Chapter 18

EXPERIENCE WITH EMERGING LUNG DISEASES FROM THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

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INTRODUCTION

Surveillance of respiratory health or environmental conditions that impact health is efficient only when the nature of health outcomes and their causes are known. Surveillance does not establish causes. Rather, the purpose of surveillance is to follow trends over time as a means of evaluating public health interventions.[1] Interventions are often difficult to justify until specific respiratory conditions and their causes are understood. Some research studies have documented increases in respiratory symptoms and diagnoses in military personnel who have deployed to Iraq and Afghanistan,[2–4] but diagnoses and their causes remain the subject of considerable controversy,[5-6] precluding systematic preventive measures and even appropriate surveillance.

Lessons learned are from characterizing emerging occupational diseases or novel occupational efforts in new service-associated challenges, such as soldiers with constrictive bronchiolitis,[7] undiagnosed respiratory symptoms, and suspected environmental contributors. Illustrative examples of emerging diseases and causes investigated by the National Institute for Occupational Safety and Health (NIOSH) are listed in Exhibit 18-1. Like public health personnel and clinical providers in the military and Veterans Affairs facing their current challenges, NIOSH investigators could not look up answers in textbooks when these emerging problems were presented to them. Rather, some were new diseases altogether, such as chemical-associated bladder neuropathy and flock worker's lung. Others were rare or familiar diseases surfacing in an unanticipated setting, such as flavoring-related constrictive bronchiolitis and asthma related to indoor dampness. Efforts to intervene frequently failed because NIOSH knowledge had to be extended and refined, sometimes triggering experimental laboratory science to establish biological plausibility, as in control of beryllium sensitization in beryllium-exposed workers. Controversy is inevitable when previously unsuspected diseases or causes surface, because no common consensus exists regarding these phenomena among the many disciplines and institutions with stakes in the answers. Only multidisciplinary research regarding health in relation to environmental conditions will solve these challenges. Pertinent disciplines include clinical medicine, epidemiology, environmental science, and statistics. Interventions, which are often necessary to confirm cause, require military leaders, engineers, and public health personnel, among others.

This chapter illustrates several lessons from NIOSH work on emerging occupational diseases and novel causes of traditional lung diseases. It then briefly outlines the implications for surveillance and tools to identify three types of lung disease that affect service members who have deployed to southwest Asia.

LESSONS FOR APPROACHING NEW CAUSES AND NEW DISEASES

The lessons on emerging issues, distilled from investigations in occupational health practice and public health, do not apply equally to the three major respiratory health concerns discussed at the August 2012 Airborne Hazards Symposium: (1) constrictive bronchiolitis, (2) asthma, and (3) chronic obstructive pulmonary disease (COPD). However, a systematic approach to unknowns is invaluable before committing to surveillance prematurely, and confusion about cause exists for all three diseases. Consensus is often necessary to support preventive intervention and to assess benefits related to service-associated disability. These lessons include the importance of

- verifying pathology/diagnosis when cases are reported,
- interviewing patients,
- being wary of textbook descriptions,
- reviewing known etiologies,
- exploring exposure surrogates,
- generating hypotheses for epidemiological studies, and
- assessing the effectiveness of interventions.

These are steps to creating the knowledge base that will underlie consensus building regarding the allegations that service in southwest Asia has impaired respiratory health in US service persons.

EXHIBIT 18-1

EXAMPLES OF EMERGING ISSUES ILLUSTRATING LESSONS FOR SUCCESSFUL INVESTIGATION

- Flavoring-related bronchiolitis obliterans
- Bladder neuropathy related to the catalyst dimethylaminopropionitrile
- Dampness-related asthma
- Nylon flock worker's lung
- Lifeguard lung
- Beryllium sensitization via skin exposure

Verify Pathology/Diagnosis When Cases Are Reported

Environmental insults to the respiratory system may affect the larynx, the large airways, the small airways (bronchioli), the alveoli, or a combination of these compartments. Symptoms of chest illness are nonspecific and cannot differentiate among compartments reliably. For example, wheezing may have its origin in vocal cord adduction, asthma, bronchiolitis, and emphysema—all of which reflect damage at different levels of the respiratory tract. Additional information is usually necessary for differential diagnosis, such as age of the patient, onset and time course, cigarette smoking history, reversibility of symptoms, whether exacerbations exist, physiological measurements, and pathology. For example, to differentiate asthma from other respiratory diseases with common symptom presentations requires demonstration of reversible airflow limitation by spirometry in serial clinic visits, with a bronchodilator, or a test of airways hyperreactivity with methacholine or mannitol. Without distinguishing between asthma and other respiratory diseases, the investigator may misclassify the disease outcome, making it less likely that associations with environmental conditions can be demonstrated. An example of potential misdiagnosis is respiratory symptom data from a Veterans Affairs hospital, in which specific diagnostic tests *for* asthma (eg, methacholine challenge) were unavailable, and diagnosis was required on the form requesting spirometry to evaluate the diagnosis.[8]

An example of the need to verify diagnosis is the recognition of microwave popcorn-associated constrictive bronchiolitis. Several cases of severe respiratory illness had occurred over 8 years among workers who had manufactured microwave popcorn in a small plant in rural Missouri. In 2000, eight former workers were recognized as having constrictive bronchiolitis, a rare disease that is usually the late sequel of massive overexposure to irritant gases.[9] Misdiagnoses of more common diseases (eg, asthma, bronchitis, and COPD) were the norm in these cases.[10] Clinicians and public health investigators had no inkling about cause. The only way to establish that a new cause of occupational constrictive bronchiolitis existed was to epidemiologically evaluate the current workforce. The investigation documented that current workers had a 3.3-fold excess of obstructive spirometric abnormalities, that exposure to the flavoring chemical diacetyl (2,3-butanedione) was associated with abnormality in an exposure-dependent manner, and that exposed rodents had respiratory epithelial necrosis.[10]

Verifying the pathological diagnosis is particularly important for exploring constrictive bronchiolitis. Controversy about this unsuspected diagnosis in US soldiers serving in Iraq and Afghanistan dates from 2008[11,12] and is finally being resolved by an independent pathology panel. If the pathology is confirmed that this rare disease exists in a number of soldiers who served in Iraq and Afghanistan, exploration of cause will be required, regardless of whether case-patients had fixed airways obstruction, high-resolution computerized tomography (HRCT) findings of mosaic attenuation, or expected clinical course. The absence of some of the classic characteristics of constrictive bronchiolitis has been used to question the diagnosis, but the pathology findings are the gold standard in this instance. Discovery of new causes of constrictive bronchiolitis or attribution of case-patients to known causes must follow this first step.

