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Immunobiological Consequences of Sulfur Mustard Contamination

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ABSTRACT

Sulfur mustard has been employed in chemical warfare in certain regions including Iran. The short and long term biological effects of sulfur mustard contamination have been studied in both basic and clinical aspects. Sulfur mustard has been shown to induce a vast array of pathological effects in affected persons. In addition to skin, lung, eyes and gastrointestinal disturbances, sulfur mustard has been shown to induce hematological complications and a severe suppression of the immune system. The short and long term immunological (both cellular and humoral), hematological, genetic and biochemical consequences of persons exposed to sulfur mustard are extensively reviewed here. The long term complications of these patients indicate the need to develop effective preventive and therapeutic strategies in the clinic. These strategies may be based upon immunopotentiating intervention and therapy.

Key words: Chemical warfare; Hematological complications; Immune response; Immunopotentiation; Sulfur mustard

INTRODUCTION

Sulfur mustard is a colorless to light yellow oily liquid. Its melting point and boiling point are 13-14^{o}C and 215-217^{o}CmmHg, respectively. Sulfur mustard is only sparingly soluble in water (0.68/L at 25^{o}C). However it is soluble in fat and fat solvents.[1] Several reports concerning the clinical situation of patients exposed to sulfur mustard have been published in Iran during the eight years of war against Iran (1980-1988).

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The main acute pathological findings reported are: depigmentation and wet lesions on the skin,[2] lung function disturbances,[2] ophthalmologic manifestations, conjunctivitis and corneal abrasion,[2,3] gastrointestinal symptoms (dysplagia, diarrhea and vomiting), hematological complications (leukopenia, bone marrow depletion),[2,3] septicemia[3,4] and liver and kidney failures.[2] One of the most threatening effects of sulfur mustard exposure has been determined, by many clinicians and investigators, to be a severe suppression of the immune system which can, in the case of lesions and blisters, lead to opportunistic infections (resistant to conventional antibiotic therapy), septicemia and consequently death.[2,3] Drasch Frominsitute Fur

Rechtsmedizin (F.R.G) has reported the presence of unmetabolized sulfur mustard in the biopsy of the tissues in Iranian patients.[5] The tissue of choice in this study was any lipid rich tissue. Sulfur mustard has been found in the fat of thigh, abdominal skin, and subcutaneous fat. Lung, spleen, liver, blood and urine specimens also showed low concentrations of unmetabolized sulfur mustard.[4,6] Patients admitted to hospitals have been classified into three groups (severe, moderate and mild) according to the clinical features of the skin burns as well as ophthalmologic symptoms, respiratory and gastrointestinal problems and hematological complications (Table1).

Table 1 Classification of patients exposed to sulfur mustard. ***The value present in this table represents lung efficiency. Percentage of severity was assessed according to spirometry and clinical manifestation system.***

Classification	Spirormetry	Severity (%)
NALD	FVC>80 or FEV1>80	0
Mild	65<FVC<80 or 65<FEV1<80	5-20
Moderate	50<FVC<65 or 50<FEV1<65	25-45
Severe	40<FVC<50 or 40<FEV1<50	50-70

Note: FVC, forced vital capacity;
FEEVI forced expiratory volume in the first second;
NALD, no active lung disease

Immunological Consequences of Sulfur Mustard

A- Short-term consequences of sulfur mustard

Cellular Status

Studies on the status of immunocompetent cells in the blood of the patients exposed to sulfur mustard within the day 1 up to the 7th week of exposure showed that; T cell numbers decreased in 54% of the patients and monocytes decreased in 95% of the patients.[7] Also eosinophil counts decreased in 35% of the patients in the first week and in 65%of them in the 7th week after exposure.[7] Neutrophil counts decreased in 89% of patients and 60%of the patients in the first week and the 7th week, respectively. B lymphocyte levels were normal up to the 7th week after exposure[8] (Table 2)

