Acute and Late Complications of Chemical Warfare Agents

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Financial conflict of interest

--- None

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Introduction

Chemical Warfare Agents (CWA) including sulphur mustard gas were used against both Iranian soldiers and civilians during the Iran-Iraq War of 1980-88, by the regime of Saddam Hussein.

This presentation aims at discussing almost 30 years of observing clinical manifestations and management of patients including successes and failures in both military and civil setting from this unique tragedy.

Cornicle of chemical warfare in Iran

August 1983 to July 1988

For a period of about 5 years, Iran (military and civilian settings) was attacked several times with chemical weapons by the Iraq (regime of Saddam Hussein)

July 1987 and June 1988

- ✓ *Sardasht* (one of the Kurdish cities in the North West of Iran) was attacked by several Sulfur mustard bombs that was released in the city center. At the time of the attacks, 8 025 people of 12 000 residents in this town were chemically injured and 130 civilians were killed.
- ✓ The last chemical attack on civil population was in Feb 1988 in the town of *Oshnaviyeh* (in the North West of Iran) which left 2 680 injured civilians. The use of chemical weapons against civilian population in 8 locations at Sheikh Othman District in Oshnaviyeh has been confirmed by United Nation's experts.

Razavi SM et al. Iraq-Iran chemical war: calendar, mortality and morbidity. Chin J Traumatol. 2014;17(3):165-9.

Chemical Warfare Agents (CWA)

- Kill
- Injure
- Incapacitate

- Threaten
- Balance the power

Compared to other weapons of mass destruction, CWA are different in terms of the following issues

- ✓ Act rapidly (minutes to hours)
- ✓ Easier to identify (due to rapid effect, odor and availability disclosures)
- ✓ Different sustainability rates in the environment
- ✓ Distinct victims distribution (close to the release point and the wind direction)
- ✓ Medical approach; Evacuation, Decontamination, Antidotes and symptomatic and supportive treatment are recommended.

History

The first well-documented intentional use of chemicals as weapons occurred in 429 B.C. when ***Spartans*** besieging Athenian cities burned pitch-soaked wood and brimstone to produce sulfurous clouds[1].

Haller JS: Gas warfare: Military-medical responsiveness of the allies in the great war 1914-1918. NY State Med J 1990;90:499-510. Pics from the net

Homicide and assassination

Madam Giulia Toffana

- ✓ Selling her poison (Aqua toffana (arsenic trioxide?)) to women who wanted to murder their husbands.
- ✓ Under torture, she confessed to killing 600 men in Rome alone (controversial)
- ✓ She was executed in 1659

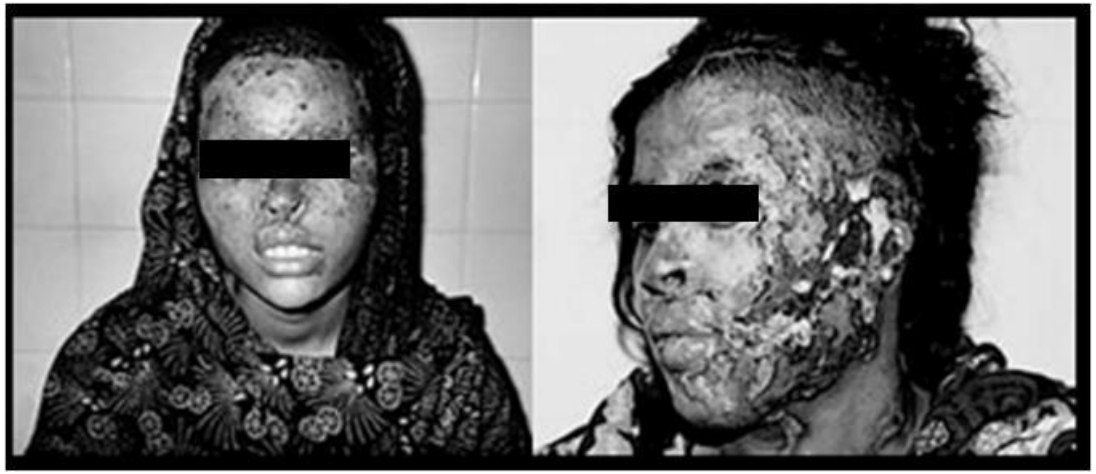
Napoleon Bonaparte (controversial)

- ✓ 1821, Died
- ✓ 1840, hid body exhumed for reburial in Paris, which was in A remarkable condition “arsenic mummification
- ✓ 2008, samples showed high arsenic levels (??)

Victor Yushchenko

Ukraine Presidential Candidate, 2004 (3rd President of Ukraine)
A British scientist declared “chlorane” as a result of dioxin poisoning.
They found dioxin levels in his blood 6,000 times above normal.
His poisoning is controversial.

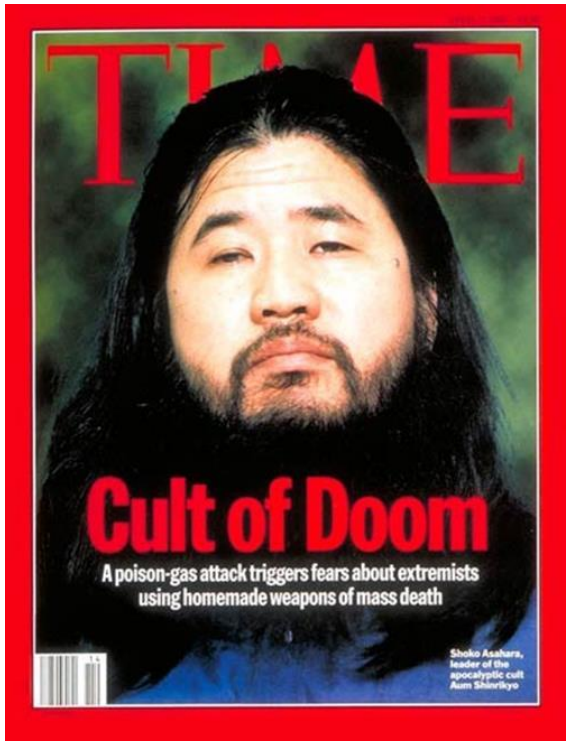
Posting contaminated packages



Using Acids for Terror
Infamous Love Stories in South and Central Asia

Tokyo subway Sarin attack

March 20, 1995 in Tokyo, Japan,
by members of the cult movement Aum Shinrikyo



- Killed 12
- Major injury 50
- Temporary vision problems for 5,000

Pictures from the net

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Different types of CWA

Blood agents	***Vesicants***
✓ Cyanogen chloride ✓ Hydrogen cyanide	✓ Lewisite ✓ Sulfur mustard
Pulmonary agents	***Incapacitating agents***
✓ Phosgene	✓ Quinuclidinyl benzilate
Lachrymatory agents	***Nerve agents***
✓ Pepper spray: OC ✓ Tear gas: CN, CS, CR	✓ Sarin: GB, ✓ VE, VG, VM, VX

Methods

- Literature reviewed via PubMed in spring, 2016.
- Personal experience and data are also discussed.

CWA attack

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Acute effects following exposure

Ocular findings

- ✓ Conjunctivitis
- ✓ Edema of the eyelids
- ✓ Closure of the eyes

Acute effects following exposure

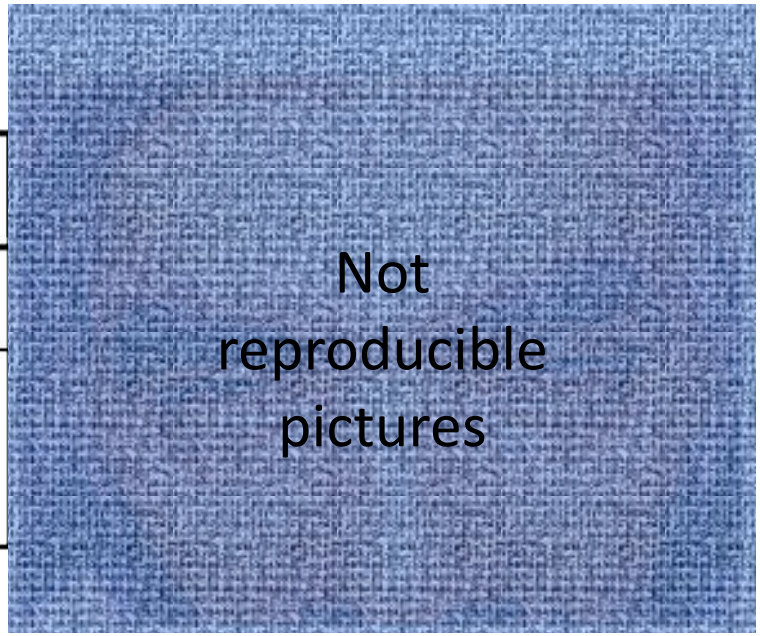
Ocular findings

Conjunctivitis, edema of the eyelids and closure of the eyes were observed in the majority of the cases.

Table 3.—Ophthalmic Manifestations of Mustard (Yperite) Gas*

Clinical Manifestations	No. of Patients	%
Conjunctivitis	455	85.04
Photophobia	332	62.05
Eyelid edema	64	11.96
Corneal abrasion	43	8.03

*Five hundred thirty-five patients were exposed to mustard gas.