Interview Patients

The cases of constrictive bronchiolitis diagnosed at Vanderbilt University (Nashville, TN) puzzled military pulmonologists because they largely had normal pulmonary functions and radiology studies.[7,11] When patients have symptoms that do not "make sense" in light of conventional medical practice, it is especially important to obtain their health and exposure histories in an open-ended fashion (ie, interview patients to obtain their insights). Standardized questionnaires are limited for emerging issues because they only work when you know what to ask, and they may not be appropriate for new patterns of disease, such as indolent onset of constrictive bronchiolitis.

A chemically induced bladder neuropathy illustrates this lesson.[13] Nine workers from a factory manufacturing foam automobile seats came to an emergency room together saying that they could not urinate. However, they all produced urine specimens, which appeared to contradict their chief complaint. Each individual worker had consulted his or her physician without resolution of urinary symptoms, but they knew that most of their co-workers had developed the same chronic symptoms in the same time course. Their clinicians had never heard of a chemical that caused patients to complain that they could drink a six-pack of beer and feel no need to void. Some workers had undergone surgery for prostatic obstruction without resolution of urinary symptoms. The county health department had investigated and reported that the restrooms were sanitary. Interviewing these sentinel nine patients led to clues about both the diagnosis and the potential causes. The investigators could only devise a questionnaire to collect systematic information from the workforce after interviewing them and their managers. An investigation of the current workforce showed that half of the workers in the facility had developed abnormalities of urination beginning shortly after a new catalyst was introduced, and incident cases paralleled the volume of its use (Figure 18-1). Workers had bladder neuropathy following introduction of dimethylaminopropionitrile, a chemical catalyst that had been used as a grouting agent for decades outdoors in construction without recognition of a sensorimotor neuropathy of the bladder. When the catalyst was removed from production, new cases immediately fell to zero.

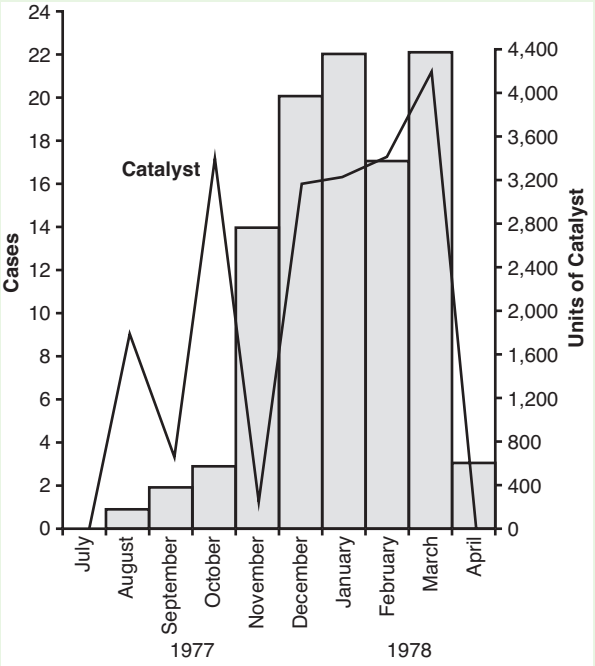

Figure 18-1. Number of incident cases of urinary symptoms and dimethylaminopropionitrile catalyst used by month during bladder neuropathy outbreak in automobile seat manufacturing plant.[13]
Data source: Kreiss K, Wegman DH, Niles CA, Siroky MB, Krane RJ, Feldman RG. Neurological dysfunction of the bladder in workers exposed to dimethylaminopropionitrile. *JAMA*. 1980;243:741–745.

The 38 Vanderbilt-diagnosed soldiers with pathological constrictive bronchiolitis were not systematically queried, but this was to be expected for an emerging condition that was likely recognized as a potential "outbreak" only after a number of similar cases had come to thoracoscopic biopsy. A challenge in this outbreak was the confusion about military versus Veterans Affairs jurisdiction to follow up these soldiers after they left the Army, which has delayed the ability to learn as much as possible from those affected. Among the 38 patients, 28 reported having been exposed to smoke from a sulfur mine fire near Mosul. Their probable chemical exposures include sulfur dioxide and hydrogen sulfide, both known causes of bronchiolitis.[14,15] In the instance of new-onset respiratory symptoms in soldiers deploying to southwest Asia, case-patients can

- report the circumstances of their recognizing new dyspnea on exertion and any associated symptoms;
- communicate whether co-workers had similar symptoms;
- reveal work assignments and exposures preceding or concurrent with the symptoms;
- describe progression or stabilization in relation to deployment dates; and
- report suspected causes.

Be Wary of Textbook Descriptions

Emerging issues are not described in textbooks, and prudence requires careful consideration of the basis of textbook knowledge. This is particularly evident for occupational constrictive bronchiolitis. Those individuals writing textbooks convey knowledge from case reports with recognized causes. In individual cases, the clue to cause has been acute pulmonary edema from an overwhelming accidental exposure; such cases seemingly recover and then develop fixed obstruction weeks or months later. The drama of acute presentation in previously healthy farmers or workers makes it easy to identify the cause of constrictive bronchiolitis, even though it is a rare condition. Without a dramatic acute event, persons with constrictive bronchiolitis would not be diagnosed or would be considered to have an idiopathic lung disease.

In flavoring-related constrictive bronchiolitis, there were no accidental high exposures, and yet 25% of plant workers had abnormal spirometry, many without chest symptoms.[10] They reported no work-aggravated chest symptoms and had no idea that they had work-related disease. The clue to a common etiology was the cluster of eight former workers with severe fixed obstruction, half on lung transplant lists, among a small workforce. Only epidemiological investigation in several microwave popcorn plants established the cause to be diacetyl. Diacetyl is an alpha diketone used in artificial butter flavorings. This example of chemical exposure-related constrictive bronchiolitis may be similar to the military case series of soldiers in Iraq with indolent development of dyspnea that subsequently precluded their meeting military requirements for exercise performance. Without an acute overexposure resulting in clinical contact for acute symptoms, only epidemiological investigation can resolve confusion about contributing exposures. In the example of diacetyl-related constrictive bronchiolitis, the cluster of severe lung disease in former workers motivated epidemiological investigation of current workers whose distribution of abnormal lung functions was related to current and estimated past exposures to flavoring ingredients of microwave popcorn production.

