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Review Article

The Evolving Spectrum of Pulmonary Disease in Responders to the World Trade Center Tragedy

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On September 11, 2001, events at the World Trade Center (WTC) exposed residents of New York City to WTC dust and products of combustion and pyrolysis. The majority of WTC-exposed fire department rescue workers experienced a substantial decline in airflow over the first 12 months post-9/11, in addition to the normal age-related decline that affected all responders, followed by a persistent plateau in pulmonary function in the 6 years thereafter. The spectrum of the resulting pulmonary diseases consists of chronic inflammation, characterized by airflow obstruction, and expressing itself in different ways in large and small airways. These conditions include irritant-induced asthma, non-specific chronic bronchitis, aggravated pre-existing obstructive lung disease (asthma or COPD), and bronchiolitis. Conditions concomitant with airways obstruction, particularly chronic rhinosinusitis and upper airway disease, and gastroesophageal reflux, have been prominent in this population. Less common have been reports of sarcoidosis or interstitial pulmonary fibrosis. Pulmonary fibrosis and bronchiolitis are generally characterized by long latency, relatively slow progression, and a silent period with respect to pulmonary function during its evolution. For these reasons, the incidence of these outcomes may be underestimated and may increase over time. The spectrum of chronic obstructive airways disease is broad in this population and may importantly include involvement at the bronchiolar level, manifested as small airways disease. Protocols that go beyond conventional screening pulmonary function testing and imaging may be necessary to identify these diseases in order to understand the underlying pathologic processes so that treatment can be most effective. Am. J. Ind. Med. 54:649–660, 2011.

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INTRODUCTION

On September 11, 2001, the attack, explosion, fire, and subsequent structural collapse of the World Trade Center (WTC) towers exposed response personnel, survivors, and bystanders to toxic substances in the form of dusts and gases. Continued exposures occurred in the days, weeks, and months that followed, but the exact nature of these exposures remains only partially characterized. This perspective study presents a consensus among the authors, who reserve their individual opinions on specific issues. In this study, we review the chronic and potential late developing lower respiratory tract diseases observed in former WTC site workers and speculate upon their possible causes.

Although WTC exposed individuals initially reported a wide-range of respiratory symptoms [Centers for Disease Control Prevention, 2004; Salzman et al., 2004], they mostly reported severe cough, which was given the eponym, ''World Trade Center Cough Syndrome'' [Prezant et al., 2002; Webber et al., 2009]. With time, however, the prevalence of this sentinel symptom decreased and the predominant respiratory symptom is shortness of breath [Webber et al., 2009]. While cough can be due to upper or lower airway disease, persistent shortness of breath increases concern that lower airway and/or alveolar injury has occurred.

The survivors of the WTC events are demonstrating a wider but still discrete spectrum of these responses [de la Hoz et al., 2008a; Prezant et al., 2008]. For upper respiratory diseases, chronic rhinosinusitis [de la Hoz, 2010], gastro-esophageal reflux disease associated with laryngeal involvement, and pharyngolaryngitis in isolation [de la Hoz et al., 2008b; de la Hoz, 2010] have been the predominant conditions. For lower respiratory diseases, chronic obstructive disease has become the hallmark WTC-related disease, affecting thousands of exposed individuals [Herbert et al., 2006; Oppenheimer et al., 2007; Aldrich et al., 2010; Rom et al., 2010; Weiden et al., 2010]. This condition is probably distinct from the more familiar forms of obstruction that are strongly (but not exclusively) associated with cigarette smoking [Thurlbeck, 1982; Wright, 2001]. The chronic obstructive airways disorder observed among WTC responders is a persistent inflammatory condition found among non-smokers as well as smokers and may express itself in large airways as asthma, or a non-specific chronic bronchitis, or as an aggravated pre-existing chronic obstructive pulmonary disease or asthma. Many WTC responders are also demonstrating disease of the small airways, and in a subset this appears to be emerging as a cause of significant impairment, as will be discussed. These conditions, which became apparent up to several months after September 11, 2001, are now chronic and will require long-term treatment.

Other lower respiratory diseases have also been reported post-9/11 but their frequency is not known. Sarcoidosis, affecting approximately 100 individuals, has been reported by the three largest WTC responder monitoring programs [Izbicki et al., 2007; Miller and Palecki, 2007; Jordan et al., 2008; Bowers et al., 2010; Crowley et al., 2010] and cases are probably present in other series [Safirstein et al., 2003]. There has been a report of two cases of acute eosinophilic pneumonia [Rom et al., 2002].

Two diseases, bronchiolitis and interstitial pulmonary fibrosis, have been reported in very few cases, [Mann et al., 2005; Izbicki et al., 2007; de la Hoz et al., 2008a,b; Wu et al., 2010] but remain biologically plausible as potential late-presenting diseases. If the currently observed WTC-related chronic inflammation of the upper and lower airways results in widespread bronchiolitis, airway remodeling, or interstitial fibrosis, it would be necessary to modify our current diagnostic and treatment approach [Friedman et al., 2008; de la Hoz, 2010; de la Hoz et al., 2010].