Pauser et al.[2] reported a loss of immunocompetent cells leading to almost complete bone marrow suppression in the puncture material. Some clinicians have first reported a pattern of initial leukocytosis up to $25x10^3/mm^3$, followed by decreasing leukocytopenia and eventually total bone marrow depletion.[3] Studies on mouse models indicated that sulfur mustard caused a significant suppression of DTH responses to sheep RBC.[9]

Antibody Status

Studies on antibody levels indicated an initial increase in IgM levels followed by a decrease during a six month period. IgG levels were also initially higher than normal, but dropped to normal in most studies.[7,11-12] The levels of IgA, measured in the first week, and subsequently 3rd and 6th months, were high in 7% of the patients (12). The level of C3, C4 and CH50 during the first week and up to the six month were however normal (Table 3). Studies on the mice also indicated a decrease in the antibody titers to sRBC following low levels of sulfur mustard contamination (Table 3).[9]

B- Long-term consequences of sulfur mustard

Cellular Status

Studies on the peripheral WBCs of the people highly exposed to sulfur mustard showed a significant decrease in the normal WBC level as compared to unexposed populations .WBC of the moderate and mild patients were within the normal levels. There was also an increase of immature WBCs and RBCs such as myelocytes, metamyelocytes and B cell and microcytes. Also anisocytosis was observed.

Table 2. Cellular status of the patients exposed to sulfur mustard.

	Short term contamination				Long term contamination		
	% lower than normal	% higher than normal			% lower than normal		
		severe	moderate	mild	severe	moderate	mild
T cell	54%	0%	0%	0%			
B cell	1%	7%	12%	9%	8%	12%	21%
NK cell	_	0%	0%	0%	80%	91%	83%
Monocyte	95%	40%	16%	16%	4%	0%	0%
Granulocyte	89%	48%	72%	76%	12%	8%	2%

Table 3. Humoral status of patient exposed to sulfur mustard.

	Short term contamination (higher than normal)			Long term contamination (higher than normal)		
	1 week	14 week	6 month	severe	moderate	mild
IgG	75%	50%	33%	19%	10%	9%
IgM	41%	38%	16%	25%	21%	22%
IgA	7%	7%	7%	8%	10%	3%
IgE	_	_	_	27%	19%	31%
C3		27%	19%	23%		
C4		23%	1%	1%		

Flow cytometric studies on the CD markers of immunocompetent cells indicated a decrease in the cell numbers, while in the severely affected patients showed a significant decrease in the absolute count of CD56+, whereas CD56+/CD25+ cells increased comparing to the normal population . No differences were noticed in the level of CD 56+ and CD56/CD25 in the moderate and mild patients compared to the normal population.[13] The absolute counts of CD15+ and CD15/CD16 in the gate of leukocytes were in the normal level in the severe, moderate and mildly affected patients.[14] In the gate of monocytes, the absolute number of CD14 was in normal level in severe, moderate and mild patients. The levels of CD14/HLA-DR in the monocyte of severe and moderate patients were lower than the mild patients and normal population.[15] The absolute numbers of CD3/CD4 and CD3/CD8 in the gate of lymphocytes were in normal levels in all groups of the patients, while the levels of CD4/CD25 in the moderate and mild patients were decreased, but in the severely affected patients it was significantly reduced as compared to the normal population.[16]

The levels of CD19, CD19/CD25 and CD19/HLA-DR were in normal levels in the entire groups (Tables 2 and 4).[17]

Antibody Status

After the third year of exposure, the Iranian Ministry of Health and Medical Education held a check up survey for all exposed patients .The results indicated that the severely affected patients still demonstrated elevated levels of IgM, while in the moderate and mildly affected patients levels of IgM dropped to normal.[12] IgG levels also decreased to normal in most of the population studies. IgA levels in all the contaminated patients were in normal range,[12] while mucoid IgA demonstrated a significant decrease comparing to the normal population.[18] The levels of IgE were high in 27% of the patients, 15% of the moderately exposed and only 13% of the mildly exposed. The levels of C3 and C4 increased in the severe patients; while in the moderate and mild patients these levels were normal.[12]

