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CME Article #1

Incidence of Lung, Eye, and Skin Lesions as Late Complications in 34,000 Iranians With Wartime Exposure to Mustard Agent

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Learning Objectives

- Recall the frequency and severity of chronic pulmonary, ocular, and cutaneous lesions in this study of 34,000 Iranians exposed in war to mustard agent and followed up after 13 to 20 years.
- Relate the physical and chemical properties of mustard agents to their biological effects in exposed persons.
- Describe the chronic clinical sequelae of mustard exposure as observed in the lungs, eyes, and skin.
- Describe a categorizing method for determining the severity of lung, eye, and skin lesions based on clinical criteria.

Abstract

Approximately 34,000 Iranians known to have sustained mustard agent exposure during the Iran–Iraq war of 1980–1988 and survived over a decade afterwards were screened for distribution of the most commonly occurring medical problems. In order of greatest incidence, these include lesions of the lungs (42.5%), eyes (39.3%), and skin (24.5%). Within each subpopulation, patients were ranked according to severity of lesions. Twenty-three percent to 37% of patients exhibited at least mild coverage, with 1.5% to 4.5% classed as moderate, and a much smaller population (0.023–1.0%) of the 34,000 patients exhibiting extensive (severe) lesional coverage. These results provide a comprehensive overview of the medical problem most common among mustard victims and could serve as a predictor of the likely impact of these weapons on health status of populations exposed to them during ongoing military conflicts. (J Occup Environ Med. *2003;45:1136–1143*)

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During the 8-year war between Iran and Iraq (1980–1988), Iraqi forces were known to have frequently used chemical weapons against Iranian targets, which included both military personnel and civilians in Iranian border towns. The agents used by the Iraqis fell into 2 major categories based on chemical composition and casualty-producing effects. The most frequently-used were "nerve" agents, which act by complexing with essential enzymes necessary for nerve transmission, causing death as a result of failure to maintain control of major organ systems, particularly the lungs. "Mustards," or vesicant agents, which degrade tissue of exposed personnel causing severe chemical burns, were also used extensively. The tactical use of mustards is the result of their low manufacturing cost, ease of dissemination, and ability to force target personnel into protective posture for prolonged periods of time, thus reducing combat effectiveness by making logistics very difficult.[1,2] Consequently, they became the weapon of choice by Iraq, as documented by United Nations fact-finding missions in 1984–1987[3] By contrast, nerve agents were often used in a different battlefield mode. Their high toxicity relative to mustards made them ideal for rapidly causing mass casualties among target personnel, particularly when protective gear was absent or marginally effective. The psychologic effects of such weapons are in and of themselves excellent combat multipliers

and thus could be accurately classed as "terror weapons." Iraq made use of these agents in combat with Iranian forces, primarily using a weaponized organophosphate called Tabun (ethyl N, N-dimethylphosphor amidio ciyanidate), sometimes in mixtures with mustards[3]; however, they refrained from more widespread use of these weapons. Both acute and latent medical effects of chemical warfare agents arise from their biochemical properties. Mustards such as bis (2-chloroethyl) sulfide are alkylating compounds, which act on exposed persons by addition of an alkyl group to cellular components. Their physical properties also affect tactical use and impact. Most are liquid at room temperature, producing casualties as a result of either inhalation of vapor, when absorbed by the skin (percutaneous), or both. Generally, the lower the compound's volatility (and hence its inhalation threat), the greater its percutaneous toxicity and time of persistence. Toxicity of mustard agent is considerably greater when absorbed through moist tissues such as the respiratory tract, axillary areas, genitals, and eyes. Their acute toxic effects result from irreversible alkylation of protein and nucleic acids, mediating monoadduct formation with components such as ring nitrogens or extracyclic oxygens of nucleotide bases.[4] Collectively, this causes loss of structural and functional integrity of cells and tissues, resulting in intense pain and burning with blister formation.[5] Death often occurs as a result of suffocation as a result of respiratory damage. Both nerve and mustard agents are known to cause long-term medical complications related to, but separate from, the acute effects of battlefield exposure. Exposure to mustards is associated with development of chronic health problems, including chronic neuropathic pain,[6] increased susceptibility to cancers,[7–13] defective spermatogenesis,[14] ocular injury,[15–21] skin lesions,[22–26] and respiratory disease.[27–37] During our war with Iraq, reports from Iranian combat aid stations, field hospitals in battle zones, and reports by civil authorities (where noncombatants had endured chemical weapon [CW] exposure), more than 100,000 military and civilian personnel had received treatment for acute effects of CW agents.[38] These reports, which included both inpatient and outpatient populations, were compiled primarily in frontline military medical facilities and hospitals in population centers close to the front lines (which were also subjected to chemical attack). Today, more than 15 years postwar, an enormous number of Iranians, both military veterans and civilians, are afflicted with medical problems arising from exposure to Iraqi chemical weapons.[38] During the course of the war with Iraq, greater numbers of Iranians sustained exposure to nerve agents than mustards.[38] However, our observation has been that of those who survived, a substantially larger number of mustard agent victims have reported chronic health problems since the time of the war.[38] In the present study, we investigated the occurrence of chronic effects among these personnel, in which the pathologies of their illnesses are presumed to have arisen as a result of mustard agent exposure. Predominant disorders among this population are persistent lesions of the eye, skin, and respiratory tract. We report the distribution of these pathologies according to severity and offer insight into novel approaches to therapy for affected individuals. For the purpose of this study, we focus exclusively on occurrence and extent of lesions because in the experience of Iranian primary care facilities, this is the most commonly shared symptom exhibited by survivors of mustard agent exposure. We nevertheless recognize that mustards are known to induce a diverse range of pathologies, and in future investigations, we will examine each major disease among this population.

