Chapter 4

PULMONARY RESPONSE TO AIRBORNE HAZARDS: INTERPRETING CASES OF SUSPECTED DEPLOYMENT-RELATED LUNG DISEASE

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SUMMARY

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INTRODUCTION

Respiratory complaints following deployment are common, and most are attributable to known risk factors. However, a small minority of cases in returning veterans of south Asia and the Middle East may suggest a novel or at least unexplained pathology. This chapter is directed largely at these cases and what they may tell us about the following:

- Exposures and pulmonary responses that we do not understand.
- Exposures of concern for future health that can be prevented during employment.
- Directions in which new technology or deployment management strategies may need to go.
- Sentinel cases, early clinical signs, biomarkers, and population-based indicators that can identify warriors and veterans who are at risk.
- Disease processes that might be addressed by appropriate and specific treatment rather than by general suppression of inflammation.
- Preventive measures (either primary, secondary, or tertiary) that reduce risk of disability among the deployed.

EXPOSURE CHARACTERISTICS

Some of these cases were associated with particular events that may have presented exposure to specific hazards, such as the Mishraq Sulfur Mine, in which sulfur dioxide would have been the relevant exposure. Others, however, were not. One universal in theater, however, was the presence of burn pits.[1] These are trenches in which combustible trash (undoubtedly with some noncombustible materials as well) is doused with diesel fuel and set on fire, producing emissions that consist of diesel fuel combustion products, products of combustion of the trash stream, and possibly entrained particles of dirt and other material of crustal origin.

Any consideration of the inhalation toxicology of combustion products begins with two phases: (1) particulate matter and (2) gases. However, particles should be understood not as a distinct and unrelated phase, but as a complex consisting of a particle core onto which is adsorbed other substances, including gases and volatile organic compounds. Emissions from burn pits are determined by several characteristics.

- Because burn pits are at or below ground level, their dispersion plumes are likely to spread laterally and to fumigate the area downwind, especially in the early morning, when an inversion would be expected.
- Burn temperatures are variable. Because of the use of accelerants (diesel fuel), they probably burn hotter than simple trash fires, but not as hot as diesel engines or furnaces.
- Efficiency of a burn pit is much less than that of an engineered incinerator, leading to production of carbon monoxide, more complex hydrocarbon species, and coarser particulate matter than might be expected from a more structured incineration process.
- In keeping with other combustion sources, toxic emissions are most likely to occur when the fire is beginning from a cold start and when it is cooling down, because this is when polycyclic aromatic hydrocarbons condense and are not consumed. Carbon monoxide is more likely to be formed from incomplete combustion, and thermal updrafts are less.
- Combustion of diesel fuel in the burn pit does not occur under pressure, as it would in a diesel engine. Thus, the emissions profile may be less rich in fine particulate matter compared with coarse particulate matter. Also, secondary fine particles from agglomerated sulfate are less likely to be an issue with emissions from burn pits compared with ambient air pollution derived from diesel engine exhaust.
- Content of the trash being burned—including plastic materials (such as vinyl chloride, which is a chlorine source for polychlorinated dioxins and furans), electronic components, human waste, and materials containing metals—may make the composition of emitted particulate matter variable in composition.

Toxic effects of particulate matter will be emphasized in this chapter because it is more complex, and toxicology is more consistent with longer term, subchronic health effects. Gaseous emissions from the burn pit are more likely to result in acute hazards and to be recognized at the time. Carbon monoxide, in particular, is a systemic poison rather than a pulmonary hazard. Therefore, it probably plays little if any role in open-air trash burning.

MODELS FOR UNDERSTANDING THE PULMONARY RESPONSE

There are several possible models for understanding the effects of particulate matter from burn pits on the lungs. They include learning from the following:

- occupational health experience of firefighters, including responders to the World Trade Center (WTC) tragedy;
- ambient air pollution;
- diesel engine exhaust studies;
- combustion of crude oil, as in oilfield fires; and
- cigarette smoking (this is both an important confounder for any study of combustion-related health effects and a model for effects of combustion products).

Table 4-1 describes the dominant chemical species for each of the two phases for each of these model pollution regimes.

These models overlap considerably and individually approximate exposures likely to occur from a burn pit. But none of them exactly replicates the exposure regime characteristic of a burn pit. Care should also be taken not to fall into the trap of *paradigm blindness*, wherein enthusiasm for an explanatory model that seems to fit the situation reduces awareness of differences and anomalies that may be significant in practice.

Firefighters Model

Firefighters represent an attractive model for healthy warriors because of their stringent selection for fitness. Obviously, the exposure profile of career firefighters is different from that of soldiers maintaining or downwind of burn pits, but the constituents of the smoke may not be much different. Firefighters are exposed to many inhalation hazards, most related to combustion products of fires, diesel exhaust, or airborne hazards from unusual fires (eg, pesticides) that occur on occasion throughout a firefighter's career, which of course is much longer than a tour of duty.[2,3]

It is well established that firefighters have an increased risk of myocardial infarction that persists about 24 hours or more after exposure to a fire.[4] It is not entirely clear, however, whether this is attributable to combustion products or to the stress response and catecholamine sensitization, because arrhythmias can be demonstrated from the stress of responding to the alarm alone. In terms of chronic disease, there appears to be an elevated risk of cancer for the kidney,

TABLE 4-1

CONSTITUENTS OF EMISSIONS FROM COMBUSTION IN FOUR MODEL EXPOSURE REGIMES AND CATEGORIES OF HEALTH EFFECTS

Phase	Firefighting	Ambient Air Pollution	Diesel Engine Exhaust	Cigarette Smoking
Particulate	Coarse and fine particulate matter with PAHs, chlorinated hydrocarbons	Coarse and fine particulate matter with PAHs, adsorbed metals	Coarse and fine particulate matter with PAHs	Coarse and fine particulate matter with PAHs, cadmium
Gas	Carbon monoxide, 1,3-butadiene, vinyl chloride	Carbon monoxide, oxidant gases* (air toxics)	(Carbon monoxide) Nitric oxide	Carbon monoxide, acrolein, numerous other gases
Health effects attributable to exposure	(Cardiovascular) Cancer	Cardiovascular respiratory cancer	(Acute lung inflammation) Cancer	Cardiovascular respiratory cancer

