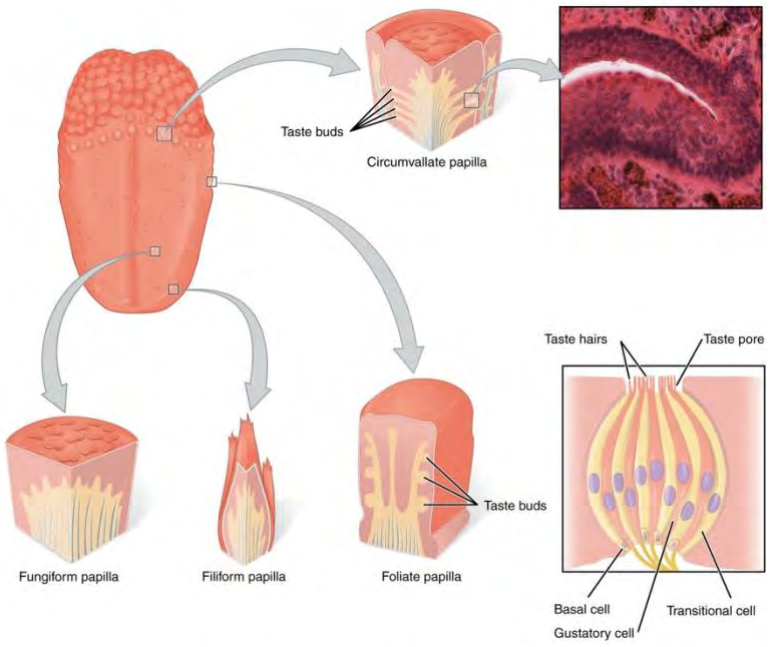
honey and vegetables, is about three-quarters as sweet; and lactose, a milk sugar, is one-half as sweet.

The sourness of a substance can be rated by comparing it to very dilute hydrochloric acid (HCl).

Relative saltiness can be rated by comparison to a dilute salt solution.

Quinine, a bitter medicinal found in tonic water, can be used to subjectively rate the bitterness of a substance. Units of dilute quinine hydrochloride (1 g in 2000 mL of water) can be used to measure the threshold bitterness concentration, the level at which the presence of a dilute bitter substance can be detected by a human taster, of other compounds. More formal chemical analysis, while possible, is difficult.

There may not be an absolute measure for pungency, though there are tests for measuring the subjective presence of a given pungent substance in food, such as the Scoville scale for capsaicin in peppers or the Pyruvate scale for pyruvates in garlics and onions.



Taste buds and papillae of the tongue © Wikipedia

Taste is a form of chemoreception which occurs in the specialized taste receptors in the mouth. To date, there are five different types of taste these receptors can detect which are recognized: salt, sweet, sour, bitter, and umami. Each type of receptor has

a different manner of sensory transduction: that is, of detecting the presence of a certain compound and starting an action potential which alerts the brain. It is a matter of debate whether each taste cell is tuned to one specific tastant or to several; Smith and Margolskee claim that "*gustatory neurons typically respond to more than one kind of stimulus, [a]lthough each neuron responds most strongly to one tastant*". Researchers believe that the brain interprets complex tastes by examining patterns from a large set of neuron responses. This enables the body to make 'keep or spit out' decisions when there is more than one tastant present. "*No single neuron alone is capable of discriminating among stimuli or different qualities, because a given cell can respond the same way to disparate stimuli*." As well, serotonin is thought to act as an intermediary hormone which communicates with taste cells within a taste bud, mediating the signals being sent to the brain. Receptor molecules are found on the top of microvilli of the taste cells.

