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Occupational Exposures in Rheumatoid Arthritis-related Airway Disease: A Missing Link?

To the Editor:

We read with great interest the recently published, "A Focused Review: Airway Disease in Rheumatoid Arthritis" (1). In this review, Matson and colleagues deftly summarize the pathophysiology and myriad clinical manifestations of airway disorders that cooccur with rheumatoid arthritis (RA). The authors note that asthma, chronic obstructive pulmonary disease (COPD), bronchiolitis, and bronchiectasis are all well-known manifestations or comorbidities in patients with RA. As part of their discussion of the complicated and incompletely understood pathogenesis of rheumatoid arthritis, the authors reference environmental insults and, specifically, tobacco smoke as triggers for autoantibody-mediated immune responses that lead to the development of autoimmune disease and potentially airway disease. Although the review was by definition focused, a discussion of occupational exposures that cooccur with RA and airway disease is warranted both to assess risk of airway disease and potentially prevent pulmonary disease progression.

Work exposures have been well described as a risk factor for RA. One telephone survey in an area with high mortality from coal workers' pneumoconiosis found that residents with a history of coal

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mining exposure had more than threefold odds of reporting a diagnosis of RA, leading to a population attributable fraction of 33% of those studied (2). Military inorganic dust exposure has also been associated with the development of RA compared with other occupations within the armed forces (3). Prolonged exposure to the World Trade Center disaster site has also been associated with an increased rate of autoimmune disease, the most prevalent of which was RA (4). Other occupations have demonstrated gender-specific associations with RA: bricklayers and concrete workers have an increased risk of RA among men, whereas nurses and medical attendants have increased risk among women (5).

Occupational-associated lung disease in patients with connective tissue disease is increasingly recognized (6), and the well-known association between occupational exposures and asthma, COPD, and bronchiolitis suggest a shared causative environmental antigen may exist among patients with RA and airway disease. Ascertaining the association between RA and occupational exposures has enormous implications for assessment of those at high risk of disease development, such as individuals with a family history of autoimmune disease. Furthermore, more novel occupational exposure–pulmonary disease dyads in women may reveal more exposure–autoimmune disease connections in the future, given the female-predominant nature of connective tissue disease. Systematic assessment of lifetime occupational exposures, starting in clinic and continuing in research registries, is the key to further codifying exposure–disease relationships and early identification and ultimately prevention of airway disease in patients with RA. ■

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Reply: Occupational Exposures in Rheumatoid Arthritis-related Airway Disease: A Missing Link?

From the Authors:

We thank Drs. Lee and Strek for their thoughtful reading of our review highlighting the current knowledge of airway disease manifestations in patients with rheumatoid arthritis (RA) (1). In their response to our review, Drs. Lee and Strek aptly highlight an unexplored part of this discussion: the association between occupational and inhalational exposures beyond cigarette smoking and the development of RA. In fact, this paradigm of exposure to concentrated inhalational exposure such as seen in World Trade Center disaster site workers, followed by the development of RA, fittingly supports one of the conceptual models we presented in our review article. In our proposed model of RA autoimmunity development, bronchus-associated lymphoid tissue responds to local inflammatory pressures that can be triggered by a variety of inhaled factors with the production of RA autoantibodies such as antibodies to citrullinated peptide antigens. In this review, we highlighted the potential role of neutrophil extracellular trap formation (NETosis) in connecting chronic lung inflammation to development of antibodies to citrullinated peptide antigens, and although cigarette smoking has been shown to induce NETosis in models, there is a paucity of data regarding the role of other inhalational injuries on NETosis (2).

We read the recent publication from Drs. Lee and Strek regarding the spectrum of occupational and inhalational exposures found in a large interstitial lung disease registry with great interest (3). We believe their data highlight the underexplored role of inhalational exposures in chronic lung disease regardless of etiology, including RA lung manifestations such as interstitial lung disease (3). The themes in Drs. Lee and Strek's response highlight the need to understand the role of inhalational injury in NET formation and subsequent development of autoimmunity across chronic lung disease states. Importantly, NET cargo release varies based on the antigenic trigger (4); therefore, it would follow that unique inhalational risks may confer specific autoimmune risk based on the nature of the NET response induced.

We believe, as Dr. Lee and Strek point out, that ongoing clinical exploration of lung disease in patients with RA, including inhalational exposure assessment, remains paramount when approaching the many questions remaining in this realm. Airway disease in RA