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Dear Editor:

We are grateful for the research report contributed by Pauna et al. titled “Evidence Against the Mucosal Traction Theory in Cholesteatoma,” which commented upon our 2015 paper published in The Laryngoscope titled “A New Theory on the Pathogenesis of Acquired Cholesteatoma,” which postulated that mucosal interactions may underlie cholesteatoma formation. We enthusiastically welcome experimental evaluation of our theory to help determine whether or not it is valid. The authors have contributed a well-executed study evaluating the density and distribution of ciliated mucosa middle ear cleft in archived human temporal bone specimens in a variety of pathological conditions including cholesteatoma and chronic otitis media. The authors concluded, “[t]he paucity of ciliated epithelial cells on the medial side of the tympanic membrane and the lateral surface of the ossicles in the epitympanum in cases with cholesteatoma and/or chronic otitis media do not support the mucosal migration theory of cholesteatoma formation.” Although their findings are both relevant and of interest, we do not agree with the conclusions they drew from their observations.

Our mucosal traction theory postulates that interactions between the opposing mucosal surfaces redundant of the tympanic membrane with the lateral surface of the ossicles may propel cholesteatoma pouch formation. We considered three possible drivers of mucosal traction: mucous blanket migration, mucosal epithelial migration, and sequential adhesion of opposing surfaces. The study of Pauna et al. has relevance to only one of these postulated mechanisms: the dynamics of the mucous blanket motility.

The density of ciliated cells varies widely among airway tracts lined with respiratory epithelium. In the nose, where the mucosa is exposed continuously to environmental air, 20% to 50% of epithelial cells are ciliated. The paranasal sinuses, with less air flow, have cilia concentrated in proximity to their ostia. In the middle ear and mastoid, which are exposed to intermittent low-volume flows of filtered air, almost all of their cilia are concentrated in proximity to the eustachian tube (ET). Thus, the middle ear and mastoid are analogous to the paranasal sinuses in that cilia are richest on pathways converging on a narrow drainage tract, with mucous blanket flow from the walls of the cavity often swept against gravity.

The mucosal envelope of the middle ear has been shown to have robust mucociliary clearance, which rapidly expels secreted material from the tympanum. The anterior two-thirds of the middle ear have the most active clearance. In a human endoscopic study of mucous blanket migration in the middle ear observed during stapes surgery, the rate of mucociliary transport on the promontory was 1 to 1.5 mm/sec. There was intersubject variability of which pathways were dominant, but when a single route predominated, the epitypanic route toward the ET was the most common.

Even though the mucosa of the posterior middle ear and mastoid are depleted of cilia, they still possess a moist mucous blanket lining their aerated cavities that, if obstructed, fill with secretions. Without a mechanism for migration, mucous would desiccate, thicken, and be prone to infection. Despite the paucity of cilia, the mucous blanket of the posterior middle ear and mastoid is in continuous motion toward the tubal orifice, albeit at varying velocities. Although gravity may play a role, it seems more likely that the ciliated mucosal tracts proximate to the ET pull upon the viscoelastic blanket, much as pulling on the corner of a large rug moves its entire fabric. Hence, an acceleration of the peritubal ciliary beat in response to a noxious stimuli (e.g., infection) could exert a force upon the mucous blanket on the medial surface of the pars flaccida even though it possesses only a modest population of cilia.

Based upon the Pauna et al. study, it is possible that variations in the number of cilia and the vigor of mucociliary transport may be biphasic, accelerated during acute infection and decelerated in the chronic phase. A limitation of studying human temporal bone specimens is that it records the status of the middle ear at the time of death, not necessarily during the critical initial period of cholesteatoma pouch formation. Experimental evidence reveals that cilia may proliferate and become more active in response to noxious stimuli. Hermansson et al. reported that in experimentally induced pneumococcal otitis media in rats, “[t]he normally flat epithelium had become more cuboidal or cylindrical, and numerous ciliated cells occurred in areas originally devoid of these cells.” Importantly, the otitis-induced cilia persist at least 2 months after the infection. In an
investigation by Grote et al., also in rats, which showed similar findings, the authors report that “[a]fter the onset of a S. aureus infection, the number of ciliated and secretory cells increased first and most prominently in the pars flaccida, but also in the superior part of the annular region of the pars tensa.”

The effect upon cilia in acute otitis may be pathogen specific. A rat study with Haemophilus influenzae type B showed initially depleted cilia, whereas at 7 days the pars flaccida was thickened and possessed ciliated cells.

The Pauna et al. study confirmed the presence of a small population of cilia on the medial surface of the tympanic membrane as well as on the ossicles, a finding that has been inconsistently observed in earlier studies. Although the paucity of cilia on mucosa of the tympanic membrane and ossicular chain in temporal bone studies of cholesteatoma is informative, we continue to believe that mucous blanket migration of coapted mucosal surfaces may play a role in cholesteatoma pouch formation. It may also be predicted that the cilia count may be less after the acute phase once the mucosal layers have coapted. We do think that the finding of decreased numbers of mucosal cilia in cholesteatoma and chronic otitis media described in the Pauna et al. study makes an important contribution in that long-term mucosal metaplasia does not appear to play a role in cholesteatoma progression. Nevertheless, as we have explained above, a paucity of cilia in the chronic phase does not exclude dynamic mucosal interaction.

Two other mucosally based mechanisms not addressed in the Pauna et al. study need to be explored further. One is stasis and desiccation with sequential adhesion of opposing mucosal surfaces. Another is migration of the mucosal epithelium itself, as opposed to its mucous blanket, which occurs physiologically as well as in response to injury. Infections in the upper airway with virus or bacteria often lead to necrosis and sloughing of mucosa. Re-epithelialization progresses via vigorous cellular migration and proliferation from adjacent intact mucosa.

Established theories of cholesteatoma formation have all focused on the role of the squamous epithelium. The widely cited obstruction-vacuum theory does not explain many attributes of acquired cholesteatoma. Why, if cholesteatoma formation is driven by squamous proliferation, do they arise exclusively in proximity to the ossicles and not from the anterior and inferior portions of the tympanic membrane? How is a pouch drawn into a fluid-filled mastoid if not by vacuum? Why do tympanostomy tubes not prevent cholesteatoma or its recurrence? Why does anatomical closure of the ET not lead to cholesteatoma? Why does the ET often appear normal in cholesteatoma?

We continue to believe that mucosal traction remains a plausible mechanism for cholesteatoma formation and that, on a theoretical basis, it better explains the observed properties of the disease than earlier theories. We wholeheartedly welcome experimental efforts to clarify the pathophysiology of cholesteatoma such as that undertaken by Pauna and colleagues.

**Bibliography**