EXPOSURES

Most studies of the WTC responders divide the population being studied into exposure categories by the day and time of arrival at the scene [Prezant et al., 2002, 2008; Wheeler et al., 2007; de la Hoz et al., 2008a; Aldrich et al., 2010]. Respiratory health outcomes (symptoms, pulmonary function and disease) have shown exposure-response gradients, with initial arrival time or, less strongly, duration of work time at WTC, both showing associations with symptom frequency across all studied WTC cohorts [Prezant et al., 2002; Brackbill et al., 2006], or with diagnosis of WTC-related asthma [Wheeler et al., 2007], or lower airway disease [de la Hoz et al., 2008a].

The WTC dust was derived mostly from pulverized cement, and so consisted largely of calcined calcium carbonate. It does not contain more than trace high-atomic weight elements and so the dust itself is not visible on chest imaging. A unique feature of the WTC particulate matter is the generation of a highly alkaline pH in water, a characteristic it shares with cement dust, from which it was derived [McGee et al., 2003; Gavett et al., 2003]. The WTC dust therefore generated a high pH on the mucosal surface although it was of moderate intrinsic irritant potential in experimental laboratory animals [Gavett, 2006]. It thus falls into a middle range likely to lead to chronic effects. In general, the body responds less effectively to alkaline chemical injuries than to acidic chemical injury, because of the limited buffering capacity of blood and body fluids for substances of high pH [Lioy et al., 2002].

The known composition of the particle phase (dust) of the complicated mixture of dusts and gases that arose from constituents released in the WTC event is listed in

TABLE I. Known Constituents of the Plume Following the WTC Events

1. Pulverized cement dust (principally calcined calcium carbonate)
2. Pulverized and vaporized iron
3. Pulverized and combusted synthetic organic materials (plastics)
4. Combustion products
   - 4.1. Origin from jet fuel
   - 4.2. Origin from building contents
   - 4.3. Origin from structural fires
   - 4.4. Coagulated ultrafine organic particles, which may resemble fine particulate air pollution
5. Asbestos (chrysotile)
6. Synthetic vitreous fibers
7. Silica, crystalline
8. Glass fibers
9. Organic fibers (textile, cellulose of paper origin)
10. Hydrochloric acid and other chlorinated products
11. "Heavy metals," each limited to certain samples, including antimony, lead, chromium
12. Organochlorine compounds (dioxins, furans, PCBs)
13. Polycyclic aromatic hydrocarbons
14. Other organic compounds (mostly of lower toxicity than those mentioned above)

Table I [Lioy et al., 2002; McGee et al., 2002]. The concentrations of some toxic substances detected in representative dust samples are high but those of other toxic substances, such as the organohalide compounds, are low when compared to background levels in the environment. The predominant sources of toxic gases were the byproducts of combustion or pyrolysis from burning jet fuel and from secondary creation of irritant gases, fumes, and vapors resulting from the burning, vaporization, and pulverization of materials within the towers.

Exposure in the area was clearly very heterogeneous for days after the event [Chen and Thurston, 2001; Landrigan et al., 2004]. Local meteorological factors, such as wind and rain, also modified the exposure potential over time. For 4 months, smoldering fires continued to burn, diesel fumes were released, and WTC dust was re-aerosolized until the rescue/recovery efforts finally ended on May 30, 2002. Unfortunately, the intensity of exposure and the mixture of chemical substances both gaseous and coated to aerosolized dust to which WTC responders were exposed will never be known accurately because distributed environmental monitoring was either not in place or not appropriate for this type of exposure and the proximate monitoring stations that were available could not capture transient volatile components. For particles, ambient air pollution monitoring data from nearby regional monitoring stations generally included only airborne particle mass concentrations at two size cuts, PM_{10} ($PM \leq 10$ μm) and $PM_{2.5}$ ($PM \leq 2.5$ μm), and therefore could not capture the important contributions of ultrafine particles ($PM < 0.1$ μm) [Oberdörster, 2001] and volatile gaseous chemicals to morbidity and mortality studies [Sarnat et al., 2000, 2001].

The plume that enveloped lower Manhattan changed in composition rapidly as volatile components dissipated, larger particles settled, and fine particles, which remain aloft far longer, dispersed, all at different rates over short time periods. Ultrafine dust particles, which behave aerodynamically more like gases than dusts, would also have quickly dispersed. These physical factors make it challenging to reconstruct exposure to the dust itself, to volatile chemicals adsorbed onto the dust particles, and to potentially toxic constituents of the dust, including transition metals, particularly iron, which have a pro-inflammatory effect.

Individual exposure levels and composition of the inhaled materials were also subject to extreme variation, a natural consequence of plume behavior and the different exposure sources and locations relative to the individual. Additional variable factors include local air currents related to the explosion and collapse, wind eddies, re-entrainment (re-suspension in air) of dust during the rescue and recovery phases, release of trapped gases and dust in confined or poorly ventilated spaces during the rescue, recovery, and cleaning efforts. There were also differences in an individual's minute ventilation depending on the nature and the location [de la Hoz et al., 2008c] of the assigned duties.