Sweetness is produced by the presence of sugars, some proteins, and other substances such as alcohols like anethol, glycerol and propylene glycol, saponins such as glycyrrhizin, artificial sweeteners (organic compounds with a variety of structures), and lead compounds such as lead acetate. It is often connected to aldehydes and ketones, which contain a carbonyl group. Many foods can be perceived as sweet regardless of their actual sugar content. For example, some plants such as liquorice, anise or stevia can be used as sweeteners. Rebaudioside A is a steviol glycoside coming from stevia that is 200 times sweeter than sugar. Lead acetate and other lead compounds were used as sweeteners, mostly for wine, until lead poisoning became known. Romans used to deliberately boil the must inside of lead vessels to make a sweeter wine. Sweetness is detected by a variety of G protein-coupled receptors coupled to a G protein that acts as an intermediary in the communication between taste bud and brain, gustducin. These receptors are T1R2+3 (heterodimer) and T1R3 (homodimer), which account for sweet sensing in humans and other animals.

Saltiness is a taste produced best by the presence of cations (such as Na^+, K^+ or Li^+) and is directly detected by cation influx into glial like cells via leak channels causing depolarization of the cell. Other monovalent cations, e.g., ammonium, NH^+_4, and divalent cations of the alkali earth metal group of the periodic table, e.g., calcium, Ca^{2+}, ions, in general, elicit a bitter rather than a salty taste even though they, too,

can pass directly through ion channels in the tongue.

Sourness is acidity, and, like salt, it is a taste sensed using ion channels. Undissociated acid diffuses across the plasma membrane of a presynaptic cell, where it dissociates in accordance with Le Chatelier's principle. The protons that are released then block potassium channels, which depolarize the cell and cause calcium influx. In addition, the taste receptor PKD2L1 has been found to be involved in tasting sour.

Research has shown that TAS2Rs (taste receptors, type 2, also known as T2Rs) such as TAS2R38 are responsible for the ability to taste **bitter** substances in vertebrates. They are identified not only by their ability to taste certain bitter ligands, but also by the morphology of the receptor itself (surface bound, monomeric).

The amino acid glutamic acid is responsible for **savoriness**, but some nucleotides (inosinic acid and guanylic acid) can act as complements, enhancing the taste. Glutamic acid binds to a variant of the G protein-coupled receptor, producing a savory taste.

The **receptors** for the basic tastes of bitter, sweet and savory have been identified. They are G protein-coupled receptors. The cells that detect sourness have been identified as a subpopulation that express the protein PKD2L1. The responses are mediated by an influx of protons into the cells but the receptor for sour is still unknown. There is some evidence for a sixth taste that senses fatty substances.

In 2010, researchers found **bitter taste receptors in lung tissue**, which cause airways to relax when a bitter substance is encountered. They believe this mechanism is evolutionarily adaptive because it helps clear lung infections but could also be exploited to treat asthma and chronic obstructive pulmonary disease.

The tongue can also feel **other sensations** not generally included in the basic tastes. These are largely detected by the somatosensory system. In humans, the sense of taste is conveyed via three of the twelve cranial nerves. The facial nerve (VII) carries taste sensations from the anterior two thirds of the tongue, the glossopharyngeal nerve (IX) carries taste sensations from the posterior one third of the tongue while a branch of the vagus nerve (X) carries some taste sensations from the back of the oral cavity.

The trigeminal nerve (cranial nerve V) provides information concerning the general

texture of food as well as the taste-related sensations of peppery or hot (from spices).

Substances such as ethanol and capsaicin cause a **burning sensation** by inducing a trigeminal nerve reaction together with normal taste reception. The sensation of heat is caused by the food's activating nerves that express TRPV1 and TRPA1 receptors. Some such plant-derived compounds that provide this sensation are capsaicin from chili peppers, piperine from black pepper, gingerol from ginger root and allyl isothiocyanate from horseradish. The piquant ("hot" or "**spicy**") sensation provided by such foods and spices plays an important role in a diverse range of cuisines across the world—especially in equatorial and sub-tropical climates, such as Ethiopian, Peruvian, Hungarian, Indian, Korean, Indonesian, Lao, Malaysian, Mexican, New Mexican, Singaporean, Southwest Chinese (including Sichuan cuisine), Vietnamese, and Thai cuisines.