*Including oxidants that play no role in fresh diesel engine exhaust: ozone, peroxyacetyl nitrates, and aldehydes; nitrogen dioxide formed photochemically from nitric oxide.
PAHs: polycyclic aromatic hydrocarbons
Note: Parentheses indicate variability or uncertain associations.

bladder, and possibly the lung.[5] Lung disease, however, has proven elusive as an occupational association among firefighters, possibly reflecting a healthy worker effect of both selection and retention. Previous generations of firefighters tended to smoke less than the general population, and those in the current generation rarely smoke.

A population of particular concern has been surviving New York Fire Department members who responded to the WTC catastrophe. Their exposure profile was distinctly different from that of career firefighters and included heavy exposure to coarse particulate matter and heavier exposure to contaminants (eg, metals). Their exposure also most often occurred at the scene without personal protection.[6]

A disproportionately large number of these workers have experienced respiratory impairment in the years since, often diagnosed as asthma but reflecting a variety of conditions. At least some WTC responders, including firefighters who were athletic prior to exposure, subsequently developed serious, disabling disease as their underlying condition progressed. These have been attributed to asthma, but this explanation does not cover all cases.[6]

The known toxicology of the agents satisfactorily explains why WTC responders have experienced a high incidence of respiratory disease characterized by airways hyperreactivity. However, a progressive obstructive defect analogous to irritant asthma may not be the whole story. It does not explain why the frequency of symptoms appears to be getting worse in a subset of WTC responders or the anomalous findings that have emerged.

Many WTC responders are showing a decrease in forced vital capacity (FVC), which is usually indicative of restrictive disease, in the presence of a progressive decrease in forced expiratory volume in 1 second (FEV_1) that is more likely an indicator of air trapping in atypical obstructive airways disease.[6] The significance of the pattern and the importance of heterogeneity in the population as air trapping evolved may not have been appreciated at first because of the high level of statistical aggregation, wherein results were reported. Clinical deterioration has not been reported for the majority of surviving WTC responders, but a few have had unexplained disabling respiratory symptoms; the records of two responders came to the author's attention during preparation for litigation between the firefighters and the City of New York that ended with the settlement reached in 2010. Observations in these cases suggest findings at the bronchiolar (small airway) level that may or may not have their counterpart in cases of lung disease possibly arising from deployment and burn pit–associated exposures.

Constrictive bronchiolitis may be developing in at least some of the WTC cases, as suggested by findings consistent with air trapping at the bronchiolar level.[6] One case of bronchiolitis obliterans has already been reported among WTC responders, a possible sentinel event. The significance of these findings is that bronchiolar, or "small airway," disease may be more significant and more important as a response to toxic inhalation than previously appreciated, with implications for the deployed population in which constrictive bronchiolitis has already been reported.[7] Unfortunately, little is known of this condition in the context of toxic lung injury.

Constrictive bronchiolitis is characterized by a silent period, with latency depending on the underlying disease. It is possible that some WTC responders are in a silent period for the condition as the latency elapses. One reason for the silent period may be evolving inflammation, whereas cellular signals are released and stimulation of scar tissue is occurring. In this sense, latency would be similar to fibrogenic pneumoconioses (eg, asbestosis or silicosis), wherein proliferation of fibrosis takes at least 10 years until it can be seen on chest X-ray film. But a latency period can also be seen for toxic gases (eg, nitrogen dioxide) that result in interstitial fibrosis, thus presenting radiologically as *honeycombing*. Another reason for the silent period may be the time required for a sufficient number of functional units to be compromised enough to show a defect on testing. Functional reserve, in the form of numerous redundant units, preserves lung function until damage is advanced. Only when a sufficient and rather large number of bronchioles close down does an abnormality become apparent (eg, shortness of breath or pulmonary function testing). This logically would take longer for subjects whose bronchiolar walls are not weakened by smoking. Latency is not consistent with reactive airways dysfunction syndrome (RADS) or the onset of irritant asthma that provokes an airway response immediately after exposure that then persists. Firefighters other than WTC responders have not demonstrated apparent increased mortality from lung disease.[8]

Most of the functional disturbance that is a consequence of either conventional or WTC-related exposure of firefighters is likely to be reflected in changes in airways function, particularly airways' reactivity or inflammation, the major form of which is asthma. The cardinal symptoms of asthma are episodic: shortness of breath, wheezing, and coughing. The cardinal symptoms of bronchitis are cough and sputum production. However, these are not the only manifestations of hyperactive or inflamed airways. Other symptoms and signs may be present that interfere with daily life, especially fitness for duty as a firefighter or in another active job.

Monitoring pulmonary function is the most practical test to identify and track the evolution of this type of respiratory disease in this population. But care must be taken when interpreting the results. Firefighters, like healthy warriors, are a prescreened population, selected to be fit for duty in a strenuous occupation that favors strength and stamina. A firefighter who has supranormal pulmonary function (a vital capacity greater than the upper limit of that predicted in a big man) may have significant and progressive impairment that does not show up as abnormal on pulmonary function

tests. A firefighter with a vital capacity of 120% predicted would have to lose 36% of lung function before reaching 80% of predicted, which is a conservative definition of abnormal, instead of 20% for a person who began at 100%. The individual trend may be more revealing than a comparison against population norms.