The potential for toxicity is not always adequately reflected by measured or estimated airborne concentration levels for these chemicals or by analogy to more familiar dust-related disorders such as pneumoconioses or irritant-induced or aggravated asthma. For example, ultrafine particulate air pollution derived from jet fuel is likely to have characteristics similar to diesel-derived particulate matter, which is much more potent compared to coarse particulate matter than its mass would suggest [Frampton et al., 2004; Delfino et al., 2005]. Among metals, chromium, present in Portland cement, is a major cause of dermatitis with possible implications for chronic inflammation when deposited in the respiratory tract. Iron, if inhaled as fine particles and deposited intracellularly is associated with a catalytic effect (the Fenton reaction) generating free radicals in the presence of peroxide during inflammation, contributing to oxidant stress. These exposures may have effects out of proportion to their mass and their potential to contribute to toxicity must be considered.

Finally, for the individuals exposed there are differences in pre-exposure co-morbidity, including pre-existing respiratory disease [de la Hoz et al., 2008a], as well as differences in the host inflammatory response (although apparently not by atopic status [de la Hoz et al., 2009]). Thus, it is to be expected that there would be some

diversity among WTC responders in symptom profile and/or disease severity.

LUNG FUNCTION

The inhalation of irritant gases and fine particles produce effects not only on the upper (nose, pharynx, and throat) and larger airways (trachea and bronchi) of the respiratory system, but also depending on their depth of penetration, on the small airways (bronchioles) and lung parenchyma (alveoli). Depending on the host inflammatory response, airway injury can result in obstructive diseases and alveolar injury in interstitial diseases. Table II summarizes the elements of ''toxic inhalation'' [Guidotti, 1995, 2007]. Cough usually implies irritation of larger airways, although the symptom is entirely non-specific. The role of smaller airways and perhaps even the lung parenchyma may be equally as important in this population.

Pulmonary function decline and observed abnormalities since first exposure are profound in all exposure categories although significantly associated with exposure intensity as measured by initial arrival time at the WTC or duration of work at the WTC site. This remains true even after accounting for pre-existent disease and/or cigarette smoking [Banauch et al., 2003; Herbert et al., 2006; Rom

TABLE II. Pulmonary Response to Injury, Germane to Exposure Associated With WTC Events

1. Functional airway abnormalities
   - 1.1. Upper airway
     - 1.1.1. RUDS ("reactive upper airways dysfunction syndrome")
     - 1.1.2. Voice problems (dysphonia)
     - 1.1.3. Sleep apnea, obstructive
     - 1.1.4. Aerodigestive disorders, such as gastroesophageal reflux (complex interactions with the epiglottis, esophagus, the "lower esophageal sphincter," and reflux of stomach acid)
     - 1.1.5. Pharyngolaryngitis (isolated or in combination with above)
   - 1.2. Lower airway
     - 1.2.1. Large and central airways
       - 1.2.1.1. Airways hyperreactivity, acute and subacute inflammation
         - 1.2.1.2.1. Asthma-like wheezing (acute)
         - 1.2.1.2.2. Asthma-like airways hyperreactivity to environmental irritants (such as cigarette smoke, dust, smoke), cold, and exercise
           - 1.2.1.2.2.1. Irritant-induced asthma
           - 1.2.1.2.2.2. Reactive airways dysfunction syndrome
         - 1.2.1.2.3. Bronchitis and sputum production
       - 1.2.1.2. Bronchiectasis
     - 1.2.2. Small airways
       - 1.2.2.1. Bronchiolitis, expressed as "small airways disease"
       - 1.2.2.2. Constrictive bronchiolitis (progressive)
       - 1.2.2.3. Bronchiolitis obliterans (end stage)
       - 1.2.2.4. Fixed airways obstruction due to loss of alveolar elasticity and tethering (classic lesion of cigarette smoking)
2. Disorders of the tissue of the lung (parenchyma) other than airways
   - 2.1. Pulmonary edema
   - 2.2. Interstitial fibrosis
     - 2.2.1. Non-pneumoconiotic (not associated with retained dust and reaction to its presence)
       - 2.2.1.1. Granulomatous lung disease
       - 2.2.1.2. Diffuse fibrotic lung disease ("honeycombing")
     - 2.2.2. Pneumoconioses (specific disorders associated with dust retention and response)
       - 2.2.2.1. Disorders associated with particle overload in the lung
       - 2.2.2.2. Granulomatous disease due to dust (beryllium disease, zirconium as isolated granuomata, tungsten as giant cell interstitial pneumonia)
   - 2.3. Impaired immune function
   - 2.4. Oxidant stress injury
3. Migration of fine particles and secondary cardiovascular effects
4. Cancer
   - 4.1. Initiation of malignancy by a chemical carcinogen
   - 4.2. Promotion of a malignancy by a chemical promoter or co-carcinogen

