

Can Exposure to Very Low Levels of Asbestos Induce Pleural Mesothelioma?

Asbestos is a recognized human carcinogen, causally related to pleural and peritoneal mesothelioma and to lung cancer (1). Mesothelioma is of particular interest, as it is a specific outcome of asbestos exposure and no other causal factor except for exposure to asbestos (and erionite, a naturally occurring mineral fiber found in Turkey) (2) has been established or even convincingly suspected.

The vast majority of asbestos-induced mesotheliomas in the industrialized world is caused by occupational asbestos exposure, and occurs among workers engaged in extracting and manufacturing asbestos, or performing tasks involving contact with asbestos-containing materials (3). Concern used to be focused on the occupational environment, but it is now recognized that asbestos fibers are widely distributed in the general environment. Persons can be exposed to asbestos in different nonoccupational circumstances: living with asbestos workers, with regular exposure to soiled work clothes brought home; environmental exposure in the neighborhood of industrial sources (asbestos mines and mills, asbestos processing plants); passive exposure in buildings containing asbestos; and natural environmental exposure to geological sources (4).

Studying the effects of nonoccupational asbestos exposure on mesothelioma risk is important because it could provide information about the nature of the exposure–response relationship that cannot be obtained from studies of workers whose exposures begin in adulthood, are limited to working hours, are typically much higher in concentration, and who are mainly male. Natural environmental exposure to geological sources is of special interest, since populations subjected to natural sources present specific temporal exposure characteristics: exposure can start during childhood and be lifelong, and it can occur around the clock, seven days a week. Evidence on environmental exposure of natural origin thus provides information about the effect of early exposure on cancer risk and on latency periods, susceptibility according to sex, or the potentially different effect of asbestos fiber types (chrysotile, or amphiboles such as crocidolite, amosite, or tremolite, which are considered to be more potent carcinogens for mesothelioma than chrysotile fibers).

The main findings of studies in rural areas of Turkey (5), Greece (6), some Mediterranean islands (7–9), China (10), and New Caledonia (11), where occupational exposure to asbestos is rare, even nonexistent, show that asbestos exposure starting at birth does not seem to influence the latency period of mesothelioma. The data also indicate that susceptibility does not differ according to sex, and confirm that the much higher rates of mesothelioma among males in the industrialized countries are most probably due to sex differences in occupational exposure to asbestos.

Studies of mesothelioma related to environmental exposure to geological sources of asbestos have yielded important findings.

However, some important issues remain unresolved. Thus, it would be of utmost importance, from a scientific and public health point of view, to know whether exposure to low levels of asbestos is able to induce pleural mesothelioma. There is still controversy regarding this question (12, 13). While exposure in environmental settings is generally much lower than in occupational circumstances, the levels may not be negligible. In studies in which elevated risk of mesothelioma was demonstrated, people typically lived in close vicinity of naturally occurring asbestos sources, and may have had direct contact with asbestos, when whitewashing houses with material containing asbestos or working in polluted fields. It is thus likely that lifelong cumulative exposure may have been as high (if not higher) as in some occupational settings, but it was not—or not adequately—measured, and nonoccupational studies have not yet provided adequate answers.

This is why the work of Pan and coworkers, reported in this issue of the *Journal* (pages 1019–1025) (14), showing a relationship between mesothelioma risk and residential distance from naturally occurring asbestos, and suggesting that there is an excess risk of mesothelioma even at a long distance from the asbestos source, is important. To our knowledge, this study is the first one that demonstrates such an effect quite convincingly.

While this study has some limitations (occupational exposure was only partially taken into account, no residential history was available for the subjects, no cases under 35 years of age could be included, and asbestos exposure was indirectly assessed), many features are strong. It relied on a register-based selection of a very large number of mesothelioma cases, and their localization was quite precise, thanks to the geocoding of residency and to the use of advanced GIS techniques. The results show a convincing internal consistency. The role of occupational exposure is clear and the risk varies with exposure, showing that even if it was not completely controlled for, the study captures its main effect. There was a linear relationship between distance and the pleural mesothelioma risk, still evident when different methods were used or when restricted to some subgroups; the distance–effect relationship was similar among men and women, even if not statistically significant among the latter due to smaller numbers.