Hematological Consequences of Sulfur Mustard

A- Short-term consequences of sulfur mustard

Leukopenia was the first manifestation to appear between 10 to 14 days after the exposure, in patients most of them had severe skin burns. Thrombocytopenia and anemia appeared later among the surviving patients (WBC of some patients decreased to less 1000/cm^3). Physicians also reported cases that had minor skin lesions and yet developed leucopenia.[19] Bone marrow biopsies revealed a decrease in cell numbers and cellular atrophy.[19] High-dose exposure was shown to induce a cytotoxic effect on hematopoietic stem cells and pancytopenia was reported in affected Iranian soldiers.[20] One study showed initial marked lymphopenia in 36% of the exposed patients, while during the recovery phase, lymphocyte counts increased to greater than 40% in 18% of the patients'.[21]

Increase in lymphocyte protease activity in human peripheral blood due to mustard exposure has also been reported.[22] In another study, neutrophil function tests remained intact despite mustard poisoning.[23] An animal study showed that, leukocyte count depression occurred on days four, five and six after the exposure to SM, following a leukocyte elevation on the day 1.[24] Low-dose effects on this system may appear years later, therefore follow-up studies are needed to determine these adverse effects.

Table 4. The number and activity of immunocompetent cells in patients with long term exposed to sulfur mustard.

Cells	Phenotype	Percentage± Standard Deviation			
		Severe	Moderate	Mild	Control
T Cell	CD3/CD4	34.05±8.3	38.72±7.6.	34.65 ±7.2	37.26 ±4.6
T Cell	CD4/CD25	8.41±5.2 [a]	5..94±4.1	5.03±4.3	5.35±2.8
T Cell	CD3/CD8	27.92±8.8	27.25±8.1	30.78±9	28.11±9.6
Granulocyte	CD15	52.0±19.57	44.68±15.	51.4±11.94	43.72±7.28
NK Cell	CD56	4.8±2.8[b]	2.4±1.7[a]	4.16±3.2	3.3±2.2
NK Cell	CD56/CD25	0.35±0.3 [a]	0.51±0.6[a]	0.43±0.5	0.24±0.09

[a] P<0.05; b P<0.1 indicates a significant difference in comparison with control group as shown by Kruskal-Wallis test.

B- Long-term consequences of sulfur mustard

Most studies performed on people exposed to sulfur mustard paid attention to the status of WBC, RBC and platelets. Other factors included haemaglobulin and hematocrite. The results of a 5 year follow-up study indicated that these patients reached a stable state (semi normal state).[25] However, as depicted in table 4, the mean values of WBC, lymphocytes and neutrophils were decreased, but monocytes were increased in comparison with the first evaluation at the beginning of the study.[25] Moreover, in some patients, atypical lymphocytes comprised more than 20% of the total lymphocytes. Ten year follow up studies on the clinical conditions of the sulfur mustard victims of the Iraq-Iran war displayed the long term consequences of sulfur mustard contamination. Studies indicate that surviving Iranian victims are still suffering from two major problems: high incidences of malignancies and recurrent infections. Reports have shown that the incidence of AML is 18 fold and the incidence of ALL is 12 fold comparing to normal population (Tables 2 and 5).[26]

Biochemical Consequences of Sulfur Mustard

A- Short-term consequences of sulfur mustard

The main clinical and pathological findings among the patients exposed to sulfur mustard were depigmentation and wet lesions of the skin, lung function disturbance, ophthalmologic manifestations, conjunctivitis and corneal abrasions,[2,3] gastrointestinal symptoms (dysphlagia, diarrhea and vomiting), hematological complications (leukopenia, bone marrow depletion), septicemia and liver and kidney complications. Several body organs and systems including the pancreas, liver, kidney, and heart enzymes, immune system as well as endocrine system of these patients have been studied.