et al., 2010]. The trend in decline in airflow has been measured longitudinally in rescue workers from the Fire Department of the City of New York (FDNY), both firefighters and Emergency Medical Services (EMS) workers. In the FDNY WTC Monitoring Program, 12,781, 92% of the 13,954 present at WTC between September 11 and September 24, 2001, contributed 61,746 quality-screened spirometry measurements [Aldrich et al., 2010]. Median follow-up from 9/11 was 6.1 years for firefighters and 6.4 years for EMS workers. Over the first year following the event on September 11, 2001 (hereafter ''post-9/11''), FEV_1 decreased substantially, more for non-smoking firefighters [−439 ml (95% CI:: −471 to −408)] than for non-smoking EMS [−267 ml (95% CI: −271 to −263)], both $P < 0.001$. On average this decline was 12–15 times the annual age-associated rate when compared to pre-9/11 measures in this cohort. There was little or no recovery in FEV_1 over the subsequent 6 years, with average annualized change in FEV_1 −25 ml/year for Fire and −40 ml/year for EMS. Reductions of similar magnitude were found for the forced vital capacity (FVC). The proportion of non-smokers with FEV_1 less than the lower limit of normal increased over the first year from 3% to 18% for firefighters and from 12% to 22% for EMS, stabilizing at about 13% for firefighters and 22% for EMS at 7 years [Aldrich et al., 2010]. Similar patterns were noted for FEV_1 <70%predicted. These changes were independent of smoking. Smoking had a small but significant effect on lung function in this population; the effect was small probably because most of the responders were relatively young. These results are consistent with those found in the ''NY/NJ Responder'' cohort or WTC responders studied in New York and New Jersey, in whom high rates of abnormal spirometry among non-FDNY workers at WTC, and little change over 3 years of follow-up post-9/11 were noted. In this same cohort, continued smoking, weight gain, and failure to respond to bronchodilators on baseline spirometry were associated with decline in FEV_1 over time [Skloot et al., 2004].

In most WTC responders the post-9/11 decrease in the FVC and the FEV_1 has been of similar magnitude, thereby leading to a preserved ratio (FEV_1/FVC) [Prezant et al., 2002; Banauch et al., 2006; Aldrich et al., 2010; Rom et al., 2010]. In most patients, this is a sign of a restrictive defect, but in the population of WTC responders this pattern, combined with the presence of symptoms of airways reactivity, responsiveness to bronchodilators, demonstration of airway hyperreactivity, and air-trapping, are more consistent with an obstructive pathophysiology [Banauch et al., 2003; Weiden et al., 2010]. In the general population of pulmonary patients, and in many patients in the WTC responder population, such findings are often associated with obesity (increasing chest wall impedance) or asthma (air trapping) [Miller, 2007; Hyatt et al., 2009]. Clinically, this pattern is more consistent in the WTC-responder population with air trapping and the diagnoses of asthma, chronic bronchitis, and bronchiolitis.

High-resolution CT scans with inspiratory and expiratory views [Prezant et al., 2002; Mendelson et al., 2007; Weiden et al., 2009], frequency-dependent compliance, and forced oscillometry [Skloot et al., 2004; Oppenheimer et al., 2007] demonstrate that the small airways or bronchioles are the zone most affected by WTC inhalational exposure.

When obstruction involves the small airways, an ''all or nothing'' phenomenon results. The bronchiolar wall becomes an all-or-nothing valve (i.e., a Starling resistor) controlled by the pressure across the bronchiolar wall [Lopez-Muniz et al., 1968; Howard, 1971]. When pressure during forced expiration in the surrounding alveoli is less than in the bronchiolar lumen, flows are normal (or nearly so because there may be other causes of impedance). During forced expiration, when pressure in the surrounding alveoli is greater, the diaphanous wall of the membranous bronchiole collapses and shuts off airflow. Airways that close off at a higher than normal closing volume during the FVC maneuver do not contribute to the full measure of vital capacity during the FVC test or to FEV_1 after closing volume is reached [Howard, 1971]. Paradoxically, this maintains the FEV_1/FVC ratio even though flows are actually reduced in absolute terms. The result is a rough balance or offset, in which the FVC is reduced proportionate to the population of airways in which flow stops, masking the obstruction to flow. Air trapped behind an obstruction in the lung creates a volume displacement, which can be observed as an increase in residual volume (RV) on forced expiration. This process does not occur uniformly throughout the lung, but instead develops by recruitment, as more and more small airways close prematurely leading to higher closing volumes [Hyatt et al., 2009].