Urban Air Pollution Model

Urban air pollution has a number of similarities with burn pit emissions, specifically the health risk of particulate matter in ambient air pollution, especially derived from diesel emissions. Although the two situations share the characteristic that both have an admixture of pollutants from sources other than diesel, the sources of combustion products are not similar. The two differ in other important ways because exposure to burn pit emissions involves fresh emission of combustion products, and urban air pollution involves predominantly air pollutants that have "aged" in the atmosphere for a period, usually hours. The aging process in air pollution is important in the particulate phase for agglomeration of larger particles from fine particle nuclei and for increasing adsorption of volatile and aerosolized contaminants. The aging process is important in the gas phase for photochemical processes that lead to secondary pollutants (eg, ozone, nitrogen dioxide, and aldehydes). To the extent that these secondary processes modify the pathophysiological response, they render analogy to air pollution health effects less certain.

The epidemiological evidence for health effects is robust and provides clues to health outcomes of concern. However, the experimental evidence may be of greater value because of the acute high exposures that may be associated with burn pits.[1] Emissions from diesel engine exhaust are mixed with other air pollutants to produce a characteristic mix in urban air pollution. The composition of this mix is summarized in Table 4-1. It should be noted that, in addition to primary pollutants such as particulate matter, ambient air pollution contains many secondary pollutants that would not be expected to be present in emissions from burn pits. These include ozone, nitrogen dioxide, and other potent oxidizing photochemicals that are responsible for much of the effect of urban air pollution.

The particulate phase of urban air pollution is derived in part, and until recent changes in diesel technology, largely from diesel engine exhaust emissions. Fresh diesel engine exhaust produces coarse and fine particulate matter, nitric oxide (nitrogen dioxide is a secondary product not present in diesel exhaust), carbon dioxide, some carbon monoxide (much less than gasoline engines), and oxidized sulfur compounds (sulfur dioxide and sulfates), which vary depending on the sulfur content of fuels.

Ambient air pollution consists of particulate matter in three somewhat overlapping distributions characterized as cut points, but best understood as distinct particle populations: (1) coarse (£10 mm aerodynamic diameter, containing the bulk of the particulate mass); (2) fine (£2.5 mm); and (3) ultrafine (£0.1 mm, representing the largest number of individual particles). Each cut point represents a particular mode or population of particulate matter differentiated by composition and size. Particles in the coarse mode penetrate efficiently to the lower respiratory tract and are efficiently retained in the alveoli. However, they are also large enough to be deposited efficiently on the epithelial surface of bronchi and small airways, and are thus likely to have airways effects, alveolar effects (mediated in part by macrophage uptake), and systemic effects. Particles in the fine range penetrate to the alveoli efficiently, but are less likely to deposit in airways and more likely to migrate from the deep lung into the circulation and adjacent structures through intracellular junctions and cells.

Ultrafine particles behave more like gases than particles in their flow behavior and penetration to the deep lung. They migrate relatively freely, with the potential for systemic effects. However, evidence for significant health effects is weaker than for fine particulate matter.[9]

The smaller the particle size, the larger the surface area. Surface adsorption is critical to the biological effects of particulate matter because the surface of these particles has a high affinity for many biologically active chemicals. Fine and ultrafine particulate matter have many orders of magnitude greater capacity for binding volatile organic compounds in their surface and delivering them to deeper structures.

Coarse particulate matter predominantly consists of dust, particles of crustal origin (basically, very small dirt particles), bioaerosols, and, of interest in this context, carbonaceous particles formed by combustion on which are adsorbed a variety of volatile and organic materials. Ultrafine particles consist largely of aggregated or agglomerated structures of sulfate or nitrate, some with carbonaceous nuclei. These agglomerated particles tend to stick together when they touch, forming larger agglomerates over time. Fine particulate matter consists of both carbon-derived particles, on which are adsorbed volatile and organic materials, and agglomerated sulfate and nitrate ultrafine particles that build by accretion into the fine size range.

The adsorbed chemical species on both coarse and fine particles are biologically significant. The particle forms a carrier with a large surface area onto which are adsorbed many constituents, particularly

- volatile organic compounds,
- polycyclic aromatic hydrocarbons (PAHs) and nitroarenes,
- metals (particularly transitional metals and iron that may be proinflammatory),
- sulfate, and
- oxides of nitrogen.

Particulate matter in modern urban air pollution is closely associated on a population basis with mortality risk, the risk of cardiovascular and respiratory disease, pneumonia (indicating an effect on susceptibility), emergency department admissions for asthma, and lung cancer risk. On one hand, a few individual episodes of severe air pollution in the past (eg, the London fog [also known as the Great Smog of 1952] that occurred from December 4 to 9, 1952) have been so severe that mortality was obvious. On the other hand, the effect—although highly significant—is not readily apparent in short-term windows of observation, which resulted in it being overlooked for many years. To hear the signal against background noise, it is necessary to average out mortality and disease incidence data over long periods of time. It is convenient to report the data as attributable risk rather than relative risk because elevation is 5%. These effects, including and especially mortality, are linearly related to the concentration in air of fine particulate matter. (The relationship is not so clear for coarse or ultrafine particles.[9]) They are most apparent in the aged and chronically ill, but are also visible in healthy younger populations that have led to various theories of mechanism. One explanatory theory is that the timing of exposure is critical because people pass into and out of previously unrecognized stages of susceptibility for many factors, including and especially blood coagulability and thresholds for inflammation.[10] Figure 4-1, a schema for pathophysiology developed for the US Environmental Protection Agency (USEPA), integrates these factors into a model of how fine particulate air pollution may cause cardiovascular disease.

Based on the findings of the most recent studies, the USEPA recently dropped the air quality standard for fine particulate matter (level 2.5 or $PM_{2.5}$) from 15 to 12 mg/m^3, with an expected saving of thousands of lives, most of them from cardiovascular disease,[11] many of them from lung cancer,[12] and some from acute lung disease.

Diesel Engine Exhaust Model

Combustion of diesel fuel in a diesel engine takes place at high temperatures and under high pressure. Although probably different from the lower temperature, lower pressure combustion regime in a burn pit, the literature on toxic effects from diesel engine exhaust may suggest health outcomes and mechanisms of concern.

