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Olfactory dysfunction in COVID-19: new insights into the underlying mechanisms

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The mechanisms of olfactory dysfunction in COVID-19 are still unclear. In this review, we examine potential mechanisms that may explain why the sense of smell is lost or altered. Among the current hypotheses, the most plausible is that death of infected support cells in the olfactory epithelium causes, besides altered composition of the mucus, retraction of the cilia on olfactory receptor neurons, possibly because of the lack of support cell-derived glucose in the mucus, which powers olfactory signal transduction within the cilia. This mechanism is consistent with the rapid loss of smell with COVID-19, and its rapid recovery after the regeneration of support cells. Host immune responses that cause down-regulation of genes involved in olfactory signal transduction occur too late to trigger anosmia, but may contribute to the duration of the olfactory dysfunction.

Loss of smell in COVID-19: why?
The frequency of olfactory dysfunction in the coronavirus disease 2019 (COVID-19) pandemic is unprecedented [1,2]. Previous pandemics caused by other viruses have resulted in olfactory loss at a much lower rate [1–8], primarily by nasal congestion and obstruction, or by loss of smell and taste as a sequel after the acute infection; regardless, they did not give rise to the sudden and extensive loss of smell on the scale of the hundreds of millions of cases seen in COVID-19. What is different about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus; see Glossary) compared with previous coronaviruses? Why does this virus have such a devastating impact on the sense of smell? Most of the mechanisms that have been proposed to explain the unique features of anosmia in COVID-19 are not fully consistent with the data that have been reported from humans and animal models.

In this review, we first describe the shortcomings of previous hypotheses attempting to explain anosmia in COVID-19; we then present evidence indicating that largely overlooked properties of support cells may account for all major features of SARS-CoV-2-induced anosmia in both humans and animals. Olfactory receptor neurons depend on two types of support cell: sustentacular cells (Figure 1) and Bowman gland cells. This dependence is much more intricate than traditionally appreciated. The olfactory neurons engage in a series of complex interactions with their support cells. When this intimate symbiosis is disrupted by the infection of support cells with SARS-CoV-2, neuronal function is compromised. Given that multiple variants of SARS-CoV-2 have evolved with various mutations, it has been possible to dissect the contributions of viral factors to the effectiveness of host cell entry and tropism, and how these determine the extent of olfactory dysfunction. The COVID-19 pandemic has revealed crucial roles of support cells for neuronal function that were not previously obvious, and this has helped to inform about fundamental workings of the olfactory system. Here, we examine the merits of five hypotheses that may explain the olfactory dysfunction associated with COVID-19. We contend that, among the hypotheses, the most plausible one involves the death of infected support cells in the olfactory epithelium and, as a result, temporary disruption...
of olfactory receptor neuron function. We also discuss how viral mutations modify the extent of such dysfunction. From a historical perspective, the impact of SARS-CoV-2 on olfaction appears to be unprecedented among the pandemics of recent history.

**Previous hypotheses about underlying mechanisms**

During the first year of the pandemic, when reports of olfactory dysfunction permeated the literature and the media, a variety of potential mechanisms was considered. These included: congestion of the nasal mucosa due to swelling and obstruction of the olfactory cleft; infection and death of olfactory receptor neurons; viral neuroinvasion along the olfactory nerve; infection and death of neurons in the olfactory bulb and cortex; altered neuronal function due to cytokine release and inflammation; reduced neuronal function due to vascular changes in the olfactory bulb; reduction in mucus that dissolves odorants, due to infection and the death of cells that produce it; immune-mediated downregulation of odorant receptors and other signaling molecules; autoimmune reactions due to the resemblance of viral proteins to odorant receptors; inflammation and damage of the olfactory epithelium; and infection and death of sustentacular support cells [9–18].

**Scenarios or mechanisms that have been discounted**

Any hypothesis about the mechanism of anosmia in COVID-19 must account for the high prevalence, sudden onset, and remarkable transience of the olfactory dysfunction [9,19]. Most of the above-listed hypotheses turned out to be implausible, for various reasons. The olfactory cleft does not become obstructed in most patients with COVID-19 with olfactory dysfunction; thus, congestion cannot explain most cases of anosmia [13,15,20–22]. Olfactory receptor neurons do not express the virus entry proteins and, therefore, become infected rarely or not at all [13,22–26]. Current evidence indicates that SARS-CoV-2 has very limited neurotropic potential in humans, if any, unlike other viruses that target the olfactory circuits [13,22–24]. Since the regeneration of olfactory receptor neurons takes 2–3 weeks, the mostly short-lived loss of smell cannot be caused by death and subsequent regeneration of the olfactory receptor neurons [9,11]. SARS-CoV-2 does not invade the olfactory nerve in patients with COVID-19, and this nerve remains largely intact during anosmia [22–24,27]. In animal models and also in humans, many regions of the olfactory epithelium retain half or more of their olfactory receptor neurons after inoculation or infection [22,28], which is thought to be more than sufficient to maintain a basic sense of smell [29–31]. Effects of the virus on axonal pathology in the olfactory bulb and cerebral cortex, whether directly by viral infection or indirectly through host immune responses, were not significantly different between patients with COVID-19 with loss of smell and patients without loss of smell [32]. Infection of the olfactory epithelium in animal models causes longer-term changes of microglia activation in olfactory targets in the brain [28], apparently mediated through systemic inflammatory responses [33], but the timing of such events is not compatible with the early abrupt onset of complete anosmia and its recovery just days later [21]. In conclusion, since most of the hypotheses fail to explain COVID-19-associated anosmia, which scenarios remain? Before we examine five hypotheses that deserve further scrutiny, we first discuss key features of anosmia in COVID-19 that any mechanism has to explain.

**The unique features of COVID-19-associated anosmia**

One of the most peculiar characteristics of the olfactory dysfunction in COVID-19 is that it typically starts very abruptly, lasts for only a few days (mean or median ranges: 7–21.6 days [34,35]), and smell can recover just as abruptly as it was lost. The olfactory dysfunction may be quantitative, with reduced function (hyposmia) or complete loss (anosmia), or the dysfunction may be qualitative, with altered smell (parosmia); it may be accompanied by dysfunction of taste; and it may last shorter or longer, and with sudden...
or gradual recovery. Typical temporal features of anosmia are illustrated in Figure 2 using data from a controlled clinical study on humans [36]. Volunteers underwent objective testing of olfaction daily or every 2 days post inoculation (dpi). As expected from epidemiological meta-analyses of the same virus variant based on subjective recall of patients [37,38], two-thirds of volunteers infected with SARS-CoV-2 lost their sense of smell. The onset of loss of smell varied, but occurred between 5 and 12 dpi. Two main patterns became apparent. In most volunteers with anosmia, smell was lost abruptly (within hours) for an average duration of 8 days, followed by either an abrupt (Figure 2A) or gradual recovery (Figure 2B).

