

Clinical management of mustard gas casualties

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FOREWORD

Dr. J.L. Willems has earned a well deserved reputation of expertise in the medical treatment of victims of the use of chemical weapons.

This field is uniquely sensitive for Belgian people, given the memories of the use of chemical weapons during World War I. It is indeed most regrettable that it has still taken place more than seventy years after the first use on April 22, 1915, in our country.

Expertise and dedication to the cause of curing victims of a particularly horrible weapon is most valuable. It would naturally be preferable if such expertise was no longer needed but we have to see reality as it is. International commitments such as the Protocol of Geneva can be broken, as we sadly know.

The aim of the Belgian foreign policy with respect to chemical weapons is the prevention of their use, first and foremost through compliance with the existing prohibition embodied in the Protocol of Geneva of 1925. Belgium seeks additional guarantees of compliance with this prohibition, mainly through the conclusion of a total ban on chemical weapons that would induce states to close this military option entirely and for good.

In a way, diplomats and scientists work at opposite ends of the same problem. The ones are trying to prevent, the others to cure what could not be prevented. Compassion for the victims is the common denominator.

It is a source of pride for Belgium that the tradition of scientists dedicated to humanitarian causes is still very well alive today. I thank Dr. Willems for the testimony his work bears to this.

L. TINDEMANS
Minister of Foreign Affairs
of Belgium

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ABSTRACT

About 170 chemical warfare casualties, presumably victims of sulfur mustard exposure, were evacuated from Iran to European hospitals during 1984-86. The casualties chosen for evacuation had moderate to severe injuries. The clinical files of 65 of these casualties who were treated at 9 European hospitals are summarized in this report. Patients arrived at European hospitals 4 to 17 days after exposure. For those arriving within 5 days, the most prominent symptoms were mucocutaneous lesions of the eyes, skin, and upper airways; and coughing and sore throat. Skin lesions ranged from dark brown areas of epidermal lysis, beneath which was regenerating epithelium, to deep erosive lesions. Leukopenia was present in almost half the patients, and usually resolved quickly; in contrast, the seven patients with severe leukopenia (200 or less cells/ml) later died. Ventilatory insufficiency requiring artificial ventilation also indicated a poor prognosis. Treatment regimens varied because of the number of institutions that treated these patients, and because of the absence of clinical experience with mustard casualties. For instance, systemic drug administration was most extensive for patients in intensive care units, less for those on burn wards, and least for those on general and dermatology wards. Evaluation of treatment outcomes in this study was precluded by the small sample sizes. Detoxification procedures to remove any remaining mustard were attempted at some centres. However, contamination of newly arrived patients by unmetabolized mustard could not be established by the toxicological assays performed. Thus the efficacy of these treatments could not be determined, and the need for such treatments is questionable. A high frequency of septicemia was observed for patients who received hemoperfusion, the most invasive decontamination treatment. Nine patients died, all but one within 15 days after exposure. Patients were discharged after 2-10 weeks; the length of hospitalization was determined by the healing time for deep skin lesions.

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ACKNOWLEDGEMENTS

I would like to thank all the clinical centres and laboratories that allowed me to use their data, and particularly the physicians who provided me with the summaries of their clinical files (see section 1.1). I would like to thank also the following persons who provided me with a great deal of personal information, and were very helpful in making the necessary contacts :

Prof. Dr. G. Bloom (Medical Board of the Armed Forces, Sweden), Dr. U. Helm (University of Bonn, Germany),

Dr. D. Ligtenstein (Prins Maurits Laboratory, TNO, The Netherlands), Dr. S.A. Persson (FOA 4, Sweden).

As a physician trained in pharmacology and toxicology, I have been confronted with a variety of less familiar clinical and analytical problems when preparing this work. I therefore gratefully acknowledge the close collaboration of the following colleagues in the preparation of this report :

Dr. R. Biersack (München), Dr. W. Buylaert (Ghent), Dr. T. Chevolet (Liège), Dr. F. Colardyn (Ghent),

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Dr. L. Mortelmans (Antwerpen), Dr. M. Roman (Brussels), Dr. K. Vossaert (Ghent).

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CHAPTER I : INTRODUCTION

In March 1984, February 1985 and March 1986, Iranian casualties from the Iran-Iraq conflict were sent to hospitals in Ghent (Belgium) and to other West European hospitals for treatment. Others followed in 1987. They were part of the evidence for the accusations made by Iran that Iraq had used chemical warfare agents on the battlefield.