The International Agency for Research on Cancer (IARC) is a body of the World Health Organization that has as its primary purpose the evaluation of world knowledge to determine cancer risk from exposures to various agents. IARC is essentially universally considered authoritative in the field of cancer research, and its findings are accepted by agencies such as the USEPA. In June 2012, IARC reclassified diesel engine exhaust as a class 1 carcinogen, meaning that there is sufficient evidence to conclude that diesel exhaust causes cancer in humans, drawn from both epidemiology studying exposed populations and toxicology using animal studies. The evidence for concluding that diesel exhaust presents a human cancer risk will be summarized in the soon-to-be published IARC Monograph 105.

However, this finding was not a surprise. In 1988, IARC concluded that diesel exhaust was *probably* carcinogenic to human beings, but the evidence was not completely conclusive.[13] The case is made most strongly for lung cancer. Because of the putative exposure regime, the risk of other cancers is likely to be raised as well, specifically in the upper airway, kidney, and bladder that share many risk factors with the lungs.

It is well established that specific chemicals present in diesel exhaust cause cancer. In addition to many compounds already known to cause cancer, there are also PAHs and 1,3-butadiene. Evidence has accumulated that the class of compounds called nitroarenes are also present in diesel exhaust and are potently carcinogenic. Nitroarenes are nitrogenated versions of complex organic compounds called PAHs that are formed by combustion and comprise a mix of organic chemicals, several of them potently carcinogenic. It had long been known that diesel exhaust was rich in PAHs and their corresponding nitroarenes, several of which are potent carcinogens known to cause human cancers—such as lung, skin, and bladder cancer—and significantly for this case kidney and upper airway cancer (including nasopharyngeal cancer).

Several developments since 1988 persuaded IARC that the case for the carcinogenicity of diesel fuels had been fully made and was no longer speculative. The most important was the availability of studies that got around major methodological issues that limited earlier studies of occupations involving exposure to diesel engine exhaust. These earlier limitations had to do primarily with subtracting the obvious effect of cigarette smoking and determining an exposure–response

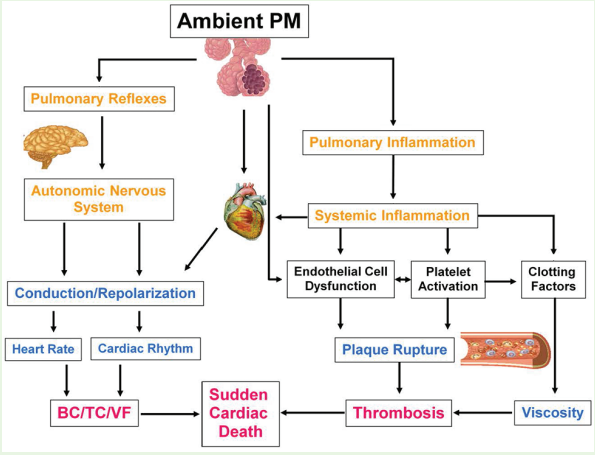

Figure 4-1. Plausible pathophysiological pathway.
BC: bradycardia (slow heart rhythm); PM: particulate matter; TC: tachycardia (fast heart rhythm); VF: ventricular fibrillation (chaotic rhythm)

relationship (basically asking the question: "Do more people get cancer the higher the exposure they experience?"). This gap was answered by a series of studies taking as their endpoint lung cancer, the cancer most likely to be caused by diesel engine exhaust. The populations studied were railroad workers, truckers, and underground miners who use diesel-powered equipment. Numerous studies were conducted, of which the most definitive version of the most important study for railroad workers[14] showed an excess risk of 1.40 (corresponding to a 40% elevation above expected). This level of risk was very similar to that found for the other two occupational groups in other studies. Thus, it is now firmly established that railroad workers have a 40% greater risk of developing lung cancer than they would otherwise, taking smoking into account. This number also means (mathematically) that approximately 29% of lung cancers in this population can be attributed to diesel exhaust, as opposed to tobacco or other causes.

Also, there has been resolution of a long-standing issue in inhalation toxicology over whether diesel exhaust itself was carcinogenic or whether diesel particles simply overloaded the protective cells of the lung and caused a sequence of events that induced cancer indirectly because these cells malfunctioned. It is now known that the particle overload problem is unique to mice and is not seen in human beings; thus, the findings of animal studies might not apply to human beings. The particle overload mechanism was therefore not so important in diesel exhaust toxicology and was not likely to be confusing to human studies. It is no longer questioned if the carcinogenic effect of diesel engine exhaust comes from chemicals in or on the surface of particles.

Stimulated by the attention to diesel brought by IARC's interest, the literature on diesel effects has grown for cancer risk, but not for acute and subchronic effects. Few studies are available for human beings on acute respiratory and cardiovascular responses to fresh diesel engine exhaust because this has not been seen as a pressing problem. However, it is clear that fresh diesel engine exhaust has potentially significant acute effects and small particles have effects distant from the lung and into kidney tissue.[14–18]

The gas phase of diesel exhaust may not contain secondary pollutants that are important in urban air pollution. However, depending on running conditions, they may be rich in formaldehyde (a potent respiratory and mucosal irritant and upper airway carcinogen) and acetaldehyde.[19]

The particle phase of diesel exhaust also has irritant potential and may induce inflammation. Recent subchronic and acute animal studies suggest that fresh (nonaged) diesel engine exhaust—administered in deployment-relevant time periods (1 month)—is associated with relatively mild, in context, proinflammatory and prothrombic effect. These effects overall were indicated by expired airway nitric oxide[20] and increased circulating cytokines that may paradoxically be attenuated by asthma-like airway reactivity. Of additional concern are findings that diesel engine exhaust may interfere with proliferation and remodeling of lung epithelial cells, thus setting the stage for subchronic and chronic health effects. Such studies require replication and integration into a hypothetical mechanism to be useful, but this is elusive in the absence of a specific respiratory outcome consistently observed with acute exposure.[10,21]

The conclusion from this still incomplete model is that inflammatory and thrombotic respiratory and cardiovascular effects are plausible with exposure to fresh diesel engine exhaust. This may be relevant to the effects of emissions from burning diesel fuel at open-fire temperatures and atmospheric pressure, but this has not been demonstrated. An experimental model using diesel fuel alone would not be complete, because the exposure was not confined to diesel fuel. The purpose of burn pits is to dispose of all types of trash, leading to diverse and variable composition in the emissions.