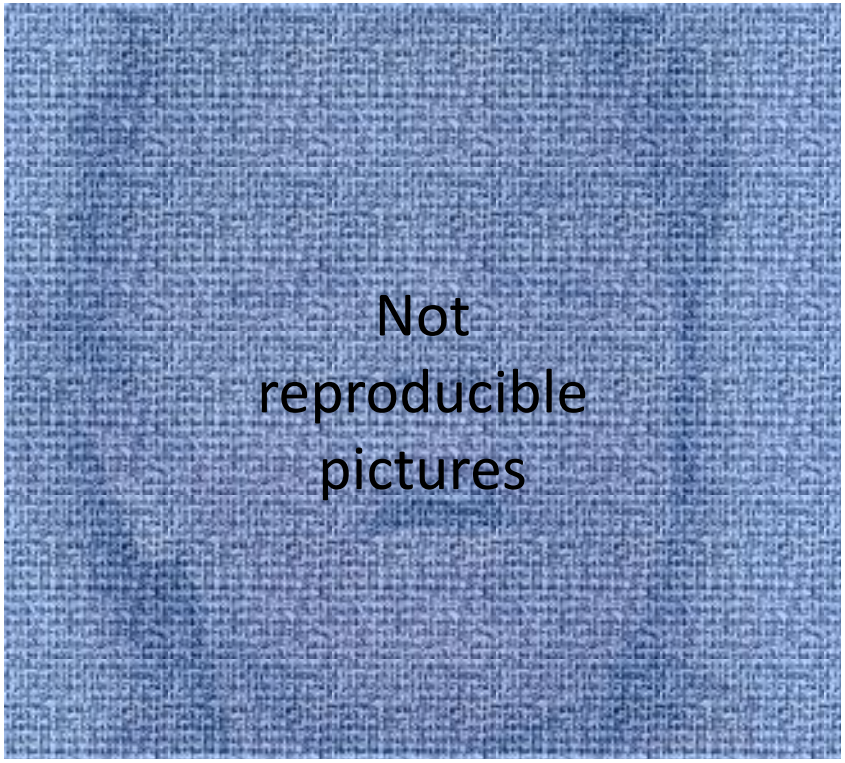


Blepharokeratoconjunctivitis

Momeni AZ et al, Skin manifestations of mustard gas. A clinical study of 535 patients exposed to mustard gas. Arch Dermatol.1992 Jun;128(6):775-80.

Acute effects following exposure

Ocular findings



Severe photophobia. lacrimation, and facial skin lesions in a girl following exposure to mustard gas

Azizi F &, Amid MH. Clinical Warfare Presentation Of Chemical Injuries In Children And Teenagers. Medical Journal of the Islamic Republic of Iran. 1990 summer 4 (2)103-108.

Acute

Table I. Admission vital signs in children injured with vesicants.

No:	Day (s) After exposure	Age	Sex	Pulse rate Per minute	Respiratory rate per minute	Temp. erature (C)	Remarks
1	1	8	M	120	42	40.0	Died
2	1	12	F	106	36	40.0	Died
3	2	5	F	120	36	39.5	
4	3	0.4	F	140	30	39.0	Died
5	3	10	F	140	40	38.0	
6	3	10	M	110	30	38.0	
7	4	9	F	100	36	37.5	
8	8	3	M	140	60	39.5	Died
9	9	5	F	120	36	38.5	
10	10	6	F	110	37	37.5	
11	10	3	F	110	36	38.0	
12	10	3	F	120	36	37.0	
13	10	9	M	90	24	37.5	
14	12	4	F	134	40	38.0	
15	12	9	F	100	20	37.0	
16	20	5	F	140	20	36.8	

tions were performed every three to five days in those who survived.

RESULTS

Table II. Clinical findings in 16 children injured with vesicants.

Sign	Number	Percent
Ocular:		
Conjunctivitis	15	94
Edema of the eyelids	13	81
Closure of the eyes	10	63
Keratitis	6	38
Blepharospasm	4	25
Corneal ulcer	3	19
Chemosis	1	6
Cutaneous:		
Erythema	15	94
Hyperpigmentation	12	75
Ulceration	11	69
Erosion	10	63
Blister	9	56
Edema of the skin	8	50
Vesicle	5	31
Hypopigmentation	2	13
Respiratory:		
Dyspnea	10	63
Crepitation	8	50
Wheezing	4	25

Results

Acute effects following exposure

Cutaneous manifestation

- ✓ Erythema
- ✓ Blisters
- ✓ Hyperpigmentation

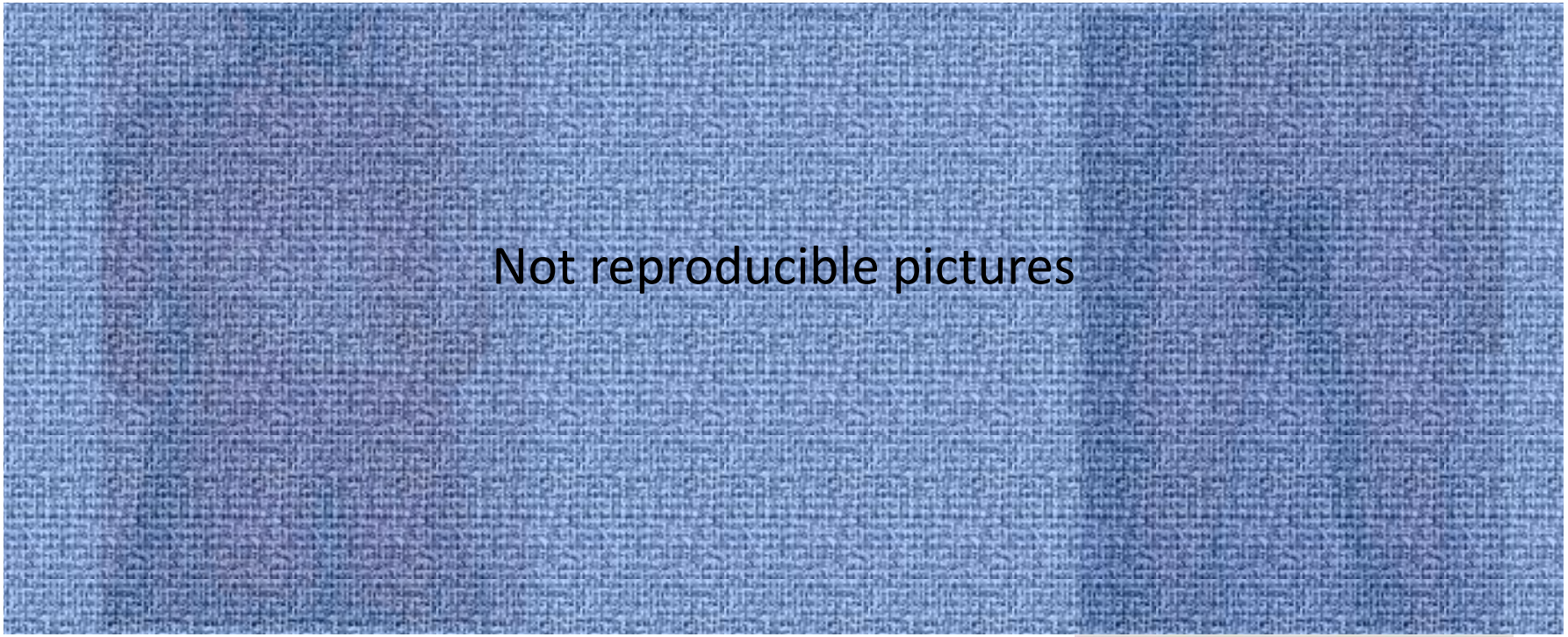
Table 1.—Skin Manifestations of Mustard(Yperite) Gas*

Clinical Manifestations	No. of Patients	%
Erythema	423	79.06
Bulla	295	55.14
Pigmentation	109	20.37
Scale	60	11.21
Urticaria	26	4.85
Purpura	6	1.12
Mucosal lesion	6	1.12

*Five hundred thirty-five patients were exposed to mustard gas.

Table 2.—Location of Bullous Lesions of Mustard (Yperite) Gas*

Location	No. of Patients	%
Axillary	266	90.16
Genital	213	72.20
Face	104	35.25
Chest	89	30.16
Trunk	36	12.20
Other parts of the body	18	6.10



Diffuse erythema and ulcerating lesions over the back

Diffuse erythematous lesion over the genital area

Momeni AZ et al. Skin manifestations of mustard gas. A clinical study of 535 patients exposed to mustard gas. Arch Dermatol. 1992 Jun;128(6):775-80.

Not reproducible pictures

Generalized hypopigmented and hyperpigmented macules over the trunk

Postinflammatory hypopigmented and hyperpimentation

Not reproducible pictures

Blisters

Erythematous lesion over the chest with ulceration of the face

Table I. Clinical manifestations, sequelae, and special therapeutic measures

Case	Manifestations		
	Ocular	Oral mucous	Cutaneous
1	Palpebral edema, conjunctivitis	Erythema, lip erosions	Widespread blisters, erosions
2	Conjunctivitis	—	Sunburnlike erythema, widespread blisters
3	Conjunctivitis	—	Sunburnlike erythema, widespread blisters
4	Corneal erosion, conjunctivitis	—	Sunburnlike erythema, widespread blisters
5	Conjunctivitis	—	Sunburnlike erythema, erosions on the neck
6	Palpebral edema, conjunctivitis	Erythema, lip erosions	Facial blisters, erosions on the scrotum
7	Conjunctivitis	—	Sunburnlike erythema
8	Corneal perforation of the right eye, corneal erosion of the left eye	—	Ulcers on the scrotum and on the lower extremities

Requena L et al. Chemical warfare. Cutaneous lesions from mustard gas. B. J Am Acad Dermatol. 1988 Sep;19(3):529-36.

Respiratory	Otorhinolaryngology	Gastrointestinal	Sequelae	Special therapeutic measures
Respiratory distress, paroxysmal cough	Earache, laryngitis, hoarseness	—	Residual pigmentation	Oxygen inhalations
Respiratory distress, radiologic evidence of pneumonia	Laryngitis, hoarseness	—	Residual pigmentation	Oxygen inhalations, amoxicillin
Respiratory distress, paroxysmal cough	Adhesive otitis	Vomiting	Residual pigmentation	Oxygen inhalations
Paroxysmal cough	Swollen pharynx	Vomiting	Residual pigmentation, corneal hairiness	Corneal transplantation
Paroxysmal cough	Swollen pharynx	—	Residual pigmentation	—
Paroxysmal cough	Laryngitis, hoarseness	Dysphagia	Residual pigmentation	Parenteral nutrition
Paroxysmal cough	—	—	Residual pigmentation	—
Paroxysmal cough	Laryngitis, hoarseness	—	Residual pigmentation, corneal hairiness, hypertrophic scar	Corneal transplantation

Requena L et al. Chemical warfare. Cutaneous lesions from mustard gas. B. J Am Acad Dermatol. 1988 Sep;19(3):529-36.