The hospital physicians confronted with these casualties were totally unfamiliar with this kind of lesion. Indeed, since World War I the clinical experience with regard to chemical warfare injuries had nearly completely disappeared, and this is expressed in the multitude of treatment policies that have been applied to these casualties. However, the use of chemical warfare agents, i.e., mustard gas and tabun, in this conflict, as officially stated by three UN missions (United Nations, 1984; 1986; 1987), proves that chemical warfare agents remain a threat in any future armed conflict even if most countries have abandoned the first use of chemical agents by signing the Geneva Convention of 1925 (Robinson, 1973). Moreover, the use of chemical agents in densely populated areas, e.g., in Europe, would produce even more victims within the civilian population than within the military services, which generally deploy some protective equipment, and would pose a heavy burden on the medical services of the countries affected.

It therefore seemed of interest to us to gather all the clinical information available on these Iranian casualties and to present it to the medical profession. The first purpose of this report is to describe in some detail the clinical course of the patients and the different treatment schemes that have been followed, and to discuss the diagnosis and optimal therapy. The second purpose is to provide the physician confronted with this type of war casualty with some guidelines to decide upon the most appropriate treatment.

1. CENTRES PARTICIPATING IN THIS STUDY

This work started with the observations made in 1984 at the Hospital of the University of Ghent Medical School (Universitair Ziekenhuis, Ghent). The clinical files of the patients treated in 1984, and later in 1986, were summarized using a standardized form, which permitted the necessary reduction in amount of data without losing relevant information. In 1986, 1987 and 1988 I was able to visit several clinical centres in Belgium and in other European countries that had also been involved in the treatment of Iranian casualties. The physicians of these centres kindly allowed me to share their experience by discussing their observations, by granting me the permission to study their patient files or by sending me the completed standardized patient forms. They agreed that that information would be included in this report.

The collaboration of the following clinical centres and physicians, and of their staff, is gratefully acknowledged.

- Academisch Ziekenhuis Utrecht, Utrecht, The Netherlands.
Department of Cardio-Pulmonary Resuscitation and Clinical Toxicology : Prof. Dr. B. Sangster.
- Akademiska Sjukhuset, Uppsala, Sweden.
Division of Plastic Surgery : Dr. A. Hedlund.
- Hôpital Erasme, Université Libre de Bruxelles, Bruxelles, Belgium.
Department of Intensive Care : Prof. Dr. R. Kahn.
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Department of Traumatology : Dr. M. Ledoux.
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- Universitair Ziekenhuis, Rijksuniversiteit Ghent, Ghent, Belgium.
 - Department of Dermatology : Prof. Dr. A. Kint
 - Department of Intensive Care : Prof. Dr. F. Colardyn.

- Ziekenhuis De Bijloke, OCMW Ghent, Ghent, Belgium.
Department of Intensive Care : Dr. B. Neyrinck.

The diagnosis of mustard gas poisoning has been possible on the basis of the history obtained from the patient and Iranian medical personnel, clinical symptomatology and analytical results obtained in several laboratories of toxicology. The following laboratories and scientists and their staffs kindly agreed to discuss the analytical procedures they applied and the positive and negative results they obtained. The authorization to include these data in this report is gratefully acknowledged.

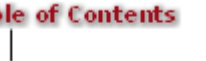
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2. REPORT CONTENTS

Besides the introductory chapter this report contains the following parts :

- Chapter II gives background information that was available at the time of arrival of the patients at the European hospitals. It contains reliable information from the three UN reports, and medical history data from the patients and the Iranian physicians regarding exposure, development of initial lesions and early treatment. It also mentions unconfirmed rumours that circulated in the media.
- Chapter III describes the patients at the moment of their admission at the European hospitals. A detailed description of the clinical picture and the clinical examinations, and analytical data from the toxicology laboratory are given. Since the patients were transferred at different times after their exposure to the chemical agent, and since symptomatology changed with time, they are grouped according to this time interval. This chapter ends with a discussion regarding differential diagnosis.
- Chapter IV describes in detail the different treatment policies that were followed, the evolution of the clinical situation, the treatment adaptations and the final outcome. Since not only the initial clinical condition but also the kind of treatment determined the clinical outcome, patients will be grouped according to the treatment policy that was applied. This chapter ends with a comparison of the different treatments.
- Chapter V summarizes the most important data concerning the clinical situation at the time of arrival and the treatments applied.
- The annex document gives in more detail the conclusions of the three UN Reports. In order to preserve medical confidentiality the patients are identified by a code number, which indicates the group to which they belonged without identifying the centre in which the group was treated. The letter code was given at random.

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CHAPTER II : MEDICAL HISTORY OF THE PATIENTS AND BACKGROUND INFORMATION

1. INTRODUCTION

At the time of arrival of the first casualties in Europe in 1984, allegations of the use of chemical warfare agents in the Iran-Iraq conflict and pictures of casualties were circulating in the press (Time, 1984). This was rapidly followed by televised pictures of the first arrivals, and a few days later by the press release of the first laboratory results. It was against this sometimes chaotic background of unconfirmed rumours and statements that physicians with no experience in treating chemical warfare casualties had to make decisions with regard to diagnosis and treatment policy. In the following years, although unconfirmed rumours continued to circulate, important and reliable information became available which, together with the past experience, allowed a more straightforward approach of the casualties in 1985, 1986 and 1987.