Pan and colleagues (14) bring new findings in favor of the carcinogenic role of low levels of exposure to asbestos, as it is most likely that level of exposure to asbestos at the remote distances where excess risk of pleural mesothelioma was apparent is very low. The fact that the risk of peritoneal mesothelioma, which is induced by higher exposure than pleural mesothelioma (1), is not related to the distance of the asbestos source gives more weight to the hypothesis that very low levels of asbestos may cause mesothelioma of the pleura. Additional work is now necessary for an accurate assessment of the levels of cumulative exposure that people experience in areas where an excess risk of pleural mesothelioma was observed.

Conflict of Interest Statement: Neither of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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DOI: 10.1164/rccm.2507003

Surfactant Dysfunction Mutations in Children's Interstitial Lung Disease and Beyond

Surfactant has been an important focus in pediatrics since the recognition of surfactant deficiency in premature infants (1). It seemed logical that derangements in this system could contribute to other types of pediatric lung disease, and this hypothesis has been substantiated over the last 15 years. Mutations in the surfactant protein B (SPB) and C (SPC) genes result in significant morbidity and mortality for newborns and young children (2–4). Mutations in the ABCA3 gene, an ATP-binding cassette transporter of lipid found in alveolar type II cell lamellar bodies, have recently been recognized as a cause of fatal neonatal interstitial lung disease (ILD) (5).

Children with ILD (chILD) have a range of rare and diverse diagnoses (6). They initially present with a constellation of findings called chILD syndrome. The chILD research network has defined chILD syndrome as a lung condition in children with at least three of the following criteria in the absence of any identified etiology as the primary cause: (1) symptoms of impaired respiratory function, (2) hypoxemia, (3) diffuse infiltrates, (4) presence of adventitious sounds, and (5) abnormal lung function. Primary causes to be excluded include cystic fibrosis, cardiac disease, asthma, acute infection, immunodeficiency, neuromuscular disease, scoliosis, typical bronchopulmonary dysplasia or premature respiratory distress syndrome, and confirmed significant aspiration.

To determine a more specific diagnosis, chILD syndrome prompts an extensive evaluation, usually including a lung biopsy. Until recently, children were retrofitted into an adult histologic classification system for ILD (7). As young children with ILD have distinct diagnostic entities not seen in adults (8, 9), and conversely, no documented evidence for usual interstitial pneumonitis, it is not surprising that this adult classification system was limiting (10). A new chILD classification system developed by the chILD imaging and pathology cooperative is based on a retrospective multidisciplinary review of 187 lung biopsies from children younger than 2 years who underwent lung biopsy during a 5-year period at 11 pediatric centers in North America (11). Characteristic

histologic features of surfactant dysfunction mutations were documented in 10% of this population, with a 100% mortality noted for ABCA3 patients (12). A category for surfactant dysfunction disorders in infancy is included in the new chILD classification.

The work of Bullard and colleagues in this issue of *AJRCM* (pp. 1026–1031), examining the role of ABCA3 mutations in older surviving children with ILD, now extends the importance of the ABCA3 mutations beyond infancy (13). DNA samples from 195 children with chronic lung disease of unknown etiology were analyzed. First, ABCA3 was sequenced from DNA samples of children with desquamative interstitial pneumonitis who were older than 10 years at the time of enrollment. Three of four patients had a common missense ABCA3 mutation (E292V) on one allele and a second unique mutation identified on the other, consistent with an autosomal recessive disorder. Second, the remaining DNA samples, not positive for other SPB or SPC mutations, were screened for the E292V mutation, with seven more children identified. Interestingly, a second mutation was not found in two patients, possibly due to missed mutations, other genetic or environmental influences, or decreased rather than absent ABCA3 function causing disease. Clarifying these issues could have major implications for E292V as a genetic modifier for other pediatric and adult lung diseases.

In this population of children with chronic lung disease, 5% had the common ABCA3 mutation (E292V) in contrast to 14% who had an SPC mutation and 1% who had an SPB mutation. This likely recognizes only a small fraction of ABCA3 mutations, as only the E292V mutation was screened for and only SPC and SPB genes fully sequenced. If the CFTR in cystic fibrosis, another large gene in the ATP-binding cassette family, is analogous to ABCA3, there will likely be an extensive number of additional mutations capable of causing diverse disease in children and adults (14).