Based on animal studies, it is thought that more than 90% of the olfactory epithelium has to be impaired to lose the sense of smell [29–31]. In adult rats, when 30–40% of sustentacular cells were eliminated, with loss of ~25% of olfactory receptor neurons, olfaction was found to be normal [39]. There appears to be redundancy (or a ‘safety buffer’) in that only 10% or less of functional olfactory receptor neurons are needed for a basic sense of smell. Humans have ~10 million olfactory neurons and 10 million support cells in the olfactory epithelium. To lose the sense of smell, as often occurs in COVID-19, it is likely that, by extrapolation from animal studies, at least 90% of the human olfactory receptor neurons (i.e., 9 million cells) must be dysfunctional.
Since it is known that, in COVID-19 patients with anosmia, the number of olfactory receptor neurons is not reduced to such an extent [22,24], the neurons appear to become temporarily disabled by a mechanism that differs from those known for other viruses. Any viable hypothesis has to account for these peculiar features of anosmia in COVID-19.

Timing of recovery of smell: implications for the mechanism involved

Another important feature of anosmia in COVID-19 is the way in which smell recovers, because this recovery profile rules out several mechanisms. What kind of insult can rapidly disable 90% or more of the olfactory receptor neurons, causing an anosmia that may last only 4 days, on average 9 days [37], and mostly shows an abrupt, not gradual, recovery of the sense of smell (objectively verified in humans [36])? Keeping in mind the ‘safety buffer’, one can conclude that, for subjective or objective recovery of smell, in as few as 4 days, at least 5–10% of olfactory neurons (500 000 to 1 million neurons) must have become functional or have regained their functionality. Under normal conditions, both the adult olfactory receptor neurons and their support cells constantly regenerate with a neuronal turnover of ~30–90 days [40]. Regeneration of these two cell types follows a very different time course. The sustentacular cells rapidly regenerate, within 4–8 days after lesion (Figure 3). Regeneration of olfactory receptor neurons is much slower [41–43], due to the need for growth of the apical dendritic process toward the nasal cavity, odorant receptor expression and trafficking, and enwrapping of the dendrite by sustentacular support cells [44,45]. The growth of the axon, along the olfactory nerve, through the cribriform plate and into the glomeruli of the olfactory bulb, takes an additional 5–7 days, even in small rodents [43,45–47]. These differences in regeneration between cell types provide clues to the plausibility of the proposed mechanisms.

Focus on elimination of support cells and host immune responses

The currently viable hypotheses aiming to explain anosmia in COVID-19 can be divided into two major categories with five different ‘flavors’ that are not mutually exclusive: (i) elimination of support cells with consequences for neuronal function: (a) reduction or alteration of the mucus covering the olfactory epithelium; (b) loss of energy (glucose) that normally powers olfactory cilia, due to death of sustentacular cells and Bowman gland cells; and (c) retraction of olfactory cilia due to the death of sustentacular cells and loss of a maintenance factor
for the cilia; and (ii) host immune responses affecting olfactory receptor neuron function: (a) downregulation of gene expression for odorant receptors (and other signaling molecules) in olfactory receptor neurons; and (b) immune cytokine-caused inflammation and destruction of the olfactory epithelium, including loss or damage of olfactory receptor neurons.

We review these five hypotheses in sequence. The first three envision a central role of the support cells and propose that damage to two types of support cell, sustentacular cells

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**Figure 3. Timetable of the events that ensue when the sustentacular support cell (SUS) is damaged or eliminated.** This figure summarizes the events when the SUS is damaged by either a toxin or due to virus infection. Notably, damage of the SUS causes within 2–3 h a physical separation of the SUS from the olfactory receptor neuron (ORN), swelling of the knob and its degeneration, and retraction of the cilia [27,51,63–65]. Deciliation continues from 2 to 48 h. The ORN resumes an immature stage of its dendritic extension, with focus on growth of its processes rather than on neurotransmission and sensory transduction. Gene expression of odorant receptors (ORs) is downregulated at 2 days (mouse [52]), 3 days (zebrafish [63]), and 4 days (hamster [22]) after inoculation. Odorant-binding proteins (OBPs) and receptor transporting protein 1 (RTP1) are also reduced [52]. In most animal models, loss of smell is evident as early as 2 days after lesion of SUS (mouse) and, depending on the animal model, anosmia lasts from 2 to 8 days. In humans, it lasts from 7 to 10 days (mean values) after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [27]. The stem cells in the basal layers begin to divide at 3 days after SUS damage [66], and the first newly regenerated SUS appear at 4–8 days [22,64]. Recovery of smell begins at 4 days after SUS lesion in the mouse, at 8 days in the hamster [75], and the olfactory epithelium appears fully intact in the hamster at 7 days [74] or 14 days [51]. Human data on recovery of smell are according to pertinent studies [36,37,120,121].
Mucus reduction

The mucus that covers the olfactory epithelium is produced by sustentacular cells and Bowman gland cells. These cell types abundantly express the viral entry proteins, angiotensin-converting enzyme 2 (ACE2) and TMPRSS2 [19,48–50] and, therefore, are the prime target of SARS-CoV-2 within the olfactory system. The virus rapidly and extensively infects and destroys these cells in animal models [25,27,51,52] and humans [22,24]. This could lead to reduction and/or alteration of the mucus, impede diffusion of odorant molecules, and alter processing and signal transduction induced by odorants [53,54]. The amount of mucus after SARS-CoV-2 infection has been quantified in an animal model and was found to be significantly reduced after infection [55], suggesting that changes in the quantity and chemical composition of the mucus contribute to the olfactory dysfunction [51,56].

Loss of glucose normally supplied by sustentacular cells and Bowman gland cells

The dendritic knob of olfactory receptor neurons lacks a sufficient number of mitochondria to supply energy for olfactory transduction in the cilia, which extend up to 100 μm from the knob within the mucus [57,58]. Instead, glucose has to be transported from blood vessels below the basal lamina through the sustentacular cells and Bowman gland cells to the mucus. These cells import glucose at their basal domain via glucose transporters (GLUT1) and export (secrete) the glucose at their apical surface via GLUT3 into the mucus [57–59] as illustrated for sustentacular cells in Figure 4. Impairing the glucose transporters and reducing the glucose concentration in the mucus is thought to rapidly abolish the energy-dependent olfactory signal transduction that normally ensues upon binding of odorants to their receptors. When this energy supplementation is disrupted by the infection of the support cells with SARS-CoV-2, the cilia become dysfunctional. Consistent with this hypothesis, genes for glucose transporters are among the earliest downregulated genes according to single-cell RNA-sequencing analyses of support cells after SARS-CoV-2 infection in hamsters [22]. Since ACE2, abundantly expressed in support cells, is part of the renin–angiotensin–aldosterone system (RAAS), RAAS-associated peptidases may be linked to anosmia because of their potential involvement in the regulation of ion/water content and glucose metabolism [60]. SARS-CoV-2 is known to hijack host metabolic pathways to maximize glucose utilization for virus replication [61]. Therefore, it is possible that glucose within infected support cells is diverted even before they die, preventing the glucose from being released and making it unavailable for cilia. The dependence of olfactory signal transduction on energy supplied by the support cells provides a plausible mechanism for COVID-19-induced anosmia [10,11,24,62].