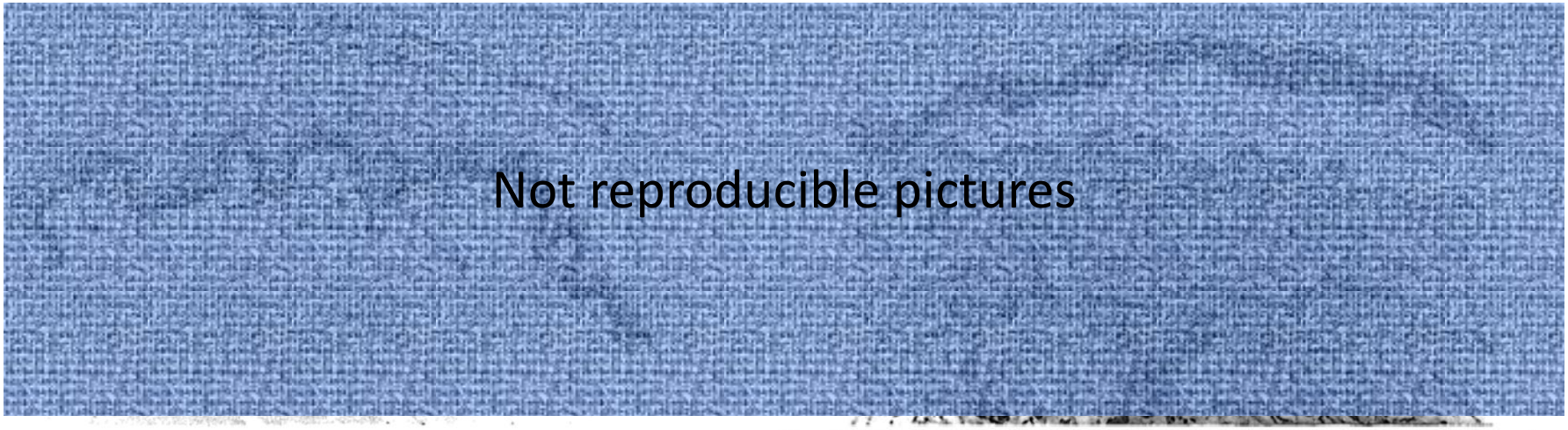


Fig. 10. Abundant melanin granules in all layers of the epidermis, even in the horny layer. There also were numerous melanophages in the papillary dermis. (Masson-Fontana stain; ×200.)

Fig. 4. Subepidermal blister with the PAS-positive basement membrane zone located on the floor of the blister. (PAS stain; ×100.)

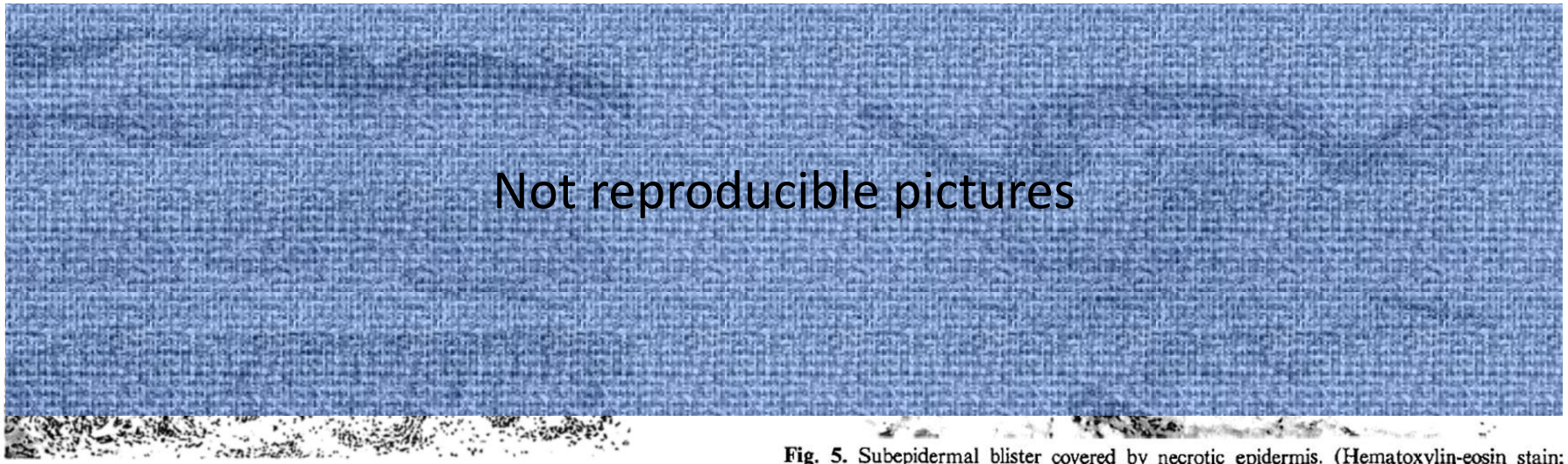


Fig. 6. Epidermal regeneration has caused an intraepidermal blister location. This blister contained a fibrin network and few neutrophils. (Hematoxylin-eosin stain; ×100.)

Fig. 5. Subepidermal blister covered by necrotic epidermis. (Hematoxylin-eosin stain; ×100.)

Requena L et al. Chemical warfare. Cutaneous lesions from mustard gas. B. J Am Acad Dermatol. 1988 Sep;19(3):529-36.

Not reproducible pictures

Fig. 7. Poikilodermatous scar on the lower extremities.
Fig. 8. Punctate pigmentation around the pores of hair follicles.
Fig. 9. Striking pigmentation on the neck.

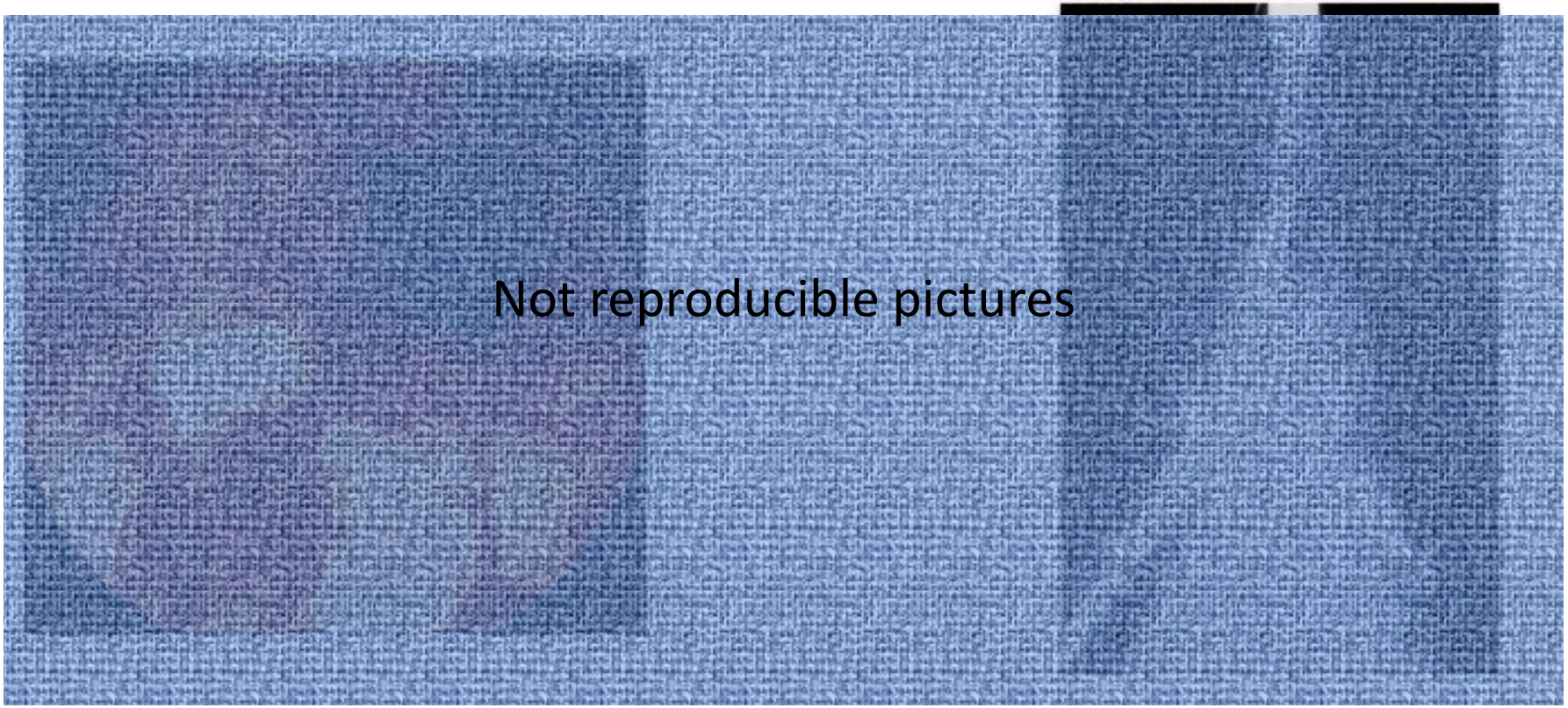
Fig. 1. Sunburnlike erythema in the mild cases.
Fig. 2. Extensive involvement of cutaneous surface.
Fig. 3. Sheets of separated epidermis on the hand.

Requena L et al. Chemical warfare. Cutaneous lesions from mustard gas. B. J Am Acad Dermatol. 1988 Sep;19(3):529-36.