Air trapping and increased resistance and obstruction in the small airways may only be detected by special diagnostic studies. Spirometry is a poor screening test for small airway flow limitations as there may be only minor changes in the shape of the flow-volume loop or in mid-expiratory flow rate reductions. It may also be silent when lung volumes are measured by helium dilution and underestimated when measured by body plethysmography. Air trapping at an elevated closing volume increases the actual physiological RV during forced expiration, but measurable RV (which is the difference between total lung capacity and vital capacity) may not show much change because intrathoracic pressures are not forced during measurement of total lung capacity by either gas dilution or plethysmography [Wanger et al., 2005]. Given how these conventional tests are conducted, an elevated RV would be highly significant when present [Weiden et al., 2010] but may be

absent altogether. Even if present, the magnitude of elevation would underestimate the actual degree of air trapping at closing volume. Interpretation of changes in RV is complicated by the absence of reference standards, interlaboratory variation, and compounded uncertainties in measurement of lung volumes.

While no test of function is specific for small airways diseases, some findings would indicate that air trapping and small airways obstruction at the bronchiolar level are present and may be evolving in this population [Wanger et al., 2005]. These are summarized in Table III.

Air trapping can be detected radiographically by high resolution, thin section CT scans, especially if images are compared between inspiration and expiration [Konen et al., 2004; Parambil et al., 2009]. This technique has also been used to demonstrate air trapping in WTC-exposed individuals [Mendelson et al., 2007; Weiden et al., 2010]. The technique has been demonstrated to identify bronchiolitis obliterans at an early stage in lung transplant patients, who are at high risk for a form of constrictive bronchiolitis on an immune basis and shows a high specificity for that condition (80–100% in a series of 26 cases) [Parambil et al., 2009]. Unfortunately the sensitivity of the test was much too low for a viable screening test (44–64%). Since the method is based on detection of air trapping and not the specific characteristics of the bronchiolitis, the test would be expected to perform with the same characteristics for WTC dust-related disease [Konen et al., 2004].

Perhaps the most compelling demonstration of increased small airways resistance has been shown using forced oscillometry, a non-invasive, inexpensive technique that results in no patient discomfort or radiation exposure and that correlates closely with frequency dependence of compliance, the gold standard to demonstrate small airways obstruction [Oppenheimer et al., 2007]. Two studies of WTC respondents have found small airways resistance to be increased (elevated resistance at 5 Hz (R5), a global index influenced by both small and large airways; elevated resistance at 5–20 Hz (R5–R20), an index of frequency dependence of resistance that reflects small airways function; and an integrated area of low-frequency reactance (AX) that provides a complementary measure of small airways obstruction) [Skloot et al., 2004; Oppenheimer et al., 2007]. As both of these studies were on non-randomized subsets, it remains to be determined whether these averages apply to the large population of WTC responders.

OBSTRUCTIVE AIRWAYS DISEASES

WTC responders have demonstrated airways reactivity as shown by positive response to bronchodilators by spirometry (FEV_1) and bronchial hyperreactivity by methacholine challenge, or suggested by elevated RV with normal diffusion capacity by pulmonary function testing, and air trapping and bronchial wall thickening by chest CT imaging [Weiden et al., 2010]. Using initial arrival time at the WTC, an exposure-response gradient was demonstrated. Similar symptoms (nasal drip/congestion, sore throat, cough, wheeze, chest tightness, and shortness of breath) have been described in every group of WTC rescue/recovery workers [Skloot et al., 2004; Herbstman and Schwab, 2005; Tapp et al., 2005; Herbert et al., 2006; Buyantseva et al., 2007; Kelly et al., 2007; Webber et al., 2009] as well as in exposed community residents, children, and office workers [Centers for Disease Control Prevention, 2002; Reibman, 2003; Szema et al., 2004]. The WTC Health Registry confirmed that adults with significant WTC exposure reported increased rates of newly physician-diagnosed asthma was associated with (1) being caught in the dust cloud on 9/11/01; (2) earlier arrival time relative to the collapse; (3) work on the pile; and (4) cumulative exposure [Wheeler et al., 2007]. The Registry

TABLE III. Findings Suggesting Air-Trapping and Small Airways (Bronchiolar) Disease

Standard pulmonary function tests used for screening
The flow-volume loop paradoxically does not show signs of either "small airways disease" or restriction despite the reduction in FVC
Mid-expiratory flow rates are reduced
A bronchodilator response in the FVC or FEV_1 is not evident on spirometry
A significant discrepancy is present in vital capacity (VC) measured by different techniques, with the forced vital capacity (FVC) being much smaller than the "slow" VC obtained when lung volumes are measured by means that do not require forced expiration
Diagnostic testing and physiological studies
RV is variable on conventional volume testing with higher RV measured by body plethysmography than helium dilution and this variability is otherwise unexplained
RV is increased by more sensitive and reliable tests, such as body plethysmography during controlled breathing maneuvers
Closing volume is elevated on the closing volume ("nitrogen washout") test, which is seldom used in clinical medicine
Forced oscillometry demonstrates an increase in peripheral small airways resistance and of frequency dependence
Air trapping out of proportion to pulmonary function is observed on HRCT scanning, performed with inspiratory and expiratory views
Frequency dependence of dynamic compliance is the "gold standard" for small airways dysfunction but it is an invasive technique only available in a few centers

also demonstrated an increased incidence of asthma exceeding expected population incidence until late 2003 [Brackbill et al., 2009].