Retraction of neuronal cilia after damage to sustentacular cells

Several studies of anosmia in COVID-19, in both animal models and humans, have reported rapid deciliation (retraction of cilia from olfactory receptor neurons) after infection of sustentacular cells with SARS-CoV-2 [27,51,52,63] (Figure 3). Such data suggest that the sustentacular cells provide a maintenance factor for olfactory cilia. Surprisingly, deciliation has rarely been discussed as a mechanism for COVID-induced anosmia, with few exceptions [11,27,51,52,60].
Previous studies have shown that toxins that primarily target and destroy the sustentacular cells (e.g., dibasic esters, methimazole, and nickel sulfate) rapidly lead to deciliation of the olfactory receptor neurons [64–66] (Figure 3). Olfactory neurons lose contact with their sustentacular cells, dendritic knobs begin to swell and degenerate, losing their cilia within 2 h after treatment with methimazole [65]. Likewise, after destruction of support cells with dibasic esters, cilia disappear within 24 h [64]. Such loss of cilia cannot be an artifact of tissue processing, because cilia are preserved in vehicle control cases, and because specifically those neurons lose their cilia when their adjacent sustentacular cell has died [64], which suggests the existence of a local, contact-mediated maintenance signal between the two cell types [60]. Tight contacts between the two cell types have been described in the rodent [44] as well as in the human olfactory epithelium [67]. SARS-CoV-2 causes deciliation in animals with the same rapid time course as described for the above-listed toxins [27,51,52] (Figure 3). Importantly, the key transcription factor for ciliogenesis, Forkhead box J1 (Foxj1), is already downregulated in olfactory receptor neurons 1 dpi [22]. Although originally proven to be essential only for motile cilia [68], Foxj1 is expressed in some, and possibly most, olfactory receptor neurons, as shown by transcriptome analyses [22,69,70] and examination of tissue sections [69,71]. Rapid deciliation also occurs in the SARS-CoV-2-infected respiratory epithelium [72,73]. Since cilia are required for olfactory signal transduction [45], deciliation after elimination of support cells may be primarily responsible for anosmia in COVID-19.

Can this mechanism also explain the rapid and often abrupt recovery of smell? It is important to consider two possibilities: after deciliation, the recovery of smell may be due to a sufficient number of immature receptor neurons that develop over time to become functional; alternatively, there may be regrowth of cilia on surviving receptor neurons. Regarding the first possibility, assuming a 30–90-day turnover of 10 million olfactory receptor neurons [40], this amounts to 110 000–330 000 new neurons per day. Normally, it would take only 4–10 days to achieve 500 000 to 1 million new functional olfactory receptor neurons with cilia (i.e., 5–10% of the total required for smell [29–31]). However, because of the substantial destruction of the olfactory epithelium, numbers of immature neurons in the pipeline may be considerably lower, since some of them become infected or damaged and die during the desquamation of the epithelium [51,52,74] and their maturation may be delayed.

As an alternative, regrowth of cilia may occur on surviving deciliated mature olfactory receptor neurons. Since most of the mature neurons are thought to survive [22,24,25,28], only a small fraction of them (10%) need to regrow their cilia to provide basic olfactory functionality. The abrupt recovery of smell in many cases of anosmia [36] (Figure 2A) is more consistent with a synchronized regeneration of support cells, allowing the regrowth of the cilia on surviving neurons, rather than the gradual increase in regenerating neurons that were already in the pipeline (before infection). Thus, the time course of smell recovery favors the scenario of surviving neurons regrowing their dendrites.

Regardless which of the two scenarios applies (and they are not mutually exclusive), there is strong evidence from animal models that, after having been largely deciliated at 3–5 dpi, the cilia are fully intact at 14 dpi in hamster [51]. Since olfaction returns at 8 dpi in the hamster [75], the time course of cilia recovery (between 5 and 14 dpi) is consistent with the notion that reciliation is involved in the fast recovery of smell in COVID-19.

**Downregulation of odorant receptor genes**

Increased levels of some cytokines, such as interferons (IFNs), in the olfactory epithelium can reduce the expression of odorant receptors in olfactory receptor neurons [76]. Such
downregulation of odorant receptors was proposed as a potential mechanism for anosmia in COVID-19 [9]. This hypothesis was first tested in a mouse model [52], and it was found that not only odorant receptor genes, but also additional molecules involved in olfactory signal transduction were downregulated. However, in humans, normal expression of odorant receptor genes was reported [24], unchanged between infected and non-infected olfactory epithelium. Likewise, no downregulation of odorant receptor genes was found in COVID-19 patients with persistent (12 weeks) loss of smell [56], but ADCY3 (an odorant receptor-related signaling molecule) was reduced. In hamster, downregulation of odorant receptor genes did not occur.
until 4 dpi [22], and it was concluded that systemic proinflammatory cytokines can induce downregulation of odorant receptor genes as well as genes encoding other signaling molecules, such as ADCY3 [22]. Several studies reported impaired olfactory signal transduction due to a reduction in signaling molecules [22,52,77].

The cellular source of the cytokines in the host has not yet been identified, and neither have the relevant cytokines. Sustentacular cells may be the only, or the main, source of such cytokines [9], or sustentacular cells may contribute among various other cellular sources [22]. Most studies reported increased levels of IFNs in the olfactory epithelium after SARS-CoV-2 infection [22,51,52], with one exception (to our knowledge) [74]. Some IFN-stimulated genes encode proteins (such as IFITM or LY6E) that inhibit viral entry along the endosomal route [78,79]. Since IFITMs are abundantly expressed in support cells [22], this would reduce endosomal virus entry, but may not prevent virus entry after surface membrane fusion via TMPRSS2 [21,79,80] (Figure 5). The importance of viral entry mediated through TMPRSS2 is underscored by the reduced olfactory dysfunction in patients with COVID-19 treated with the TMPRSS2 inhibitor, camostat [81]. Besides IFN, several other cytokines, such as IL6 and TNFα, may be involved in anosmia, although their roles are somewhat controversial and await clarification [76,82–85].

A mechanism involving immune responses is an attractive hypothesis, because it would explain the sudden onset of complete anosmia. However, there are inconsistencies with the timing. If immune-mediated release of cytokines silences olfactory signaling, one would expect that downregulation of odorant receptor genes occurs before the onset of anosmia, and there should be some delay between reduced gene expression and actual depletion of odorant receptor proteins, because of the turnover rate of these proteins [86]. One would also expect that smell does not recover until gene expression has normalized. However, in hamster, the onset of anosmia precedes the gene expression changes by 2 days and extends beyond the time of smell recovery. At 8 dpi, the sense of smell in hamsters has already recovered [75], while odorant receptor genes are still downregulated at 10 dpi [22]. Apparently, smell can recover before normal odorant receptor expression has resumed.