Acute effects following exposure

- ✓ Dyspnea
- ✓ Wheezing

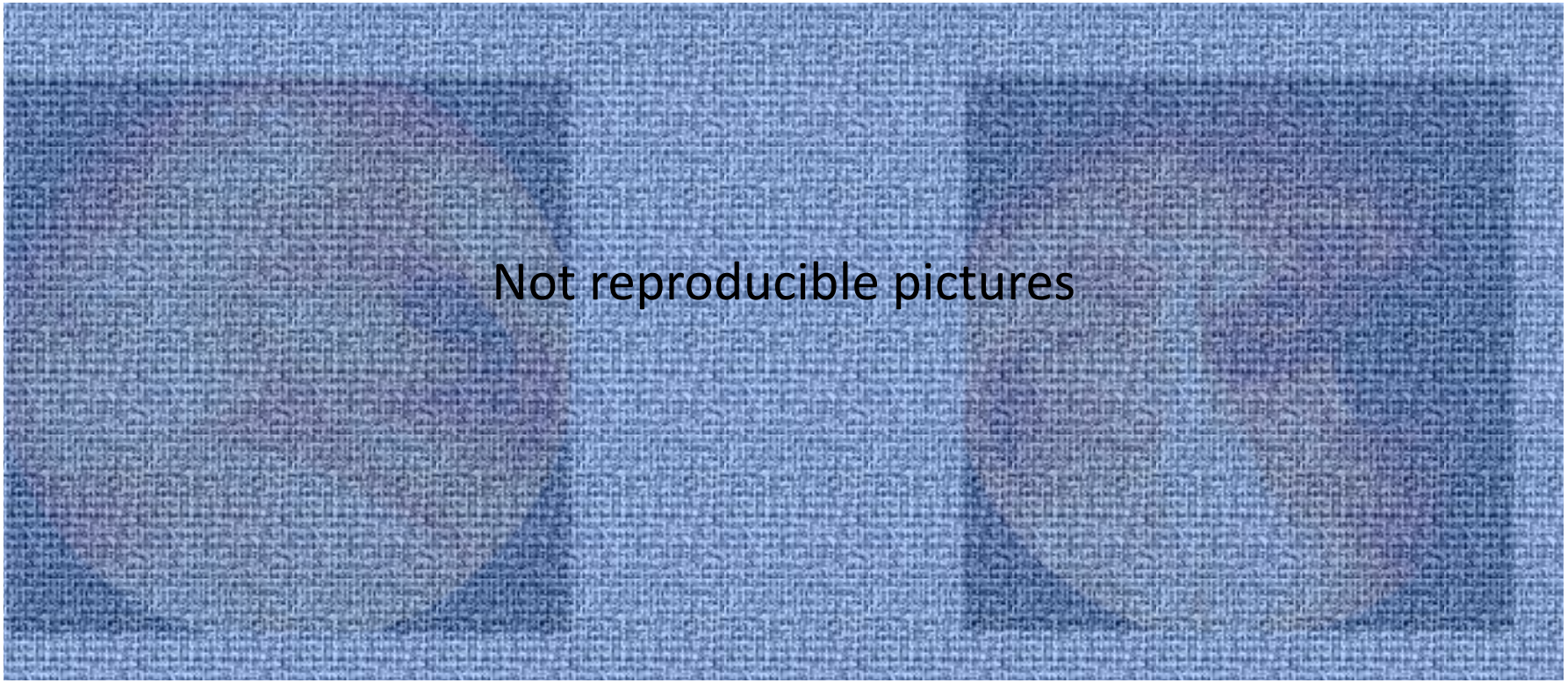
were the most frequent respiratory manifestations



Bronchoscopic view of distal trachea three weeks after exposure to mustard gas showing severe hemorrhagic bronehitis, mucosal necrosis, and early development of scaring tissue.

Bronchogram of central airways revealing structural damage and generalized narrowing of the tracheobronchial tree; massive shrinking.

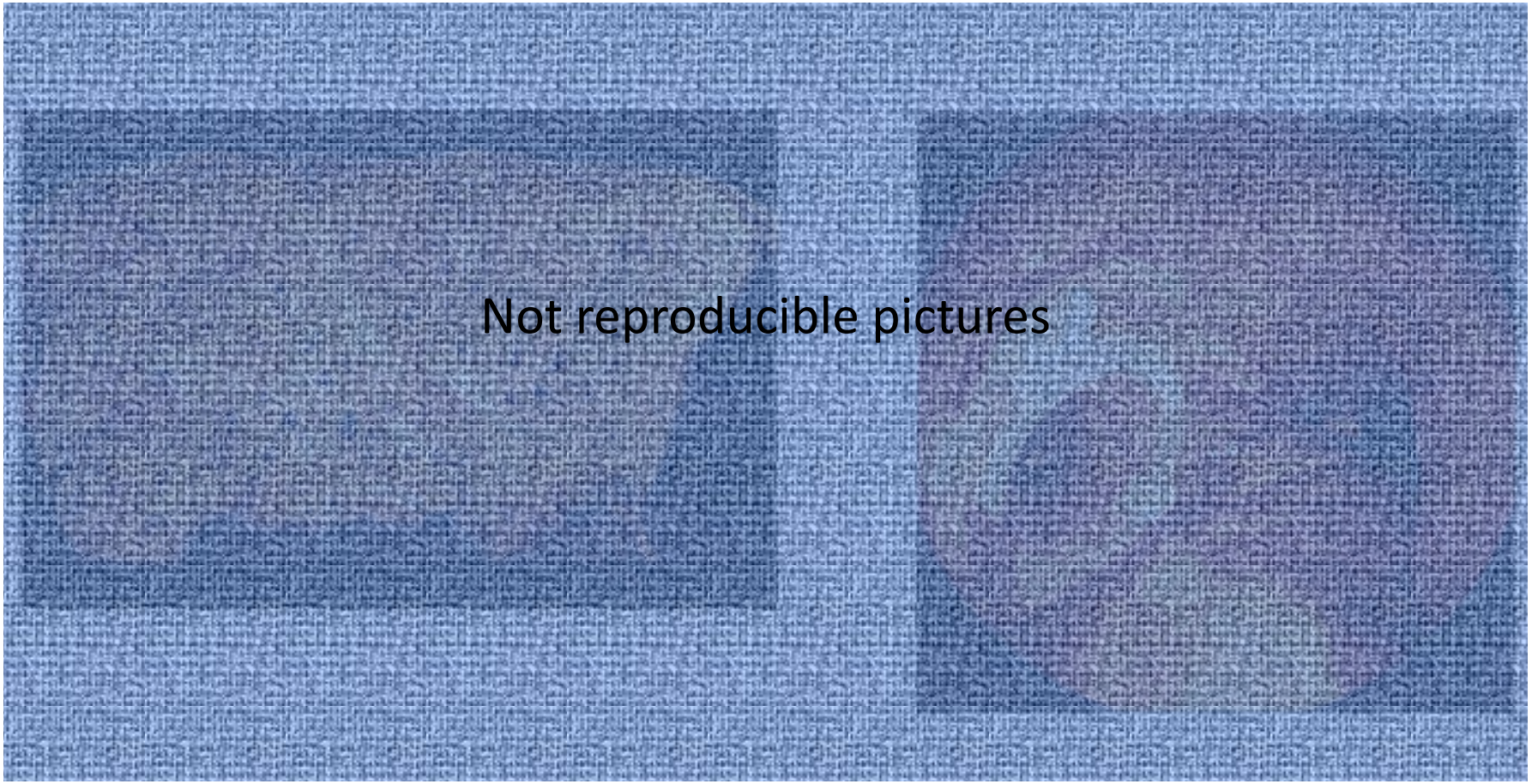
Freitag L1, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. Chest. 1991 Nov;100(5):1436-41.



Bronchial tree several months after exposure (bronchial lumen filled with purulent material)

Severe subglottic tracheal stenosis immediately below the vocal cords five years after exposure to mustard gas

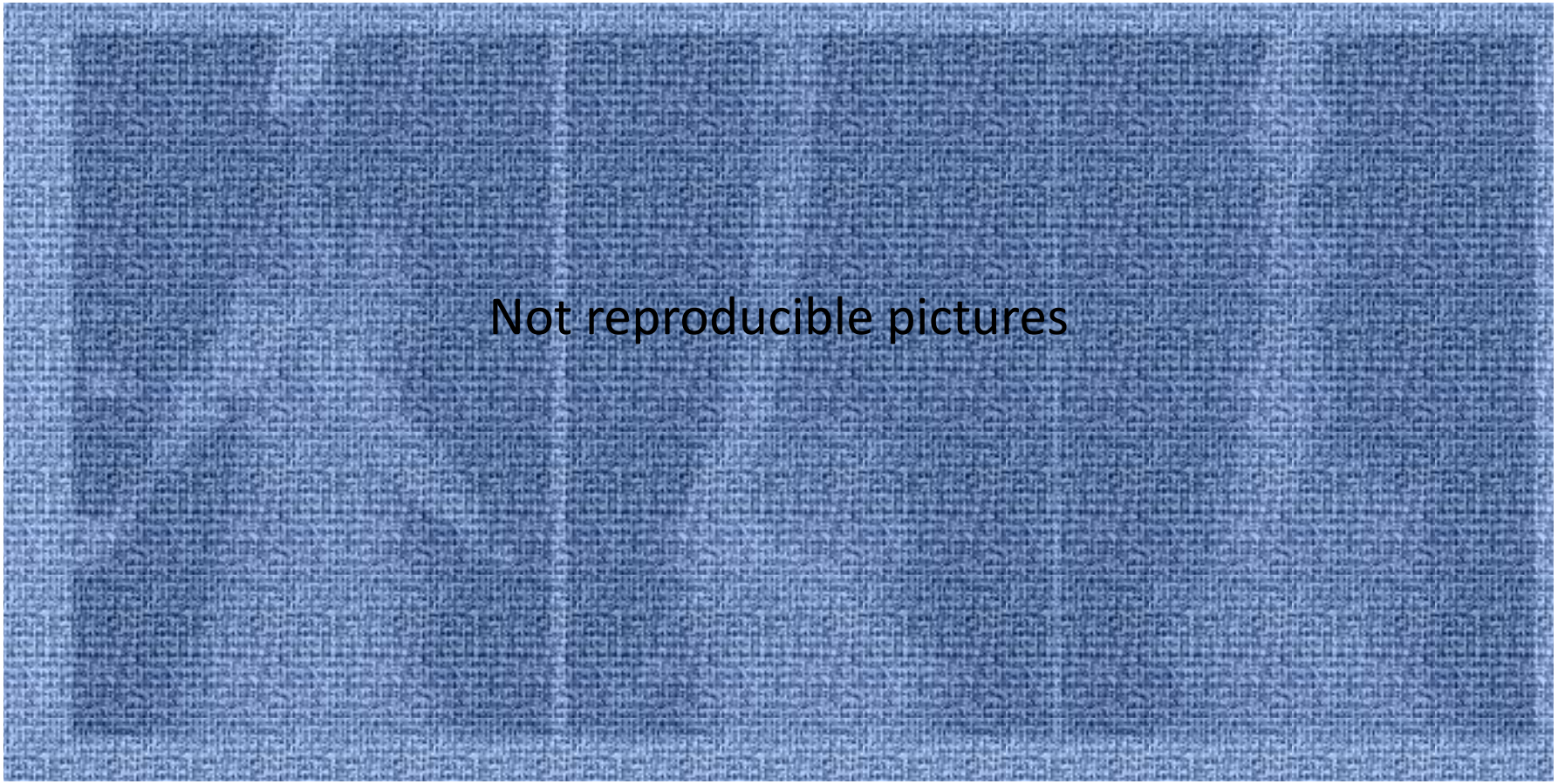
Freitag L1, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. Chest. 1991 Nov;100(5):1436-41.