Materials and Methods

Subject Identification and Approach to Data Collection

Subjects for this investigation constituted the entire pool of 34,000 individuals with confirmed exposure to mustard agent during the war with Iraq and who subsequently were evaluated for exposure to mustard agent by medical authorities as described subsequently. Approximately 95% of these subjects were males between 17 and 30 years of age and serving in the armed forces of Iran, but we also include civilians evaluated under this program. All exposures occurred as a result of hostilities during the war with Iraq, and participants were long-term survivors of mustard attack; thus, no mortality data is included. As a result of the large number of subjects surveyed as part of this study, the protocol for evaluation was not completely uniform. We therefore focus exclusively on data concerning extent of skin, eye, and lung lesions because this was generated using a standardized medical evaluation sheet. These individuals were identified and medically evaluated as part of a nationwide survey sponsored by the Iranian Ministry of Veterans Affairs through the Health and Treatment Agency (Janbazan Organization). Identification and collection of clinical data on this population was preceded by a workshop at which medical personnel participating in the survey established uniform standards for evaluation of mustard-exposed persons and convention for interpretation of results. Expert medical teams were then dispatched to each province of the country for data collection. Each team included a dermatologist, an ophthalmologist, a pulmonologist, a general practitioner, and support personnel. Each team coordinated activities with local medical facilities in communities to be visited, allowing thorough screening of each region of the Iran for survivors of chemical attacks and

TABLE 1
Respiratory Effects—Assessed as Severity of Lung Lesions (Individuals presenting with spirometry and physical exam findings as indicated below are classified into one of three diagnostic categories as shown)

Diagnostic category (lesional involvement of lungs)	Spirometry		Physical exam findings
MILD	65 =/< FEV1<80 or =/< FVC < 80	65	Abnormal lung sounds
MODERATE	50 =/< FEV1<65 or =/< FVC <65	50	Abnormal lung sounds
SEVERE	40 =/< FEV1 <50 or 40 =/< FVC <50		Abnormal lung sounds. May include cyanosis and intercostal retraction; or tracheal stenosis in bronchoscopy

incorporation into the survey database. The entire survey was accomplished during the timeframe 1997–2000. An individual was designated as "mustard-exposed" only if the criteria for exposure designated by the aforementioned workshop were met. Persons who could have had some degree of battlefield exposure to mustard, but were in full mission-oriented protective posture at the time and who suffered no adverse health effects, were not considered to have exposure to the agent. Case definition criteria include: 1) documentation of blister at time of exposure, and 2) signs and symptoms compatible with mustard toxicity (latency period followed by skin erythema–vesicle and blister formation, coughing).

Additional Exclusion Criteria

In addition to the aforementioned clinical attributes, the following subject categories were excluded from the study:

1. Smokers;
2. Persons with confirmed nonchemical-related lung disease (asthma, congestive heart failure, occupational disease) based on job history, familial disease, or chronic obstructive pulmonary disease with other known etiology;
3. Persons with dermatologic disease with nonchemical-related etiology; and
4. Persons with ophthalmologic disorders with other known etiology.