Textbook knowledge of constrictive bronchiolitis from inhaled toxins is largely based on case reports; it is not informed by population-based research on those at risk of indolent constrictive bronchiolitis. Only within the last decade has investigation of flavoring-exposed populations and population-based case series allowed characterization of the

broader spectrum of findings in constrictive bronchiolitis. These recent findings contradict and thus must extend the classic descriptions of occupational constrictive bronchiolitis. Specifically, biopsy-confirmed cases do not always have fixed airways obstruction, expiratory mosaic attenuation on HRCT scans, or relentlessly progressive disease.[7,16,17] These three characteristics, detailed in the following paragraphs, are no longer required for diagnosis.

The spectrum of spirometric findings in biopsy-confirmed constrictive bronchiolitis now includes normal pulmonary function and spirometric restriction, as well as fixed obstruction and mixed obstruction and restriction (as described in textbooks). In a consecutive clinical case series, Markopoulou and co-authors[17] described 19 cases: 4 had normal spirometry, 2 had isolated gas trapping, 1 had restriction, 1 had mixed obstruction and restriction, and the remaining 11 had airflow obstruction. Similarly, among 7 biopsied mustard gas cases from the Iraq-Iran war with constrictive bronchiolitis, Ghanei and co-workers[16] showed that all had normal spirometry; of 4 additional cases with chronic cellular bronchiolitis on biopsy after mustard gas exposure, 2 had normal spirometry, 1 had restrictive abnormalities, and 1 had obstructive abnormalities. Distribution of spirometric findings among 38 US soldiers in Iraq and Afghanistan with biopsy-documented constrictive bronchiolitis included 32 with normal spirometry, 3 with restriction, 2 with obstruction, and 1 with mixed obstruction and restriction.[7] This last case series was unusual in that invasive workups were conducted to describe unexplained decreases in exercise performance. All of these case series reflect the limitations of spirometry (and a textbook requirement for fixed obstruction in constrictive bronchiolitis) in identifying bronchiolar abnormalities.[18]

In NIOSH work on flavoring-related lung disease starting in 2000, researchers concentrated on fixed obstructive spirometric abnormalities because they were guided by textbook descriptions, and their efforts preceded the publications just cited. In the sentinel microwave popcorn plant investigation, researchers found nearly equal numbers of current workers with spirometric obstruction, restriction, and mixed obstruction and restriction.[10] NIOSH investigators classified those with mixed abnormalities with the obstructed because it was assumed that air trapping explained the restrictive component. With the advent of publications on biopsy-confirmed constrictive bronchiolitis, researchers have reexamined the spectrum of spirometric abnormalities in the many flavoring-exposed worker populations now studied.[19] Distribution of spirometric abnormalities in many flavoring-exposed worker populations parallels that of the sentinel microwave popcorn plant. In addition, we found one flavoring manufacturing plant in which 28% of the workers had abnormal spirometric restriction; those workers in jobs or areas with higher potential for flavorings exposure had a 5.8-fold risk of excessive decline in forced expiratory volume in 1 second (FEV_1) during employment, compared to workers with lower potential for flavorings exposure.[20] In retrospect, we underestimated the burden of disease associated with flavoring chemical exposure by concentrating on obstructive and mixed spirometric abnormalities. In addition, we neglected the excesses of exertional dyspnea in flavoring-exposed workers in microwave popcorn and flavoring manufacturing industries because we had not recognized the insensitivity of spirometry abnormalities in biopsy-documented constrictive bronchiolitis. The insensitivity of spirometry was demonstrated in a study of 34,000 Iranians who developed respiratory complications of sulfur mustard gassing in the 1980s: 57.5% had normal pulmonary function testing, 37.0% had mild impairment, 4.5% had moderate impairment, and 1.0% had severe pulmonary function testing impairment, primarily obstructive but occasionally mixed and purely restrictive in pattern.[21,22]

Radiographic diagnostic tests, the second classic criterion for constrictive bronchiolitis, are also insensitive for identifying bronchiolar abnormalities, as reflected in the biopsy-documented case series described previously. In the consecutive clinical case series, air trapping reflecting mosaic attenuation was found in only 5 of 10 cases.[17] Similarly, Ghanei and co-workers[16] showed that biopsy-confirmed cases in Iran did not all have HRCT abnormalities. In US soldiers with southwest Asia experience, 25 of 37 (68%) had normal HRCT scans, and 6 (16%) had mild air trapping.[7] Similarly, in flavoring worker surveillance in California, only 4 of 7 cases with moderate-to- severe obstruction had abnormal HRCTs consistent with constrictive bronchiolitis.[23] Our conclusion is that workers and soldiers with unexplained dyspnea and normal radiological studies and physiology may require thoracoscopic biopsies for a diagnosis.

The third presumed characteristic of constrictive bronchiolitis, unrelenting progression, has its origin in the experience of persons who have undergone lung or bone marrow transplant. This common source of posttransplant demise is thought to reflect an immune-mediated phenomenon. In contrast, we have found that the natural history of flavoring-related constrictive bronchiolitis is quite different. Even the sentinel former worker cases of constrictive bronchiolitis in 2000 and 2003 appeared to have stabilized in their physiological impairment with the cessation of exposure,[24] and none of them have received lung transplants to date to our knowledge. Similarly, an incident case of flavoring-related lung disease during the eight cross-sectional surveys of the sentinel microwave popcorn plant had much slower deterioration in FEV_1 2 years after he left employment (Figure 18-2).

As factory exposures were brought under control, excessive lung function declines normalized for the aggregate population with spirometry over all eight surveys (Figure 18-3).[25,26] Thus, there is good reason to suspect that

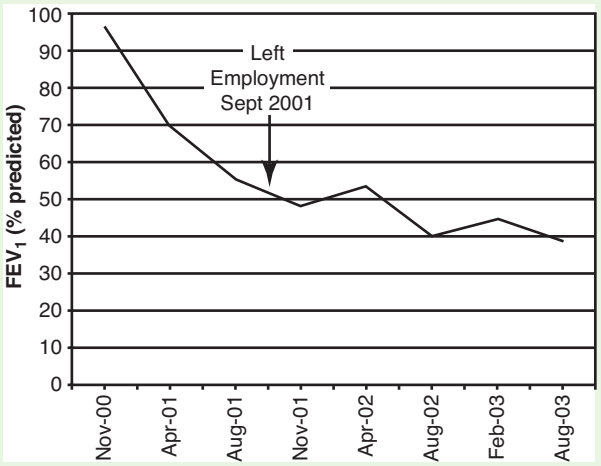

Figure 18-2. Serial forced expiratory volume in 1 second (FEV_1) by month of employment of incident case of fixed obstruction in microwave popcorn plant. *Arrow* indicates cessation of employment.