The most interesting information certainly resides in three official UN reports relating the findings of an official investigation team of four experts sent to Iran in 1984, 1986 and 1987. The first mission went to Iran from March 13 to March 19, 1984 and released its official report, S/16433 (United Nations, 1984) on March 26, 1984. They returned to Iran in 1986, from February 26 to March 3, and released their second report, S/17911 (United Nations, 1986) on March 12, 1986 (see also Dunn, 1986). The third mission took place from April 22 to May 3, 1987, and the official report S/18852 (United Nations, 1987) was released on May 8, 1987. The conclusions, based on field inspection, clinical examination of casualties and laboratory analysis of chemical ammunition, can be summarized as follows (see Annex) :

- Chemical weapons, in the form of aerial bombs, had been used in the areas inspected in Iran by the official UN team.
- The main type of chemical agent used was bis (2-chlorethyl) sulfide, or mustard gas.
- On some occasions evidence was found for the use of the nerve agent ethyl N, N-dimethylphosphoroamido cyanidate, or tabun.

On the basis of this information, one could expect that the patients had been poisoned either by the vesicant mustard gas or by the nerve agent tabun.

It remained possible, although not probable, that other agents also had been used. Soon after the arrival of the first victims in 1984, one laboratory reported that mycotoxins had been found in biological samples of some of the casualties (Heyndrickx et al. 1984b). After the publication of the first UN report, these patients were reported to show combined lesions of mustard, tabun and mycotoxins (Heyndrickx et al. 1984b). During the second mission the expert team received oral information about isolated cases that had shown signs consistent with hydrogen cyanide intoxication (United Nations, 1986). During the third mission some Iraqi patients were observed to show lesions compatible with phosgene exposure (United Nations, 1987). As chapters III and IV make clear, however, the patients evacuated to Europe were mustard gas casualties.

Taking the medical history of these patients was rather difficult because of language and communication problems. Moreover, most of them could hardly describe the evolution of their clinical symptoms or the treatment they had received. For a few patients, the Iranian clinical dossier was available. Therefore, I felt it justified to include in this chapter also the clinical information on similar casualties provided by the UN experts. Indeed, in the UN reports three groups of patients are described; the largest one had a clinical picture compatible with an exposure to a vesicant. Since the patients transferred to Europe belonged to this group, the description of the initial symptomatology in the UN report is almost certainly applicable to our patients. In the same way, information from Iranian physicians about the treatment that was given to these patients may be of interest.

2. MEDICAL HISTORY

2.1. PATIENTS TRANSFERRED TO EUROPE

Table II-1 lists the different patient groups transferred to European hospitals that are included in this report. As stated in chapter I, a code is used to identify the patients. The table also gives some information with regard to the time course of hospitalization.

TABLE II-1 : Patients in the study. The time course of hospitalization with regard to the time of exposure to the chemical agent is given.

PATIENT		NUMBER OF DAYS AFTER EXPOSURE			DAYS IN HOSPITAL
GROUP	NUMBER	ADMITTED	DISCHARGE	DEATH	
A	1	10	27		17
	2	10		12	2
	3	10		16	6
	4	5	21		16
	5	7		13	6
B	1	7	22		15
	2	7	33		26
	3	7	33		26
	4	7	28		21
	5	7		185	178
	6	7	28		21
	7	6	21		15
	8	6	41		35
	9	7	42		35
C	1	10		15	5
	2	10	47		37
	3	10	36		26
	4	10	47		37
	5	10	36		26
D	1	5	26		21
	2	5	26		21
	3	5		6	1
	4	5	71		66
	5	5	41		36
	6	5	26		21
	7	5	76		71
	8	5	26		21
	9	5	48		43
	10	7	34		27
	11	16	43		27
	12	15	42		27
E	1	7	38		31
	2	7	38		31
	3	10	41		31
I	1	9	39		30
	2	9	27		18
	3	9	34		25
	4	9	27		18
	5	9	39		30
K	1	5		12	7
	2	5	50		45
	3	5	50		45
	4	x			5
	5	16	43		27
L	1	6	26		20
	2	6	17		11

	3	6	25		19
	4	6	34		28
N	1	6	69		63
	2	6	54		48
	3	6	69		63
	4	17	51		34
	5	6	40		34
	6	4	45		41
	7	4	50		46
	8	4	45		41
	9	4	50		46
	10	6	66		60
	11	5		7	2
	12	4	52		48
P	1	*	*		*
	2	*		+	*
	3	*	*		21
	4	*	*		14
	5	14	28		14
	6	14	28		14

* : exact time of exposure unknown, but most likely within 5 days.

+ : time of death unknown.

x : had not been exposed to a chemical agent (see section III.2.3).