In contrast to the significant mortality in young children with ABCA3, there were only two deaths (6 mo and 11 yr) in this series, suggesting a milder phenotype. The current age of survival

for the E292V group was reported as 6 to 32 years. Many patients had symptoms in infancy, but two patients reportedly became symptomatic only later in childhood. Histologic findings of bronchiolitis obliterans and minimal change, not currently considered suggestive of a surfactant dysfunction mutation, were also found in two patients (11).

A major obstacle involves identifying patients with ABCA3 mutations. Complete genetic identification of all ABCA3 mutations in all candidate patients is currently not possible. However, the identification of a common mutation (E292V) and pathology techniques, such as surfactant protein staining patterns, as reported by Bullard, and electron microscopy to look for abnormal lamellar bodies (5), could provide a starting point. Electron microscopy should be obtained on all lung biopsies for chILD. Clinical, imaging, and histologic correlations will also be critical to better define and recognize these patients.

Bullard and colleagues have provided intriguing data that may represent the proverbial “tip of the iceberg” for pediatric and perhaps adult lung disease related to ABCA3 mutations. Even with limited patient numbers and incomplete clinical information, we suggest the following clinical conclusions. Surfactant dysfunction mutations should be considered in any patient with ILD. In older patients, the presentation may differ from younger children, requiring a higher index of suspicion. A family history is helpful, but cannot be relied on to recognize all patients, as only 50% of the patients had a family history of lung disease. Although perhaps underappreciated in adult ILD (15), now that both ABCA3 and SPC mutations have been reported in adults, surfactant dysfunction mutations should also be considered in the differential of adult ILD.

Conflict of Interest Statement: Neither of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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DOI: 10.1164/rccm.2507004

Exacerbations The Asthma Paradox

Considering the enormous amount of knowledge that has been gained in our understanding of the inflammatory mechanisms of asthma, it is disappointing that we still know very little about asthma exacerbations. This is all the more surprising when it is realized that exacerbations are manifestations of asthma that cause the greatest concern to patients, account for the largest proportion of the health costs of this disease, and can be life threatening. The majority of asthma research into mechanisms has focused on the allergic pathways, and this is also reflected in the way that the pharmaceutical industry has sought new treatments, relying largely on antigen sensitization and animal challenge models to screen new drugs. Maybe this concentration on the importance of the allergic pathways helps explain why there have been no highly innovative treatments found for asthma other than improvements made to known drug classes or those predicted from knowledge on disease mechanisms obtained over 25 years ago.

Although allergen exposure can trigger asthma exacerbations, this is not the commonest cause. Both in adults and in children, the majority of asthma exacerbations are caused by respiratory virus infections of which rhinoviruses (RVs) are by far the most frequent (1). For example, a recent Australian study has reported that 78% of acute asthma exacerbations were virus-associated, and of these, 83% were RVs (2). The marked increase in asthma exacerbations in both children and adults that occurs in the fall, winter, and early spring months is predominantly virus-related, with RVs dominating (3, 4). Beyond causing the common cold, RVs predominately infect the conducting airways, although occasionally they are responsible for pneumonia, especially in immunocompromised children (5). Virus-induced exacerbations of asthma represent a major unmet clinical need in this disease.

RVs gain access to the airway via the epithelium where they bind and are internalized by intercellular adhesion molecule-1

(ICAM-1) in the case of the major RV subclass and low-density lipoprotein receptors for the minor RV subclass. Once inside the epithelial cell, the virus triggers a set of molecular pathways leading to the activation of the transcription factor nuclear factor- κ B and the secretion of a range of cytokines and chemokines that include interleukin 17F (IL-17F), granulocyte-macrophage colony-stimulating factor, IL-8, and Gro α , which recruit neutrophils as well as CD4⁺ and CD8⁺ lymphocytes into the airways. This inflammatory signature is different from that seen with allergen exposure and helps to explain why virus-induced exacerbations in most parts are refractory to inhaled or oral corticosteroids, both in adults (6, 7) and in children (8, 9). In this issue of the *Journal* (pp. 1037–1040), Xatzipsalti and colleagues have investigated whether RV infection is accompanied by viraemia in groups of 1- to 14-year-old children experiencing an exacerbation of asthma, bronchiolitis, the common cold, or pneumonia (10). Although they were unable to grow live virus from the blood of none of the children, in a significant proportion of cases they were able to detect RV by polymerase chain reaction. Successful detection was dependent on obtaining the blood sample within 24 hours of the start of symptoms and was five times greater if the child was experiencing an exacerbation of asthma. A history of asthma also markedly increased the risk of rhinoviraemia (odds ratio, 5.8; $p = 0.012$). Neither age nor corticosteroid use proved to be a risk factor for rhinoviraemia.