Most of the biological parameters were high in the first month but began to decrease after several months and the patients reached a normal state after one year (Table 6).[3]

Table 5. Percentages of the cell type in the control group and patients under study.

Patients	Hemoglobin total no. ±SD	Hematocrit total no. ±SD	White Blood Cells total no. ±SD	Red Blood Cells total no. ±SD	Platelet total no. ±SD
Severe group					
Patient	14.858±2.292	44.923±6.711	9269.2±2457.9	$5.43x10^6$±$526478x10^3$	$252x10^3$±71381
Control	16.18±0.964	48.6±2.875	7670±1244.6[a]	$5.72x10^6$±$55478x10^3$	$224x10^3$±82970
Moderate group					
Patient	14.54±0.81	45±3.66	8752±173.14 [b]	$5,64x10^6$±$5777x10^3$	$218x10^3$±58128
Control	15.62±0.51	47.9±1.66	7480±1508	$5,73x10^6$±$56478x10^3$	$262x10^3$±58060
Mild group					
Patient	15.33±1.23	44.36±3.27	8123±1767 [a]	$5,73x10^6$±$56478x10^3$	$228x10^3$±81280
Control	15.33±1.01	44.38±3.84	7110±1507	$5,73x10^6$±$56478x10^3$	$228x10^3$±81280

[a] P<0.05; [b] P<0.1 indicates a significant difference in comparison with control group as shown by Kruskal-Wallis test. SD: Standard Deviation

B- Long-term consequences of sulfur mustard

Most of the patients, checked during later years were in normal and stable state and no significant differences with the normal populations were observed except thyroid hormone TT4 levels which showed a lower level than normal range values.[27]

Genetic Consequences of Sulfur Mustard

Previous reports suggested that human exposure to nitrogen mustard resulted in chromosomal breakage. It was concluded that following the seven years of treatments with nitrogen mustard, a significant aberration rate (specially chromosomes 5 and 7) and chromosomal breakage (specially chromosome 5, 7 and 9) developed.[28] In one study significant differences in the numerical aberration rate and chromosomal breakage among the severe patients were observed,[29] but no significant differences were noticed in the mild and moderate patients as compared to the control group.[30,31] Previous studies on the people exposed to nitrogen mustard showed an increase in the hypo- and hyperploids, which are indicative of a secondary tumor (Table 7).[28] Studies on the ploidy of the patients indicated that in the case of severe patients, 22 out of the 26 studied patients had aneuploidy cell population (hyper or hypoploid) in their peripheral blood lymphocytes.[29] Chi-square test for aneuploidy state of both the patient and control populations was significant.[29] In the moderate and mild patients there were no differences in the ploidy comparing to the control group.[30,31] These results confirm the findings of other workers, which correlate the high incidence of tumor in patients with severe exposure to sulfur mustard.

DISCUSSION

Although international regulations strictly prohibit the use of chemical warfare however, sulfur mustard has been excessively produced, stored and employed in various regions of the world.[1]

Table 6. The level of humoral parameters in patients exposed to sulfur mustard

Tests	Period of exposure			
	up to month	up to 1 year	up to 8 year	up to 12 year
Alkaline aminotransferase	Normal	Normal	Normal	Normal
Transferrin	Normal	Normal	Normal	Normal
bilirubin	High	Normal	Normal	Normal
Amylase	High	Normal	Normal	Normal
Total protein	Normal	Normal	Normal	Normal
Albumin	Normal	Normal	Normal	Normal
Beta globulin	Normal	Normal	Normal	Normal
Immunoglobulin α	High	Normal	Normal	Normal
Uric acid	Normal	Normal	Normal	Normal
Creatinine	High	Normal	Normal	Normal
Creatine kinase	High	Normal	Normal	Normal
Lactate dehyrogenase	High	Normal	Normal	Normal
TT4	Low	Low	Low	Low
TT3	High	High	ND	ND
FT4	normal	Normal	Normal	Normal
FT31T3	normal	Normal	Normal	Normal
TSH	normal	Normal	Normal	Normal