The historical data obtained from individual patients were very incomplete, but when we integrated the complementary data for similar patients a consistent overall picture was obtained.

Exposure and protection

A consistent history of exposure was obtained from the patients belonging to group C. They had been exposed to exploding bombs generating black dust and rain. The rain probably was caused by the liquid content of the bomb that was mixed during the explosion with dust and water, as they were fighting in a marshy region. Patients of group A reported that the bombs exploded on impact and generated a cloud with a colour that was described by different patients as grey, green-blue or orange. Patients of group N told a similar story and reported that the cloud, after covering the area, was somewhat persistent, and that it contaminated the equipment and the vegetation.

In 1984 most soldiers did not wear protective clothing or gas masks. Later some protection became available, but it is doubtful that this protection was fully effective, since it is not known whether the masking drill was carefully performed.

Moreover, according to Dr. Andersson (UN team, personal communication), the efficacy of protection of the airways by the mask was substantially decreased because of the beards many of the soldiers wore. For example, patients L1 and K2 wore gas masks over their beards, but L1 developed limited palpebral lesions and some coughing and expectoration, and K2 developed severe bronchial lesions.

Because of the relatively long persistence of toxic agents such as mustard gas, decontamination procedures are very important for avoiding secondary contamination. The only decontamination that was mentioned by the casualties was that they took off their clothes after withdrawal from the battlefield, and that several of them took a shower. The efficacy of decontamination by water, which can disperse the agent over the body, is dubious, however. Secondary contamination, therefore, remains an explanation for some of the lesions.

Early symptomatology

The following early symptoms were described by the patients of group C and N.

Shortly after exposure, they experienced a burning sensation in the eyes and throat and difficult respiration. Two patients complained of abdominal pain and vomiting, seven had experienced a sensation of suffocation and some had lost consciousness for some time. They remained in the contaminated atmosphere for several hours. After being evacuated, they changed clothes and took a shower.

In the following one or two days they developed the following lesions :

- itching, erythema and small blisters on the skin
- edema of the eyelids and photophobia
- hoarseness, coughing, dyspnea and hemoptysis.

None of these patients was able to describe the further evolution of the lesions, because photophobia and bandages interfered with observation of the lesions.

Eye irritation and breathing difficulties immediately upon exposure were also mentioned by others (A1, group I, L2). Loss of consciousness was also mentioned by P5.

Delay in the development of skin lesions was frequently reported (L2, K5, groups A and I).

The medical dossiers of patients D12, I1 and N4 reported that they had developed leukopenia, with a minimum of 1400 leucocytes/mm³ (9th day after exposure), 2000/mm³ (3rd day) and 800/mm³ (less than 15 days after exposure), respectively.

Initial treatment

It appeared that some soldiers carried autoinjector devices, containing at least atropine, and amyl nitrite ampules, and that they used these automedications shortly after exposure to the unknown chemical agent. They complained afterward of dry mouth and headache, as would be expected after the unjustified use of these antidotes.

According to the clinical documents of some patients of groups C, D, I and N, the following treatments were also applied :

- eye ointment or droplets, containing sulfacetamide, chloramphenicol or betamethasone.
- antitussives and mucolytics.
- skin treatment : calamine lotion.
- systemic treatment : antibiotics (an aminopenicillin, a cephalosporin, an aminoglycoside), bronchodilators (aminophylline, a beta 2-mimetic), and corticosteroids.

In groups E and K the following drugs were mentioned : sulfacetamide eye droplets, antibiotics (a penicillin, a macrolide, a tetracycline, an aminopenicillin, a cephalosporin), a bronchodilator and a corticosteroid.

Patients of group A and N mentioned that blisters had been punctured.

Patient N4 had received a transfusion with leukocytes.

2.2. PATIENTS DESCRIBED IN THE UN REPORTS

In the UN reports (United Nations, 1984; 1986; 1987) a group of patients is described that showed similar lesions to those of the patients transferred to Europe. That description was based on the medical examination of 31 patients during the first mission, 40 patients during the second, and 45 during the third.

Exposure and protection

The patients reported that they had been exposed to bombs which were dropped from aircraft. The explosion had been detected by the flash produced, by the odour of garlic, or by an acrid or pungent odour.

Early symptomatology

The first symptoms appeared from 20 minutes to 4 hours after exposure and increased in intensity in the following 8 to 48 hours. These clinical signs were conjunctivitis, a sensation of a foreign body in the eye, photophobia and palpebra1 edema.

Further symptoms that gradually developed were itching, intensive erythema and a dark coloration of the skin that became black in some areas. The areas most affected were the armpits, genitalia, groin and the flexor sites of the elbows and the knees (fossa poplitea).

Subsequently, blisters filled with yellowish fluid appeared (figures [II-1](#) and [II-2](#)). They ranged from a few millimetres to several decimetres, reaching enormous size in some cases.