Oilfield Fires Model

The intentional oil fires set in Kuwait at the end of Operation Desert Storm have provided a conceptual model for exposure to burning oil products; but, because of the short duration of the problem, field conditions, and the difficulty in reproducing conditions, there is little empirical data available.[1] Elevations in circulating proinflammatory interleukin mediators (interleukin-8) have been reported and appear to be a good match to the linear response observed in particulate matter for healthy young people in exposure studies. Similarly, fine particulate matter from oil fires may reproduce the experimental effect in animal studies of fine particulate matter in urban air pollution with respect to accelerated atherosclerosis and induction of arrhythmias.

Oilfield flaring was a common practice and still exists as a safety measure in oil and gas installations. Emissions from flares have been extensively characterized and more than 200 organic chemicals are produced from gas flares, suggesting complicated combustion chemistry for the relatively simple input.[22] Extensive studies on the health effects of flaring emissions on human health are not available, but the literature on animals is now extensive as a result of two sets of studies conducted in western Canada.[23,24] Unfortunately, these studies may be of limited use because of species differences and difficulty characterizing burn pit exposures and isolating combustion products of interest.

PAHs remain the principal biologically active chemical class in oilfield exposures, especially in fires.[25]

Cigarette Smoking Model

The health effects of cigarette smoking are well characterized, and comparative pathology is readily available. However, the application of lessons from smoking to this problem is limited, in part because smoking is an important confounding exposure.

PATHOPHYSIOLOGY OF RESPONSE

Exhibit 4-1 summarizes the common lung responses to pulmonary injury after exposure to inhaled irritants. There are two components to such injury: (1) the toxic or irritant effect of the agent on tissue and (2) an injury that may result from the lung's response to the agent, which can be dysfunctional. For fibrogenic pneumoconioses, this is overexuberant fibrosis that—like the overexuberant response to tuberculosis—causes as much or more functional impairment as the agent itself. For airways disease, increased airways reactivity and structural remodeling of the airway wall may result in a greater and more chronic functional disturbance than that caused by the initial irritant exposure. Thus, consideration of the pulmonary outcomes of concern for the deployed population should include the possibility that clinically significant responses may not be a particular named disease or defined pathological condition, but the end result of host defense mechanisms that are stressed to the point of irreversible change.

Cases of respiratory illness in returning veterans include a subset with unexplained, but functionally disabling, symptoms and no obvious diagnosis. (These cases are summarized in other chapters in this book.) Most of these cases developed their illness over time after return, but a small number (two in the Vanderbilt series of cases) became symptomatic during deployment. There is a suggestion that those who developed their respiratory disorder early had a more rapid course of illness leading to impairment.

Cases were referred for dyspnea on exertion, wheezing, and productive coughing, with one case producing pigmented sputum. Physical examination was generally unremarkable. Imaging studies were not helpful except in one case where multiple nodules were apparent on the chest film and were found to represent small areas of consolidation (this case is also anomalous in other ways). Pulmonary function studies reported for the initial 38 soldiers seen at Vanderbilt University Medical Center (Nashville, TN) showed a strikingly preserved total lung capacity but reduced FVC, FEV_1 (in isolation and as the FEV_1/FVC ratio), and diffusing capacity. This pattern suggests air trapping and early airway closure. Exercise testing showed poor maximum ventilation. There was also anecdotal reference to desaturation in the case reports. Despite these findings, however, some of the soldiers responded at least partially to treatment for airways reactivity. Desaturation on polysomnography was reported, but this was a secondary phenomenon seen in many respiratory disorders. Although there was only one subject for which it was mentioned, methacholine challenge appeared to have been negative in that one relatively typical case.

In the four cases reported in detail by Welsh and Miller (Chapter 21, Denver Veterans Affairs Medical Center Experience With Postdeployment Dyspnea Case Report) and in the two cases each added by Miller (Chapter 14, Value of Lung Biopsy in Workup of Symptomatic Individuals) and Lewin-Smith et al (Chapter 19, Follow-up Medical Care of Service Members and Veterans: Case Reports—Usual and Unusual), the pathological findings are nonspecific and nondiagnostic, but clearly abnormal and in several cases permanently disabling. If a consistent picture of pathology emerges in the cases described in detail in this book, it is air trapping, chronic inflammation centered on bronchioles, and poorly formed granulomata, more reminiscent of hypersensitivity pneumonitis than sarcoidosis. (A subset of cases with eosinophilic granulomata is not included in this series.) Particle accumulation and subsequent inflammation centered on blood vessels and surrounding bronchioles are to be expected because of lymphatic drainage channels. Polarizable material, that would indicate silica exposure or be a marker for dust of crustal origin, is reported to be absent.

Thus, counting cases is difficult because the authors have not listed them uniquely, and references are often anecdotal. In addition to at least one of the cases reported in the more than 40 cases from Denver by Welsh and Miller (see Chapter 21, Denver Veterans Affairs Medical Center Experience With Postdeployment Dyspnea Case Reports), 52 of 65 cases seen at Vanderbilt University Medical Center between 2005 and 2012 are reported to show constrictive bronchiolitis, and four cases show respiratory bronchiolitis. Constrictive bronchiolitis is not reported consistently, but is reported to be present in at least one of the eight cases reviewed by a pathologist specializing in lung studies. One case showed clear intraluminal deposition of fibrin and hypertrophy of smooth muscle narrowing the caliber of an airway, but (to this author's eye) without bronchial gland hyperplasia that would be suggestive of bronchitis.