Collection of Exposure-Related and General Information

Because this investigation was conducted retrospective more than 15 years after initial exposure, it has been difficult, and in many cases impossible, to ascertain acute mustard effects by each subject in any systematic way. Such data does in fact exist in medical records for some individuals and is the subject of a separate investigation that focuses on acute symptoms. However, because the purpose of this study was to document distribution of the most common chronic problem experienced by mustard attack survivors, we have deferred discussion of the effects occurring immediately postexposure to the aforementioned investigation. Assessment of the circumstances of exposure to chemical warfare agents was made on the basis of a standardized questionnaire, which additionally included 3 subparts, each specific to a major symptom known to be common to victims of mustard agent, specifically: 1) dermatologic symptoms, 2) ophthalmic symptoms, and 3) respiratory/pulmonary symptoms. After identification of mustard agent victims within a community, each team randomly selected exposed persons for evaluation to allow for testing of some individuals by more than one team. This was done as an internal quality control measure to ensure reproducibility of results.

Categorization by Severity of Lung, Skin, and Eye Damage

Chronic medical problems diagnosed among subjects were broadly divided into 3 subgroups: mild, moderate, or severe based on a standardized diagnostic protocol adopted by Janbazan Organization. Because anecdotal information before the present study suggested that the most common chronic ailments experienced by mustard-exposed persons are respiratory, ocular, or dermal disease; physical examinations conducted under the present investigation focused on defining the extent of each of these disorders among subjects. These evaluations were conducted according to a standardized method that included clinical and laboratory parameters. Pulmonary lesional involvement of each subject was determined by spirometry and by the presence of abnormal lung sounds during physical examination (Table 1). Severity of skin problems among mustard agent victims was assessed according to 24 dermatologic disorders with classification as mild, moderate, or severe based on the presence or absence of each condition (Table 2). Ocular effects were classified as mild, moderate, severe, and very severe according to the presence and severity of symptoms of eye damage, with lesional involvement of the cornea serving as a major index of severity (Table 3).

Results

Our evaluation of the clinical status of mustard agent-exposed Iranians reveals that a significant percentage of these individuals experience some form of chronic disease. The distribution of lung, eye, and skin lesions in a population of 34,000 Iranian mustard agent victims is shown in Table 4. Of these, 14,450 cases (42.5%) exhibited lung lesions, with 12,920 (37%) classed as mild, 1530 (4.5%) moderate, and 340 (1.0%) severe (Fig. 1). Eye lesions were diagnosed in 13,362 individuals (39.3%), with 11,900 (35%) showing

TABLE 2
Medical Classification Criteria Established by the Janzaban Organization for Skin-Related Chronic Disease Among Victims of Chemical Attacks

	Symptoms	Diagnostic category (lesional severity)
1	Itching or burning skin without clinical lesions	Mild
2	Dry skin	Mild
3	Hypo- or hyperpigmentation or both; or depigmentation less than 18% of body surface; or in covered area*.	Mild
4	Alopecia areata totalis, or universalis.	Mild
5	Generalized vitiligo.	Mild
6	Psoriasis (less than 20% of body surface).	Mild
7	Lichen simplex and limited prurigo.	Mild
8	Limited and mild eczema.	Mild
9	Limited scars in area of lesional involvement.	Mild
10	Single keloid without limitation in range of motion and in covered area*.	Mild
11	Severe acne vulgaris and nodulostic or suppurative hydradenitis.	Mild
12	Chronic hives or angioedema.	Mild
13	Vesicular lesions (localized).	Mild
14	Recurrent superficial fungal disease (chronic resistant dermatophitosis).	Mild
15	Hypo- or hyperpigmentation or both; or depigmentation more than 18% of body surface; or in uncovered areas+.	Moderate
16	Severe and diffuse eczema.	Moderate
17	Generalized prurigo.	Moderate
18	Diffuse scarring in uncovered areas+.	Moderate
19	Keloid with limitation in range of motion and in area outside of lesional involvement	Moderate
20	Generalized recurrent vesicular lesions.	Moderate
21	Generalized and chronic itching with clinical lesions	Moderate
22	Psoriasis (more than 20% of body surface).	Moderate
23	Basal cell carcinoma (BCC)	Moderate
24	Skin or mucosal cancer (except BCC)	Severe

Mustard-exposed personnel who exhibit one or more of symptoms 1–14 above are classed into the Mild lesion diagnostic category; 15–23: Moderate; and 24: Severe.

* "Covered areas" refer to portions of skin normally covered by clothing. In these areas pigmentation disorders are usually not dominant.

