released from the injured neurons (11) (Figure 1C). The increase in nasal NO levels during the recovery phase from rhinitis-induced inflammation and anosmia is already well evident (2); I believe this can secondarily be due to the normalization of tryptophan catabolism. Overall, the high nasal NO levels should not be considered as a simple marker of persistent inflammation and a risk factor for CRS in patients recovering from COVID-19–induced anosmia.

In conclusion, the proposed hypothesis explains why patients with COVID-19 with anosmia develop less severe disease than those with preserved olfaction and why higher nasal NO levels were evident in patients with COVID-19 after recovery of anosmia (1). I believe measuring the levels of nasal NO in patients with COVID-19 during the acute phase of anosmia and in patients with postacute COVID-19 syndrome with persistent anosmia could provide further understanding about the olfactory–nasal NO link in COVID-19. ■

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Reply to Jain

From the Authors:

We thank Dr. Amit Jain for his interesting hypothetical explanation of the persistently high levels of nasal nitric oxide (NO) in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and having coronavirus disease (COVID-19)–associated anosmia as compared with patients without anosmia (1). We agree with Dr. Jain that IFN-induced increase of indoleamine 2,3-dioxygenase (IDO) activity can divert tryptophan catabolism toward the kynurenine pathways in the nasal epithelium. We also concur that the resulting rise in 3-hydroxykynurenine levels could directly cause neuronal injury leading to anosmia in some patients with COVID-19. As increased IDO activity may adversely affect NO synthesis (2), Dr. Jain has proposed an alternate explanation suggesting that nasal NO is reduced during the acute phase of anosmia, and its high levels evidenced in our study (1) could be viewed as a sign of recovery from the initial neuronal injury rather than a biological proof of persistent inflammation.

Although we fully acknowledge the plausibility of Dr. Jain's interesting hypothesis, we also would like to seize this opportunity to broaden the discussion to another key player of the NO pathways, namely, the neuronal NO synthase (NOS). The gas NO stemming from the upper airways can be synthesized from three different NOS isoforms, that is, the inducible, endothelial, and neuronal NOS (3). Although inducible NOS plays a pivotal role in innate and adaptive immunity (4), neuronal NOS localized in the upper airways critically regulates NO levels to maintain normal cilia (5) and olfactory (6) functions in humans. All three NOS isoforms are highly regulated heme-thiolate proteins (7) whose enzymatic activities can be inhibited by large amounts of NO acting as a negative feedback loop on NO synthesis (8). One possible alternate explanation for our findings of high levels of nasal NO 5 months after acute anosmia (1) could be the differential implications of inducible and neuronal NOS over the time course of SARS-CoV-2 infection. During the acute phase, activation of the inducible NOS would lead to marked increase in NO synthesis, which, in turn, inhibits neuronal NOS activity and causes anosmia. Inhibition of neuronal NOS progressively wears off with reduced activity of inducible NOS, enabling olfaction

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recovery. The only way to prove this hypothesis would be measurement of nasal NO during the acute phase of COVID-19 and histopathological proofs of various NOS expression in the patients' nasal mucosa over the time course of the disease and its recovery. To conclude, we thank Dr. Jain for this opportunity to further discuss the various mechanisms underlying our initial findings (1), and we agree that measurement of nasal NO in patients with COVID-19 warrants further investigations to decipher the complex underlying mechanisms of SARS-CoV-2–induced anosmia and its recovery. ■

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