Exhibit 4-1 presents the common responses of the lung to an inhalation injury.[6,26] The lung, although a very complicated organ at the tissue or cellular level, has only a few stereotyped means of expressing injury. The expression of disease is restricted because the mechanical function of the lung is relatively simple compared with the function of some organs. Inhalation of irritant substances, either gases or particles, can produce effects on the upper airway (nose, pharynx, and throat), on the airways (trachea, bronchi, and small airways down to bronchioles), and on the tissue of the lung parenchyma, depending on the depth of penetration into the respiratory tract. Cough usually implies irritation of larger airways, although the symptom is entirely nonspecific. The role of smaller airways may be just as or more important in this population, however.[6,26]

For gases, the depth of penetration depends on the solubility of the gas in water because of clearance in the upper airway and the more proximal airways in the lower respiratory tract. The damage caused by toxic gases depends on

EXHIBIT 4-1

PULMONARY RESPONSE TO INJURY FOLLOWING AN INHALATION INJURY OR CHALLENGE

Functional airway abnormalities

- Upper airway
  - Reactive upper airways dysfunction syndrome
  - Voice problems (dysphonia)
  - Sleep apnea, obstructive
  - Aerodigestive disorders, such as gastroesophageal reflux (complex interactions with the epiglottis, esophagus, the lower esophageal sphincter, and reflux of stomach acid)
- Lower airway (airways hyperreactivity, acute and subacute inflammation)
  - Asthma-like wheezing (acute)
  - Asthma-like hyperreactivity to environmental irritants (eg, cigarette smoke, dust, smoke), cold, and exercise
    - Irritant-induced asthma
    - Reactive airways dysfunction syndrome
  - Bronchitis and sputum production
  - Fixed airways obstruction, including bronchiolitis
  - Bronchiectasis
  - Bronchiolitis
    - Constrictive bronchiolitis (progressive)
    - Bronchiolitis obliterans

Disorders of the tissue of the lung (parenchyma) other than airways

- Pulmonary edema (an extreme and lethal condition)
- Interstitial fibrosis (scarring of tissue in the parenchyma over time, with or without dust)
  - Nonpneumoconiotic (not associated with retained dust or reaction to its presence)
    - Granulomatous lung disease
    - Diffuse fibrotic lung disease ("honeycombing")
  - Pneumoconioses (specific disorders associated with dust retention and response)
- Disorders associated with particle overload in the lung
  - Impaired immune function
  - Oxidant stress injury

Migration of fine particles and secondary cardiovascular effects

Cancer

- Initiation of malignancy by a chemical carcinogen
- Promotion of a malignancy by a chemical promoter or co-carcinogen
- Facilitation or promotion of metastases

the irritation they produce on the way down (expressed as airways disease) and at the alveolar level (expressed as pulmonary edema and interstitial fibrosis), and the degree of toxicity to the body as a whole that occurs after they are absorbed. Highly toxic gases kill outright or cause acute illness. Gases that do not kill but instead primarily cause chronic lung problems—that may be permanently disabling—are usually not those that are most irritating or close to lethal concentrations, but are those that fall in the middle range of irritant potential.[26]

Medium-irritant gases may cause RADS, which is a form of irritant-induced asthma. Low-level irritant gases cause coughing and chronic lung irritation (eg, irritant-induced asthma or bronchitis) that may resolve. The usual variety of RADS (the term has been greatly overused), which follows an acute exposure to a gas or vapor, may take many years to resolve and may lead to sleep apnea, upper airway abnormalities, and other occlusive conditions.[26]

Size of the particle determines the location of maximal deposition, and particles in the predominant size range likely

to be produced from burn pits would be expected to deposit more or less efficiently in the peripheral airways, where significant local effects may occur because of inflammation. Damage caused by irritant dusts depends on the degree of irritation they produce, their inherent toxicity (eg, asbestos), and the degree of toxicity to the body as a whole that occurs after they are absorbed (for particles that contain toxic materials such as fine particulate matter.) Irritating particles typically cause coughing and asthma-like symptoms appearing acutely at the time of the exposure.[26]

Air trapping is usually a consequence of advanced obstructive lung disease or acute asthma and as such occurs against a background of reduced airflow. However, air trapping may manifest itself mostly in a reduction in vital capacity, with relatively preserved ratios of airflow to vital capacity (FEV_1/FVC, %), which has been observed among WTC responders.[27] Air trapping has also been directly documented among WTC responders by imaging methods.[28] As discussed in the next section, this may be a sign of significant, progressive, and largely silent pathology at the level of bronchioles.

The time course of the cases presented in this chapter is puzzling because a few cases presented in theater, but most developed over some months or years after return. Irritant-induced asthma is sometimes acute, but often has a gradual onset resulting from subacute or repeated irritation; however, this must be sustained.[29] Interstitial disease primarily causes a restrictive defect that develops over time as a reduced vital capacity, but would be expected to result in a pure restrictive defect showing a reduced FVC, preserved flow rates, no air trapping, and a reduced residual volume. A nongranulomatous pneumoconiosis usually takes years to develop (acute silicosis being an exception). It generally requires either a dust load over a long period of exposure or an overwhelming acute exposure of a dust load with high fibrogenic potential (eg, silica) conditions unlikely to apply in the basic deployment situation, but more likely to apply in a construction or demolition scenario.

Role of Atopy and Airways Reactivity

Between 9% and 30% of the North American population has a hereditary predisposition to develop allergies, including asthma, as measured by atopic skin reactivity.[30,31] Asthma, skin rashes, allergies, and sinusitis or other manifestations are the common symptoms of atopy. When atopy preexists, there may be interactive effects with the irritant exposures leading to an exaggerated or worse condition than that expected from atopy alone. Aggravation of existing airways reactivity is a common and important mechanism for airways response following irritant exposure[26] and is now formally recognized as *work-exacerbated asthma*.[29] Lung injury that occurs in the presence of preexisting atopy is a work-related injury regardless of predisposing factors. When consequences are greater than that arising from the underlying condition alone, the additional injury would not have occurred *but for* the exposure at work.