As mentioned previously, the altered regulation of genes enabling olfactory signal transduction is not restricted to odorant receptor genes, but involves additional proteins relevant for olfactory signal transduction, including receptor transporting protein 1 (RTP1 [52]), IFN-controlled G-protein signaling (RGS2 [77]), and ADCY3 [22,56], which is essential for maintenance of olfactory cilia [87] and is also reduced at the protein level [22]. This indicates a broad effect on gene expression in olfactory receptor neurons in response to SARS-CoV-2. Such broad changes in gene expression may be a consequence of deciliation and the regression of the olfactory receptor neurons to a less mature state, with impaired placement of odorant receptors; odorant receptor trafficking to the cilia is thought to be a critical step toward maturation of olfactory neurons [88].

**Immune cytokine-induced destruction of the olfactory epithelium**

A final possible scenario to consider is that infection of the sustentacular cells by SARS-CoV-2 rapidly causes immune cell infiltration of the olfactory epithelium, which leads to desquamation of the epithelium, with expulsion of epithelial cells into the lumen. Many of these cells die by apoptosis, including some olfactory receptor neurons. This may be part of a host defense mechanism that evolved to protect the brain from pathogens and toxins [89–92]. The destruction of the olfactory epithelium may cause the anosmia, and eventual regeneration of the olfactory epithelium...
Figure 5. Illustration of the molecular mechanisms that can explain why severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants cause different amounts of olfactory dysfunction. This figure summarizes how the properties of three SARS-CoV-2 virus variants (D614, G614, and omicron) differ in ways that likely determine to what extent sustentacular support cells (SUS) in the olfactory epithelium become infected and whether their loss will lead to anosmia. The original D614 (Wuhan) virus results in premature spike shedding, lower spike density, and, therefore, less effective virus entry [79]. This may cause less infection of SUS and, therefore, results in a low prevalence of anosmia (~10%) [37]. The G614 variant has the D614G mutation, which stabilizes the spike trimer and prevents premature spike shedding; the higher spike density allows the G614 variant to infect SUS cells effectively [79], resulting in a high (30–50%) anosmia prevalence [38]. All three variants bind to the virus entry protein angiotensin-converting enzyme 2 (ACE2), expressed by SUS, and with no significant differences in binding affinity to ACE2 [21,79,80]; thus, this cannot explain differences in anosmia. The first two variants, D614 and G614, both enter host cells by using surface membrane fusion mediated by the protease TMPRSS2 [79,110]. The new mutations in the omicron variant cause a less efficient furin cleavage, resulting in reduced surface membrane fusion mediated by TMPRSS2 [79,80,111]. Therefore, omicron prefers an endosomal route that is less efficient for SUS infection, possibly because many host cells have developed defenses for the endosomal entry [78,79,111]. As a result, the omicron variant, despite retaining the D614G mutation, is associated with a lower anosmia prevalence of ~13% [105].
may lead to recovery of smell [27,28,51,52,74,93]. Chronic immune responses in the olfactory epithelium appear to delay regeneration of the olfactory epithelium [94,95]. This may explain why an estimated 5% of COVID-19 patients with olfactory dysfunction recover from chemosensory dysfunction late or not at all [96].

While there is substantial, although patchy, damage of the infected olfactory epithelium, a major question is whether such damage indeed leads to the destruction of 90% or more of the olfactory receptor neurons, because of the safety buffer discussed previously [29–31]. Studies report that most olfactory receptor neurons do not become infected, and a sufficient large percentage of them apparently survive [22,24,27,28,51]. This indicates that anosmia in COVID-19 is unlikely to be caused by the death of olfactory receptor neurons.

**Parosmias: prevalence, time course and possible mechanisms**

The prevalence of qualitative olfactory dysfunction (parosmia) in COVID-19 is not well known. The largest cohort studies have reported 7.5–11% [97,98], and two smaller cohort studies indicate a doubling of the prevalence with COVID-19 compared with the parosmia prevalence without COVID-19 [2,99]. The pre-pandemic level was ~4% [100]. The frequency of parosmia in COVID-19 patients with persistent olfactory dysfunction is higher (11–67%), but survey-type studies likely overestimate prevalence because long-haulers are more motivated to respond [98,101,102]. The more debilitating (persistent) parosmias occur at 1–6 months after diagnosis [97–99], suggesting a correlation with smell recovery [98,101]. The mechanism of parosmia is not clear; the most plausible is a peripheral process with aberrant wiring of the olfactory axons into the ‘wrong’ glomerulus in the olfactory bulb [101,103]. A central mechanism at the cerebral level may also contribute [101,103]. Altered mucus may change the effective concentration of odorants, which can transform odorant perception [54], but mucus composition would be expected to normalize after support cell regeneration and, therefore, is not likely to be responsible for parosmias that persist for weeks and months after the infection. The aberrant wiring hypothesis is consistent with our proposal that olfactory receptor neurons become partially ‘immature’ after elimination of their support cells. The dendrite retraction may lead to a disconnection between the innervated glomerulus and the expression of the appropriate odorant receptor. In addition, after extensive destruction of the olfactory epithelium, regenerating olfactory neurons may fail to receive the appropriate signals for innervation of the correct glomerulus, leading to wiring mistakes.

**Contributions of virus and host factors to anosmia**

Studies from different countries reported widely diverging anosmia prevalences in COVID-19, indicating differences due to ethnicity and/or geographic location [37,60]. It was initially unclear whether such differences in prevalence were due to viral factors or to host factors, or both.

**Virus factors: the D614G mutation**

When the same population was infected mostly with the G614 variant rather than the D614 virus, olfaction was more often impaired [38]. This constitutes strong evidence that the difference in loss of smell between Western and Asian countries was largely due to infection with different virus variants, with the G614 virus causing a larger anosmia prevalence than the original D614 virus (which affected primarily populations in East and South Asia [38,104]). The D614G mutation in the spike protein appears to enhance entry of this variant into the sustentacular cells and the Bowman gland cells of the olfactory epithelium (Figure 5). It appears that the virus variants differ in how efficiently they infect the support cells, and the population-specific anosmia prevalence reflects such differences.
Virus factors: omicron
The omicron variant causes a lower prevalence of chemosensory dysfunction (Figure 5) [105,106], and this was confirmed by subsequent large-cohort studies [107,108]. The pooled mean is ~13%, which is a three- to fourfold reduction from the anosmia prevalence caused by the alpha and delta variants (at 35–50%; Figure 5 [107–109]). Why does omicron largely spare olfaction? The omicron variant is more hydrophobic and, therefore, may be less soluble in the mucus [105], possibly resulting in fewer virions reaching the support cells. Second, omicron has a lower cell entry efficiency in TMPRSS2-expressing cells (Figure 5), apparently due to less efficient furin cleavage, resulting in lower membrane fusion activity and a shift toward cell entry via the endosomal pathway [79,80,110,111] (Figure 5), a pathway for which support cells have more potent defenses, such as IFITM [22]. Omicron appears to be less efficient in infecting these cells [112], resulting in a lower frequency of anosmia.