In a sample of rescue workers from FDNY whose bronchial hyperreactivity was measured 6 months later, those who arrived at the WTC site on the first day of 9/11 were 7.8 times more likely to experience airways hyperreactivity than were those firefighters who arrived at a later date and/or had lower exposure levels [Banauch et al., 2003]. In this same study, persistent asthma emerged in 20% of highly exposed (present during the morning of collapse) and 8% of moderately exposed rescue workers (arrived after the morning of 9/11 but within the first 48 hr) [Prezant et al., 2002].

It is important to distinguish between reactive airways caused by the irritant effect of WTC dust and other exposures and the diagnosis of ''reactive airways dysfunction syndrome'' (RADS) as originally proposed by Brooks et al. [1985]. The condition observed among WTC responders more closely resembles an irritant asthmatic bronchitis rather than the relatively pure new-onset airways reactivity occurring within 24 hr of a single acute gas/vapor exposure proposed by Brooks. This distinction is important because ''RADS'' has become a catch-all diagnosis frequently applied uncritically to these and other respiratory conditions with a consequent loss of accuracy and prognostic value.

The known toxicology of the dust and gases present at the WTC explains why those exposed demonstrate increased incidence and persistence of obstructive airways disease most commonly characterized as asthma or asthmatic bronchitis. COPD and emphysema share many features of the chronic obstructive airways disorder observed among WTC responders but currently this population does not demonstrate reduced diffusion capacity on pulmonary function testing or evidence for general lucency and bullous disease on CT that are typical of smoking-associated COPD and emphysema in isolation, or the pathological features related specifically to cigarette smoke, such as peribronchiolar alveolitis and hypertrophy of bronchial glands.

The findings of air trapping and increased small airways resistance support the conclusion that airways obstruction has developed. Although we do not have sufficient evidence to draw conclusions at this time, our clinical analyses suggest that this is potentially evolving in WTC responders, either as a group or more likely in certain subsets, and expressing itself early on as small airways disease possibly at the level of the terminal bronchiole.

BRONCHIOLITIS

The expression of disease at the bronchiolar level is small airways disease on pulmonary function testing. Bronchiolitis occurs distal to the airways associated with asthma, reactive airways, at the level where the bronchiolar wall is membranous. Bronchiolitis, regardless of type (constrictive or obliterative) or cause (congenital, infectious, inhalational, neoplastic, autoimmune, or transplantation) shares many features and may develop into airways obstruction. Bronchiolitis also presents with cough and shortness of breath, obstruction, or a mixed process on pulmonary function testing, flat bronchodilator response, and normal diffusion until substantial disease has occurred. Chest CT imaging shows air trapping as well as possible bronchial wall thickening, bronchiectasis, ground glass opacities, centrilobular nodules from luminal impaction, and, when mucus is present, a tree-in-bud pattern [Rossi et al., 2005].

Bronchiolitis due to toxic inhalation has been reported after exposures to irritant gases, including phosgene, nitrogen dioxide, ozone, cadmium, and ammonia [Guidotti, 1995, 2007; Visscher and Myers, 2006]. Diacetyl, a component in butter-tasting food flavoring, provokes similar inflammation producing a bronchiolitis known as ''popcorn lung'' [Kreiss et al., 2002; Parmet and Von Essen, 2002; Schacter, 2002]. In fact, any irritant that can cause a bronchitis can probably cause a bronchiolitis if it penetrates to the bronchiolar level, with possible progression to bronchiolitis obliterans depending on the severity of airways damage and control of the inflammatory response.

The pathological picture of ''constrictive bronchiolitis'' (the term is variably used by pathologists) may be an underappreciated process in the chronic obstructive airways disorder that characterizes WTC responders [Colby, 1998; Schlesinger et al., 1998; Markopoulou et al., 2002; Ryu et al., 2003; Fournier et al., 2006; Visscher and Myers, 2006]. Constrictive bronchiolitis is a smoldering inflammatory process involving bronchioles, that leaves surrounding alveoli unaffected. Constrictive bronchiolitis may progress to the more familiar bronchiolitis obliterans, the end stage where the airways are completely obliterated by fibrosis [King, 1989; El-Zammar et al., 2009]. While it progresses, the condition may result in respiratory impairment, expressed as ''small airways disease'' with reduction in mid-flows on expiration. At the obliterative end stage, the airway is no longer patent. After, and probably for some time before this stage (because an incompletely occluded bronchiole will close early during expiration), all airways and alveoli distal to it are no longer ventilated through the airway during the breathing cycle. Because of collateral ventilation, however, these regions may remain inflated and may trap air and become hyperlucent on chest film.