This particular sensation, called **chemesthesis**, is not a taste in the technical sense, because the sensation does not arise from taste buds, and a different set of nerve fibers carry it to the brain. Foods like chili peppers activate nerve fibers directly; the sensation interpreted as "hot" results from the stimulation of somatosensory (pain/temperature) fibers on the tongue. Many parts of the body with exposed membranes but no taste sensors (such as the nasal cavity, under the fingernails, surface of the eye or a wound) produce a similar sensation of heat when exposed to hotness agents.

Some substances activate **cold trigeminal receptors** even when not at low temperatures. This "fresh" or "minty" sensation can be tasted in peppermint, spearmint and is triggered by substances such as menthol, anethol, ethanol, and camphor. Caused by activation of the same mechanism that signals cold, TRPM8 ion channels on nerve cells, unlike the actual change in temperature described for sugar substitutes, this coolness is only a perceived phenomenon.

Both Chinese and Batak Toba cooking include the idea of 麻 (*má* or *mati rasa*), a tingling **numbness** caused by spices such as Sichuan pepper. The cuisines of Sichuan province in China and of the Indonesian province of North Sumatra often combine this with chili pepper to produce a 麻辣 *málà*, "numbing-and-hot", or "mati rasa" flavor. Typical in northern Brazilian cuisine, jambu is an herb used in dishes like tacacá. These sensations although not taste fall into a category of chemesthesis.

Some foods, such as unripe fruits, contain tannins or calcium oxalate that cause an **astringent or puckering sensation** of the mucous membrane of the mouth. Examples include tea, red wine, rhubarb, some fruits of the genus *Syzygium*, and unripe persimmons and bananas. Less exact terms for the astringent sensation are "dry", "rough", "harsh" (especially for wine), "tart" (normally referring to sourness), "rubbery", "hard" or "styptic".

When referring to wine, *dry* is the opposite of *sweet,* and does not refer to astringency. Wines that contain tannins and so cause an astringent sensation are not necessarily classified as "dry", and "dry" wines are not necessarily astringent.

In the Indian Ayurvedic tradition, one of the six tastes is astringency (*kasaaya*). In Sinhala and Sri Lankan English it is referred to as *kahata*. In Tamil it is referred to as *Thuvarppu*.

A **metallic taste** may be caused by food and drink, certain medicines or amalgam dental fillings. It is generally considered an off flavor when present in food and drink. A metallic taste may be caused by galvanic reactions in the mouth. In the case where it is caused by dental work, the dissimilar metals used may produce a measurable current. Some artificial sweeteners are perceived to have a metallic taste, which is detected by the TRPV1 receptors. Many people consider blood to have a metallic taste. A metallic taste in the mouth is also a symptom of various medical conditions, in which case it may be classified under the symptoms dysgeusia or parageusia, referring to distortions of the sense of taste, and can be caused by medication, including saquinavir, zonisamide, and various kinds of chemotherapy, as well as occupational hazards, such as working with pesticides.

Recent research reveals a potential taste receptor called the CD36 receptor. CD36 was targeted as a possible **lipid taste receptor** because it binds to fat molecules (more specifically, long-chain fatty acids), and it has been localized to taste bud cells (specifically, the circumvallate and foliate papillae). There is a debate over whether we can truly taste fats, and supporters of our ability to taste free fatty acids (FFAs) have based the argument on a few main points: there is an evolutionary advantage to oral fat detection; a potential fat receptor has been located on taste bud cells; fatty acids evoke specific responses that activate gustatory neurons, similar to other currently accepted tastes; and, there is a physiological response to the presence of oral fat. Although CD36 has been studied primarily in mice, research examining

human subjects' ability to taste fats found that those with high levels of CD36 expression were more sensitive to tasting fat than were those with low levels of CD36 expression; this study points to a clear association between CD36 receptor quantity and the ability to taste fat. Other possible fat taste receptors have been identified. G protein-coupled receptors GPR120 and GPR40 have been linked to fat taste, because their absence resulted in reduced preference to two types of fatty acid (linoleic acid and oleic acid), as well as decreased neuronal response to oral fatty acids.