Host factors affecting anosmia: ACE2, TMPRSS2, or UGT2A1/A2?
Is there also a contribution of host factors to the anosmia variation between populations? Initially, it was thought that the levels of expression of the virus entry proteins, ACE2 and TMPRSS2, may differ in the frequency of SNPs between ethnicities and this was assumed to contribute to altered binding affinities and enhanced infectivity, and, thus, altered anosmia prevalence [113]. However, more recent studies have concluded that ACE2 expression levels within populations do not correlate with infectivity or chemosensory dysfunction and cannot explain different phenotypes [114,115]. A genome-wide association study (GWAS) on a large number of subjects showed that a different gene locus, the UGT2A1/A2 locus, correlated with differences in anosmia prevalence between populations [116]. The UGT2A1 glucuronosyltransferase metabolizes odorants and other substrates, and genetic variation in this locus differs between ethnicities, with East Asians having the lowest, and populations with European ancestry having the highest levels of expression. This pattern implicates UGT2A1/A2 as the host factor contributing to the differences in anosmia prevalence between populations, rather than ACE2 or TMPRSS2 variants. Since the sustentacular cells are the cell type with most abundant UGT2A1/A2 expression in the olfactory epithelium [24,56], the GWAS [116] further implicates this support cell as the key cell type responsible for COVID-induced anosmia, although the exact role of UGT2A1/A2 awaits clarification.

Concluding remarks
Among the hypotheses attempting to explain anosmia in COVID-19, the strongest evidence favors a lack of support cell-derived cilia-maintenance factors. Immune responses are possibly involved, but appear to occur too late to act as the trigger for anosmia. Broad gene expression changes take place after the olfactory receptor neuron loses its support from sustentacular cells and Bowman gland cells, and the deciliation propels the olfactory neuron back to a less mature state of gene expression, geared toward process growth and away from neurotransmission and signal transduction. When support cells have regenerated, the regrowth of cilia from surviving olfactory neurons enables rapid recovery of smell. SARS-CoV-2 has evolved a novel and unique mechanism of support cell damage, lacking any apparent historic precedent (Box 1). While the broader picture of the underlying mechanisms is emerging, many details remain to be clarified (see Outstanding questions). Nevertheless, COVID-19 has revealed a much more intimate relationship between the olfactory neuron and its support cells than previously appreciated.

Author contributions
All authors contributed to the writing of this article.

Outstanding questions
When mucus quantity and composition is assessed in animal models of COVID-induced anosmia, is there a correlation between mucus properties and anosmia?
Is glucose transport/secretion by support cells reduced after virus infection in animal models of COVID-19?
What are the signals that derive from sustentacular cells that cause the deciliation of olfactory receptor neurons?
Can deciliation be prevented by adding glucose to the mucus after SARS-CoV-2 infection?
Does ACE2 as part of the local RAAS have a role in the regulation and chemical composition of the mucus, specifically ion flux, glucose metabolism, and cilia maintenance, and thereby contribute to olfactory dysfunction?
Can deciliated olfactory receptor neurons regrow cilia when they receive signals from regenerated support cells?
The odorant receptor mRNA as well as protein need to be quantified over the course of COVID-19 anosmia; do they correlate with anosmia and with the recovery of smell?
Besides odorant receptors, additional genes and proteins involved in olfactory signal transduction may contribute to anosmia in COVID-19. When such proteins are tracked and manipulated during COVID-19 anosmia, do they correlate and contribute to the cause of anosmia and the recovery of smell?
Can the change of gene expression in olfactory receptor neurons be explained, in part, by an increased fraction of immature neurons following death of mature neurons induced by infection and damage of support cells?
Does the timing of anosmia and smell recovery after anosmia correlate with loss and subsequent regeneration of sustentacular cells and Bowman gland cells?
What is the precise role of the putative host factor UGT2A1/A2 in COVID-19 anosmia?
Box 1. Lack of widespread anosmia in previous pandemics

Viral infections can cause temporary olfactory dysfunction due to swelling, rhinitis, and obstruction [15,122]. The COVID-19-induced loss of smell differs from common postviral dysfunctions due to its sudden onset, often complete loss of smell, usually short duration, and large numbers of patients affected. Much less olfactory dysfunction was caused by previous flu pandemics (Table I).

It was suggested that COVID-19 has similarities with the 1889 pandemic. The causative agent of the 1889 flu has not been established, unlike the H1N1 influenza pandemic from 1918 (D.A. Pettit, PhD thesis, University of New Hampshire, 1976) [123]. However, circumstantial evidence indicates that the 1889 pandemic may have been caused by a coronavirus. This is based on clinical parallels between COVID-19 and the 1889 pandemic: age risk curve, with older people more affected (unlike the H1N1 pandemic [3]); neurological symptoms; more males affected; pulmonary and cardiac conditions; obesity as a risk factor; multorgan thrombosis; gastrointestinal symptoms; and long-haulers [123,124]. Based on such similarities, together with genomic similarities between human coronavirus OC43 and bovine coronavirus [125], it was suggested that this pandemic was caused by a coronavirus similar to SARS-CoV-2 [123,124,126].

Among the shared clinical symptoms between COVID-19 and the 1889 pandemic, a frequent loss of smell and taste was emphasized [123,126]. However, the notion that anosmia was frequent in the 1889 pandemic is based on a misunderstanding of one of the transcribed sources ([4], see p. 133): the quoted author [127] in fact refers to a single case ([127], see p. 90). Importantly, in a text providing precise information on the prevalence of loss of smell and taste during the pandemic in Germany [4], it was documented that 20 out of 3042 reports (<1%) mentioned this symptom, prompting the authors to consider chemoosensory dysfunction among the ‘more rarely observed nerve symptoms’ ([4], see table in p. 100). Accordingly, one can conclude that loss of smell and taste was not a frequent symptom during the 1889 pandemic. This does not argue against the hypothesis that a coronavirus caused this pandemic, but whatever the virus was, it did not attack the sense of smell and taste to anywhere near the level that SARS-CoV-2 is able to.

In other reports of the 1889 pandemic, chemoosensory dysfunction was described to be part of a long-term sequel among long-haulers rather than being an acute symptom during the initial infection [128,129]. We conclude that the widespread olfactory dysfunction caused by SARS-CoV-2 is unique in its intensity and frequency and has no truly comparable precedent during the past 150 years.