Gross appearance of the excised lung showing bronchiectasis and severe chronic inflammation
Actinomycosis was also discovered

Stent in the left main bronchus

Freitag L1, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. Chest. 1991 Nov;100(5):1436-41.



Left. Pin-hole stenosis of the proximal left main bronchus;

Center. Same patient one year later with one stent in the trachea and a second stent in the left main bronchus;

Right. Same patient six years after initial treatment; progression of diffuse stenosis proximally and distally to both stents.

Freitag L1, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. Chest. 1991 Nov;100(5):1436-41.

What to do in acute exposure

- ✓ Immediate access to personal protective equipment
  Quick Setup decontamination facilities
- ✓ The initial triage of victims
- ✓ Distribution of numbered plastic bags to separate clothes & valuables
- ✓ Monitoring of food products
- ✓ Offering psychological support and stress reduction
- ✓ Secondary triage of people in need of urgent medical treatment
- ✓ Providing information on CWA, the potential effects and treatment
- ✓ Controlling media
- ✓ Monitor and organize research

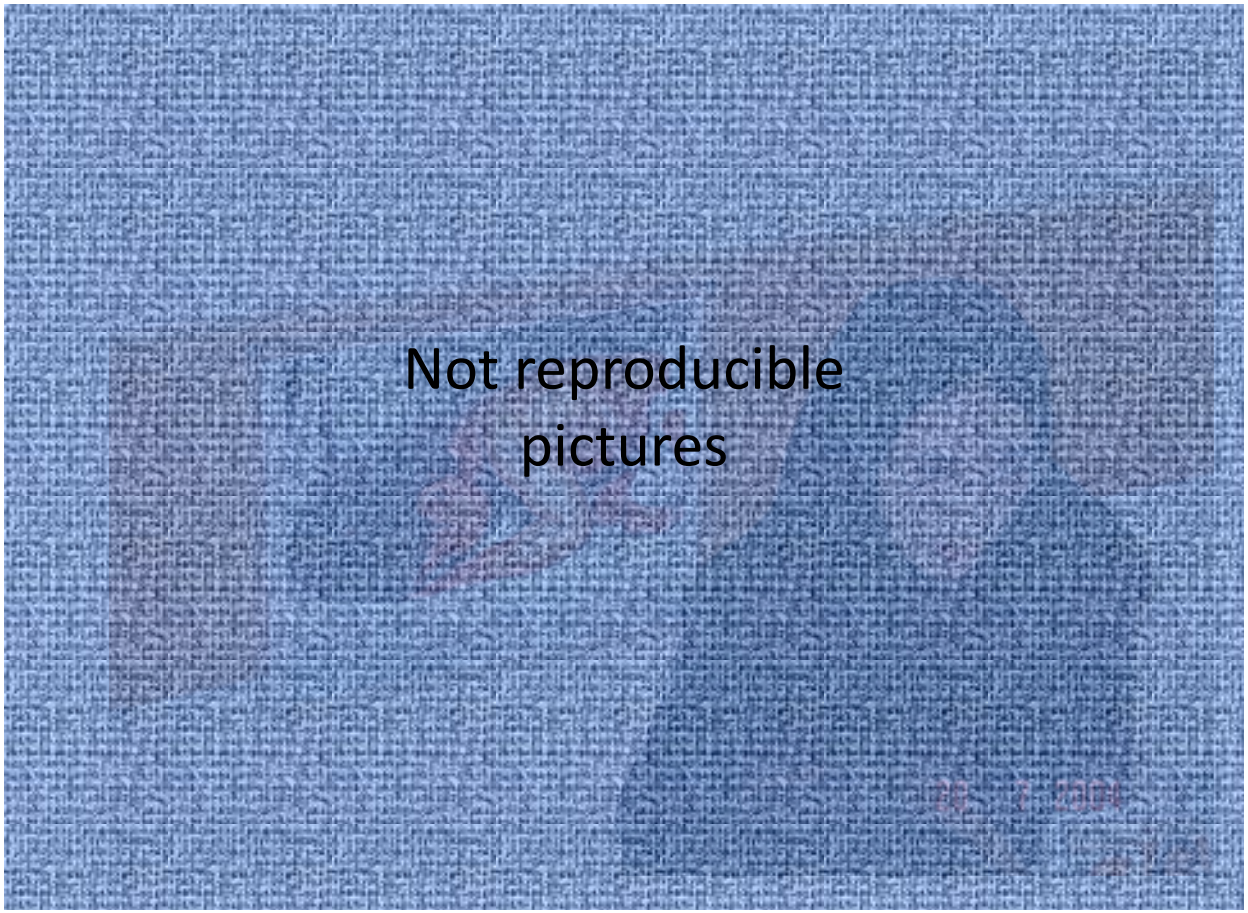
- ✓ Decontamination
- ✓ Symptomatic and supportive treatment
- ✓ Skin lesions; Keep clean, treatment with topical antibiotics, roofs larger than 1 cm
- ✓ Taking care of eye injuries
- ✓ Respiratory tract injuries; Cough, bronchodilators and inhaled bronchodilators, mucolytics, and the use of oxygen and antibiotics for bacterial pathogens
- ✓ Early stage intubation
- ✓ Bronchoscopic removal Pseudomembranes
- ✓ Anti-inflammatory
- ✓ Antioxidant factors predator sulfhydryl
- ✓ Other specific treatments such as granulocyte colony-stimulating factor for neutropenia caused by mustard gas

- Risk of Exposure

- Psychological Effects Either the threat or the actual use

Pictures from the net

Delayed effect



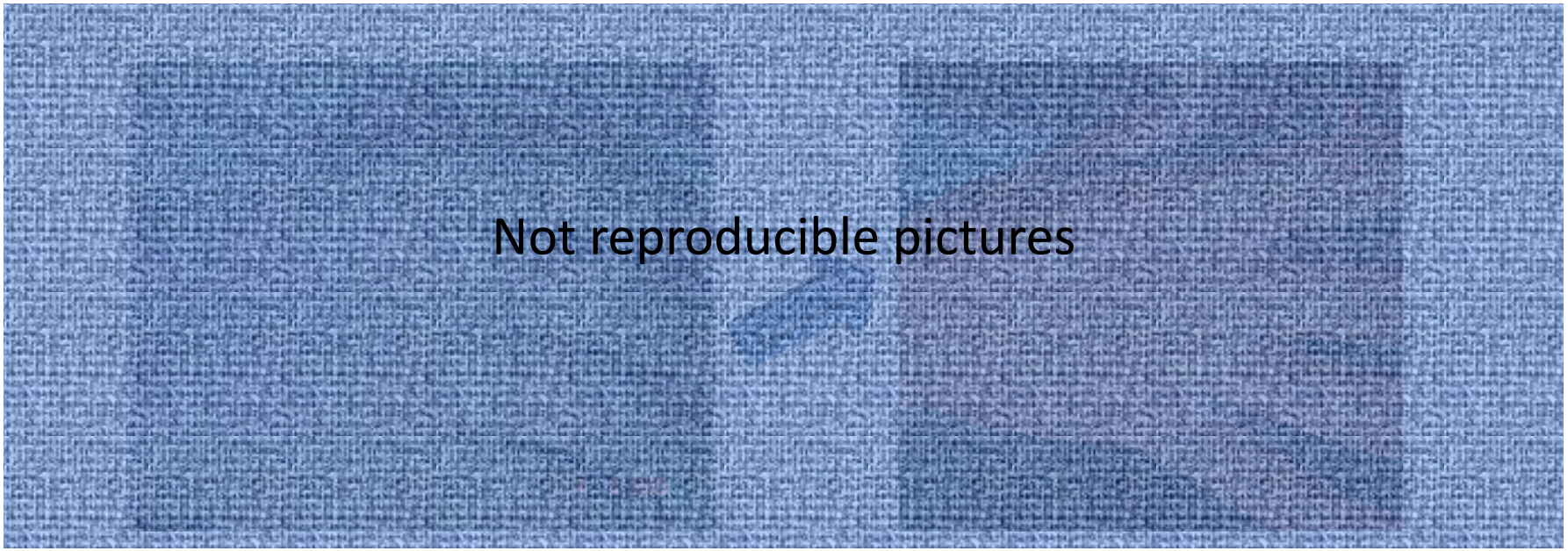
Delayed effects

Skin disorders

- ✓ Itching
- ✓ Burning sensation
- ✓ Blisters
- ✓ Dry skin
- ✓ Dermatitis
- ✓ Pigmentary changes

Table I. Long-term effects of mustard gas on the skin

Symptoms	No.	%	Anatomic locations	No.	%
Stinging, burning	7	70	Lower extremities	7	70
Itching	6	60	Genitalia	6	60
Pigmentation (light/dark)	2/3	50	Upper extremities	4	40
Blister formation	2	20	Face	2	20
Flushing	2	20	Axillae	2	20
Swelling	2	20	Chest	2	20
Thin and very sensitive skin	3	30	Abdomen	2	20
Exanthema	1	10	Neck	1	10
Numbness	1	10			
Symptoms aggravated by sunlight, heat or cold	5	50			



Thomsen AB, Eriksen J, Smidt-Nielsen K. Chronic neuropathic symptoms after exposure to mustard gas: a long-term investigation. J Am Acad Dermatol. 1998 Aug;39(2 Pt 1):187-90.