+ "Uncovered areas" in this case refer to areas of skin not normally covered by clothes. These areas are generally not severely afflicted by mustard-related pigmentation disorder.

mild lesions, 1224 (3.6%) moderate, and 238 (0.7%) severe (Fig. 2). Skin lesions were diagnosed in 8338 (24.5%) patients, with 7820 (23%) reporting mild lesions, 510 (1.5%) moderate, and a very minor population of 8 persons (0.023%) exhibiting severe skin lesions (Fig. 3).

Discussion

Military Use of Chemical Weapons

Chemical warfare is recognized as a deeply abhorrent addition to the repertoire of combat strategies, and efforts have been made to ban its use for over a century at the time of this writing. Treaties designed to do this began with the Hague Convention of 1899,[39] which failed to prevent widespread use of chemical weapons during the First World War,[40] the 1925 Geneva Protocol,[41] and numerous other agreements to refrain from battlefield application of these weapons. These efforts met with moderate success until the Iran–Iraq war in the 1980s. During the course of that conflict, UN fact-finding teams confirmed the use of chemical weapons on massive scale by the Iraqis. In 1984, 1986, and 1987, UN inspectors verified through field inspections, clinical examination of casualties, and laboratory analysis of chemical ammunition that the Iraqis had used aerial bomb-delivered chemical weapons, and that the main type of chemical agent used was mustard, with occasional use of the nerve agent Tabun.[3] This experience has inflicted an enormous toll on Iran.

Medical Impact of Chemical Weapons

In the present investigation, we have documented occurrence and severity of the 3 most common health problems experienced by individuals exposed to mustard between 13 and 20 years before physical evaluation for this study. On the basis of the criteria used in these evaluations, a total of 34,000 persons were considered unambiguously to have been exposed to mustard agent to some degree. This entire population constituted the subject base for this investigation. It is recognized, however, that although the screening protocol was thorough, operational and technical limitations resulted in an imperfect assessment of exposure effects. The most outstanding limitation was the inability to definitively assign a particular exposure level to an individual, which would have been extremely valuable for correlation of clinical effects with mustard dosage. However, despite this constraint, the report nevertheless provides a broad picture of the most obvious long-term health effects of mustard exposure.

Lung Injuries

Among Iranians exposed to mustards, respiratory disorders were the most common long-term medical complaint (Table 4), with 42.5% of the exposed population exhibiting chronic lung lesions and associated symptoms (Fig. 1). The high incidence of pulmonary disease among surviving mustard agent victims could be accounted for by the severe effects mustard is known to have on the lungs.

Because mustard in vapor form is most readily absorbed through mucous membranes, the respiratory sys-

TABLE 3
Ocular Effects—Assessed as Severity of Eye Lesions

Diagnostic category (lesional severity)	Symptoms
Mild	***Complaints:*** Photophobia; foreign body sensation; tearing; burning; itching; red eye; blured vision; vision loss; pain; difficulty in reading ***Signs:*** Conjunctival inflamation and hyperemia; sub conjunctival hemorrhage; swollen blood vessels; blepharitis; dysfunction of mibomian glands; papillary change
Moderate	Above complications, plus mild corneal involvement: Epithelial and sub epithelial opacity; anterior stroma in peripheral cornea; perilimbal hyper pigmentation; iron deposit in cornea; band keratopathy; pannus<2mm - no melting; BUT : 5–10 sec; Schirmer (with anesthesia) : 5–10 mm; red reflex : 9/10–10/10
Severe	Above complications, plus severe corneal involvement: Thinning; melting; severe hyaline-like deposit; corneal vascularization BUT <5 sec - Schirmer (with anesthesia) <5 mm; red reflex: 1/10–4/10
Very Severe	Above complications, plus very severe corneal involvement: Diffuse corneal opacity; severe thinning; desmatocele; severe vascularization Red reflex <1/10 - retina is not visible

Individuals presenting with patient complaints and signs indicated above are classified into one of three diagnostic categories as shown.

TABLE 4
Distribution by Severity of Lung, Eye, and Skin Lesions in a Population of 34,000 Iranians With Histories of Mustard Agent Exposure

Lesional severity	LUNG (percent affected)	LUNG (number affected)	EYE (percent affected)	EYE (number affected)	SKIN (percent affected)	SKIN (number affected)
No lesions	57.5%	19,550	60.7%	20,638	75.5%	25,670
Mild lesions	37%	12,580	35%	11,900	23%	7,820
Moderate lesions	4.5%	1,530	3.6%	1,224	1.5%	510
Severe lesions	1.0%	340	0.7%	238	0.023%	8

Subjects are categorized according to severity of lung, eye and skin lesions. Listed are numbers of individuals and percentage of population affected in each category.