These individuals almost universally have reactive airways and are prone to coughing, wheezing, choking, or symptoms of rhinitis (runny nose) when provoked by an irritant exposure. They are minor only in the sense that they are not part of the diagnosis and are usually not the endpoints for treatment. However, they are important in daily life and work, and should probably be called and thought of as *impairment factors* rather than minor symptoms. One important paper[32] on this topic makes the observation that, "It is widely acknowledged that the personal burden of illnesses, such as asthma, cannot be fully assessed by traditional clinical outcome variables, such as symptoms and lung function."

Constrictive Bronchiolitis and Bronchiolitis Obliterans

One pathological entity that has not been discussed much in the scientific literature on irritant exposure to combustion products is constrictive bronchiolitis. This condition is the result of inflammation at the level of small airways or bronchioles. It is very different from the more familiar small airways abnormality seen in cigarette smoking, which is what most physicians are used to when they look at an abnormal pulmonary function test. This pattern of pulmonary function is not consistent with most forms of asthma, where the airways reactivity affects somewhat larger airways.

Constrictive bronchiolitis is a less common form of intraluminal airway wall dysplastic repair. It shares with its more common form, *proliferative bronchiolitis* (perhaps more accurately called *intraluminal polypoid bronchiolitis*), a tendency to evolve into small airway effacement and destruction, leaving behind the familiar (and common) lesion of obliterative bronchiolitis. The terminology is confusing. Constrictive bronchiolitis and proliferative bronchiolitis are different processes that may follow their own pathways to arrive at similar end results, but do not necessarily progress to completion.[33–35]

Constrictive bronchiolitis is a form of bronchiolitis in which the clinical picture is dominated by inflammation in the bronchioles, abnormality of small airways function, and air trapping. Under a microscope, it looks like an inflammatory response of the smaller airways with the tissue around them relatively preserved (unlike the effect of cigarette smoking). In some of these bronchioles, the inflammation progresses to the point where the airway is completely obliterated by scar tissue and essentially disappears from where it ought to be under the microscope (its remnants can be found with special methods, specifically a stain for elastin),

a condition known as bronchiolitis obliterans. Obliterative bronchiolitis is the end result of bronchiolar effacement, not a separate process.

Bronchiolitis has many causes and is often observed together with other pathology of the lung, such as asthma, cystic fibrosis, cigarette-induced emphysema, conventional pneumonia, or bronchiolitis obliterans organizing pneumonia (a distinct condition, unrelated to what is being discussed here). Bronchiolitis comes in many forms and is not at all the same as asthma, which is characterized by variable airflow reduction that may be associated with reversible inflammation and bronchoconstriction.[34] This is also RADS and affects larger airways.

Bronchiolitis is more familiar as a medical concept, common and noticeable in children because of the high frequency of respiratory syncytial virus in infancy, the increased risk of pertussis, and the dramatic functional effects on children's much smaller airways that disappear as they grow and their airways get bigger. There are many causes of acute bronchiolitis in adults, however, and the condition may accompany almost any lower respiratory tract infections. There are fewer causes of persistent (chronic) bronchiolitis and permanent alteration of the bronchiole structure in adults; but, in many adults, the causes are never identified and in such cases are called *cryptogenic* (Greek for "hidden cause"). The known causes unrelated to toxic exposure include

- adenovirus infection (specific strains of which are associated with persistent bronchiolitis),
- cancer (associated with a type called follicular bronchiolitis),
- mycoplasma infection,
- connective tissue disorders,
- eosinophilic lung diseases (there are several),
- inflammatory bowel disease,
- graft versus host reactions in lung transplantation, and
- several forms of autoimmune vascular disease.

There is also a form called diffuse panbronchiolitis, which is seen almost exclusively in Japanese men.[34]

The more familiar form of proliferative bronchiolitis is common and frequently associated with toxic inhalation exposures.[33] There has been almost no study of constrictive bronchiolitis as a pathological entity from toxic exposures. Most of the attention in the medical literature has been on nontoxic causes (eg, rheumatological disorders). Because of this, discussions on the functional implications of constrictive bronchiolitis are necessarily speculative. However, the relationship between proliferative bronchiolitis obliterans and irritant gases is well known, and there well may be overlap.

Bronchiolitis associated with toxic exposure includes most deeply penetrating irritant gases, but is characteristic of ozone and nitrogen dioxide, both highly oxidant gases that can progress to bronchiolitis obliterans.[26] Diacetyl provokes inflammation in the bronchioles that can result in a severe lung disorder trivialized by the name "popcorn lung" because it is a constituent of butter-tasting flavoring. It may be speculated that any irritant that can cause a bronchitis can probably cause a bronchiolitis if it penetrates to the bronchiolar level.

Invoking constrictive bronchiolitis as a process in some of these cases also explains another anomaly: latency period. It is striking that so few cases first became symptomatic during the period of deployment. An acute bronchiolitis is usually experienced by shortness of breath and coughing, followed by recovery. If they progress along the path to obliterative bronchiolitis, subjects experience the return of shortness of breath, in one form or another, and coughing months or years later. Some cases of toxic bronchiolitis (especially those associated with oxidant gases such as nitrogen dioxide and ozone) present minimal symptoms at the time of exposure, but may progress to classic hyperlucent lung over time. This time course would be inconsistent with RADS or irritant asthma, which provokes an airway response immediately after exposure. However, it would be consistent with advanced constrictive bronchiolitis.