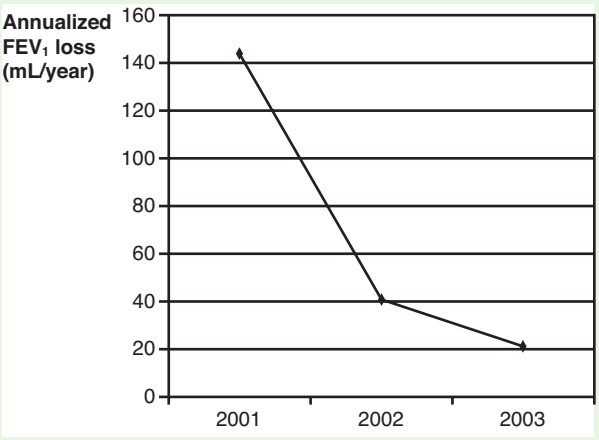

Figure 18-3. Annualized decline in forced expiratory volume in 1 second (FEV_1) by year of follow-up in sentinel microwave popcorn plant, November 2000–August 2003 for participants in all eight cross-sectional studies.

exposure-related indolent evolution of constrictive bronchiolitis does not progress after exposure ceases, and this may be true for the US soldiers in Iraq and Afghanistan who were diagnosed postdeployment. Even for constrictive bronchiolitis from an acute overwhelming exposure, long-term follow-up shows that disease can be stable.[14,21,27–29] In the case of follow-up studies of patients gassed with chlorine from transportation accidents, the absence of progressive disease from 2 to 6 years postexposure has been taken as lack of evidence of chronic effects, even when excessive declines in pulmonary functions were evident in the first 2 years postexposure and did not improve.[30]

In summary, classic characteristics of constrictive bronchiolitis in textbooks are incomplete. Without findings from population-based epidemiology and biopsy-documented case series, conclusions about the extent of disease, its characteristics, and its causes may be inaccurate.

Review Known Etiologies

In approaching unidentified causes of respiratory disease, exploration of known or suspected causes is the first step. Because environmental sampling is never available for unsuspected causes, the known causes may suggest exposure surrogates that can be explored in epidemiological studies. In turn, exposure surrogates that are associated with increased incidence or prevalence of health outcomes can form the basis of intervention studies. Effectiveness of interventions in interrupting adverse health outcomes in longitudinal surveillance can form evidence that the causal hypotheses were correct.

For constrictive bronchiolitis, known etiologies based on case reports of acute injury followed by delayed fixed obstruction include nitrogen dioxide, sulfur dioxide, the halogens, ammonia, methyl isocyanate, hydrogen sulfide, and sulfur mustard (see Table 18-1[14–18,21,26–29,31–58]). All of these are gases, with the exception of sulfur mustard aerosols.

Gases are also associated with constrictive bronchiolitis without recognition of acute injury (see Table 18-1). Many of these causes of insidious disease required epidemiological investigation to substantiate cause or assembly of case series in particular industrial settings. The best studied is diacetyl, a constituent of artificial butter flavoring, with cases and risk associated with microwave popcorn production, manufacturing of flavorings, and diacetyl manufacture.[26] With substitution of other alpha diketones for diacetyl (2,3-butanedione) in flavoring manufacture, experimental laboratory work documents that compounds with similar structure, such as 2,3-pentanedione, have similar epithelial toxicity in rodents and are likely no safer.[59]

Chemicals associated with reinforced plastic resins used in fiberglass boat building likely include a cause of constrictive bronchiolitis, and this may be styrene. Diagnoses of constrictive bronchiolitis were made in five boat builders in four fiberglass boatyards; in a worker building fiberglass water towers using similar chemicals; and in someone who burned Styrofoam insulation indoors, liberating styrene gas.[55,60] Another fiberglass boat builder was diagnosed on clinical grounds with hypersensitivity pneumonitis.[61] Two mortality studies of workers exposed to styrene in boat building document excess deaths from "other chronic obstructive disease" (not emphysema, bronchitis, or asthma) in short tenure workers with high exposure.[62,63] This pattern is consistent with a short latency, exposure-related, severe

TABLE 18-1

KNOWN OR SUSPECTED CAUSES OF CONSTRICTIVE BRONCHIOLITIS BY GASEOUS OR PARTICULATE FORM AND COURSE OF INJURY

Gaseous or Particulate Form and Course of Injury	Illustrative Setting	References
Irritant Gases Causing Acute Injury		
Nitrogen dioxide	Explosive detonation, silage decomposition, nitric acid use, nitrocellulose fires, welding gases	Lowry & Schuman, 1956 Grayson, 1956 Becklake et al, 1957 Darke & Warrack, 1958 Milne, 1969 Ramirez & Dowell, 1971 Horvath et al, 1978 Yockey et al, 1980 Zwemer et al, 1992
Sulfur dioxide	Paper mill bleaching, sulfur mine fire	Woodford et al, 1979 Charan et al, 1979
Thionyl chloride	Lithium batteries	Konichezky et al, 1993
Chlorine	Transportation spill	Jones et al, 1986 Seaton, 2008
	Industrial accident	Chester et al, 1977
Bromine and compounds	Flavoring research and development	Kraut & Lilis, 1988
Ammonia	Chemical industry; refrigerant	Kass et al, 1972 Monforte et al, 2003
Methyl isocyanate	Bhopal pesticide manufacture leak	Weill, 1987 Cullinan et al, 1997 Mishra et al, 2009
Polymethylene polyphenol isocyanate	Plastics factory maintenance	Markopoulou et al, 2002
Hydrogen sulfide	Crude oil, natural gas, manure pits, toilets	Arnold et al, 1985 Parra et al, 1991 Richardson 1995 Doujaiji & Al-Tawfiq, 2010
Sulfur mustard	Chemical war gassing (with aerosol)	Thomason et al, 2003 Ghanei & Harandi, 2007 Ghanei et al, 2008 Weinberger et al, 2011 Tang & Loke, 2012
Dimethyl disulfide		Seaton, 2008
Hydrochloric acid		Seaton, 2008
Irritant Gases Causing Subacute Injury		
Diacetyl and other alpha diketones	Microwave popcorn, flavoring, and diacetyl manufacture	Kreiss, 2007
Oxides of nitrogen	Silo filling	Zwemer et al, 1992 Ramirez & Dowell, 1971