Delayed effects

Pulmonary findings

- ✓ Dyspnea,
- ✓ Cough and expectorations
- ✓ Various obstructive and restrictive lung diseases


Not reproducible pictures

Treatments

Respiratory complications

- ✓ N-acetyl cysteine
- ✓ Bronchodilators
- ✓ Corticosteroids
- ✓ Interferon-gamma
- ✓ Furosemide
- ✓ Morphine

Ocular complications

Invasive procedures treating

- ✓ Corneal complication
- ✓ Limbal ischemia
- ✓ Stem cell deficiency

Dermatological complications

- ✓ Anti-depressants
- ✓ Pimercrolimus
- ✓ Unna's boot
- ✓ Capsaicin
- ✓ Phenol and menthol
- ✓ Aloevera and olive oil
- ✓ Curcumin
- ✓ Interferon-gamma

Shiyovich A et al, Long-term complications of sulfur mustard exposure: a therapeutic update]. Harefuah. 2014 Mar-Apr;153(3-4):199-205, 237.

Current treatment strategies

- ✓ Symptomatic management to relieve symptoms
- ✓ Prevent infections
- ✓ Promote healing (returning damaged tissue to)
  - ➢ Optimal appearance
  - ➢ Normal function
  - ➢ In the shortest period of time
  - ➢ Ameliorating chronic effects

Graham JS, Schoneboom BA. Historical perspective on effects and treatment of sulfur mustard injuries. Chem Biol Interact. 2013 Dec 5;206(3):512-22.

Pulmonary involvement

- ✓ Prevalence 43%
- ✓ The most common complaints
  - ➢ Cough and dyspnea.
- ✓ Major respiratory complications
  - ➢ Chronic obstructive pulmonary disease,
  - ➢ Bronchiectasis
  - ➢ Asthma
- ✓ Spirometry
  - ➢ Restrictive and obstructive pulmonary disease.
- ✓ Plain chest X-ray
  - ➢ Does not help in about 50% of lung diseases.
- ✓ High-resolution CT
  - ➢ Is the best modality for diagnostic assessment of parenchymal lung and bronchi

Razavi SM, Ghanei M, Salamati P, Safiabadi M. Long-term effects of mustard gas on respiratory system of Iranian veterans after Iraq-Iran war: a review. Chin J Traumatol. 2013;16(3):163-8.

Pulmonary treatment regimens

- ✓ Oxygen administration
- ✓ Vaporized moist air
- ✓ Respiratory physiotherapy
- ✓ Mucolytic agents
- ✓ Bronchodilators
- ✓ Corticosteroids
- ✓ Long-acting beta-2 agonists
- ✓ Antioxidants
- ✓ Surfactant
- ✓ Magnesium ions,
- ✓ Therapeutic bronchoscopy
- ✓ Laser therapy
- ✓ Placement of respiratory stents
- ✓ Early tracheostomy in laryngospasm
- ✓ Lung transplantation

Razavi SM, Ghanei M, Salamati P, Safiabadi M. Long-term effects of mustard gas on respiratory system of Iranian veterans after Iraq-Iran war: a review. Chin J Traumatol. 2013;16(3):163-8.
Razavi SM, Salamati P, Harandi AA, Ghanei M. Prevention and treatment of respiratory consequences induced by sulfur mustard in Iranian casualties. Int J Prev Med. 2013 Apr;4(4):383-9.

Delayed effects

Ocular problems

- ✓ Photophobia,
- ✓ Red eye
- ✓ Tearing
- ✓ Corneal ulcers
- ✓ Blindness

Eye symptoms	No.	%	Airway symptoms	No.	%	Systemic symptoms	No.	%
Conjunctivitis	8	80	Asthma, bronchitis	4	40	General feeling of cold or warmth	5	50
Photophobia	6	60	Frequent infections	4	40	Impaired short-term memory	8	80
Impaired vision	3	30	Dyspnea	3	30			
			Cough	3	30			
			Dryness	2	20			
			Hoarseness	1	10			
Eye symptoms	9	90	Airway symptoms	7	70	Systemic symptoms	8	80

Thomsen AB, Eriksen J, Smidt-Nielsen K. Chronic neuropathic symptoms after exposure to mustard gas: a long-term investigation. J Am Acad Dermatol. 1998 Aug;39(2 Pt 1):187-90.

Not reproducible pictures

Porcelain-white episcleral changes and adjacent peripheral corneal ulceration (arrow) in the right eye of the patient initially seen in December 1998, 10 years after mustard gas exposure.

Confocal images of the patient's right eye in December 1998.
Left; Spindle-shaped irregular keratocytes (↑) of the anterior stroma
Right; Fibroblasts are interconnected by a three-dimensional network of fibrils and surrounded by highly reflective diffuse fibrillar material (Confocal microscopy; objective 40/0.75)

Pleyer U, Sherif Z, Baatz H, Hartmann C. Delayed mustard gas keratopathy: clinical findings and confocal microscopy. Am J Ophthalmol. 1999 Oct;128(4):506-7.

TABLE I. *Mean basal serum hormone levels and semen quality in three groups of subjects and sperm count in oligospermic patients with normal reference ranges provided*

Variable	Normal Reference Ranges	Intensity of Exposure		
		Mild	Moderate	Severe
LH (mIU/mL)	3–11	4.7 ± 0.8 (3.7–5.8)	4.6 ± 0.9 (3.5–6)	5.7 ± 0.9 (4.4–6.8)
FSH (mIU/mL)	3–10	14.8 ± 1.8 (13.4–17)	15.6 ± 2.0 (13.4–18)	18 ± 2.8 (15–21.5)
Testosterone (ng/mL)	4–12	6.8 ± 1.8 (4.7–9)	8.4 ± 1.8 (6.4–10.4)	6.4 ± 2 (4.2–9)
Sperm count in oligospermic men (10^6/mL)	>20	5.9 ± 1.8 (4.8–6.8)	4.8 ± 2.4 (3.2–5.5)	3.9 ± 1.8 (2.8–4.2)
Sperm motility (%)	>50	20.9 ± 3.7 (26.6–56)	16.1 ± 3.3 (16–48)	14.6 ± 4.1 (1–46)
Normal morphology (%)	>30	41.2 ± 4.9 (18–71)	30.2 ± 4.8 (16–68)	8.4 ± 3.8 (2–35)

Data presented as the mean ± SD, with the range in parentheses.
KEY: LH = luteinizing hormone; FSH = follicle-stimulating hormone.

Not reproducible pictures

Testicular biopsy from an azoospermic patient. Testicular tubule lined by Sertoli cells only. Groups of Leydig cells are present in the interstitial tissue

Testicular biopsy from an oligospermic patient. Atrophy of seminiferous epithelium with a significant decrease in the amount of cellularity

Safarinejad MR. Urology. 2001 Jul;58(1):90-4. Testicular effect of mustard gas.

Delayed effects

Psychological

- ✓ Caregivers of war veterans suffer from poor QOL. Chemical warfare agents contribute to more persistent poor QOL in caregivers than the injuries caused by conventional weapons.

- ✓ Quality of life in 532 caregivers of Iran Iraq war

Mousavi B, Seyed Hoseini Davarani SH, Soroush M, Jamali A, Khateri S, Talebi M, Montazeri A5. Quality of life in caregivers of severely disabled war survivors. Rehabil Nurs. 2015 May-Jun;40(3):139-47.

Long-term effects of sulfur mustard on civilians mental health 20 years after exposure

Table 3 Psychological disorders according to the GSI index cut-off values in exposed and controls

	Control (n = 128)	Exposed (n = 397)	
	No. (%)	No. (%)	P*
Psychological status			0.006
Normal (global severity index < 0.4)	20 (15.5)	27 (7.3)	
Probable case (global severity index ≥ 0.4)	108 (84.5)	340 (92.7)	

* Comparison with control group derived from chi square test.