The blisters subsequently broke open, leaving a cutaneous detachment over wide areas. These ulcerations were painful and the patients complained when they were moved or when the lesions were dressed.

Some patients developed nasal obstruction, rhinorrhea and nasal scall. A number of them showed tracheitis and laryngitis accompanied by hoarseness, coughing, hemorrhagic expectorations and expectoration of dead mucosa.

The most seriously affected developed leukopenia, especially of the lymphopenic type.

Initial treatment

It is clear that in 1984 the use of a chemical warfare agent was unexpected by the Iranian Medical Services and that no systematic treatment was available. In 1985 and 1986, however, the following scheme was officially proposed (Balali, 1986b).

- Eye treatment : rinsing with water and Ringer solution, application of sulfacetamide ointment and of a mydriatic collyrium, eyes kept closed and bandaged for 2-3 days.
- Skin treatment : skin decontamination with water (shower), application of chloramine (0.2 %) or sodium thiosulfate (2 %), aspiration of the contents of the blisters and removal of the necrotic skin, application of silver sulfadiazine cream.
- Systemic treatment, if necessary : inhalation of moist air enriched with oxygen; bronchodilator drugs and systemic corticosteroids in the case of bronchoconstriction; antitussives, mucolytics and expectorants; antibiotics in the case of bronchopneumonia; intubation and artificial ventilation with PEEP if needed; hemoperfusion in very severe cases.
Blood or white cell transfusions to counteract bone marrow depression.
- Intravenous fluids and electrolytes to stabilize the water and electrolyte balance; calorie-rich feeding.

It was, however, impossible to tell for an individual case whether this treatment had been applied, or to what extent.

*Figure II-1 :
Blisters on the forehead
and cheek, 17 hours after
exposure to the chemical
agent. Picture kindly
provided by Dr. U. Helm.*



*Figure II-2 :
Blisters on the back and
buttocks, 16 hours after
exposure to the chemical
agent. Patient n° 30 of the
UN Report S/16433
(1984). Picture kindly
provided by Dr. U. Helm.*

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CHAPTER III : OBSERVATIONS AT THE TIME OF ADMISSION AT THE EUROPEAN CLINICAL CENTRES

1. INTRODUCTION

This chapter gives a detailed description of the clinical observations, the results of specialized investigations, biochemistry, and toxicological findings at the time of arrival of the Iranian patients at European hospitals. Some degree of data reduction was necessary, but we tried to retain all relevant information. Since the general clinical aspects of all these patients were similar, a common description, taking into account the different time intervals at which these patients arrived after their exposure to the chemical agent, is acceptable.

The chapter ends with a discussion of the diagnosis, taking into account the clinical picture, the laboratory findings, the information given in chapter II, and information available from the literature.

2. CLINICAL DATA

2.1. ARRIVALS WITHIN FIVE DAYS AFTER EXPOSURE

The basic description which follows is based on groups of patients who were transferred to Europe within five days after exposure to the chemical warfare agent (patients A4, D1-D9, K1-K3, N6-N9, N11 and N12, P1-P4).

2.1.1. General Clinical Condition

Clinical symptoms

These casualties were conscious, showing a blood pressure within normal range but with a variable degree of tachycardia, paralleled by a moderate increase in body temperature between 37 and 38° C. In some patients temperature fluctuated between 37 and 39° C. Respiratory symptoms included sore throat, abundant aqueous white sputum and coughing. In a few cases green expectorations and slight dyspnea were observed, with diffuse crepitations and rhonchi on auscultation. There were no abdominal problems. The frequencies of these symptoms, explicitly mentioned in the clinical file, are given in table III-1.

TABLE III-1 : Symptomatology and chest X-ray findings. The number of patients is given in whom the particular finding was mentioned in the clinical files (% within brackets).

i : patients of section 2.1, n = 23.

ii : patients of section 2.2, n = 38.

iii : patients of section 2.3, n = 4.

	i	ii	iii
Temperature < 38° C	8 (35)	24 (63)	2 (50)
Temperature > 38° C *	11 (48)	11 (29)	1 (25)
Aqueous sputum	6 (26)	15 (39)	
Purulent sputum	4 (17)	8 (21)	
Coughing	8 (35)	19 (50)	1 (25)
Symptoms on auscultation	8 (35)	15 (39)	
Lung infiltrates	9 (39)	6 (18)	1 (25)
Mucosal lesions of the upper airways	11 (48)	16 (42)	2 (50)

* : In class i this symptom was closely linked to the lung symptoms.

X-ray examination

Chest radiography revealed relatively few abnormalities, except for a few discrete basal and perihilar infiltrates. The frequencies of these findings are given in table III-1.

