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Turning the Lungs Inside Out: The Intersecting Microbiomes of the Lungs and the Built Environment

Ignore the protestations of our colleagues in gastroenterology: when it comes to surface area, the lungs beat the gut. While out-of-date textbooks claim that the gut lumen has a surface area comparable to that of a tennis court (260 m^2), some brave heretics recently used modern morphometric methods to show that prior estimates were greatly exaggerated (1). In the authors' words: "the total area of the human adult gut mucosa is not in the order of [a] tennis lawn, rather is that of half a badminton court": a modest 32 m^2 (Figure 1). In contrast, no one has dared challenge Philip Hasleton's 1972 estimate of the internal surface area of human lungs, 70 m^2, roughly that of a racquetball court (2). When it comes to surface area, the lungs take the prize at twice that of the gut and 30 times that of the skin. (Dermatologists have recently attempted to assert the supremacy of the skin by counting *intrafollicular* surface area (3), yet even this estimate is still only 25 m^2, merely one-third of a pickleball court.)

This vast surface area is also far more exposed to the outside environment than is the gut. To reach the lower gut lumen, ambitious microbes must traverse 6 m of bowel, enduring acidic and enzymatic assault, finally penetrating a thick, protective mucous layer. By contrast, no physical barrier (other than the intermittently closed larynx) separates the most distant alveoli from the outside environment, a mere half-meter away. Each day, the lungs are barraged by 7,000 L of air and all it contains. If your interest is the interface between the body and its environment, the lungs are where the action is.

It is fitting, then, that both sides of this interface—the lungs and the outside environment—have enjoyed recent revolutions in our microbiologic understanding. In the past decade, study of the lung microbiome has revealed that the lungs, long considered sterile, harbor diverse and dynamic communities of bacteria (4, 5), altered in disease (6–9), correlated with alveolar immunity (5, 10), predictive of clinical outcomes (6–8), and participating in pathogenesis (8, 11). Meanwhile, similar techniques interrogating "the microbiome of the built environment" have demonstrated that our residences, hospitals, and places of work have their own unique microbial communities. These environmental microbiomes are influenced by geography, season, outside air, building ventilation, and the animals and humans that inhabit the space (12, 13). The environmental microbiome contributes to the skin, nasal, and oral microbiota of its occupants (14, 15) and has been correlated with differences in health outcomes, including respiratory disease (16). Surprisingly, these fields have not yet intersected. We know next to nothing about whether and how the microbiota of our inhabited spaces influence the microbiota of our lungs.

In this issue of the *Journal*, Wu and colleagues (pp. 1678–1688) perform a remarkable double feat (17). First, they use microbiome methods to answer questions of pathogenesis in a rare occupational lung disease characterized by bronchiolitis, alveolar ductitis, and emphysema with B-cell primary lymphoid follicles (BADE) among patients exposed to metalworking fluids. Second, they provide the first evidence in humans that the microbiome of one's environment can seed and shape the lung microbiome.

The authors discovered that the lung microbiome in patients with BADE is distinct from that of matched BADE-free subjects, more closely resembling microbial communities detected in on-site metalworking fluid. To hone in on a microbial culprit, they used whole genome sequencing to show that BADE-associated bacteria in the lungs are genetically identical to *Pseudomonas pseudoalcaligenes*, a bacterial species known to dominate metalworking fluid, both in the literature (18) and in the facility in which the patients with BADE worked. Lastly, they established *in vitro* evidence of biologic plausibility by showing that B-cells (implicated in BADE) proliferate and are activated by in-use metalworking fluid. Together, these data link BADE not only to metalworking fluid but also the microbiota that inhabit it.

In addition to advancing our understanding of BADE, this study represents a step forward in our ecologic understanding of the human lung microbiome. Prior experimental work has demonstrated that manipulation of the environment can alter lung microbiota in mice and horses (10, 19), supporting our intuition that lung microbiota should reflect their outside environment. The current study takes the vital next step of testing this association in humans, using an impressive and exhaustive sampling strategy. To characterize the environment, they sampled microbiota from various types of metalworking fluid and air throughout the facility. Using these environmental taxa as a candidate "source community," they showed that the microbiome of the skin and nares of workers with close contact to metalworking fluid differed from those of more remote coworkers. Workers' physical proximity to metalworking fluid correlated with enrichment of the skin, nose, and lung microbiota with metalworking fluid–associated taxa.