ND: Not Done

Table 7. The ratio of Ploidy in metaphase of the peripheral blood of severe, moderate, mild and control groups

Subject	no. of cases	hypoploid ratio±SD	diploid ratio±SD	hyperdiploid ratio±SD
Severe group				
Patient	25	0.89±0.109	1.00±0.04	1.08± 0.08
Control	10	0.89±0.045	1.00±0.02	1.08±0.01
Moderate group				
Patient	25	0.05±0.064 [a]	0.9 ±0.09	0.06±0.036
Control	10	0.155± 0.065	0.93±0.07	0.06±0.01
Mild group				
Patient	25	0.89±0.03	0.90±0.13	0.99±0.79
Control	10	0.92 ±0.03	0.99± 0.056	1.26± o.1

[a] P<0.05.indicates a significant difference in comparison with control group as shown by Kruskal-Wallis test.
SD: Standard Deviation.

Weapons of mass destruction such as chemical arsenal are still a potential threat to world peace and human health. Therefore effective therapeutic measures must be established to counter the short and long term effects of sulfur mustard contamination. Since suppression of various functions of the immune system occurs in patients exposed to sulfur mustard early after the contamination, its short and long term consequences must be well defined. The administration of immunostimulating drugs as a preventive measure could substantially decrease the incidence of severe infections, malignancies and other complications. Long term follow up studies on the clinical conditions of the patients exposed to different degrees of sulfur mustard can reveal the physiological and cellular aspects of these pathological conditions.

Today, approximately two decades after the Iranian victims' exposure to sulfur mustard, they face two major problems: high incidence of tumors[26] and recurrent infections.[33] In addition, there is a possible shift in the severity of the illnesses from mild to either moderate or severe forms. Available data also suggest a strong correlation between the cancers of the upper respiratory tract and the level of the individuals' exposure to sulfur mustard gas during the World War II.[1] Certain reports have also been published concerning long term effects on workers exposed to sulfur mustard and sufferings from multiple skin tumors such as basal cell carcinoma, and Bowen's disease.[32] Considering the particular affinity of mustard derivatives for lymphoid cells and for DNA molecules, further immuno-toxicological studies on sulfur mustard contaminated patients will shed light on the observed clinical conditions. Studies on the immunological aspects of sulfur mustard contamination have been focused on both basic and clinical aspects and various parameters of immune function. Efforts to obtain a reliable and reproducible animal model for sulfur mustard contamination proved successful and a murine model for these studies is currently established.[9] Basic research on the use of immunomodulators for reversing the immunosuppression induced by sulfur mustard has also revealed noticeable findings, which could be applied to clinical cases.[35] Cimetidine, a histamine antagonist widely used for the treatment of duodenal ulcer and other hyper secretory conditions,[36] has also been implicated in the augmentation of cell mediated cytotoxicity and abrogation of suppressor cell functions [36,37],and has exhibited immuno-enhancing properties in the sulfur mustard contaminated patients.[38] Pyrimethamine an anti malarial agents, which exerts their effects through the inhibition of dihydroplate enzyme;[39] also displayed immuno-potentiation properties in the sulfur mustard patients. So far, studies have been mostly focused on the quantitative rather than the qualitative aspects of hematopoietic system disorders as a result of mustard intoxication. These studies indicate the importance of degrees of contamination or dose of sulfur mustard. Since no exact measurement could have been done in clinical cases, determination of degrees of exposure is difficult and only approximate classification has been possible, indicating the importance of animal models and basic research. For example, a previous study on the antioxidant enzymes in blood cells showed that sulfur mustard at a sub-lethal dose inhibited antioxidant enzyme activities in WBCs and cells of the spleen .The study also suggested the formation of reactive oxygen radicals in cases of sulfur mustard intoxication.[40] Sound and well established animal models are indispensable tools for future research in this area.