Biochemistry

Several patients showed a moderate alkalosis, increased standard bicarbonate and base excess, compatible with a contraction alkalosis presumably caused by an aldosterone reaction on dehydration. In several patients moderate decreases in plasma electrolytes, blood protein and albumin were observed, and were interpreted as the results of a lack of caloric intake. Small increases in serum enzymes such as glutamic-oxaloacetic transaminase (SGOT), glutamic-pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH) showed a general state of illness. A high plasma fibrinogen, with no abnormalities in blood coagulation tests, is probably explained by the inflammatory status of the patients.

Most patients showed low to normal PO₂ and normal PCO₂. This, together with the aforementioned auscultatory symptoms, absence of radiological signs, and lesions of the walls of the airways (see section III.2.1.4) suggested a certain degree of bronchial obstruction, e.g., by bronchiolitis.

The frequencies of the most important findings are given in table III-2.

TABLE III-2 : Most relevant blood and biochemical data.

i, ii, iii : see table III-1.

Numbers of patients are given (% within brackets). Normal values are only indicative. Small differences in these normal values existed between different clinics.

NORMAL VALUES UNITS		BELOW NORMAL	ABOVE NORMAL	TOTAL NUMBER DETERMINED
Hematocrit 37-54 %	i	4 (21)	1 (5)	19
	ii	17 (47)	2 (6)	36
	iii	0	0	3
Erythrocytes 4-6.2 x10 ⁶ /μl	i	2 (15)	0	13
	ii	11 (38)	3 (10)	29
	iii	0	0	3
Leukocytes 4-10 x10 ³ /μl	i	5 (28)	3 (17)	18
	ii	5 (14)	11 (31)	36
	iii	1 (25)	2 (50)	4
Platelets 150-350 x10 ³ /μl	i	3 (21)	1 (7)	14
	ii	8 (26)	11 (31)	35
	iii	2 (50)	1 (25)	4
Sodium 139-147 mmol/l	i	9 (50)	0	18
	ii	15 (41)	2 (5)	37
	iii	3 (100)	0	3

Potassium 3.9-5 mmol/l	i	7 (39)	1 (6)	18 37 3
	ii	9 (24)	0	
	iii	0	0	
Total proteins 6.4-8.2 g/dl	i	7 (64)	0	11 29 4
	ii	8 (28)	1 (3)	
	iii	3 (75)	0	
SGOT 8-33 IU/l	i	0	6 (55)	11 29 3
	ii	0	10 (34)	
	iii	0	3 (100)	
LDH 0-195 IU/l	i	0	4 (25)	16 36 3
	ii	0	11 (31)	
	iii	0	2 (67)	
pH 7.35-7.42	i	0	15 (83)	18 35 2
	ii	5 (14)	13 (37)	
	iii	0	2 (100)	
Base excess -2-2 meq/l	i	0	13 (72)	18 22 2
	ii	4 (18)	14 (64)	
	iii	0	1 (50)	
Bicarbonate 21-25 meq/l	i	1 (6)	12 (67)	18 35 2
	ii	3 (9)	12 (34)	
	iii	0	1 (50)	
PCO ₂ 33-45 mmHg	i	2 (11)	0	19 35 2
	ii	6 (17)	1 (3)	
	iii	0	0	
PO ₂ 65-100 mmHg	i	4 (21)	0	19 35 2
	ii	22 (63)	0	
	iii	1 (50)	0	

Hematology

In several patients leukocytosis was seen as a reaction to infection. Others showed leukopenia, which is discussed in more detail in chapter IV (see also table III-2).

Bacteriology

Patient K2 showed a positive blood culture with *Staphylococcus albus*. In the other patients bacteriological examinations showed negative blood cultures and normal throat flora; in some patients *Haemophilus influenzae*, streptococci and aspergillus were cultured from the

expectorations. Samples taken from the skin lesions showed some of the following microorganisms : *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus fecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus rettgeri*, and coliforms such as *Escherichia coli* and *Enterobacter cloacae*. These bacteria were sensitive to several of the classical antibiotics.

It is difficult to judge the clinical importance of these findings. They indicate the rapid colonization of skin and upper airway lesions with the usual innocuous bacteria, but also with bacteria of nosocomial origin. Even the positive hemoculture of patient K2 might have been due to needle contamination from the skin. This patient, however, showed tachycardia and high temperature.

In tables IV-5 to IV-8 of the following chapter an overview is given of the bacteriological findings in blood and sputum, covering both the time of arrival and the time of hospitalization.

Very ill patients

Patients D3 and K1 were in poor condition. Patient D3 had a heart rate between 140-170 beats/min, body temperature above 39°C, severe ventilation problems and bladder distention. He showed a severe leukopenia, 300/μl. Patient K1 was mentally confused upon arrival, with a body temperature of 38.8°C, respiratory problems and a leukopenia of 1500/μl.