Table 4 Severity of the mental health disturbances among the study participants by Severity of the exposure

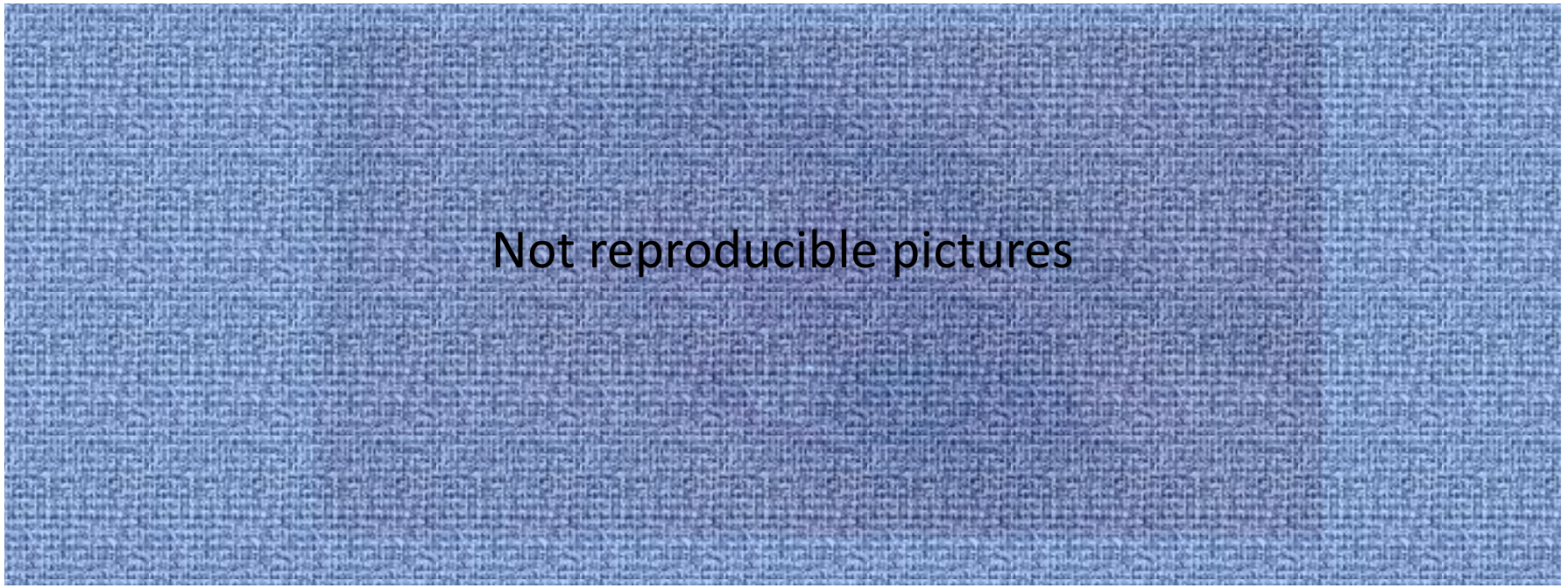
	Control (n = 128)	Exposed (n = 367)				
		Non-hospitalized (n = 192)		Hospitalized (n = 162)		
	Mean (SD)	Mean (SD)	P*	Mean (SD)	P*	P**
Somatization	1.50(0.88)	1.78(0.83)	0.014	1.78(0.82)	0.016	0.998
Obsessive-compulsive	1.37(0.85)	1.54(0.81)	0.155	1.56(0.77)	0.109	0.963
Interpersonal sensitivity	1.08(0.76)	1.19(0.75)	0.428	1.15(0.75)	0.707	0.891
Depression	1.20(0.75)	1.40(0.80)	0.073	1.45(0.82)	0.024	0.840
Anxiety	1.24(0.81)	1.41(0.78)	0.184	1.42(0.81)	0.146	0.978
Hostility	1.10(0.84)	1.37(0.79)	0.013	1.36(0.78)	0.019	0.999
Phobic anxiety	0.76(0.72)	0. 75(0.81)	0.999	0.71(0.82)	0.883	0.883
Paranoid ideation	1.20(0.80)	1.31(0.75)	0.431	1.20(0.74)	0.998	0.339
Psychoticism	0.78(0.66)	0.82(0.69)	0.891	0.84(0.70)	0.795	0.972
Global severity index (GSI)	1.16(0.70)	1.31(0.68)	0.160	1.31(0.68)	0.188	1.000
Positive symptom total (PST)	51.10(23.25)	53.05(19.75)	0.695	52.73(19.93)	0.788	0.989
Positive symptom distress index (PSDI)	1.94(0.46)	2.14(0.50)	0.001	2.15(0.46)	0.001	0.986

* Comparison with control group derived from t-test.
** Comparison between hospitalized and non-hospitalized group derived from t-test.

Roshan R, et al. Long-term effects of sulfur mustard on civilians' mental health 20 years after exposure (The Sardasht-Iran Cohort Study). Health Qual Life Outcomes. 2013 Apr 24;11:69.

Delayed effects (Cancer)

Despite the earlier reports rejecting additional cancerogenic effects in this population, the relative cancer risk has been reported to be 1.7 to 4 times, two decades after the exposure (significant)



38 male-SCC

Delayed neurological complications

Table 2.
Common observed signs and symptoms in 43 male veterans with delayed neurological complications of sulphur mustard and tabun poisonings in Mashhad, Iran.

Symptoms	N (%)	Signs	N (%)
Fatigue	40 (93.0)	Hyperaesthesia	31 (72.1)
Paraesthesia	38 (88.3)	Impaired Deep-tendon reflex	25 (58.1)
Headache	36 (83.7)	Tremor	23 (53.4)
Weakness	35 (81.3)	high blood pressure	17 (39.5)
Impotency	32 (74.4)	Palmomental reflex	11 (25.5)
Loss of concentration	28 (65.1)	Babinski reflex	8 (18.6)
Loss of memory	25 (58.1)	Glabella reflex	6 (13.9)
Emotional stability	23 (53.4)	Hypoesthesia	5 (11.6)
Hearing loss	23 (53.4)	Paresis	5 (11.6)
Depression	19 (44.1)	Dysarthria	3 (6.9)
Hyposmia	18 (41.9)	Ataxia	2 (4.7)
Insomnia	13 (30.2)	Nystagmus	1 (2.3)
Anxiety	12 (27.9)	Paralysis	1 (2.3)
Sphincter disorder	10 (23.2)		
Loss of libido	8 (18.6)		
Seizure	2 (4.6)		

Biochemical findings

Table 3.
Biochemical findings in 43 male veterans with delayed neurological complications of sulphur mustard and tabun poisonings in Mashhad, Iran.

Findings	Mean ± S.D.	Normal ranges[1]	*p*-value
SGPT	26.25 ± 1.18	0–40 U/l (optimal = 21)	0.999
SGOT	22.90 ± 9.80	0–31 U/l (optimal = 24)	0.999
LDH	460 ± 103.2	94–500 U/l	0.435
Total bilirubin	0.61 ± 0.26	0–1 mg/dl	0.999
Direct bilirubin	0.19 ± 0.06	0–0.3 mg/dl	0.999
Cholesterol	222.90 ± 3.47	<200 mg/dl	0.002
HDL cholesterol	38.57 ± 7.7	>39 mg/dl	0.258
LDL cholesterol	149.05 ± 3.33	<130 mg/dl	0.017
Triglyceride	188.44 ± 1.15	<150 mg/dl	0.041

[1]Normal ranges are according to National Health and Nutritional Examination Survey, conducted by the National center for Health Statistics (NCHS), USA. SGPT, serum glutamate pyruvate transaminase; SGOT, serum glutamic-oxaloacetic transaminase; LDH, lactic dehydrogenase.

sensory polyneuropathy and four patients had sensory-motor distal polyneuropathy of axonal type. NCV-disrupted patterns

Darchini-Maragheh E et al Delayed neurological complications of sulphur mustard and tabun poisoning in 43 Iranian veterans. Basic Clin Pharmacol Toxicol. 2012 Dec;111(6):426-32.

Not reproducible pictures

Table 1. Characteristics of the Assessed Articles (n=7)

Author(s)	year	City	Gap between the exposure and study (years)	Sample Volume	Mean age±SD	Cutaneous Complications (%)	Respiratory Complications (%)	Ocular Complications (%)	Prevalence of Cancers in Exposed population (%)
Namazi et al.	2009	Shiraz	17-22	134	37.2±9	82.8	100	77.6	1.5
GhasemiBroumand et al.	2006	Sardasht	17	600	41.03±14.3	83.2	81.7	69.2	-
GhasemiBroumand et al.	2008	Iran-BonyadeShohada	10	500	5.2±36.5	99.2	100	100	2
Riazi et al.	2008	Different Iranian cities	-	2252	34.31±9.05	-	-	89.8	-
Agin et al.	2004	Different Iranian cities	15	500	5.2±36.5	99.2	69.2	80	-
GhasemiBroumand et al.	2007	Marivan	17-22	476	-	90.8	96.6	89.2	0.75
Ghilasi et al.	2006	Isfahan	24±13	500	41±10	-	96.3	71.2	3

Panahi Y et al. Complications and Carcinogenic Effects of Mustard Gas--a Systematic Review and Meta-Analysis in Iran. Asian Pac J Cancer Prev. 2015;16(17):7567-73.