Clinical studies display the observations and trends of the follow up of the Iranian victims in addition to the short term studies performed.[41] Further studies on bone marrow cells and cell markers as well as long-term follow-up of these patients are also required to assess the definite hematological and immunological complications of mustard gas exposure in humans. These trends highlight the importance of follow-up studies on immunological parameters and therapeutic interventions with due consideration to these parameters and immunopotentiating strategies.

REFERENCES

1. Meselson M, Robinson JP. Chemical warfare and chemical disarmament. Sci Am 1980; 242(4):38-47.
2. Pauser G, Aloy A, Carvana M, Graninger, Harvel W, Koller W, et al. Lethal intoxication by war gases on Iranian soldiers. In: Heyndriks A, editor. Toxicological evaluation. Proceedings of the first world congress on biological and chemical warfare. Ghent: Ghent University Press, 1984: 341-51.
3. Sohrabpoor H. Observations and clinical manifestations of patients injured with mustard gas. Med J IR Iran 1987; l:32-7.
4. Vycudilik W. Detection of mustard gas Bis (2-chloroethyl) sulfiede in urine. Forensic science Int. 1985; 28(2):131-6.
5. Drasch G; Kretschmer E; Kauert G; von Meyer L. Concentration of mustard gas (Bis-2-chloroethylsufide) in

the tissues of a victim of a vesicant exposure. Forensic Science Int 1987; 32(6):1788-93.
6. Wils ER, Hulst AG, de Jong AL, Verweij A, Boter HL. Analysis of thiodiglycol in urine of victims of an alleged attack with mustard gas. J Anal Toxicol 1985; 9(6):254-7.
7. Al Yassin. Immunostatus of people exposed to sulfur mustard. In: Chemical warfare book. Tehran: Loghman Hospital, University of Tehran Press, 1984.
8. Razavimanesh A. Evaluation of immune system on patient exposed to sulfur mustard. Tehran: University of Tehran Press, 1988.
9. Hassan ZM, Ebtekar M. Modeling for immunosuppression by sulfur mustard. Int Immunopharmacol. 2001; 1(3):605-10.
10. Motakallem MH. Evaluation of 17 patients severely injured with sulfur mustard. Med J IR Iran 1988; 2:2.
11. Ghannadpour SJ. Studies on the biochemical factors of people exposed to sulfur mustard. Tehran: Tarbiat Modares University Press, 1986.
12. Sohrabpour H. Observation of the immunological changes in the people exposed to sulfur mustard. In: Proceedings of first congress on the effect of biochemical warfare on human beings environment and society. Ghent: Ghent University Press, 1990: 41-51.
13. Ghotbi L, Hassan ZM. The immune status of natural killer cells in people exposed to sulfur mustard. Int Immunopharmacology 2002; 2:981-5.
14. Hushyar A, Hassan ZM. Studies on the immune-status of granulocytes in the people exposed to sulfur mustard. Med Res 2004; 11(39):165-71.
15. Pour K, Hassan ZM. Studies on the immune status of monocyte CD45/CD14, and CD14/HLA-DR in the people exposed to sulfur mustard. Tehran: University of Shahid Beheshti Press, 1998.
16. Shaker Z, Hassan ZM, Sohrabpoor H, Mosaffa N. Immune status of T helper and T cytotoxic cells in the patients ten years after exposure to sulfur mustard. Immunopharmacol Immunotoxicol 2003; 25(3):423-30.
17. Hamzapour M, Hassan ZM. Studies on the immune status of B cell, CD19/CD25 in the people exposed to sulfur mustard. Tehran: University of Tehran Press, 1998.
18. Pakzad F. The level of secretary IgA in the lung of people exposed to sulfur mustard. Pulse 1995; 3(4):102-7.
19. Sohrabpoor H. Clinical manifestations of chemical agents on Iranian combatants during Iran-Iraq conflict. Arch Belg 1984; (Suppl):291-7.
20. Tabarestani M. Stem cell and erythroid precursors disorders in three patients with sulfur mustard poisoning. Mashhad: Proceeding of first International Medical Congress of Chemical Warfare Agents, 1988: 10.
21. Tabarestani M. Hematologic findings of sulphur mustard poisoning in Iranian combatants: Med J IR Iran 1990; 3: 185-9.
22. Cowan FM. Effect of sulfur exposure on protease activity in human peripheral blood lymphocytes. Cell Biol Toxicol 1991; 7(3):239-48.
23. Mousavi T. Study of cellular immunity in Iranian combatants poisoned with mustard gas. Mashhad: Proceeding of first International Medical Congress of Chemical Warfare Agents, 1988: 60.
24. Gold MB, Schrarf BA, Hematological profile of the euthymic hairless guinea pig following mustard vesicant exposure. J Appl Toxicol 1995; 15(6):433-8.
25. Ghanei M. Delayed Haematological Complications of Mustard Gas. J Appl Toxicol 2004; 24(6):56-8.
26. Zakery Neia M. Statistical data of malignances of the people exposed to sulfur mustard. Iran: Proceedings of the 5th congress of long-term consequences of chemical warfare, 1995: 32-4.
27. A study on serum T3, T4, TSH and humoral immunity of patients exposed to sulfur mustard. Teb Nezami, 1997; 12:101-5.
28. Fox M, Scott D. The genetic toxicology of nitrogen and sulfur mustard. Mut Res 1980; 75(2):131-68.
29. Rostam-Zadi F, Hassan ZM, Noori-Daloii M. Immunohaematological and cytogenetical studies on people severely exposed to sulfur mustard. Biology 1999; 9(1):30-8.
30. Rezwani M, Noori-Daloii M, Hassan ZM. Immunohaematological and cytogenetical studies on people moderate exposed to Sulfur mustard. Biology 1999; 9(1):1-4.
31. Jalilian N, Rostam-Zadi F, Hassan ZM, Noori-Daloii M. Immunohaematological and cytogenetical studies on people mild exposed to sulfur mustard. Tehran: Tarbiat Modares University, 2000: 65-9.
32. Klehr NV. Cutaneous late manifestations in former mustard gas workers. Z Hautkr 1984; 59(17):1161-70.
33. Sohrabpoor H. Studies of humoral immune system changes in 179 victims of chemical warfare 3 years after the injury and compression with control group. In: Seminar on the influence of biological and chemical war on human environment and society. Tehran: Tehran University Press, 1992.
34. Hassan ZM, Nori-Daloii M, Nadery Manesh A, Bidaky SK, Rostamzada J, Jalilian N, et al. Immunohaematological and cytogenetical studies on