Table I. Comparison of anosmia prevalence in previous pandemics

| Pandemic       | Years          | Virus       | Variant/Sequence | Anosmia (%) | Refs for anosmia prevalence |
|----------------|----------------|-------------|------------------|-------------|-----------------------------|
| Pandemic of 1889 | 1889-1892      | Corona?     | <1%              |             | [4]                         |
| Pandemic of 1918 | 1918-1920      | Influenza   | Not common       |             | [3]^                        |
| SARS           | 2002           | SARS-CoV-1  | <0.1%            |             | [5,6]                       |
| HCoV-NL63      | 2004           | Corona      | No reports found |             | N/A                         |
| MERS           | 2012           | Corona      | Not listed       |             | [7]                         |
| COVID-19       | 2019-2020      | SARS-CoV-2  | D614             | ~10%        | [37,38]                     |
|                | 2020-2021      |             | G614             | 30-50%      | [37,38,105]                 |
|                | 2021-?         |             | Omicron          | ~13%        | [105,107,109]               |

Abbreviations: D614, original SARS-CoV-2 (Wuhan) strain with an A nucleotide at position 614 of the spike; G614, SARS-CoV-2 variant with a G nucleotide at position 614 of the spike; MERS, Middle East Respiratory Syndrome; N/A, not applicable.  

[^]: D.A. Pettit, PhD thesis, University of New Hampshire, 1976 (https://scholars.unh.edu/dissertation/1145/).

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Declaration of interests

The authors declare no competing interests.

Resources

https://doh.wa.gov/sites/default/files/2022-02/420-316-SequencingAndVariantsReport.pdf
References

1. Dhruv, V. et al. (2021) Two worst pandemics—Spanish Flu and COVID-19: a review. Magna Sci. Adv. Biol. Pharm. 4, 1–12

2. Haehner, A. et al. (2022) SARS-CoV-2 leads to significantly more severe olfactory loss than other seasonal cold viruses. Life (Basel) 12, 461

3. Edwards, S.N. (2022) Understanding the present through the past: a comparison of Spanish news coverage of the 1918 flu and COVID-19 pandemics. J. Mass. Commun. Q. 99, 12–43

4. Leyden, E. and Gutmann, S., eds (1892) Aufsage des Vereins für Innere Medizin in Berlin, Verlag J.F. Bergmann

5. Hwang, C.S. (2006) Olfactory neuropathy in severe acute respiratory syndrome (SARS). SN Compr. Clin. Med. 2, 4–8

6. Leyden, E. and Guttmann, S., eds (1892)

7. Edwards, S.N. (2022) Understanding the present through the past: a comparison of Spanish news coverage of the 1918 flu and COVID-19 pandemics. J. Mass. Commun. Q. 99, 12–43

8. Leyden, E. and Gutmann, S., eds (1892)

9. Hwang, C.S. (2006) Olfactory neuropathy in severe acute respiratory syndrome (SARS). SN Compr. Clin. Med. 2, 4–8

10. Cooper, K.W. (2022) Postmortem assessment of olfactory tissue degeneration and microvascularopathy in patients with COVID-19. JAMA Neurol. 79, 544–553

11. Mutiawati, E. et al. (2021) Olfactory training for olfactory neuron and its cilia.

12. Ojha, P. and Dixit, A. (2022) Olfactory training for olfactory neuron and its cilia.

13. Liang, F. and Wang, Y. (2021) COVID-19 anosmia: high prevalence, but spares the olfactory bulb. Cell 184, 5932–5949

14. Xydakis, M.S.

15. Zugaj, M.

16. Ojha, P. and Dixit, A. (2022) Olfactory training for olfactory neuron and its cilia.

17. Mutiawati, E. et al. (2021) Olfactory training for olfactory neuron and its cilia.

18. Liang, F. and Wang, Y. (2021) COVID-19 anosmia: high prevalence, but spares the olfactory bulb. Cell 184, 5932–5949

19. Butowt, R. and van Bartheld, C.S. (2021) Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. Neurosci. Lett. 618, 582–603

20. Keshavarz, P.

21. Karimian, A.

22. Butowt, R. and van Bartheld, C.S. (2021) Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. Neurosci. Lett. 618, 582–603

23. Butowt, R. and van Bartheld, C.S. (2021) Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. Neurosci. Lett. 618, 582–603

24. Khan, M. et al. (2021) Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosaes but spares the olfactory bulb. Cell 184, 5932–5949

25. Chen, M. et al. (2022) Evolution of nasal and olfactory infection characteristics of SARS-CoV-2 variants. bioRxiv Published online on April 12, 2022. https://doi.org/10.1101/2022.04.12.487379

26. Dolgin, E. (2022) The science behind COVID’s assault on smell. Nature 595, 55–56

27. Breyne, B. et al. (2020) Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. Brain Behav. Immun. 89, 579–586

28. Kishimoto-Urata, M. et al. (2022) Prolonged and extended impacts of SARS-CoV-2 on the olfactory neurocircuit. Sci. Rep. 12, 5728

29. Harding, J.W. et al. (1978) Derivation of the primary olfactory pathway in mice. V. Long-term effect of intranasal ZnSO4 irrigation on behavior, biochemistry and morphology. Brain Res. 140, 271–285

30. Youngentob, S.L. et al. (1997) Odorant threshold following methyl bromide-induced lesions of the olfactory epithelium. Physiol. Behav. 62, 1241–1252

31. Fishechmann, A. et al. (2008) Mice with a ‘monocular nose’: perturbations in an olfactory map impair odor discrimination. Neuron 60, 1069–1081

32. Ho, C.Y. et al. (2022) Postmortem assessment of olfactory tissue degeneration and microvascularopathy in patients with COVID-19. JAMA Neurol. 79, 544–553

33. Spudich, S. and Nath, A. (2022) Nervous system consequences of COVID-19. Science 375, 267–269

34. Lee, Y. et al. (2022) Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J. Korean Med. Sci. 35, e174

35. Luchin, J.R. et al. (2020) Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur. Arch. Otohnsiaryngol. 277, 2251–2261

36. Killingley, B. et al. (2022) Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. Nat. Med. 28, 1031–1041

37. von Bartheld, C.S. et al. (2022) Prevalence of chemosensory dysfunction in COVID-19 patients: a systematic review and meta-analysis reveals significant ethnic differences. ACS Chem. Neurosci. 11, 2944–2961

38. von Bartheld, C.S. et al. (2021) The D614G virus mutation enhances anosmia in COVID-19 patients: evidence from a systematic review and meta-analysis of studies from South Asia. ACS Chem. Neurosci. 12, 3535–3549

39. Evans, J.E. et al. (1995) Behavioral, histological, and neurochemical effects of nile (4) on the rat olfactory system. Toxicol. Appl. Pharmacol. 130, 209–220

40. Brann, J.H. and Freston, S.J. (2014) A lifetime of neurogenesis. In The olfactory system in humans and animal models. Acta Neuropathol. 128, 6, eabc5901

41. Keshavarz, P.

42. Schwob, J.E. et al. (1995) Reconstitution of the rat olfactory epithelium after methyl bromide-induced lesion. J. Comp. Neurol. 359, 15–37