Four cases of constrictive and obliterative bronchiolitis have been reported among WTC responders [Mann et al., 2005; de la Hoz et al., 2008a]. Recently, histological findings from seven WTC responders who developed

severe respiratory impairment were reported from a study initially designed to identify mineral dusts in lung tissue [Wu et al., 2010]. Although the presence of carbon nanotubules attracted greater attention, the presence of a severe, evolving inflammatory process centered on bronchioles and progressing to fibrosis was also noted in 2 of the 7 subjects [Wu et al., 2010]. Thus, it appears that at least some WTC responders are already demonstrating a progressive bronchiolitis but whether this is a broader pattern is not known.

The paucity of recognized cases to date may be construed as evidence against constrictive bronchiolitis being a significant contributor to future lung disease among WTC responders. Most cases of bronchiolitis occur within months to a few years post-insult, but this is highly variable, and there are no studies of subjects following inhalation of alkaline particulate matter, such as the WTC dust [Epler and Colby, 1983; Meyers and Colby, 1993; Guidotti, 1995; Parmet and Von Essen, 2002]. This suggests that constrictive bronchiolitis in this population, which may well affect a subset of WTC responders, is not progressing quickly overall and has not resulted in mucus plugging.

Diagnosing or identifying small airways disease indicative of a progressive bronchiolitis presents a challenge. Although increased peripheral airways resistance on forced oscillometry or air-trapping on CT may be the most sensitive findings for bronchiolitis, and have been documented in WTC responders [Mendelson et al., 2007; Oppenheimer et al., 2007], they are not specific for the condition. Oscillometry is not readily available or fully standardized with normative data. CT scanning involves radiation exposure and is too expensive and impractical for screening large populations. Biopsy for pathologic examination may differentiate among these diseases but invasive procedures would not be clinically indicated unless the patient is progressing to impairment and is unresponsive to standard therapy, or there is another reason, such as a nodule, to obtain tissue for diagnosis. This has been uncommon to date in this cohort.

Thus, taken together, the radiological and pathological evidence suggest that a bronchiolitis component, if present, may be evolving for some members of this population in an unusually slow time course but this cannot be demonstrated definitively until such time as cases come to biopsy or autopsy. Confirmation would ideally be obtained by open lung biopsy, which additionally offers the opportunity for mineralogic analysis. It is likely that biopsies will not be limited to patients with progressive symptoms and functional loss but also obtained from patients with incidental nodules and tumors. The opportunity to determine the prevalence and progression of constrictive bronchiolitis by systematically examining tissue from these cases must not be overlooked.

Among WTC-exposed patients for whom the conventional diagnoses of asthma, RADS or chronic bronchitis are inappropriate, bronchiolitis offers an appropriate diagnostic alternative for an obstructive disorder characterized by dyspnea, cough, air-trapping, small airway changes on oscillometry with abnormal frequency dependence of compliance, and characteristic changes on CT scan.

INTERSTITIAL PULMONARY DISEASE

A normal FEV_1/FVC ratio also raises the possibility that a restrictive defect from interstitial lung disease may be present in symptomatic individuals with WTC exposure. In a restrictive defect the reduction in FEV_1 occurs due to reduced lung volumes, but not due to obstruction. The FEV_1/FVC (%) may eventually become supra-normal because elastic recoil is increased even though lung volumes (FVC, TLC, FRC, RV) are reduced.

The use of chrysotile asbestos for insulation was discontinued midway during the construction of the WTC Tower 1 and was not used in the WTC Tower 2. WTC dust did contain low levels of asbestos fibers (0.8–3.0% chrysotile asbestos by mass [Lioy et al., 2002]), some crystalline silica, and higher levels of man-made vitreous fibers [Lioy et al., 2002; McGee et al., 2003; Lowers et al., 2010]. Therefore, a slowly evolving form of pulmonary fibrosis may occur over the next 20 years, and if this occurs would likely show features typical of early asbestosis, which also begins at the bronchiolar level.

Interstitial pulmonary fibrosis can occur after inhalation of chemicals and dusts with varying latency periods ranging from months (toxic inhalation of oxidant gases and accelerated silicosis) to decades (simple silicosis, coal workers' pneumoconiosis, and asbestosis). A non-granulomatous pneumoconiosis resulting in rapid pulmonary fibrosis generally requires an overwhelming acute exposure of a dust with high fibrogenic potential, such as silica or asbestos, which were not present at high levels in air following the WTC event. A more slowly evolving or delayed form of pulmonary fibrosis may, however, occur.

Following WTC exposure, imaging methods suggest that some degree of interstitial fibrosis has already occurred in a small number of WTC responders, 19 of 29 individuals who underwent CT scan for diagnostic purposes, showing mild interstitial changes [Mendelson et al., 2007], but evidence for an increased prevalence of diffuse pulmonary fibrosis overall is lacking. The NYC Fire Department has reported 2 cases of eosinophilic pneumonitis, both resolving with treatment with systemic corticosteroids [Rom et al., 2002], and 4 cases of diffuse pulmonary fibrosis, of which 2 required lung transplantation [Izbicki et al., 2007]. The NY/NJ WTC responder cohort has reported diffuse interstitial fibrosis in four patients [Wu et al., 2010].