(**Table 18-1** *continues*)

Table 18-1 *continued*

Possible Particulate Causes		
Smoke inhalation	Plastics factory fire Synthetic materials in house fire Styrofoam combustion Photography processing fire (ammonia, nitrogen dioxide)	Seggev et al, 1983 Tasaka et al, 1995 Janigan et al, 1997 Markopoulou et al, 2002
Overheated cooking oil fumes	Commercial cooking	Simpson et al, 1985
Fly ash	Incineration of coal and oil; particulate (may have adsorbed toxic gases)	Boswell & McCunney, 1995
Dusts and combustion products	World Trade Center collapse	Mann et al, 2005
Food production dusts	Animal feed manufacture (could have been flavorings)	Spain et al, 1995
Powder of chlorine-liberating disinfectant	Cleaning	Seaton, 2008

Data sources: Arnold IM, Dufresne RM, Alleyne BC, Stuart PJ. Health implication of occupational exposures to hydrogen sulfide. *J Occup Med*. 1985;27:373–376. Becklake MR, Goldman HI, Bosman AR, Freed CC. The long-term effects of exposure to nitrous fumes. *Am Rev Tuberc*. 1957;76:398–409. Boswell RT, McCunney RJ. Bronchiolitis obliterans from exposure to incinerator fly ash. *J Occup Environ Med*. 1995;37:850–855. Charan NB, Myers CG, Lakshminarayan S, Spencer TM. Pulmonary injuries associated with acute sulfur dioxide inhalation. *Am Rev Respir Dis*. 1979;119:555–560. Chester EH, Kaimal J, Payne CB, Kohn PM. Pulmonary injury following exposure to chlorine gas. Possible beneficial effects of steroid treatment. *Chest*. 1977;72:247–250. Cullinan P, Acquilla S, Dhara VR. Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: a cross sectional survey. The International Medical Commission on Bhopal. *Br Med J*. 1997;314:338–342. Darke CS, Warrack AJ. 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respiratory disease in which those affected leave employment. Epidemiological studies in the plastic-reinforced fiberglass industry are needed to refine the causal hypotheses by looking at exposure–response relations.

Finally, causes of acute injury (eg, nitrogen oxides) have also been reported to result in constrictive bronchiolitis in workers who did not seek medical attention for acute illness following causative exposures.[36,38,40,41] Such workers presented with fixed obstruction weeks after exposure without recognized acute injury, as happens with indolent constrictive bronchiolitis in flavoring-exposed workers.

There is much poorer evidence for particulate etiologies for constrictive bronchiolitis. Case reports exist for smoke inhalation, overheated cooking oil fumes, fly ash inhalation, World Trade Center exposures, a plastics factory fire, and an animal feed worker (see Table 18-1). Interestingly, cases involving animal feed manufacture,[58] overheated cooking oil fumes,[56] and bromine compounds[41] occurred in settings with likely artificial flavorings exposure before diacetyl was recognized as causing constrictive bronchiolitis. It is difficult to separate particulate and gaseous exposures in situations involving combustion effluents. It is uncertain whether aerosols and particulates, independent of their combination with or source of toxic gases, are capable of eliciting a constrictive bronchiolitis response.[29,57,58]

Thus, the existing literature documents a multitude of associations of gas exposures and perhaps a few particulate exposures with constrictive bronchiolitis. Some of these exposures almost certainly existed in Iraq and Afghanistan. Exposures to burning plastics, burning batteries, burning Styrofoam, and nonspecific combustion products were surely episodic from burn pits. The possibility of nitrogen dioxide exposures from explosions might also need exploration, whether in the setting of improvised explosive devices or conventional fire fights. The oil field fires in Iraq and Kuwait may have been a source of hydrogen sulfide exposures. In all of these cases, episodic or single exposure may have been sufficient to result in epithelial cell injury in the distal airway with subacute evolution of constrictive bronchiolitis.

Attributing incident cases of asthma and COPD among service members is usually limited to known etiologies. These diseases are common in any population, unlike constrictive bronchiolitis that is a rare disease with an extremely low background rate. The usual way to find *new* occupational causes of asthma and COPD is to study new cases clustered in time and space in relation to exposure–response relationships. This is unlikely to be possible in a military situation.

Explore Exposure Surrogates

When no measurements of suspected causal agents are available, nearly always the case in the setting of an unexpected health outcome, markers or surrogates of exposure may be suggested by case-patient interviews and knowledge of deployment conditions in which known causes might be present. In industry, process-related risks and work practices are sometimes clues to exposures that may be associated with illness. Associations of health outcomes with such surrogates of exposure can guide further investigations and interventions. Sometimes exposure measurements are impossible to obtain or useless because they are not biologically relevant.

An example of this situation was an investigation of a pathologically unique new disease, lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia, dubbed "flock worker's lung." Several cases of this interstitial pneumonitis occurred in four plants in the nylon flock industry in which long filaments of nylon were cut into short fibers and impacted onto adhesive-covered cloth to make a velvet upholstery for automobile seats.[64–66] The nylon fibers were too large to be respirable, and no one suspected a respirable dust in the plants. In searching for a cause, we found an unexpected respirable dust from milling the cut flock. Fibrils generated in the cutting of nylon into fibers were broken off in milling (Figure 18-4).[67] This respirable dust melted at the precise melting point of nylon, suggesting that it was nylon particulate, for which no analytic method existed.

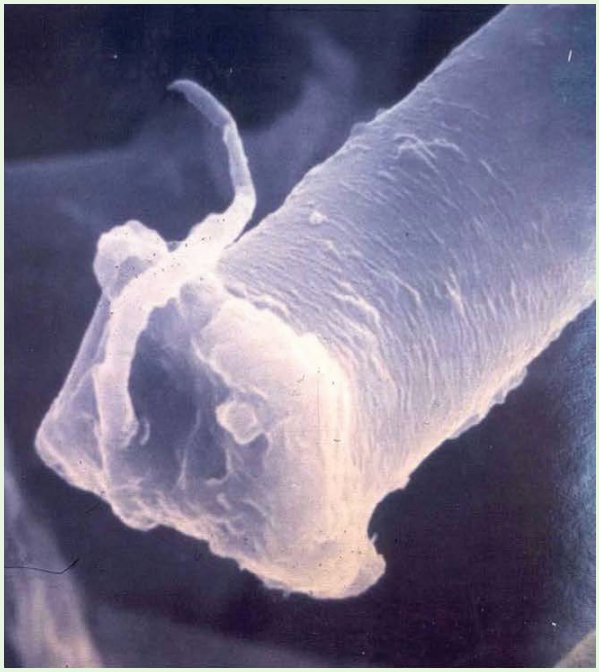

Figure 18-4. Scanning photomicrograph of nylon flock fiber with fibril on cut end that can be dislodged to form a respirable dust associated with flock worker's lung.
Data source: Burkhart J, Piacitelli C, Schwegler-Berry D, Jones W. Environmental study of nylon flocking process. *J Toxicol Environ Health*. 1999;57:1–23.