43. Schwob, J.E. (2006) Neural regeneration and the peripheral olfactory system. Anat. Rec. 296, 33–49

44. Schwob, J.E. and Jiang, W. (2006) Stem cells of the adult olfactory epithelium. In Olfactory Development and Stem Cell (2nd edn) (Rao, M.S., ed.), pp. 219–233, Humana Press

45. McClintock, T.S. et al. (2020) Maturation of the olfactory sensory neuron and its cilia. Chem. Senses 45, 405–422

46. Konoko, K. et al. (2013) Age-related changes in cell dynamics of the postnatal mouse olfactory neuroepithelium: cell proliferation, neuronal differentiation, and cell death. J. Comp. Neurol. 518, 1962–1975

47. Libera, T. et al. (2019) Sequential maturation of olfactory sensory neurons in the mature olfactory epithelium. eNeuro 6 E1061–0619.2019

48. Bilinska, K. et al. (2020) Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: identification of cell types and trends with age. ACS Chem. Neurosci. 11, 1565–1562
49. Klingenstein, M. et al. (2020) Evidence of SARS-CoV2 entry protein ACE2 in the human nose and olfactory bulb. Cells Tissues Organs 209, 165–164
50. Chen, M. et al. (2020) Elevated ACE-2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. Eur. Respir. J. 56, 2001648
51. de Mello, G.D. et al. (2021) COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. Sci. Transl. Med. 13, eabi936
52. Ye, Q. et al. (2021) SARS-CoV-2 infection in the mouse olfactory system. Cell Discov. 7, 49
53. Nagashima, A. and Touhara, K. (2010) Enzymatic conversion of extracellular glucose. FEBS Lett. 580, 601–610
54. Villar, P.S. et al. (2021) Energy requirements of odor transduction in the chemosensory cilia of olfactory sensory neurons rely on oxidative phosphorylation and glycolytic processing of extracellular glucose. J. Neurosci. 37, 5736–5743
55. Anzalone, C. et al. (2019) Possible ATP trafficking by ATP-shuttles in the olfactory cilia and glucose transfer across the olfactory mucosa. FEBS Lett. 590, 3799–3812
56. Luchini, H.R. et al. (2021) Does the RAAS play a role in loss of taste and smell during COVID-19 infections? Pharmacogenom. J. 21, 109–115
57. Krishnan, S. et al. (2021) Metabolic perturbation associated with COVID-19 disease severity and SARS-CoV-2 replication. Mol. Cell. Proteomics 20, 100159
58. Baxter, B.D. et al. (2021) Transcriptomic profiling reveals potential involvement of microvillus TRPM5-expressing cells in viral infection of the olfactory epithelium. BMC Genomics 22, 224
59. Kraus, A. et al. (2022) Intranasal delivery of SARS-CoV-2 spike protein is sufficient to cause olfactory damage, inflammation and olfactory dysfunction in zebrafish. Brain Behav. Immun. 102, 341–359
60. Lee, K.P. et al. (1992) Nasal lesion development and reversibility in rats exposed to aerosols of dibasic esters. Toxicol. Pathol. 20, 378–393
61. Bergström, U. et al. (2003) Methimazole-induced damage in the olfactory mucosa: effects on ultrastructure and glutathione levels. Toxicol. Pathol. 31, 257–267
62. Jia, C. et al. (2010) Nickel sulfate induces location-dependent atrophy of mouse olfactory epithelium: protective and proliferative role of purinergic receptor activation. Toxicol. Sci. 115, 547–558
63. Morrison, E.E. and Costanzo, R.M. (1990) Morphology of the human olfactory epithelium. J. Comp. Neurol. 297, 1–13
64. Chock, S.P. et al. (2014) Switching on cilia: transcriptional networks regulating ciliaogenesis. Development 141, 1427–1441
65. Nickels, M.D. et al. (2017) Genomics of mature and immature olfactory sensory neurons. J. Neurosci. 500, 2608–2629
66. Saravia, L.R. et al. (2015) Hierarchical deconstruction of mouse olfactory sensory neurons: from whole mucosa to single-cell RNA-seq. Sci. Rep. 5, 16178
67. Larson, E.D. et al. (2019) A subset of olfactory sensory neurons express forkhead box J1-driven eGFP. Chem. Senses 44, 665–671
68. Robinot, N. et al. (2021) SARS-CoV-2 infection induces the differentiation of multi-labeled cells and impairs mucociliary clearance. Nat. Commun. 12, 4354
69. Schreiner, T. et al. (2022) SARS-CoV-2 infection dysregulates cilia and basal cell homeostasis in the respiratory epithelium of hamsters. Int. J. Mol. Sci. 23, 5124
70. Zhang, A.J. et al. (2021) Severe acute respiratory syndrome coronavirus 2 infects and damages the mature and immature olfactory sensory neurons of hamsters. Clin. Infect. Dis. 73, e503–e512
71. Reyna, R.A. et al. (2022) Recovery of anosmia in hamsters infected with SARS-CoV-2 is correlated with repair of the olfactory epithelium. Sci. Rep. 12, 628
72. Pozharskaya, T. and Lane, A.P. (2013) Interferon gamma causes olfactory dysfunction without concomitant neuroepithelial damage. Int. Forum Allergy Rhinol. 3, 861–866
73. Avnat, E. et al. (2022) Elevated expression of RG52 may underlie reduced olfaction in COVID-19 patients. J. Pers. Med. 12, 1590
74. Majda, S. and Compton, A.A. (2021) Lessons in self-defense: inhibition of virus entry by intrinsic immunity. Nat. Rev. Immunol. 13, 1–14
75. Jackson, C.B. et al. (2022) Mechanisms of SARS-CoV-2 entry into cells. Nat. Rev. Mol. Cell. Biol. 23, 3–20
76. Meng, B. et al. (2022) Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts tropism and fusogenicity. Nature 603, 706–714
77. Chopp, G. et al. (2022) A phase 2 randomized, double-blind, placebo-controlled trial of oral cannabidiol for early treatment of COVID-19 outpatients showed shorter illness course and attenuation of loss of smell and taste. medRxiv Published online January 21, 2022, https://doi.org/10.1101/2022.01.28. 22270305
78. Henkin, R.I. et al. (2013) Interleukin 6 in hypersomnia. JAMA Otolaryngol. Head Neck Surg. 139, 728–734
79. Cazzolla, A. et al. (2022) Taste and smell disorders in COVID-19 patients: role of interleukin-6. ACS Chem. Neurosci. 11, 2774–2781
80. Torsbi, A. et al. (2020) Proinflammatory cytokines in the olfactory mucosa result in COVID-19 induced anosmia. ACS Chem. Neurosci. 11, 1909–1913
81. Sanii, D.E.T. et al. (2021) Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. Am. J. Otalaryngol. 43, 102796
82. Frances, A. et al. (2017) Daily oscillation of odorant detection in rat olfactory epithelium. Eur. J. Neurosci. 45, 1613–1622