Interstitial lung disease due to sarcoid-like granulomatous inflammation has occurred at increased frequency among WTC responders but not in large numbers. Sarcoidosis is a disorder of the immune system of unknown cause but specific pathology, characterized by the formation of structured aggregates called granulomas, of inflammatory cells, called giant cells, that mimic the characteristic response to a persistent antigen in the lung and often other organs, although no such antigen has been identified. In a cohort of nearly 14,000 FDNY rescue workers (firefighters and EMS workers) studied during the first 5 years post-9/11, pathologic evidence consistent with new-onset sarcoidosis (or sarcoid-like granulomatous lung disease) was found in 26 FDNY rescue workers, all with intra-thoracic adenopathy and 6 (23%) had additional disease outside the chest [Izbicki et al., 2007]. Thirteen were identified during the first year post-9/11 (yielding an incidence rate of 86/100,000) and 13 during the next 4 years (yielding an average annual incidence rate of 22/100,000; as compared to 15/100,000 for FDNY personnel during the 15 years pre-9/11 and 5–7/100,000 for a male Caucasian population). These studies do not account for reporting and detection biases inherent to the compensation and disability claims post-9/11. Similar findings were suggested by studies in two other cohorts, the WTC Registry and the NY/NJ WTC Responders [Jordan et al., 2008; Crowley et al., 2010]. The three studies have recruitment, surveillance, and reporting biases that make comparisons among them and to referent populations difficult but the consistency of their findings is impressive. The component(s) of WTC dust that may be responsible for this granulomatous reaction remains unknown since substances known to produce granulomatous or giant cell reactions, such as beryllium, zirconium, or tungsten, were not found in WTC dust [Lioy et al., 2002]. Whether sarcoidosis is an outcome causally associated with exposure to WTC dust therefore remains to be determined.

MONITORING AND MANAGEMENT

Given the already documented accelerated decline in lung function in the first year after the attack to the WTC and its persistence over 7 years [Aldrich et al., 2010], continued long-term monitoring of pulmonary function in WTC exposed cohorts is critical. It is the most practical way to track the evolution of airways disease and to identify those in need of additional diagnostic testing and treatment. The initial inflammatory process reflected by the decline in pulmonary function may progress to airway remodeling (bronchiolitis, chronic bronchitis), emphysema, or interstitial lung disease in a proportion of exposed subjects.

Because many WTC responders were previously healthy and often athletic, care must be taken in the interpretation of pulmonary function results. A healthy worker effect will be present, with many above normal pulmonary function tests after adjusting for age, gender, height, and race. Thus, declines in pulmonary function to levels that typify respiratory impairment in the general population may not occur for some time. For example, an exposed individual with a vital capacity of 120% predicted would have to lose 36% of lung function before reaching 80% of predicted, a conservative definition of abnormal, instead of 20% for a person who began at 100%. For these reasons, the longitudinal change in pulmonary function is far more revealing than a cross-sectional comparison with population norms.

Because of the type of workers who performed the physically demanding jobs of WTC rescue/recovery work are typically healthy, many exposed individuals have substantial pulmonary reserve and additional time may be required for sufficient numbers of functional units to be compromised enough to lead to symptoms and limitations on pulmonary testing. Only when the inflammatory process involves a sufficiently large enough number of bronchioles or alveoli do symptoms and pulmonary function abnormalities become apparent. Latency periods of months to several years are typical of bronchiolitis secondary to toxic inhalation exposure [Guidotti, 1995]. Latency periods measured in decades are common for interstitial lung disease. Asthma may have a latency period before becoming clinically apparent if the process requires cumulative exposure to irritants. Progression is likely to be discontinuous, with symptoms arising abruptly, either because a threshold is reached or because decompensation occurs with acute illness or other precipitating factors resulting in acute inflammation, occlusion, or mucus plugging, and at end-stage in severe airway remodeling, emphysema, or interstitial fibrosis [Walters et al., 2007]. Whether these latency periods will hold true for WTC exposure remains unknown. WTC dust was unique. Airway remodeling, chronic bronchitis, and perhaps even emphysema may develop over time in those with continued accelerated decline in lung function.

Unfortunately, the literature on early treatment to prevent airway remodeling in diseases, such as asthma, bronchiolitis, COPD, or the development of other pulmonary diseases such as emphysema or interstitial fibrosis is sparse. Thus, clinical trials should be offered to those WTC dust-exposed individuals who demonstrate an unfavorable trend in lung function or who are refractory to standard treatment.

A critical step in managing the problem of chronic obstructive airways disease in the WTC responder population is to identify the underlying disease processes. Converging evidence from epidemiology, clinical medicine, pulmonary pathology, respiratory physiology, and inhalation toxicology points to a broader spectrum of diseases

than previously appreciated and to the bronchiole or possibly interstitium as targets.

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