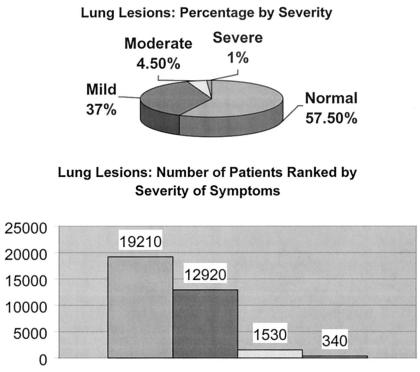

Fig. 1. Occurrence of pulmonary lesions in a population of 34,000 mustard agent-exposed Iranians.

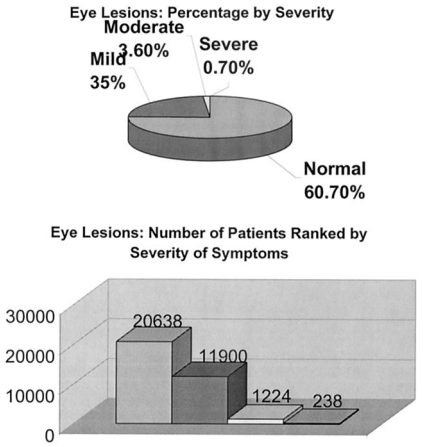

Fig. 2. Occurrence of ocular lesions in a population of 34,000 mustard agent-exposed Iranians.

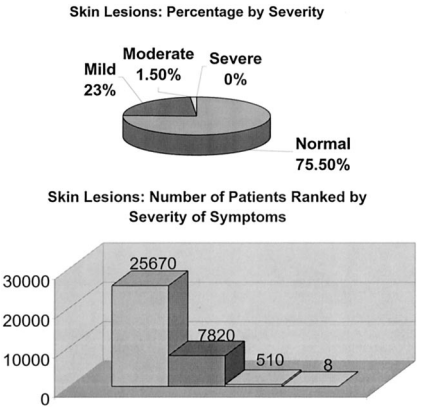

Fig. 3. Occurrence of skin lesions in a population of 34,000 mustard agent-exposed Iranians.

tem provides an enormous surface area for entry of agent and reaction with cellular components. Mustard agent chemically reacts with proteins,[42] contributing to massive damage to all tissues. In the lungs, sulfur mustard is observed to induce severe inflammation of the tracheobronchial epithelium with heavy leukocyte infiltrate, alveolar hemorrhage with thrombi formation, and vacuolation of lung parenchymal cells.[43] Such injury is often fatal; however, should the victim survive, substantial scar tissue remains, often with degradation of pulmonary function and development of pulmonary fibrosis.[34] Individuals who have sustained mustard injury to the lungs generally

have greatly increased susceptibility to pulmonary disease, particularly chronic fibrosis and bronchitis.[27] Chronic bronchitis, in fact, is the most common chronic pulmonary consequence of mustard gas exposure, occurring in greater than 50% of those exposed and often associated with marked physical deterioration.[29] Interestingly, it has been found that bronchitis among Iranian mustard agent victims exhibits pathology distinct from idiopathic pulmonary fibrosis (IPF) and other types of infiltrative lung disease (ILD).[27] Our experience with pulmonary disorders among mustard-exposed patients is that their pathology can be characterized by a number of unique features not seen in other patients with lung disease. For example, we have found by analysis of bronchoalveolar lavage (BAL) fluid from patients with pulmonary fibrosis (PF) as a late sequelae of massive sulfur mustard gas inhalation, that these patients exhibit an ongoing local inflammatory process of the lower respiratory tract. Collectively, this observation and others argues for adoption of a novel case definition applicable to mustard agent-induced lung damage. Such a definition, which has been tentatively called "mustard lung,"[27] would aid primary care physicians in defining maximally effective therapies for patients with known exposure to chemical warfare agents, and during wartime allow for a smoother flow of triage in field hospitals.