83. Zhang, Z. et al. (2017) Detection of type 3 adenylyl cyclase perturbs the postnatal maturation of olfactory sensory neurons and olfactory cilium ultrastructure in mice. Front. Cell. Neurosci. 11, 1
84. McClinchey, T.S. and Sammata, N. (2005) Trafficking prerequisites of olfactory receptors. Neuron 41, 1547–1552
85. Mori, I. et al. (2002) Olfactory receptor neurons prevent dissemination of neuroinfluenza A virus into the brain by undergoing virus-induced apoptosis. J. Gen. Virol. 83, 2109–2116
86. van Rooi, D. et al. (2019) The olfactory nerve: a shortcut for in flammation reveals reversible functional impairment associated with viral persistence and in parametric cure modelling of recovery curves. BMJ 365, l5002
87. Bon, S.D. and Horoi, M. (2020) Is anosmia the price to pay in an immune-induced scorched-earth policy against COVID-19? Trends in Neurosciences, January 2023, Vol. 46, No. 189
97. Pierna, V. et al. (2020) More than smell-COVID-19 is associated with severe impairment of smell, taste, and chemesthesia. Chem. Senses 45, 609–622
98. Raad, N. et al. (2021) Parosmia in patients with COVID-19 and olfactory dysfunction. Int. Forum Allergy Rhinol. 11, 1497–1500
99. Gurrola, J.G., 2nd et al. (2021) Short-term chemosensory distortions and phantoms in COVID-19. Laryngoscope Investig. Otolaryngol. 6, 172–176
100. Nordin, S. et al. (2007) Prevalence of parosmia: the Skövde population-based study. Rhinology 45, 50–53
101. Lemer, D.K. et al. (2022) Clinical features of parosmia associated with COVID-19 infection. Laryngoscope 132, 633–639
102. Ohia, K. et al. (2022) A follow-up on quantitative and qualitative olfactory dysfunction and other symptoms in patients recovering from COVID-19 smell loss. Rhinology 60, 207–217
103. Parker, J.K. et al. (2022) Insights into the molecular triggers of parosmia based on gas chromatography olfactometry. Commun. Med. (Lond). 2, 50
104. Korber, B. et al. (2020) Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 182, 812–827
105. Butowt, R. et al. (2022) Why does the omicron variant largely spare olfactory function? Implications for the pathogenesis of anosmia in COVID-19. J. infect. Dis. 226, 1304–1308
106. Rodriguez-Serrilla, J.J. et al. (2022) Is there less alteration of smell sensation in patients with omicron SARS-CoV-2 variant infection? Front. Med. 9, 852998
107. Menni, C. et al. (2022) Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2: a prospective observational study from the ZOE COVID Study. Lancet 399, 1618–1624
108. Whitaker, M. et al. (2022) Variant-specific symptoms of COVID-19 among 1,542,510 people in England. medRxiv Published online May 23, 2022. https://doi.org/10.1101/2022.05.21.22275368
109. Vihta, K.D. et al. (2022) Omicron-associated changes in SARS-CoV-2 symptoms in the United Kingdom. Clin. Infect. Dis. Published online August 3, 2022. https://doi.org/10.1093/cid/ciaa013
110. Zhang, J. et al. (2022) Structural and functional impact by SARS-CoV-2 Omicron spike mutations. Cell Rep. 39, 110729
111. Peacock, T.P. et al. (2022) The altered entry pathway and antigenic distance of the SARS-CoV-2 Omicron variant map to separate domains of spike protein. bioRxiv Published online May 13, 2022. https://doi.org/10.1101/2021.12.31.474603
112. Armando, F. et al. (2022) SARS-CoV-2 Omicron variant causes mild pathology in the upper and lower respiratory tract of hamsters. Nat. Commun. 13, 3519
113. Butowt, R. et al. (2020) Chemosensory dysfunction in COVID-19: integration of genetic and epidemiological data points to D614G spike protein variant as a contributing factor. ACS Chem. Neurosci. 11, 3190–3194
114. Hashizume, M. et al. (2021) Population-specific ACE2 single-nucleotide polymorphisms have limited impact on SARS-CoV-2 infectivity in vitro. Viruses 13, 67
115. Braga-Paz, L. et al. (2022) Negative correlation between ACE2 gene expression levels and loss of taste in a cohort of COVID-19 hospitalised patients: new clues to long-term cognitive disorders. Front. Cell. infect. Microbiol. 12, 90577
116. Shelton, J.F. et al. (2022) The UGT2A1/UGT2A2 locus is associated with COVID-19-related loss of smell or taste. Nat. Genet. 54, 121–124
117. Getchell, T.V. et al. (1984) Perireceptor and receptor events in vertebrate olfaction. Prog. Neurobiol. 23, 317–345
118. Heydel, J.M. et al. (2013) Odorant-binding proteins and xenobiotic metabolizing enzymes: implications in olfactory perireceptor events. Anat. Rec. (Hoboken) 296, 1333–1345
119. Strotmann, J. and Breer, H. (2011) Internalization of odorant-binding proteins into the mouse olfactory epithelium. Histochem. Cell Biol. 136, 357–369
120. Al-Ami, R.M. and Acharya, D. (2020) Prevalence of anosmia and ageusia in patients with COVID-19 at a primary health center, Doha, Qatar. Indian J. Otolaryngol. Head Neck Surg. Published online August 19, 2020. https://doi.org/10.1007/s12070-020-02064-9
121. Zayet, S. et al. (2020) Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes Infect. 22, 481–488
122. Hummel, T. et al. (2016) Position paper on olfactory dysfunction. Rhinology 56, 1–30
123. Brüssow, H. and Brüssow, L. (2021) Clinical evidence that the pandemic from 1889 to 1891 commonly called the Russian flu might have been an earlier coronavirus pandemic. Microb. Biotechnol. 14, 1860–1870
124. Erikköla, A. et al. (2022) Coronavirus as the possible causative agent of the 1889–1894 pandemic. Infect. Dis. Rep. 14, 453–469
125. Vigen, L. et al. (2022) Complete genomic sequence of human coronavirus OC43: molecular clock analysis suggests a relatively recent zoonotic coronavirus transmission event. J. Virol. 79, 1595–1604
126. Ramasy, L. et al. (2022) Paleoserology points to Coronavirus as possible causative pathogens of the ‘Russian flu’. Microb. Biotechnol. 15, 1943–1945
127. Habermann, J. (1890) Zur Erkrankung des Ohres bei Influenza. Br. Med. J. 1, 355–367
128. Anonymous (1892) The influenza epidemic. Br. Med. J. 1, 355–367
129. Dowse, T.S. (1894) On Brain and Nerve Exhaustion (Neurasthenia); and on the Nervous Sequelae of Influenza, Bailliere, Tindall and Cox