human populations exposed to sulfur mustard. J Sci IR Iran 2002; 13(4):303-9.
35. Ebtekar M, Hassan ZM. Effect of immunomodulators pyrimethamine and cimetidine on immunosuppression induced by sulfur mustard in mice. Int J Immunopharmacol 1993; 15(4):533-41.
36. Douglas W. Histamine and 5 hydrocytryptamine and their antagonists. In: Goodman, Gillmann, Macmillan, editors. Pharmacological basis of therapeutics. USA, NY 1985: 68.
37- Sahasrabudhe DM, McCune CS, O'Donnell RW, Henshaw EC. Inhibition of suppressor T lymphocytes (Ts) by cimetidine. J Immunol 1987; 138(9):2760-3.
38. Brockmeyer M. Immunomodulatory properties of Cimetidine in ARC patients. Clin Immunol Immunother 1988; 48:50-60.
39. Webster L. Drugs used in the chemotherapy of protozoal infections. In: Goodman, Gillmann, Macmillan, editors. Pharmacological basis of therapeutics. USA, NY 1985.
40. Husain K, Dube SN, Sugendran K, Singh R, Das Gupta S, Somani SM. Effect of topically applied sulphur mustard on antioxidant enzymes in blood cells and body tissues of rats. J Appl Toxicol 1996; 16(3):245-8.
41. Keyhani A, Eslami MB. Short-term effects of mustard gas on the humoral immune system. Personal communication, 2005.