prevents the long-term cognitive impairment and disability that currently affect a large number of critical illness survivors (4). When the sandman visits the ICU, he will ideally leave critically ill patients with better outcomes both in the short term and for many years to come. Though delirium prevention, whether through promotion of sleep or via other mechanisms, has important short-term benefits, its greatest benefits may very well come from effects on long-term outcomes. For this reason, we recommend that long-term outcomes be included in every clinical trial of an intervention directed at delirium in the ICU.

With only one randomized trial available at this time to inform us about the effects of nocturnal dexmedetomidine in the ICU, it would be premature to recommend nocturnal dexmedetomidine for all ICU patients. But the strategy shows promise and should be considered an evidence-based alternative to other drugs that are sometimes used in the ICU to minimize delirium and/or promote sleep, such as antipsychotics and melatonin. We now need confirmatory trials that examine not only delirium but also mechanisms, multiple schedules, and patient populations, and, perhaps most importantly, long-term outcomes. ■

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The Long-Term Effects of Cleaning on the Lungs

Past studies have demonstrated that cleaning in a variety of work settings is a risk factor for adverse respiratory health effects, most notably asthma (1, 2). Excess asthma and respiratory symptoms have also been documented in persons cleaning at home (2, 3). In this issue of the *Journal*, Svanes and colleagues (pp. 1157–1163) examine the long-term effects of cleaning, using data from the European Community Respiratory Health Survey (ECRHS) (4). The authors showed that for women, but not men, both occupational and domestic cleaning were associated with accelerated declines in spirometric parameters over the course of 20 years. They found that the size of the effect was comparable to smoking 10 to 20 cigarettes daily during the study period.

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ECRHS is a large, multicenter, population-based cohort study that began in the 1990s to address the increasing burden of asthma and its potential environmental causes (5). In their study, Svanes and colleagues included more than 6,000 adults recruited in 1992–1994 at ages 20 to 44 years (ECRHS I) and followed-up in 1998–2002 (ECRHS II) and 2010–2012 (ECRHS III) (4). Interviews and spirometry were conducted at each of the three time points, and self-reported cleaning activity information was collected during ECRHS II. Serial spirometric data were available for more than 85% of the participants.

At baseline, the study population was relatively young and healthy, with a mean age of 34 years, doctor-diagnosed asthma prevalence of 6%, and mean spirometric parameters exceeding 100% of predicted. Women, who made up 53% of the participants, were more likely than men to report cleaning occupationally (9% vs. 2%) or at home (85% vs. 47%). In models accounting for potential confounders, women who cleaned had accelerated declines in FEV_1 and FVC compared with women who did not. Occupational cleaning was associated with an additional loss of 3.9 ml/yr for FEV_1 and 7.1 ml/yr for FVC; cleaning at home was associated with an additional loss of 3.6 ml/yr for FEV_1 and 4.3 ml/yr for FVC. Similar accelerated declines were noted for at least weekly use of spray cleaners (for FEV_1) and other types of cleaners (for both FEV_1 and FVC). As the authors note, differential sensitivity to respiratory toxins or methodological issues might explain the absence of effect for men. The study may not have been sufficiently powered (just 57 men reported occupational cleaning), or the male reference group may have had other hazardous exposures that contributed to their rates of decline. Indeed, contrary to expectation (6), the rates of decline for noncleaners were considerably higher in men (26.4 ml/yr for FEV_1 and 17.8 ml/yr for FVC) than women (18.5 ml/yr for FEV_1 and 8.8 ml/yr for FVC), suggesting that the effects of cleaning may have been underestimated for men.

Changes in spirometric parameters are nonspecific, so this study cannot determine the underlying disease process. Women who cleaned reported more doctor-diagnosed asthma in ECRHS II than women who did not (up to 13.7% vs. 9.6%). However, women with and without asthma had the same relationships between cleaning and spirometric parameters. Asthma may go undiagnosed, so inclusion of asthma symptoms might have been illuminating. Recently, occupational cleaning has been identified as a risk factor for chronic obstructive pulmonary disease (7, 8). Odds ratios for incident chronic airway obstruction were elevated among female cleaners, but there were few cases, and differences were nonsignificant. Furthermore, declines in FEV_1 and FVC occurred in parallel, raising the possibility that cleaning led to interstitial changes, as occurred with humidifier disinfectant (9). In addition, bronchiolitis has been reported with some cleaning chemicals, and protean spirometric findings are possible (10). Tools such as oscillometry, specific inhalation challenge testing, analysis of particles in exhaled air, and quantitative chest computed tomography may complement spirometry in future studies.

Cleaning exposures include chemicals that are known sensitizers and irritants, chemicals with poorly characterized respiratory effects, and mixtures of all three, in addition to indoor allergens and pollutants (11). In this study, cleaners likely used a range of cleaning products for variable frequency and duration. This spectrum of exposures might have resulted in a spectrum of outcomes, with some participants' accelerated decline related to airway obstruction and others' to interstitial changes, as with other complex inhalational exposures (12). That such a blunt exposure metric performed as well as it did is remarkable, and highlights the tremendous value of a well-designed prospective observational study such as ECRHS to detect associations that would not be evident using a cross-sectional approach or with a smaller cohort. Nonetheless, many questions about exposures remain unanswered, and Svanes and colleagues' findings provide strong support for expanded exposure assessment in future studies (4).