Some of the apparently affected individuals show a pattern of pulmonary function that is consistent with air trapping. These are the firefighters who have a reduced FVC, but apparently well-preserved flow rates, of which the FEV_1 is the best understood. These cases present a puzzle because the net effect of the changes is to create a reduction in FVC that resembles a restrictive pattern, but that in reality is a form of obstruction. Air is trapped behind the obstruction, and the effect is as if the chest is filled with a tied-off balloon that is not emptying air.

Air trapping of this type occurs when pressure inside the chest (while breathing out) is greater than the air pressure within the airway, and it is pushed closed. In respiratory physiology, this effect is called a "Starling resistor," named after the physiologist who first described it. It shuts off the flow of air in the parts of the lung where it occurs. The bronchiolitis caused by cigarette smoking reduces the flow rate in small airways because tissue surrounding the airways disintegrates (from inflammation in the form of a focal alveolitis in tissue surrounding the small airway), and the airway loses the tethering effect that keeps it open. Thus, the airway collapses as soon as the air pressure around it in the lung exceeds the air pressure in the airway, which is the basis of emphysema. This occurs normally at the end of a breath; but where there is an abnormality of small airways, it occurs earlier before the breath out is finished and while there is still a relatively large amount of air in the lung.[36]

In a relatively isolated bronchiolitis, the structure of the airway is not weakened by inflammation around it with disintegration of supporting tissue; inflammation is confined to the airway itself. This means that, unlike in a heavy cigarette smoker, a person with constricted

bronchioles close abruptly at a higher rate of flow, but not every small airway. This regularly occurs when a person is bearing down to blow hard, as in the FVC maneuver. Those small airways that remain open have normal flow rates and because resistance at that level is so low, there is no obvious sign of obstruction on most pulmonary function tests. This does not occur or occurs to a much lesser degree when a person breathes out more slowly, as in the *slow* vital capacity maneuver, because the pressure is not as great in the lung surrounding the airway.

The phenomenon is best explained by the idea of "communication," the term for whether an airway (in this case a bronchiole) is open and transferring air back and forth into the part of the lung where it leads. Bronchioles that shut down do not communicate and behave like the neck of a tied-off balloon, trapping air behind them. Normally, this trapping occurs at the end of a breath, when the remaining volume of air in the lung is low (called *closing volume*). When the bronchiole is abnormal, it may occur at higher lung volumes before it should. Those bronchioles that close at abnormally high closing volume (and so trap air behind them) shut off all flow abruptly and are therefore invisible in the flow rates of the pulmonary function study from that point on. Their net effect is to increase the residual volume that has the result of cutting flow out of the lung prematurely with an exhaled breath. Those bronchioles that allow flow permit it at a near-normal rate, so the flow in that part of the lung that *communicates* is not reduced. This is why flow rates could be preserved in the small airways as measured by midflows. (The correct test to show this is a seldom-used physiological test called the "closing volume" test, but it is not generally available and in this case would add nothing that is not already known.) In constrictive bronchiolitis, which has been much less studied, it would be expected that the small airway might remain patent for longer and that closing volumes might be heterogeneous. (No data on this are available.)

Anatomically, this early closure of small airways (<2 mm diameter) occurs mostly at the periphery of the lung, where resistance to flow is lower (beyond the first generation of bronchioles) and the pattern does not show up as obstruction. Instead, the air-trapping effect interferes with emptying of the lung and creates a pattern on pulmonary function testing resembling a restrictive defect, which is usually (but wrongly) thought to be the opposite of obstruction.

The underlying condition causing such abnormalities is inflammation of the smaller airways, occurring in a specific location in the respiratory tract where the airways are relatively small, but there are so many of them that resistance to flow is very low, especially compared with the larger airways where asthma exerts its effects. Because it is occurring in a part of the lung where resistance is very low, because it does not affect all parts of the lung, and because those parts of the lung that are affected are immediately sealed off when they close and no longer communicate air with the larger airways, the typical signs of airways obstruction (reduction in the FEV_1) are not visible in pulmonary function tests. Signs that this is happening, however, are that the FVC is much smaller than the *slow* vital capacity, which is obtained with less force and therefore results in a much lower closing volume and preserved airflow. Another sign is that there is little change with bronchodilators, which primarily act on the larger airways important in conventional asthma.

Whether constrictive bronchiolitis, or bronchiolitis in general, could play a role in cases of lung disease that may be associated with burn-pit exposures cannot be determined from the available evidence. Symptom monitoring[37] and systematic collection of pulmonary function data[37,38] would be required to sort out these issues, with close attention to whatever biopsy material becomes available on these subjects in the future. Unfortunately, the decentralized nature of healthcare for these subjects and, more fortunately, their relative youth and lack of other morbidity makes it unlikely that there will be a clear answer to this issue for some time to come.

SUMMARY

Deployment-related lung disease presents diagnostic and pathophysiological quandaries. It is not entirely clear whether these cases represent individual anomalies or a subset of postdeployed personnel who are demonstrating a disease syndrome. The potentially sentinel cases identified to date do show sufficient commonality of symptoms and a history suspecting a consistent pathological entity. This may or may not be a form of bronchiolitis and may or may not be an exaggeration of the normal host defense and physiological response to irritant exposure, including overexuberant airways repair.

There are several models that may inform analysis and interpretation going forward: firefighters, urban air pollution, diesel engine exhaust, and oilfield fires. None of them, however, exactly match the situation of exposure downwind from a burn pit, which is the most likely and consistent exposure scenario that may be associated with these cases.

Predeployment screening, postdeployment surveillance (targeted search for specific outcomes), and ongoing monitoring (broad observation to characterize the health experience of the population, such as the Millennium Study) will be required to determine what actually happens in warrior populations after deployment and to identify subsets that may have an anomalous experience. Specific, targeted investigation will be required to characterize these potentially sentinel cases. Protocols

for clinical investigation and population monitoring are discussed elsewhere in this book. Research of a basic nature, focused on characterizing the exposures and toxicity under field conditions, may be necessary to answer the question of causation and therefore establish conditions for prevention.

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