Importantly, as the authors point out, a next step is to identify the mechanism by which small airways are lost. The proposed sequential pathological steps, which were first suggested by Saetta and colleagues in 1985 (4) and later revised by Mitzner (6), of "deposition of cigarette smoke particles in small airways→inflammation of small airways→propagation of inflammation through the entire bronchiolar wall into adjacent alveolar septa→destruction of bronchiolar–alveolar attachments→lung parenchyma degradation proceeding from the centers of the secondary pulmonary lobules toward the surrounding interlobular septa" are highly plausible. Support comes from other cross-sectional studies in advanced COPD (7–9). However, we should emphasize that this postulate must be confirmed via rigorous quantitative analyses in earlier COPD stages (10).

Other investigators and we have previously reported that volumetric microcomputed tomography imaging of tissue samples provides a unique opportunity to target specific lesions for histological examination, and therefore to assess the unique properties of the cellular composition within and around a lesion. Tanabe and colleagues demonstrated that the destruction of the alveolar attachments in the preterminal bronchioles could be driven by a B cell–mediated immune response (11). Assessment of the terminal and transitional bronchioles poses greater challenges with regard to analytic imaging techniques, but it is not impossible.

An additional crucial issue is the exact process behind the tissue destruction. What causes the alveolar attachments to "snap"? We believe the most plausible explanation is that the extracellular matrix is remodeled by infiltrating cells, leading collagen and elastin fibers to become deranged to such a degree that they cannot withstand the continual stretching and contraction during breathing. Novel methods, including nonlinear optical microscopy, which was previously applied to study airway remodeling in patients with asthma (12), may shed light on this process.

Hence, performing a targeted analysis of the remodeling, cellular infiltration, and gene expression of the terminal bronchioles, and assessing their association with PRM classifications at earlier disease stages are high research priorities for our group. We are confident that this multipronged approach will shed more light on the mystery of how destruction of the small airways and surrounding tissues occurs. ■

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Silica Exposure and Scleroderma: More Bridges and Collaboration between Disciplines Are Needed

To the Editor:

We have read with great interest Turner and colleagues' correspondence concerning connective tissue disease

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(CTD) and silica exposure in artificial stone workers (1). We totally support their call for a new awareness on silica hazards and their broadening to CTD. Indeed, silica hazards are too often, and almost systematically, narrowed to silicosis (2).

Although L. D. Erasmus was historically the first to link silica exposure with the occurrence of systemic sclerosis (SSc or scleroderma), B. Bramwell, a Scottish physician, had described an outbreak of scleroderma among stonemasons 50 years before (3). Despite this ancient association, SSc is still largely considered today to be of unknown cause. The Pasteurian paradigm (one cause, one disease) may have contributed to an oversimplified vision of causality in diseases, leading to a dichotomous vision of etiologies: either an obvious and single cause for some diseases (especially communicable diseases) or complex diseases with too many causal factors to be properly captured. Nonetheless, recent insights into the pathogenesis of SSc, including cancer-associated SSc, remind us that the search for a cause may not be totally in vain. Indeed, when silica exposure is properly explored (i.e., prospectively assessed through dedicated occupational questionnaires and/or evaluation by experts in occupational medicine and toxicology), this exposure appears to be strikingly frequent in male patients with SSc, with at least half of them having occupational silica exposure in recent European studies (4). Therefore, crystalline silica exposure may be a decisive cause or trigger, and this would be especially relevant in males, who are more often engaged in occupations involving silica. Interestingly, recent insights into the pathogenesis of silica-induced autoimmunity in mouse models have highlighted that the production of autoantibodies after silica exposure was significantly higher in males in comparison with female littermates (5). In humans, sex and gender in SSc may be especially crucial, as SSc is frequently more severe in men.

The current outbreak of silicosis and CTD after exposure to high-silica-content artificial stone dusts both demonstrates the specificity of the association of crystalline silica with autoimmunity in comparison with other mineral dusts and reminds us that silica exposure does not only concern the mining industry but also covers a wider range of sectors. In this regard, the call for systematic screening of patients for CTDs after silica exposure appears central in patients both with and without signs of silicosis and/or pulmonary involvement. Concerning SSc, the systematic screening strategy proposed for a very early diagnosis of SSc (known as VEDOSS [Very Early Diagnosis of Systemic Sclerosis]) (6) may be especially relevant for these silica-exposed patients. This VEDOSS strategy does not only include testing for antinuclear antibodies but also emphasizes the central role of capillaroscopic findings and clinical detection of "puffy fingers," a manifestation of SSc that may precede the occurrence of sclerodactyly. Such a screening would therefore imply a close collaboration of clinicians who have been trained to detect puffy fingers or other SSc early signs and who are familiar with capillaroscopic examinations with specialists of occupational diseases and silica-associated respiratory disorders likely to detect the situations of silica exposure.

Beyond preventability and diagnosis, the lack of a proper understanding of the pathogenesis of silica-associated autoimmunity may also result from missing bridges between disciplines. From a toxicant viewpoint, this question of silica has been almost exclusively studied through fibrotic pulmonary diseases or cancer or, when addressing autoimmunity, has been based on mouse models of systemic lupus, whereas SSc has long been considered the CTD most frequently associated with silica exposure. The alarming recent outbreak of silica-associated CTD may provide an opportunity to fill this gap and offer a timely lever to collectively better understand the pathogenesis of SSc. ■

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Reply to Lescoat *et al.*

From the Authors:

We thank Lescoat and colleagues for their correspondence and their interest in our work (1). We fully agree about the importance of a new awareness regarding silica hazards and their relationship with connective tissue disease (CTD) in artificial-stone workers. We certainly hope that our joint efforts in highlighting this important area result in greater collaboration among subspecialty physicians, toxicologists, and leaders in occupational medicine and public health globally.

Lescoat and colleagues are right to point out the broader history of the observed association between CTD and silica exposure. We were restricted by word limits in our report from acknowledging the work of the Scottish physician B. Bramwell, who in 1914 first noted an increased prevalence of scleroderma among stonemasons in his seminal paper (2). Increased mortality from "chronic rheumatism" in coalminers was subsequently reported by Collis and Yule in the United Kingdom in 1933 (3) and by Anthony Caplan, a physician working on the Cardiff Pneumoconiosis Panel, who described pneumoconiosis in coal miners with rheumatoid arthritis in 1953 (4). L. D. Erasmus reported a high prevalence of scleroderma among South African gold miners in 1957 (5), and the association between silica exposure and CTD, especially systemic sclerosis or scleroderma, has subsequently been confirmed in many publications.

Our suggestion regarding systematic screening of patients for CTD after silica exposure, both with and without pulmonary involvement, would not only aid interdisciplinary research but would also assist in the clinical diagnosis of CTD in line with the VEDOSS (Very Early Diagnosis of Systemic Sclerosis) strategy (6), as Lescoat and colleagues note. The VEDOSS strategy centers on a combination of autoimmune antibody testing, capillaroscopic findings, and clinical detection of "puffy fingers" preceding sclerodactyly. Importantly, longitudinal follow-up for 5 years or more is required. Applying this strategy with longitudinal follow-up of patients occupationally exposed to silica may enable earlier diagnosis of both silicosis and associated CTD and improve patient outcomes with earlier intervention. We would welcome the interdisciplinary clinical use of capillaroscopy and optimal surveillance strategies, and we hope that by working together we can gain a better understanding of the pathogenesis of both silicosis and CTD. ■

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