2.1.2. Eye Lesions

Clinical examination with the aid of an ophthalmoscope and fluorescein showed the following eye lesions :

- Eyelid edema ([figure III-1](#)).
- Irregular brown colour of the eyelids, with small erosions and scabs (figures [III-1](#) and [III-2](#)).
- Photophobia and blepharospasm (figures [III-1](#) and [III-3](#)).
- Conjunctivitis ([figure III-1](#)).
- Corneal erosions.



*Figure III-1 :
Eye lesion, palpebral edema and conjunctival injection. This picture (patient B4), taken 7 days after exposure to the chemical agent, is also representative for this group of patients.*

*Figure III-2 :
Eye lesions and skin lesions of the face, 5 days after exposure to the chemical agent. Patient D4.*



Some or all of these lesions appeared in different degrees in the patients. Of the 23 patients 2 had no ocular lesions, 1 had only palpebral lesions, 20 had conjunctivitis and 15 had corneal erosions.

2.1.3. Skin Lesions

The following skin lesions were observed :

- Erythema ([figure III-3](#)).
- Irregular brown colour of the epidermis with small areas of desquamation (figures [III-2](#) and [III-4](#)).
- Dark-brown colour of large skin areas, showing epidermolysis exacerbated by pressing and friction ([figure III-4](#)).
- Smooth, pink surface beneath the exfoliated area, with epithelial regeneration that started from the hair follicles and proceeded to a variable extent ([figure III-4](#)).
- Yellow and white areas of deeper necrosis; here epithelial regeneration started from the few remaining skin adnexa and from the surrounding intact skin ([figure III-4](#)).
- Denuded dermal erosions showing exudations and scabs.
- Large blisters with a rough surface; some of them contained a yellow liquid, but most were no longer intact (figures [III-5](#), [III-6](#) and [III-7](#)).
- Erosive lesions appearing after disruption of the blisters. The white-red dermal lesion showed exudations, bleeding, scabs and sometimes a yellowish precipitate. Regeneration started from the surrounding skin ([figure III-8](#)).



*Figure III-3 :
Erythema of the chest, 5
days after exposure to the
chemical agent. Patient D2.*

*Figure III-4 :
Desquamation (buttocks)*



and epidermolysis over large areas (back), 5 days after exposure to the chemical agent. Patient D5.



Figure III-5 : Large blister, partially disrupted, over the back of the hand and wrist, and edema of the fingers, 5 days after exposure to the chemical agent. Patient D4.



Figure III-6 : Large blisters, edema, and discoloration of the upper side of the right foot, 5 days after exposure to the chemical agent. Patient D7.

Figure III-7 : Extensive blistering of the upper side of the left foot, 5 days after exposure to the chemical agent. Patient D7.



*Figure III-8 :
Large disrupted blister on
the back of the hand,
edema and discoloration, 5
days after exposure to the
chemical agent. Patient D7.*

In general, the lesions were rather painful, but no examination was done to find out whether the deepest lesions had lost their sensitivity. They appeared at different sites all over the body. Erythema, brown coloration and superficial erosions were seen in face and neck; dark brown exfoliating epidermis occurred over large areas of the chest, abdomen, back and buttocks; erosive and necrotic lesions were observed at the belt region, thighs, upper arms and legs, and the genital region; the blisters and the underlying erosive lesions, which were seen in two casualties of group D, occurred at the dorsal side of hands and feet. It appeared that lesions frequently occurred in areas covered by clothing and humidified by transpiration, e.g., upper arms and limbs, back and buttocks, the genital area (see [figure III-9](#)), and the belt region (see [figure IV-11](#)).

The percentage of the total body surface involved was between 5 and 80 %. In most cases, however, the more severe lesions such as deeper erosive lesions, necrotic areas and blisters constituted only a limited part of that total surface.

It would be normal to attempt to make a correlation between the extent of the skin lesions and the severity of the general clinical condition. This was not done because most files had insufficient information about the percentage of superficial or deep skin lesions. Moreover, it is my impression that the severity of the poisoning, and its impact on the general condition, was determined more by the presence or absence of leukopenia and/or lung lesions than by the total surface area of the skin lesions. The non-dermal lesions, particularly the degree of leukopenia, are probably the best indicator of the amount of toxicant that has been absorbed.

Figure III-9 :



Lesions of the genital regions, 12 days after exposure to the chemical agent. Patient C1.



Figure III-10 : Darkening of the skin, extensive epidermolysis, and reepithelialization from the hair follicles, 12 days after exposure to the chemical agent. Patient C1.



Figure III-11 : Darkening of the skin, desquamation, pink areas showing regeneration of the epidermis, and yellow-white areas of deeper necrosis, 12 days after exposure to the chemical agent. Patient C1.

2.1.4. Lesions of the upper and lower airways

Several patients showed redness of the oral cavity and redness, edema and purulent secretions of pharynx and larynx, which hampered indirect examination of the vocal cords.