Skin Injuries

As shown in Figure 3, skin lesions are observed on 24.5% of Iranian mustard agent victims. The agents react with skin proteins, degrading structure of both cells and underlying extracellular matrix. Mustards also promote severe inflammation of the skin by induction of the major proinflammatory cytokines interleukin-1-beta, IL-6, IL-8, and tumor necrosis factor alpha.[44] Pigmentation is often altered (either increased or decreased) as a late skin disorder at the sites of primary mustard lesions, although the degree of alteration does not differ from that observed in injuries caused by burns and other forms of physical and chemical insult. In the absence of melanocyte destruction, hyperpigmentation predominates. If melanocytes are locally destroyed, and inward migration from destroyed adnexal structures does not occur, depigmentation predominates. Some previously injured sites have been described as being "sensitive" to subsequent mechanical injury. These sites can show recurrent blisters after mild injury.[45] In a prospective study of delayed toxic effects from mustard exposure, Balali-Mood followed a group of Iranian solders exposed to mustard gas during the Iran–Iraq War. After 2 years, 41% of the exposed victims exhibited skin pigmentation disorders.[46] Skin cancers occurring at the site of old scar formation is also an acknowledged biologic phenomenon,[47,48] with application to study of chemical warfare injuries. It has been observed for instance that cutaneous cancers resulting from acute mustard exposure usually localize in scars, whereas those caused by chronic exposure can occur on any exposed site.[49] Hence, the results of the present investigation will greatly aid in risk analysis for prediction of cancer incidence, both among Iranian mustard victims and other populations exposed to alkylating agents.

Eye Injuries

Ocular damage, which is observed to be present in 39.3% of mustard-exposed Iranians, is another major consequence of exposure to these agents as a result of their ease of absorption through the unprotected eye. Injury to the eye by alkylating agents results in common histologic and ultrastructural effects, which account for the acute symptoms and predispose victims to development of late complications. These include nuclear pyknosis, necrosis, loss of polarity of corneal epithelial basal cells, with stromal responses, including edema, degenerating fibroblasts, and inflammatory cellular infiltrates.[50]

Results presented in this report in some cases contrast with studies of other Iranian populations with wartime exposure to mustard agent. Chronic pulmonary sequelae of exposure to mustard were characterized in a cohort of 50 sulfur mustard-exposed Iranian war veterans, 80% of whom exhibited abnormalities visible on chest x-rays with all patients manifesting high-resolution computed tomography abnormalities, including bronchial wall thickening in 100% of cases, changes suggestive of interstitial lung disease (80%), and bronchiectasis (26%).[51] This compares with a separate study of 220 mustard-exposed personnel, nearly all of whom manifested obstructive spirometry patterns accompanied by coughing, dyspnea, and suffocation to some degree, with 67% experiencing wheezing and coarse rale, and the minority exhibiting hemoptysis (2.7%) and respiratory distress with use of accessory muscles (1.8%).[52] Ocular effects studied in a group of 22 mustard-exposed veterans revealed that all members of this population experienced some degree of chronic eye problem, primarily conjunctival scarring, often accompanied by dryness and decreased visual acuity, with 41% exhibiting dysplasia (shown by conjunctival scrape cytology).[53] In the studies described here, mustard-exposed persons experienced chronic symptoms at higher rates than are reported here; however, these reports are based on smaller test populations, which in some cases included subjects who were selected for the study based on presence of active disease. Conversely, the selection criteria for the present investigation was based only on confirmed exposure to mustard agent, and inclusion in the study did not require that an individual exhibit any symptoms. In fact, as described in "Methods," individuals afflicted with disease that overlapped with known mustard-induced pathol-

ogies were excluded. However, the applicability of this investigation is further limited by lack of historical control group data for assessment of the magnitude of health risks associated with mustard exposure in an Iranian population. Specifically, it would be desirable to compare these data with an age-/gender-matched, randomly selected Iranian cohort with no exposure to mustard. These limitations are nevertheless balanced by the very large size of our subject cohort, who collectively constitute the entire surviving population of Iranian victims of mustard attack during the Iran–Iraq war. We have described a spectrum of the most common long-term symptoms exhibited by these veterans.

Conclusion

This investigation provides a description of how lesions of the eye, lung, and skin are distributed throughout a large population of mustard attack survivors measured 13–20 years after exposure to the agent. The distribution of symptoms by severity is an excellent predictor of the degree to which veterans of a conflict in which chemical agents are used are likely to be affected in postwar years. This report can be used in planning for programs for long-term care of veterans and in estimating resources necessary for such efforts. Results presented here additionally establish groundwork for a comprehensive evaluation of the full range of health problems that can be expected as a result of chemical warfare.

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