Monovalent cation channel TRPM5 has been implicated in fat taste as well, but it is thought to be involved primarily in downstream processing of the taste rather than primary reception, as it is with other tastes such as bitter, sweet, and savory.

Proposed alternate names to fat taste include oleogustus and pinguis, although these terms are not widely accepted. The main form of fat that is commonly ingested is triglycerides, which are composed of three fatty acids bound together. In this state, triglycerides are able to give fatty foods unique textures that are often described as creaminess. But this texture is not an actual taste. It is only during ingestion that the fatty acids that make up triglycerides are hydrolyzed into fatty acids via lipases. The taste is commonly related to other, more negative, tastes such as bitter and sour due to how unpleasant the taste is for humans. Richard Mattes, a co-author of the study, explained that low concentrations of these fatty acids can create an overall better flavor in a food, much like how small uses of bitterness can make certain foods more rounded. However, a high concentration of fatty acids in certain foods is generally considered inedible. To demonstrate that individuals can distinguish fat taste from other tastes, the researchers separated volunteers into groups and had them try samples that also contained the other basic tastes. Volunteers were able to separate the taste of fatty acids into their own category, with some overlap with savory samples, which the researchers hypothesized was due to poor familiarity with both. The researchers note that the usual "*creaminess and viscosity we associate with fatty foods is largely due to triglycerides*", unrelated to the taste; while the actual taste of fatty acids is not pleasant. Mattes described the taste as "*more of a warning system*" that a certain food should not be eaten.

There are few regularly consumed foods rich in fat taste, due to the negative flavor that is evoked in large quantities. Foods whose flavor to which fat taste makes a small contribution include olive oil and fresh butter, along with various kinds of vegetable

and nut oils.

Kokumi (k/u'ku:mi/, Japanese: *kokumi* from *koku* is translated as "**heartiness**", "full flavor" or "rich" and describes compounds in food that do not have their own taste but enhance the characteristics when combined.

Alongside the five basic tastes of sweet, sour, salt, bitter and savory, *kokumi* has been described as something that may enhance the other five tastes by magnifying and lengthening the other tastes, or "**mouthfulness**". Garlic is a common ingredient to add flavor used to help define the characteristic *kokumi* flavors. Calcium-sensing receptors (CaSR) are receptors for "*kokumi*" substances. *Kokumi* substances, applied around taste pores, induce an increase in the intracellular Ca concentration in a subset of cells. This subset of CaSR-expressing taste cells are independent from the influenced basic taste receptor cells. CaSR agonists directly activate the CaSR on the surface of taste cells and integrated in the brain via the central nervous system. However, a basal level of calcium, corresponding to the physiological concentration, is necessary for activation of the CaSR to develop the *kokumi* sensation.

The distinctive taste of chalk has been identified as the calcium component of that substance. In 2008, geneticists discovered a **calcium receptor** on the tongues of mice. The CaSR receptor is commonly found in the gastrointestinal tract, kidneys, and brain. Along with the "sweet" T1R3 receptor, the CaSR receptor can detect calcium as a taste. Whether the perception exists or not in humans is unknown.

Temperature can be an essential element of the taste experience. Heat can accentuate some flavors and decrease others by varying the density and phase equilibrium of a substance. Food and drink that—in a given culture—is traditionally served hot is often considered distasteful if cold, and vice versa. For example, alcoholic beverages, with a few exceptions, are usually thought best when served at room temperature or chilled to varying degrees, but soups—again, with exceptions—are usually only eaten hot. A cultural example are soft drinks. In North America it is almost always preferred cold, regardless of season.

A 2016 study suggested that humans can taste **starch** (specifically, a glucose oligomer) independently of other tastes such as sweetness. However, no specific chemical receptor has yet been found for this taste.

If we look at the **nerve supply and neural connections**, the glossopharyngeal nerve

innervates a third of the tongue including the circumvallate papillae. The facial nerve innervates the other two thirds of the tongue and the cheek via the chorda tympani.

