MUCOCILIARY CLEARANCE plays a crucial host-defense role in both the upper and lower airways, providing protection from a wide variety of airborne hazards including allergens, pathogens, and environmental toxins. Proper function of the mucociliary clearance system depends on the structure and function of the cilia as well as the composition of the airway surface liquid layer. The mucus component of this layer forms a protective netting that entraps deposited materials while a more aqueous layer underneath it facilitates the transport of the entire layer by the cilia. In healthy airways this system has been shown to be adaptive to changes in environment and very effective as a host defense under a variety of insults. However, defects in the system can quickly result in secondary disease in both the upper and lower airways. For example, rhinosinusitis and otitis media are typically reported in patients with primary ciliary dyskinesia along with increases in cough and pulmonary infection (8). Dehydration of the airway surface liquid layer is thought to contribute to impaired mucociliary clearance in cystic fibrosis, which manifests with both pulmonary and sinonasal disease (2, 6). Deficient mucociliary clearance may also play a role in more common disorders such as chronic rhinosinusitus (4, 10). Both ciliary and mucoviscous dysfunction have been implicated with the result being a pattern of immobile secretions, infection, and inflammation in the nose (3).

Clinical study methods have been used for some time to assess mucociliary clearance in the nose. These include saccharine or dye testing and imaging using radiopharmaceutical tracers. In vitro models have typically considered specific components of the mucociliary clearance system using cell cultures or ex vivo airway samples, rather than modeling the system as a whole (1). In a study in this issue of the Journal of Applied Physiology, Hua et al. (7) present a detailed description of a radiopharmaceutical imaging method for studying nasal mucociliary clearance in the mouse. Their method provides a means of assessing systemic function of the nasal mucociliary clearance system in real time and may allow for the study of specific genetic factors related to mucociliary clearance or upper airways disease. The method is also nonlethal, offering the potential for crossover study. It utilizes cannulated delivery of technetium-99m-labeled sulfur colloid (Tc-SC) into the nostrils. Tc-SC is a submicron-sized, radio-labeled particulate often used to assess pulmonary mucociliary clearance. After delivery of the tracer, clearance is externally imaged using a pinhole gamma camera. The images presented by the authors (see Fig. 1 of Ref. 7) demonstrate rapidly assessable movement of the tracer between two distinct locations on the images, one associated with the nostril and the other associated with the oropharynx of the animal. Interestingly the clearance of material from one location to the other occurred in two distinct phases. Two-phase clearance is often reported in studies of pulmonary mucociliary clearance in human subjects. In those studies the tracer is typically delivered as an inhaled aerosol, and the distinct “fast” and “slow” phases have been associated with the deposition of the aerosol in the well-ciliated large airways vs. the less-ciliated small airways or nonciliated alveoli. A two-phase pattern noted here in the nasopharynx brings this explanation somewhat into question. The authors propose that this two-phase clearance in the mouse nose may be the result of varying mucus rheology at different sites on the epithelium, or possibly by tracer material being deposited onto both respiratory and nonrespiratory (specifically olfactory) epithelium. In the study, the authors also demonstrate a transient response to 10% hypertonic saline. Osmotics like hypertonic saline are known to increase water content in the airway surface liquid layer, which in turn increases the mucociliary clearance rate. Isotonic saline did not prompt an increase in mucociliary clearance, indicating that the osmotic properties of the 10% solution caused the increased clearance rates noted and that the effect was not simply caused by hydration of the nasopharynx.

One potential limitation of the present method and likely any similar imaging method involving a small animal model is the need for anesthesia. Volatile anesthetics have been shown to slow ciliary beat frequency in vitro (9). As an element of method development, the authors (7) tested the effect of several different anesthetics on nasal mucociliary clearance, specifically pentobarbital, avertin, and different concentrations of isoflurane. Both pentobarbital and avertin significantly depressed clearance when compared with 1.1% isoflurane, which the authors suggest for this application. Another potential limitation, particularly with respect to transferability of the technique, is the skill required to deliver the technetium-99m tracer into the mouse nostril in a repeatable manner. Without proper placement, the distinct transit of the tracer reported by the authors may not be exhibited and the technique may yield less consistent results.

Measurements of pulmonary mucociliary clearance in human subjects using similar radiopharmaceutical methods have proven valuable in the development of therapies for cystic fibrosis. Large animal and more recent murine methods for measuring pulmonary clearance have proven useful for studies of lower airway physiology (5). The work by Hua et al. (7) demonstrates that radiopharmaceutical imaging can be performed within the small confines of the mouse nose using relatively accessible imaging equipment (pinhole gamma scintigraphy). The authors have demonstrated a palpable response to an intervention known to increase mucociliary clearance (hypertonic saline) and suggested a protocol for anesthesia that appears to provide a consistent starting point for study. Epithelial differences or differences in the physical properties of the nasal mucus could affect the measurements provided by this method, and therefore careful studies will be required when transferring this method to murine models of upper airway disease. Ultimately this method may help to determine

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the causes of depressed clearance in the nose and also the role of mucociliary clearance in the development of chronic sinusitis and other upper airways diseases. It may also have important applications in environmental health and toxicology studies where mucociliary clearance is an important element of host defense. Newer imaging technologies such as micro-CT-SPECT might allow for extension of the technique, providing information on the local effects of an anatomy and an even clearer picture of the physiology of clearance.

REFERENCES