Exhausting the milling procedure removed the respirable particulate in the plant. Animal studies demonstrated that respirable nylon particulate from the plant was toxic on intratracheal instillation.

For another emerging issue—damp indoor spaces in relation to asthma and hypersensitivity pneumonitis—bioaerosol measurements do not correlate with health risk; but, observational indices of dampness, mold, and mold odor do. These observational indices are a marker of presumed causal microbial constituents in water-damaged indoor environments, in which the epidemiological evidence is overwhelming that there are health risks.[68] We do not use bioaerosol measurements to recommend remediation of the source of water incursion, nor do we recommend clearance air sampling after remediation.[69]

Generate Hypotheses for Epidemiological Studies

Pathologically confirmed cases of constrictive bronchiolitis or another unexpected lung disease are an opportunity to extend our knowledge for the sake of intervention. Opportunities for exposure to known causes can be explored using surrogates of possible exposure. For potential causes requiring intervention, focusing on personal susceptibility or predeployment exposures are diversions, sometimes motivated by attempts to deny occupational risk factors and responsibility for prevention. Personal risk factors and predeployment exposures are only important in the differential diagnosis of individual cases in a clinical setting. In the epidemiology of risk factors, personal factors are usually irrelevant because persons do not sort into particular military categories of exposure by their genetics, hobbies, or prior exposure experience.

Hypothesis generation arises from exposure surrogate clues from "sentinel cases" regarding deployment processes, times, locations, and the case-patients' own ideas about risky situations. These clues should be winnowed to a reasonable number by in-depth study of known etiologies and surrogates for these potential exposures. In southwest Asia, possible exposure surrogates are the sulfur mine fire with sulfur dioxide and hydrogen sulfide ambient exposures; burn pits with many potential exposures to causes of constrictive bronchiolitis, including battery and Styrofoam combustion products; explosions with possible exposure to nitrogen dioxide; and oil fires with possible hydrogen sulfide exposures.

To identify likely candidate exposure risk factors for intervention, appropriate epidemiological designs are important for efficiency and feasibility. For rare diseases, such as constrictive bronchiolitis, case-control studies are efficient, and cross-sectional designs are not. Surveillance is not the mechanism for finding epidemiological associations, but is a way of monitoring trends in response to interventions.

Assess Effectiveness of Intervention

Knowing specific chemical or particulate cause is not required to intervene to prevent future workers or service personnel from being affected. It may be enough to find "process-related" risk, in which potential causal exposures can be lowered with engineering controls, changes in work practices, and/or personal protective equipment.

An illustrative example is flavoring-related lung disease in microwave popcorn manufacture. From the eight sentinel cases in former workers, we knew that the mixing room conferred high risk because half of these severe case-patients had been mixers, despite each shift having only one mixer.[9] The engineering recommendation was to isolate the mixing room from the packaging line so that the source of the potential cause did not contaminate the work spaces of the larger number of microwave production workers. Because microfine salt dumped into an auger in the mixing room billowed dust into the room, our industrial hygienists initially recommended particulate respirators, as had an earlier generation of NIOSH industrial hygienists investigating constrictive bronchiolitis in a company adding liquid flavors to powders for the baking industry.[70] In both of these investigations, the initial counsel for intervention was inappropriate and would have been ineffective because constrictive bronchiolitis is usually related to gases and would require organic vapor protection. Luckily, in the microwave popcorn investigation, the hypothesis that volatile flavoring exposure was the cause, rather than salt dust, surfaced quickly from the multidisciplinary team. In later microwave popcorn plant investigations, we found that some plants used encapsulated flavors that required a combination of particulate and organic vapor respiratory protection until engineering controls were put into place. In an emerging issue, evaluation of intervention is critical and can substantiate the likelihood of having found the cause.

A problem with epidemiology is that associations between exposure surrogates and health outcomes may not be causal. Granted, Sir Austin Bradford Hill gave the criteria for interpreting associations as causal, including strength of association, consistency of findings by different investigators, appropriate temporal relations between exposure and outcome, biological plausibility, and exposure–response relationships.[71] In the microwave popcorn industry with diacetyl exposure, it was years before the criteria had been met for interpreting associations as causal, and the seriousness of the health effect dictated intervention before there was proven cause.[72]

Sometimes effective interventions cement our understanding of cause. For the emerging issues listed in Exhibit 18-1, several encompassed examples of successful interventions. In the bladder neuropathy outbreak, new cases

disappeared with removal of the catalyst dimethylaminopropionitrile (see Figure 18-1).[13] In the sentinel popcorn plant, control of diacetyl exposure resulted in average annualized FEV_1 declines falling from 144 to 40 to 22 mL/yr over a 3-year follow up period (see Figure 18-3).[25,26] In a damp building with cross-sectional evaluations before and after remediation of water infiltration, new asthma cases with building-related symptoms were prevented.[73] Surveillance is an effective tool to study intervention. If interventions result in lower incidence, that finding contributes to causal criteria for associations.

If interventions fail, it generally means that the cause has not been found or that the controls have been inadequate. For example, in another damp building, incomplete remediation did not lower a seven-fold excess incidence of building-related asthma since occupancy after remediation.[74,75] For emerging occupational lung diseases, unsuccessful interventions are a stimulus to learn more to prevent them. Reexamination of hypotheses and other intervention strategies are required.