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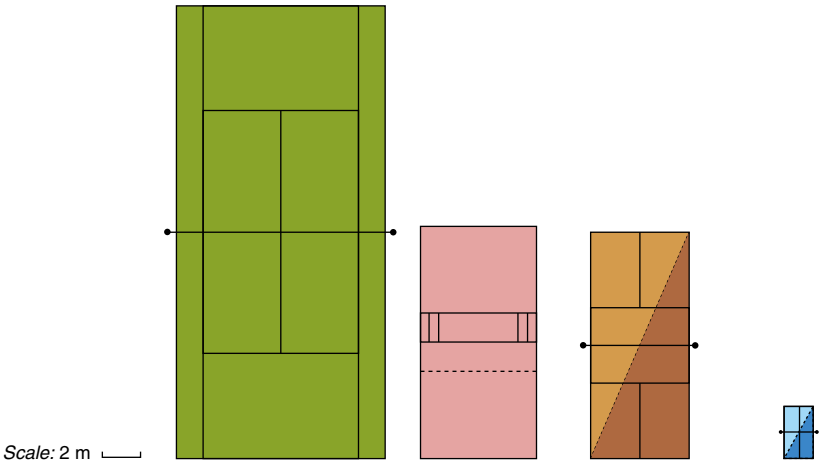

Organ	Apocryphal Gut	Lungs	Actual Gut	Skin
Surface Area	260 m^2	70 m^2	32 m^2	2 m^2
Racquet Sports Equivalent	Full tennis court	Full racquetball court	Half of a badminton court	Half of a table tennis table

Figure 1. Relative surface areas of key organs at the interface of the body and the outside environment. For decades, the surface area of the human gut lumen was overstated (260 m^2, that of an entire tennis court). We now know, via modern morphometric methods, that the gut lumen is instead a mere 32 m^2, roughly half a badminton court. The lungs are thus the body's largest interface with the outside environment: 70 m^2, the size of a full racquetball court and 30 times that of the skin. Scale bar, 2 m.

These findings strongly suggest that lung microbial communities are indeed shaped by the microbiota of the environment.

Concurrent investigation of lung and environmental microbiota could have implications and applications beyond the current clinical question. Although BADE is uncommon, many idiopathic lung diseases have undetermined etiologies; interrogation of environmental and lung microbiota may provide breakthrough insights regarding pathogenesis for some. More broadly, study of the lung–environment interface may help explain the variable susceptibility to pulmonary disease. Whereas ecologic analysis has suggested that healthy lungs experience a relatively constant, low-level dynamic turnover of pharyngeal microbiota (4, 9), microbial communities in diseased lungs diverge from those of the pharynx, indicating differential rates of elimination and proliferation of microbes. One possible interpretation of the current study is that similarity between lung and environmental microbiota in patients with BADE is attributable not merely to differential *exposure* but more a failure of at-risk lungs to adequately protect themselves from microbial assault (impaired *elimination*).

Lastly, this study raises fundamental questions regarding the route of "cross-pollination" between the environment and the lungs. Intriguingly, the authors found similarities between skin, nasal, and oral microbiomes of workers exposed to metalworker fluid but no evidence of these overlapping microbes in environmental air. This could suggest that immigration to the lungs occurs indirectly: microbiota arrive on the skin, disseminate to the upper respiratory tract, and, finally, spread to the lungs. On the other hand, prior work has shown that metalworking fluid is commonly aerosolized along with its microbes, including *Pseudomonas pseudoalcaligenes* (18). A clearer understanding of the routes by which the environmental microbiome influences the lung microbiome would be of critical utility for occupational health.

The lungs admittedly cannot compete with the gut when it comes to quantity and diversity of microbiota. However, when considering how the environment—and its microbes—impact the body, the lungs are undeniably the largest and most intimate interface. With their study, Wu and colleagues remind us that to understand how the microbial universe affects human health and disease, we would serve ourselves well to keep our attention above the diaphragm. ■

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Patient-reported Outcomes for Clinical Trials in Idiopathic Pulmonary Fibrosis: New Opportunities to Understand How Patients Feel and Function

In recent years, our understanding of the pathogenesis of idiopathic pulmonary fibrosis (IPF) has grown enormously, and this new knowledge has underpinned major clinical trials testing novel treatment approaches (1). These scientific advances have resulted in the approval of two antifibrotic therapies (2, 3), which have changed the landscape of IPF care. At the same time, our knowledge of the physical, emotional, and social impacts of IPF has also grown, primarily from the application of qualitative methods in IPF research (4). The burden of dyspnea and cough are well established, with the impact of fatigue increasingly recognized (5). Many patients with IPF also experience anxiety, frustration, sadness, a loss of independence and important life roles, financial stress, and social stigma (4). Although the emergence of antifibrotic treatments has made us feel better about the future of IPF treatments, to date we do not have convincing evidence that these therapies have delivered better health-related quality of life (HRQL) for patients (2, 3).

The development and testing of interventions to improve HRQL in people with IPF across the disease course has been hampered by a lack of confidence in our measurement tools, many of which were adopted or adapted from those for other lung diseases (6). Although purpose-designed tools are emerging (7), a comprehensive HRQL measure for IPF that is ready for use in clinical trials remains a gap in our clinical trial toolbox. In this issue of the *Journal*, Swigris and colleagues (pp. 1689–1697) describe the first steps toward this important outcome (8). The Living with IPF (L-IPF) questionnaire has 35 items scored on a five-point numerical rating scale that address important symptoms (dyspnea, cough, and low energy) and impacts of IPF. This study provides evidence that the L-IPF has excellent test-retest reliability in stable patients, together with good psychometric, concurrent, and known-groups validity. The authors have worked with the U.S. Food and Drug Administration to ensure the

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