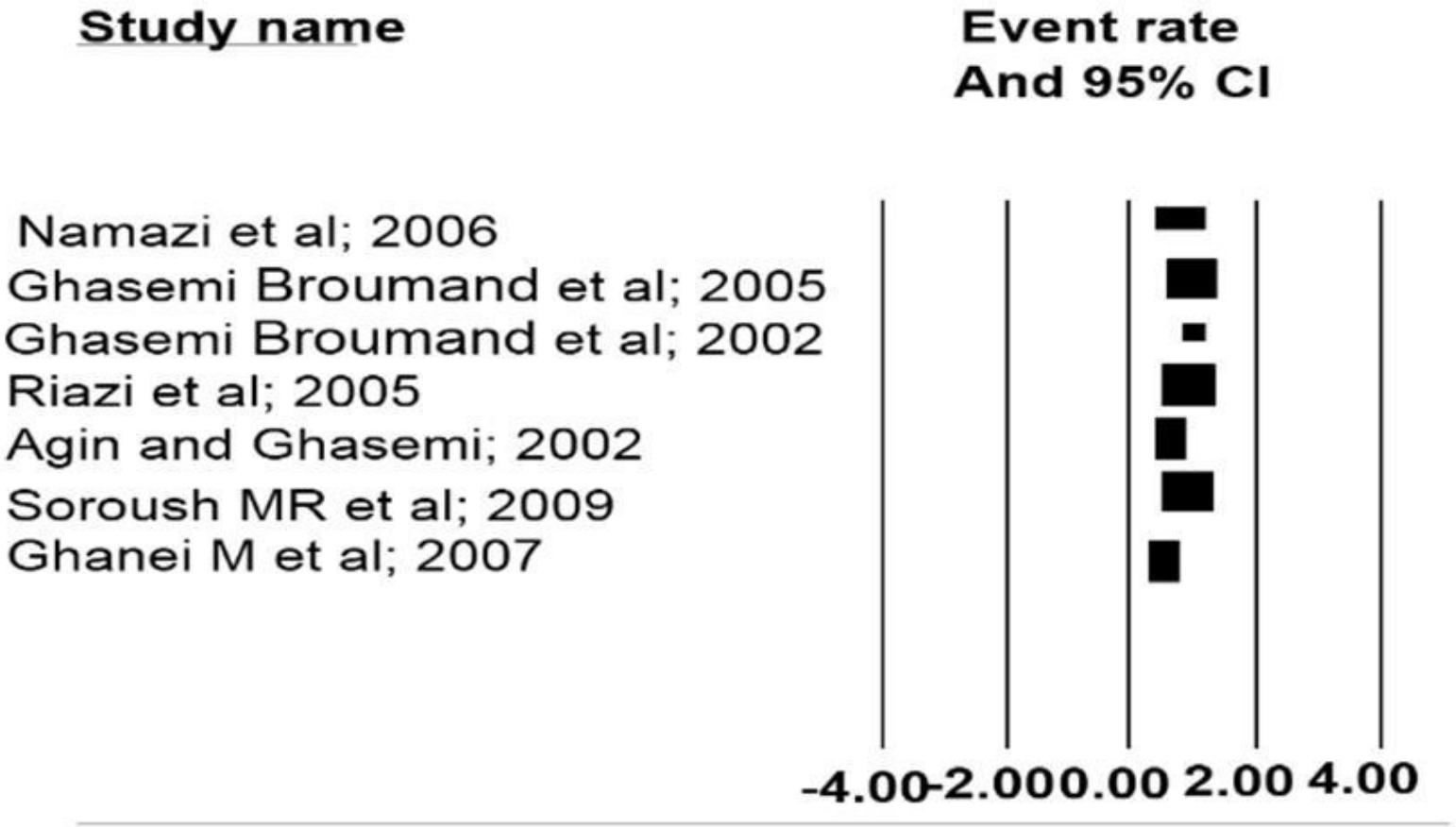


Figure 6. The Incidence of Different Types of Cancers Due to Mustard Gas in the Chemically Victims of Iraq-Iran war with a Confidence Interval of 95% (I^2=92.7 Based on Randomized Model)

Adopted from Panahi Y et al. Asian Pac J Cancer Prev. 2015;16(17):7567-73.

Table 3 Age standard incidence rates for each cancer group in SM exposed and unexposed veterans followed in the study

Cancer Group	Exposed		Unexposed	
	Obs (Exp)	Age std Inc. rate (95 % CI)	Obs (Exp)	Age std Inc. rate (95 % CI)
Head and neck	5 (5.03)	0.99 (0.12–1.86)	5 (4.97)	1.006 (0.13–1.88)
Gastrointestinal	18 (15.01)	1.2 (0.69–1.70)	10 (12.99)	0.77 (0.23–1.31)
Lung and bronchial	5 (3.49)	1.43 (0.38–2.48)	2 (3.51)	0.57 (0–1.62)
Genitourinary	9 (9.23)	0.97 (0.33–1.62)	9 (8.77)	1.03 (0.36–1.69)
Lymphatic and Hematology	22 (18.05)	1.22 (0.76–1.68)	13 (16.95)	0.77 (0.29–1.24)
Others	10 (6.33)	1.58 (0.8–2.36)	3 (6.67)	0.45 (0–1.21)
Skin	6 (4.29)	1.4 (0.45–2.34)	2 (3.71)	0.54 (0–1.56)
CNS	9 (5.85)	1.5 (0.73–2.35)	3 (6.15)	0.49 (0–1.28)
Bone and soft tissue	0 (0.93)	0 (0–2.03)	2 (1.07)	1.87 (0–3.76)

Obs observed number of cancer cases in cohort, *Exp* expected number of cancer cases in cohort, *Age std Inc. rate* age standard incidence rate in 10,000 person years, *CI* confidence interval

Zafarghandi MR, et al. Incidence of cancer in Iranian sulfur mustard exposed veterans: a long-term follow-up cohort study. Cancer Causes Control. 2013 Jan;24(1):99-105.

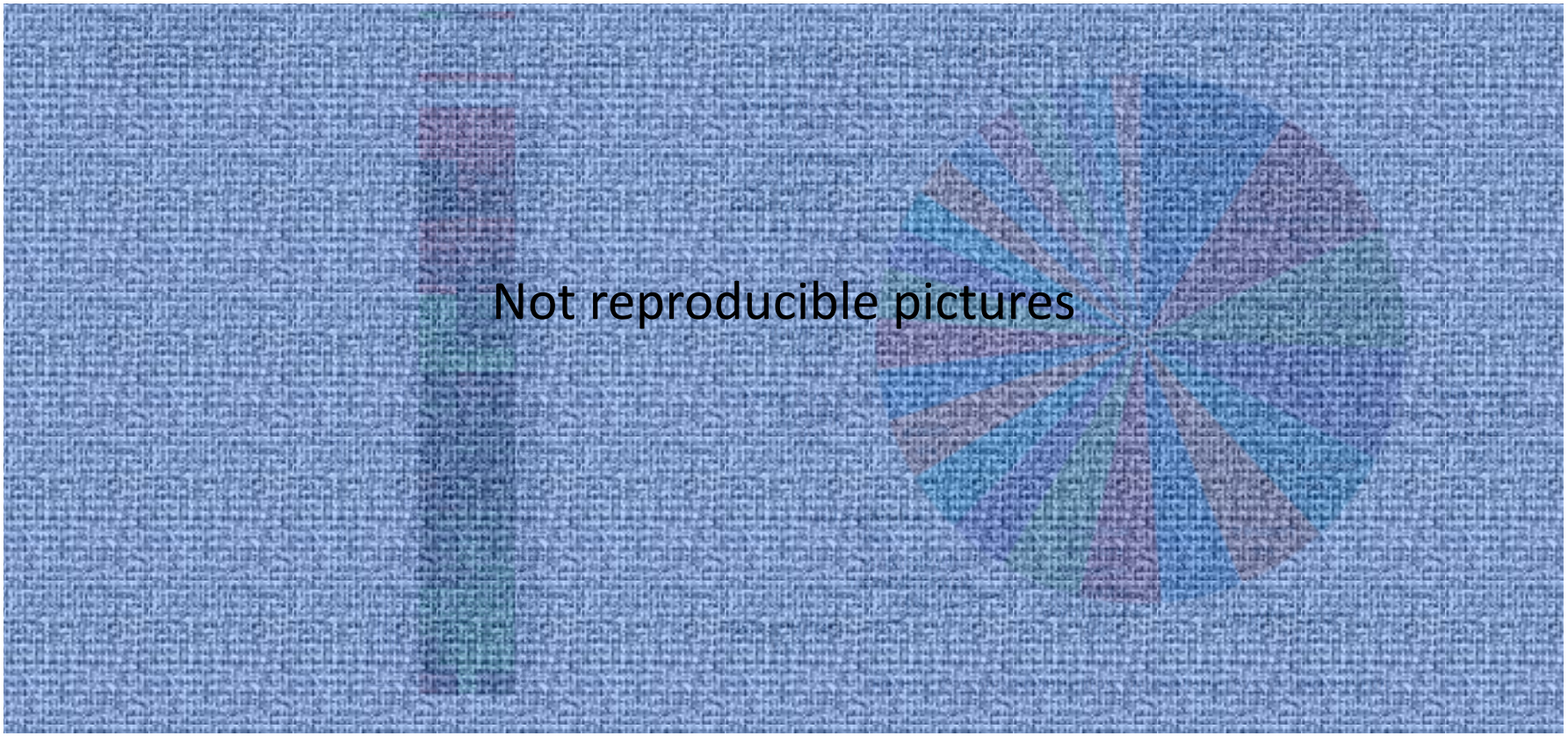
Major mechanisms responsible for the effects of SM

- ✓ DNA alkylation and cross-linking
- ✓ Protein modification
- ✓ Membrane damage
- ✓ Induction of inflammatory mediators in the target tissues causing
  - ➢ Extensive necrosis
  - ➢ Apoptosis
  - ➢ Loss of tissue structure

Shiyovich A, Rosman Y, Krivoy A, Statlender L, Kassirer M, Shrot S. [Long-term complications of sulfur mustard exposure: a therapeutic update]. Harefuah. 2014 Mar-Apr;153(3-4):199-205, 237.

Genes dysregulation

Microarray transcriptional profiling indicated that a total of 122 genes were significantly dysregulated in tissues located in the airway of patients. These genes are associated with the extracellular matrix components, apoptosis, stress response, inflammation and mucus secretion.



Adopted from Najafi A1, Masoudi-Nejad A, Imani Fooladi AA, Ghanei M, Nourani MR. Microarray gene expression analysis of the human airway in patients exposed to sulfur mustard. J Recept Signal Transduct Res. 2014 Aug;34(4):283-9.

In conclusion

- ✓ Although standardized treatment plans exist
  - ➢ none of which are curable
- ✓ Immediate preventive measures after exposure improve the following outcomes
- ✓ Supportive and symptomatic treatments for chronic manifestations are still the core of treatment plans, 30 years after the exposure

“Knowing is not enough; we must apply. Willing is not enough; we must do.”

—Goethe

- ✓ Evidence based research and educational materials are essential
- ✓ Approach to acute and delayed effects related to exposure to the CWA should be added to the medical, nursing and health curriculum

Education (professional and public) is the Key in Toxic exposure

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