An example of a failed intervention occurred in NIOSH work in the beryllium industry. Beryllium sensitization is a precondition for developing beryllium disease, a granulomatous interstitial disease. A 10% prevalence of sensitization was found in beryllium workers who had worked at least a year.[76] The company invested millions of dollars in lowering beryllium air concentrations. On a repeat cross-sectional survey, a 10% prevalence of beryllium sensitization was found in new workers regardless of tenure.[77] The intervention had failed. The company then decided that the only thing they had not considered was protecting workers' skin from beryllium exposure. Only after developing a comprehensive program that included keeping beryllium off the skin did sensitization prevalence fall in each of the three production facilities of this company.[78–80] The company did not need scientific proof of skin as a route of beryllium sensitization to institute this intervention. It was a matter of economic survival. As in the military situation with unexpected respiratory disease in southwest Asia, solving the problem with interventions is more important than developing proof of causation.

Another example of a failed intervention involved a leisure swimming pool with many water spray features. A lifeguard developed granulomatous lung disease with work-related symptoms and an abnormal chest X-ray.[81] Symptomatic co-workers were also found to have abnormal biopsies consistent with hypersensitivity pneumonitis, despite having normal chest X-rays. With systematic public health investigation, 33 lifeguards had abnormal biopsies (an attack rate of 27% of pool-exposed employees). The pool was closed for ventilation improvements, but within 3 months of the pool reopening, 65% of the lifeguards had developed work-related chest symptoms. The only abnormal industrial hygiene measurement was elevated endotoxin levels in air, particularly when the spray water features were on.

The pool was closed again, the chlorination system was replaced with ozonation, and corroded water circuits were replaced. This time the outbreak was beat. The cause could not be found, but the problem had been solved. In retrospect, it might have been wise to perform a culture for environmental mycobacteria, which was subsequently implicated in hypersensitivity pneumonitis in hot tubs, therapy pools, and machinists exposed to contaminated metal working fluids.[82] Targeted surveillance allowed a second solution to be evaluated as successful.

IMPLICATIONS FOR EMERGING CAUSES OF LUNG DISEASES

Approaches to Constrictive Bronchiolitis

Recent investigations of biopsy-documented constrictive bronchiolitis in survivors of mustard gassing in the Iraq-Iran war and in a sequential clinical case series document that spirometric results range from normal to obstructive, restrictive, and mixed abnormalities. In this disease, FEV_1 is not an indicator of severity of impairment, unlike in COPD. The spectrum of abnormalities in flavoring-exposed populations is also diverse, and NIOSH investigations of constrictive bronchiolitis ignored the many workers with similar flavoring exposures who had exertional dyspnea without obstructive abnormalities. NIOSH investigators are currently trying to rectify this oversight in their further studies of flavoring-related constrictive bronchiolitis. Spirometry and radiological imaging are both insensitive for bronchiolar pathology. In US service members with unexplained dyspnea after conventional noninvasive clinical evaluations, only open biopsies will make or exclude the diagnosis of constrictive bronchiolitis. Without looking for this disease systematically, the military and the Department of Veterans Affairs will not know the extent of the problem and will not have a rigorous case series with which to conduct epidemiological studies of possible causes, such as burn pit effluents, the sulfur mine fire, or nitrogen oxides from exploded ordinance. An efficient design for furthering understanding of associations would be case-control studies, guided by hypotheses based on known causes and surrogates of potential exposure to known or unsuspected causes. Trying to reconstruct historical exposures is usually impossible for individual cases or even groups with similar exposure levels, but surrogates of exposure may be illuminating. The

focus of some at the 2012 Airborne Hazards Symposium on individual exposure measurements being necessary to prove cause is an unrealistic distraction that ignores the potential contribution of epidemiological study.

Interventions for known causes of constrictive bronchiolitis should be implemented as quickly as possible, with efforts to evaluate effectiveness in preventing new cases. Because little is known about exposure–response relationships for chemicals causing constrictive bronchiolitis, lowered exposure measurements by themselves will not be sufficient evidence of intervention effectiveness. Furthermore, concentrations of particulate exposures may not be relevant to this health outcome, and future assessment of gaseous exposures may be of more utility. Surveillance of clinical outcomes, rather than environmental surveillance, is the means of evaluating intervention effectiveness, but depends on adequate symptom and clinical abnormality data.

Approaches to Asthma

In studies presented at the August 2012 Airborne Hazards Symposium, objective measures of lung function have not always been available to validate the reports of new-onset asthma or asthma exacerbation in Gulf War veterans. Normal spirometry does not exclude the diagnosis of asthma in which airflow limitation is episodic. When spirometry is normal, tests of airways hyperreactivity are needed. Physician misdiagnosis of asthma is common in the setting limited to history taking and stethoscopic examination. Serial spirometry is also not helpful usually, because asthmatic persons typically have normal spirometry between attacks of asthma. Case definitions should include airways hyperreactivity and not spirometry alone, unless abnormalities respond to the bronchodilator, documenting reversibility of airflow limitation.

Although allergic occupational asthma has a latency period to development after exposure begins, symptoms of occupational asthma and asthma exacerbation (in the case of preexisting asthma) occur during or within about 12 hours of the implicated exposure. Similarly, asthma caused by irritant exposures has onset in close temporal sequence to exposure. Asthma symptoms do not have **onset** weeks after the postexposure period. Thus, incident asthma cases lend themselves to hypothesis generation about causal exposures that can be addressed in case-control or cohort studies.

Allergic occupational asthma of many causes is curable if identified early in its course, and implicated exposures cease. When asthma becomes severe, steroid-dependent, and prolonged in duration, the prognosis switches to permanent asthma with many nonspecific triggers. For this reason, early identification of service members with incident asthma and removal from further exposure are critical to their long-term respiratory health. In meta-analyses of population-based asthma studies, about 21% of current asthma is attributable to indoor dampness,[83] and housing during deployment may warrant consideration.

Approaches to Chronic Obstructive Pulmonary Disease

COPD, unlike asthma, can be diagnosed with spirometry demonstrating obstruction that is not fully reversible with bronchodilators. However, even in smokers, airflow limitation below the lower limits of normal is not usually demonstrated until the fifth decade of age.[84] COPD is a long latency respiratory outcome that results from accelerated decline

TABLE 18-2

ODDS RATIOS FOR MEASURED AIRWAYS OBSTRUCTION BY INDUSTRY OR OCCUPATION IN THE US WORKING POPULATION FROM 1988 TO 1994 (EXCLUDING THOSE REPORTING PHYSICIAN-DIAGNOSED CURRENT ASTHMA)*

Industry & Occupation	Odds Ratio
Industry	
Rubber, plastics, and leather manufacturing	**2.5**
Utilities†	2.4
Office building services	2.4
Textile mill products manufacturing	**2.2**
US armed forces‡	**2.2**
Food products manufacturing	**2.1**
Occupation	
Freight, stock, and material handlers	**2.2**
US armed forces§	**2.0**
Vehicle mechanics	2.0
Records processing and distribution clerks¥	1.8

*Adjusted for age, race/ethnicity, smoking status, pack-years of cigarette smoking, body mass index, education, and socioeconomic status. **Bold font** indicates that 95% confidence intervals exclude 1.0 in comparison to office workers which is both an industry and an occupation.