The authors offer two explanations for their findings. They suggest that viraemia may be a route through which RV spreads from the nasal mucosa to the lower respiratory tract. However, as with other viruses that restrict themselves to the respiratory tract and where the principal site of viral entry is the epithelium, this seems somewhat unlikely, especially since the 2- to 3-day interval between upper and lower airway symptoms would accommodate direct viral transmission from the upper to the lower airways (1). An alternative is that virus gains access to the blood due to a defect in innate and/or adaptive immune responses designed to limit viral spread. Their finding that rhinoviraemia was more frequent in severe rather than mild asthma exacerbations (86 vs. 33%) supports this view. When compared with normal control subjects, we have recently shown that asthmatic epithelial cells in culture have an impaired ability to clear RV after infection and that this is accompanied by reduced apoptosis (11). Rather, the infected asthmatic epithelial cells hold onto the RV longer, allowing greater replication and eventually resulting in cytotoxic cell death with release of inflammatory mediators along with large numbers of intact viruses that will infect neighboring cells. If apoptosis is inhibited in RV-infected normal epithelial cells, then the asthma phenotype appears with increased cell cytotoxicity and greatly increased virus shedding. The cause of this abnormal epithelial response to RV infection in asthma has been shown to be a major defect in the virus-induced generation of the cytokine IFN- β , with exogenous IFN- β able to restore the virus protection observed in epithelial cells from normal airways. This asthma-related defect in epithelial innate immunity would be expected to facilitate virus penetration into the airway tissue and subsequently into the circulation.

In adults with asthma, there is also some evidence for an impaired adaptive immune response on RV infection with reduced IFN- α production by circulating mononuclear cells both *in vivo* (12) and when infected *in vitro* (13). Recently, Copenhaver and colleagues have reported that, in infants, impaired cord blood IFN- α responsiveness of mononuclear cells, when stimulated with the nonspecific mitogen phytohemagglutinin (PHA), is also a risk factor for RV-induced wheezing (14).

A crucial question that remains to be answered is the role of RV, and indeed other respiratory viruses, in the origins and persistence of asthma. Although at one time considered to be

protective against asthma and atopy in susceptible children, there is mounting evidence that respiratory virus infection early in life may trigger the onset of asthma. In children aged 4 to 12 years with an acute asthma exacerbation, RV was detected in nasal aspirates in 82% of cases and in over half these, RV nucleic acid was still detectable after 6 weeks. Even at 6 months after infection, 25% of the children still had RV present in their nasal secretions, with persistence correlating with initial asthma severity (15). Thus, although RV and other respiratory viruses are major causes of acute asthma exacerbations, their role in the persistence of asthma remains unknown but could be important.

It is clear from the impact that respiratory viruses, and especially RV, have on the lives of patients with asthma patients that new treatments are needed beyond corticosteroids, which have limited efficacy in this situation. Although soluble ICAM-1 has been shown to be particularly active, IFN- β or an agent that induces this in the airways is likely to be more effective because not only will it replace a cytokine crucial to antiviral defense across a range of viruses but it will also trigger secondary immune responses, including the production of IFN- α (16). A possible precedent for this approach was demonstrated by Simon and colleagues who, in an open study, have shown that 1 to 2 years of regular treatment with low-dose intravenous IFN- α in 10 patients with corticosteroid-refractory severe asthma not only resulted in an impressive increase in FEV₁, increasing from 50 to 90% predicted, but also enabled a halving of the mean daily oral prednisolone dose, accompanied by an increase in IFN- α and IL-10 production by stimulated circulating mononuclear cells *ex vivo* (17).

Conflict of Interest Statement: S.T.H. is the cofounder and consultant for Synairgen. Synairgen has an interest in the use of interferons in the treatment of lung disease. The University of Southampton is part owner of the spin-out company Synairgen.

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DOI: 10.1164/rccm.2507007