Most studies of cleaners face similar exposure assessment challenges. Contributing to these challenges are incomplete information on products used and their ingredients, an abundance of cleaning products on the market, and a lack of methods to simultaneously measure multiple chemicals (2). Yet quantitative exposure assessment is critical not only to identify causative chemicals and inform the development of exposure limits but also to identify effective strategies to prevent or manage adverse respiratory health effects. Product substitution or elimination requires knowledge of the causative agents and a mechanism to certify the safety of alternative products. Although Green Seal certifies products as asthmagen-free, numerous other "green" or "eco-friendly" labels do not necessarily shield against adverse respiratory health effects (13). For example, a new peroxygen-containing product promoted as a safer alternative to other sporicidal disinfectants was nonetheless associated with symptoms among cleaners and healthcare workers (14). Effective engineering or administrative controls require knowledge of exposure levels and the specific tasks, tools, and workplace or home characteristics leading to exposures. Efforts to raise awareness among workers, employers, and the public about the risks of cleaning, and among healthcare professionals to recognize cleaning-related respiratory disease, would also benefit from knowledge of causative agents and exposures. Future studies could incorporate direct reading instruments with advanced sensors now in development for simultaneous measurement of multiple chemicals (15).

Although more certainty about pathophysiology and exposure is welcome, it would be a mistake simply to wait for the results of future investigations. These results should prompt prudent actions to prevent long-term lung damage among cleaners, including modifying cleaning practices, such as eliminating the use of spray products; mixing products in ventilated areas or purchasing ready-to-use products; judicious and selective use of cleaning products for specific applications; increasing public awareness about hazards and dispelling misperceptions that cleaning agents for home use or "green" cleaners are "safe"; training workers, employers, and healthcare professionals about the effects of cleaning; forming stakeholder committees to make cleaning product purchasing policies; incorporating questions on use of cleaning products in population-based respiratory disease surveillance; and where other control measures are not feasible, considering the use of appropriate respiratory protection (1, 2). The time to act is now. ■

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Complementing Lung Cancer: How Tumor Cells Co-opt the Host Complement System to Reach Bone

Lung cancer remains the number one cause of cancer-related death worldwide. Despite significant advances in early detection, resection, genetics, and targeted therapies, its 5-year survival remains below 20% (1). A major reason for its grim prognosis relates to the fact that most lung cancers are detected late, often after the cancer has metastasized to other organs. Of these, bone metastasis has long been described as affecting up to 40% of patients and represents a major source of morbidity and mortality (2). The cumulative survival rates after bone metastasis in the setting of lung cancer is 11.3% at 2 years, with a mean survival of 9.7 months (3). Thus, new insights into the molecules and pathways involved in osseous metastasis in this disease should be pursued to identify potential targets for intervention.

The complement system was recently associated with poor prognosis in patients with lung cancer (4). The complement system is best known for its role in innate and adaptive immunity, as its cascade leads to activation of the anaphylatoxins C3 and C5, which participate in the formation of membrane attack complexes on the surface of target cells (5). Notably, although C3b and C5b participate in opsonization and the assembly of membrane attack complexes, C3a and C5a activate cognate G protein–coupled signaling receptors termed C3R (C3 receptor) and C5aR1 (C5a receptor 1) and C5aR2, respectively, which are implicated in diverse biological processes ranging from cellular chemotaxis and vascular permeability to atherosclerosis (6). Regarding cancer, C5a has been found to impair antitumor immune responses through modulation of regulatory T-cell function and the production of immunosuppressive cytokines (7, 8). It is through these nonopsonin pathways that the complement system is thought to affect cancer progression, but the exact mechanisms involved remain incompletely elucidated.

In this issue of the *Journal*, Ajona and colleagues (pp. 1164–1176) bring new insight into this area by setting out to explore the potential role of the C5a/C5aR1 axis in bone metastases, using experimental models of lung cancer (9), but first they showed that patients with high levels of C5aR1 mRNA in tumor cells manifest shorter recurrence-free survival and overall survival, although the exact reason for this was not investigated. Tumor cells as well as host stromal cells, epithelial cells, neutrophils, and macrophages stained positive for C5aR1 in patients diagnosed with non–small cell lung cancer. Notably, higher C5aR1 levels were found in primary lung tumors harvested from patients with bone metastases when compared with those with metastases to nonskeletal sites. Further *in vitro* studies revealed that these receptors are functional in lung A549 cells. Of interest, recombinant C5a did not affect cell proliferation, but increased cell motility and invasiveness, processes inhibited by a matrix metalloproteinase inhibitor.

To study bone metastasis, the investigators used A549M1 cells derived from a parental A549 cell line previously shown to selectively form osseous metastases; these cells were silenced for C5aR1 using lentiviral transduction. Using this system, they found that C5a-mediated induction of motility and invasiveness was

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