†Among never-smokers, odds ratio in this industry was 27.2 (confidence interval = 3.6–214).

‡Among never-smokers, odds ratio in this industry was 4.4 (confidence interval = 0.9–20).

§Among never-smokers reporting armed forces employment, odds ratio was 4.1 (confidence interval = 0.9–19.4).

¥Among never-smokers reporting records processing and distribution clerk employment, odds ratio was 2.9 (confidence interval = 1.1–7.6).

Adapted from: Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*. 2002;156:738–746.

of FEV_1, year after year, until abnormal airflow limitation manifests. In smokers, excessive annual decline usually disappears with the cessation of smoking, but recovery of lost reserves does not usually occur. Few service members are in the age range in which smokers have abnormal obstructive spirometry. This is the one health outcome that merits predeployment and postdeployment spirometry to identify excessive declines of FEV_1 within the normal range of lung function in service members who may go on to develop clinical COPD. This group with excessive declines should be targeted for smoking cessation efforts and attention to occupational exposures related to COPD.

Population-based studies suggest that occupational exposures account for 26% to 53% of COPD in nonsmokers,[85] and the nonsmoking group of soldiers would be the easiest in which to study likely military causes of obstructive lung disease. In smokers, the attributable risks of smoking and occupational exposures are at least additive. Before the advent of widespread cigarette smoking, there was clear recognition of the risk of chronic airways disease with dusty trades, and there is now good evidence for airways disease among workers exposed to silica, coal mine dusts, and asbestos, independent of pneumoconioses and smoking. In population-based community surveys in many countries, being exposed to vapors, gas, dust, or fumes at work in the longest-held job has been associated with poorer or abnormal pulmonary function comparable in size of effect to cigarette smoking. With respect to specific agents associated with occupational COPD, there is ample evidence of the hazards of cadmium for emphysema, vanadium (as in oil field fires) for bronchitis, and welding gas and fume exposures for airways obstruction.[85]

In addition to well-established causes of occupational COPD, the third National Health and Nutrition Survey data demonstrated industries and occupations with an excess of measured airways obstruction, adjusted for cigarette smoking, where causative exposures remain to be explained (Table 18-2).[86] Among these is the armed forces category, and these data—collected from a general population sample in 1988 to 1994—largely precede the conflicts in southwest Asia. The excess respiratory outcomes among veterans are likely a long-standing risk of military service independent of ambient dust storms in Iraq and Afghanistan. To begin to prevent the substantial burden of COPD in veterans, research and intervention on exposures during military service, apart from smoking, are prudent.

LIMITATIONS OF OUR TOOLS

Looking for causes of health outcomes with our limited surveillance tools may be insufficient, akin to looking for lost keys at night under a lamppost because light is available. Questionnaires can give us symptoms of constrictive bronchiolitis and asthma, but are less useful for identifying subclinical evolving COPD in the military age group. In addition, symptoms alone are nonspecific for differentiating among lung diseases. In constrictive bronchiolitis, even dyspnea may be insensitive for spirometric abnormality, as demonstrated in microwave popcorn manufacture in which one-quarter of workers with abnormal spirometry had no chest symptoms.[10] In public health surveillance of the flavoring industry, half of those with spirometric obstruction reported no chest symptoms.[23]

Questionnaires for exposure classification need different approaches for the health outcomes of constrictive bronchiolitis, asthma, and COPD. These health outcomes have different time courses of pertinent exposure and different known exposure types. Particulate exposures are more important for COPD and asthma, and gaseous exposures are likely more important for constrictive bronchiolitis.

Serial spirometry is useful for subclinical COPD to identify excessive declines in FEV_1. Spirometry alone is not useful for identifying asthmatics because they have intermittent airflow obstruction. Instead, case definitions for epidemiological studies of deployment-associated asthma should measure airway hyperreactivity in the absence of bronchodilator response to spirometry. Finally, spirometry is insensitive for constrictive bronchiolitis because case-patients can have normal, obstructive, restrictive, or mixed patterns.

Our questionnaire tools for symptoms, exposures, and spirometry must each be tailored for specific respiratory disease outcomes. Even then, their interpretation is limited, particularly for constrictive bronchiolitis because we do not have good clinical tests for bronchiolar disease apart from open lung biopsy.

SUMMARY

The reason to better understand exposures associated with health outcomes is to intervene, both to prevent US service members from having exposures and to improve prognosis of those who have developed health conditions in relation to exposure. The role of surveillance is the repeated assessment of health outcomes in a population to assess trends, and there is no reason to repeatedly assess health outcomes unless interventions are undertaken. Surveillance is not a substitute for understanding military respiratory hazards with targeted hypothesis-driven research.

Longitudinal surveillance is premature when unexpected health outcomes occur. Such health outcomes need to be acknowledged as unknowns and restated as hypotheses about plausible causes to facilitate research regarding causes and interventions. Targeted epidemiological research studies should test hypotheses about plausible causes of specific health outcomes. Past exposures that were not measured cannot be known, and this is particularly true of the uncharacterized gases that may have caused constrictive bronchiolitis, the bioaerosols in damp indoor spaces that may induce asthma, or the various occupational exposures that will eventually lead to COPD. Indices of exposure can be as simple as deployment in specific locations and dates or information about participation in exposure-generating processes gathered by questionnaires. For constrictive bronchiolitis arising in an indolent way, report of severity of exposures may not be helpful at all because respiratory epithelial toxins may not induce irritant symptoms, even in those with spirometric abnormality. For incident asthma, however, symptoms would have arisen during pertinent exposures in deployment.

Prevention of respiratory diseases in service members requires research efforts to assess causality and to evaluate the effectiveness of interventions so that fighting strength can be preserved. These efforts should take precedence over determination of compensation eligibility for service-related health outcomes. In clinical occupational medicine practice, a high level of evidence about proof of cause in the workers' compensation system is needed. The military cannot afford to risk the health of its troops, even if causal associations have not yet been demonstrated. The occurrence of pathological and objective disease requires attempts at intervention.

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