The pterygopalatine ganglia are ganglia (one on each side) of the soft palate. The greater petrosal, lesser palatine and zygomatic nerves all synapse here. The greater petrosal carries soft palate taste signals to the facial nerve. The lesser palatine sends signals to the nasal cavity, which is why spicy foods cause nasal drip. The zygomatic sends signals to the lacrimal nerve that activate the lacrimal gland, which is the reason that spicy foods can cause tears. Both the lesser palatine and the zygomatic are maxillary nerves (from the trigeminal nerve).

The special visceral afferents of the vagus nerve carry taste from the epiglottal region of the tongue.

The lingual nerve (trigeminal) is deeply interconnected with the chorda tympani in that it provides all other sensory info from the anterior 2/3 of the tongue. This info is processed separately (nearby) in the rostal lateral subdivision of the nucleus of the solitary tract (NST).

NST receives input from the amygdala (regulates oculomotor nuclei output), bed nuclei of stria terminalis, hypothalamus, and prefrontal cortex. NST is the topographical map that processes gustatory and sensory (temp, texture, etc.) info. Reticular formation (includes Raphe nuclei responsible for serotonin production) is signaled to release serotonin during and after a meal to suppress appetite. Similarly, salivary nuclei are signaled to decrease saliva secretion.

Hypoglossal and thalamic connections aid in oral-related movements. Hypothalamus connections hormonally regulate hunger and the digestive system. Substantia innominata connects the thalamus, temporal lobe, and insula. Edinger-Westphal nucleus reacts to taste stimuli by dilating and constricting the pupils. Spinal ganglions are involved in movement. The frontal operculum is speculated to be the memory and association hub for taste. The insula cortex aids in swallowing and gastric motility.

A **supertaster** is a person whose sense of taste is significantly more sensitive than most. The cause of this heightened response is likely, at least in part, due to an increased number of fungiform papillae. Studies have shown that supertasters require less fat and sugar in their food to get the same satisfying effects. However,

contrary to what one might think, these people actually tend to consume more salt than most people. This is due to their heightened sense of the taste of bitterness, and the presence of salt drowns out the taste of bitterness. (This also explains why supertasters prefer salted cheddar cheese over non-salted.)

Patients with Addison's disease, pituitary insufficiency, or cystic fibrosis sometimes have a **hyper-sensitivity to the five primary tastes.**

Aftertastes arise after food has been swallowed. An aftertaste can differ from the food it follows. Medicines and tablets may also have a lingering aftertaste, as they can contain certain artificial flavor compounds, such as aspartame (artificial sweetener).

An **acquired taste** often refers to an appreciation for a food or beverage that is unlikely to be enjoyed by a person who has not had substantial exposure to it, usually because of some unfamiliar aspect of the food or beverage, including bitterness, a strong or strange odor, taste, or appearance.

Ageusia is the loss of taste functions of the tongue, particularly the inability to detect sweetness, sourness, bitterness, saltiness, and umami (meaning "pleasant/savory taste"). It is sometimes confused with anosmia – a loss of the sense of smell. Because the tongue can only indicate texture and differentiate between sweet, sour, bitter, salty, and umami, most of what is perceived as the sense of taste is actually derived from **smell**. True ageusia is relatively rare compared to hypogeusia – a partial loss of taste – and dysgeusia – a distortion or alteration of taste.

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When Jean-Anthelme Brillat-Savarin wrote his aphorisms (in the 19th century), our knowledge of the senses involved in the pleasure of eating (and sharing a meal) was miniscule. Even a few years ago when I reported on this subject, my essays were much shorter. These days, hundreds of research teams explore the detailed complexity of pleasure, food, cooking, wine and much more, and report their findings in peer-reviewed scientific journals, at specific/specialized meetings or on TED talks. And the volume is growing exponentially.

My own contribution is just providing (mostly by copying *verbatim* Wikipedia and other sources) reliable information. This might be too much to… swallow in one reading, and I urge you to take time. Just like at a great meal.

Bon Appétit!

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