Bronchoscopy in two patients of group D showed a bilateral erythematous inflammation of the mucosa with bleeding, and purulent secretions. In several places casts of necrotic mucosa partially obliterated the airways. In two patients of group K bilateral hemorrhagic lesions of the mucosa were observed in large and small bronchi, without signs of

superinfection. Casts of necrotic mucosa were observed in one of them. In a third patient of group K only diffuse inflammation was observed without clear mucosal lesions. Edema, redness and bleeding, and necrotic areas were observed in four patients of group N. It is likely that similar lesions were present in the small distal airways, producing bronchiolitis.

2.1.5. Lesions of the gastrointestinal tract

In patient K2 an esophago-gastro-duodenoscopy was performed. It revealed a normal esophagus, a hemorrhagic erosive gastritis and acute bulbar ulceration. In patient K3 a hemorrhagic gastritis of the gastric body and an esophageal ulcer were observed.

2.2. PATIENTS ARRIVING 6-14 DAYS AFTER EXPOSURE

Patients B7-B8, L1-L4, N1-N3, N5 and N10 arrived 6 days after exposure; patients A5, B1-B6, B9, D10, E1-E2, 7 days; patients I1-I5, 9 days; patients A1-A3, C1-C5, and E3, 10 days; and patients P5-P6, 14 days. The most relevant symptoms and biochemistry are given in tables III-1 and III-2.

The general condition was similar to that described in section III.2.1.1. Biological signs of dehydration, with some degree of hemoconcentration, were seen in patients of groups C and L and in patient E3. High fibrinogen values were seen in patients in groups B, C, I, L and N. High sedimentation rates (30-90 mm the first hour) and leukocytosis (up to 12,700/ μ l) were observed in the patients of group L and N. Patients A5, C4, I3 and P5 showed decreased white cell counts (2800, 3200, 3200 and 3000/ μ l). A small decrease in renal clearances indicated a discrete nephropathy in patients of group C.

Bacteriological examinations were also similar to those seen in the earlier arrivals. In addition citrobacter was found near the anus of patient I5 and *Staphylococcus aureus* in the sputum of patient B9. Patient B2 showed a positive blood culture with enterococci, and patient C3 with *Staphylococcus aureus* and *Serratia liquefaciens*. There were, however, no clinical signs of sepsis.

Patient E3 showed skin lesions limited to the face (5 % of total body surface), but nevertheless suffered from serious lung problems and high fever (up to 40°C).

Patient C1 was disoriented and agitated. His mental condition rapidly deteriorated during transfer, requiring heavy sedation with diazepam and haloperidol.

The muco-cutaneous lesions were of the same type as those described in sections III.2.1.2 and 2.1.3.

A discrete opacity of the lens was found in the left eye of patient L2. Of the 38 patients 2 had no ocular lesions, 4 had only palpebral lesions, 32 had conjunctivitis, and 19 had corneal erosions. A purulent external otitis was seen in patients B4 and E2.

The extent of the skin lesions for patients of group A varied between 26 and 70 %; group B, 10-60 %; group I, 10-40 %; group L, 3-40 %; group E, 5-68 %; and were 40 and 18 % for patients P5 and P6. The lesions were darkening of the skin, epidermolysis, erosions and necrosis (figures [III-9](#), [III-10](#) and [III-11](#)). Single blisters were present in patients C1 and E1. Patients of group L already showed extensive reepithelialization from the hair follicles.

Bronchoscopy was performed in patient A5, in two patients of group C, and in three patients of group N. The lesions were similar to those described in section III.2.1.4.

2.3. PATIENTS ARRIVING 15 DAYS AND LATER AFTER EXPOSURE

Patients D12, D11, and N4 arrived 15, 16 and 17 days, respectively after exposure.

They showed a clinical picture similar to that described above. The general condition of

these patients was good and there were few respiratory problems. Patient D12 had a leukocyte count of 4000/ μ l. He was recuperating from a leukopenia of 1400/ μ l that had been observed on the 11th day after exposure. At the time of admission he suffered mainly from eye lesions : conjunctivitis, photophobia, corneal erosion (right eye) and keratitis punctata (left eye). Patient N4 also had cconjunctivitis

Patient K5 arrived 16 days after exposure with eye and skin lesions similar to those described above, including conjunctivitis. He showed a high body temperature of 39.7°C, abundant expectorations, and red mucosa and necrotic casts in the upper and lower airways.

The most relevant symptoms and biochemistry are given in tables III-1 and III-2.

One patient, K4, showed very few skin lesions with some erythema. A detailed questioning revealed nothing that could be related to an exposure to chemical agents. It was concluded that he was not a chemical warfare casualty. Although he is listed in table II-1, which gives an overview of all the patients admitted to the different hospitals, this patient is not included in further descriptions and tables.

3. HISTOLOGICAL EXAMINATION OF THE SKIN LESIONS

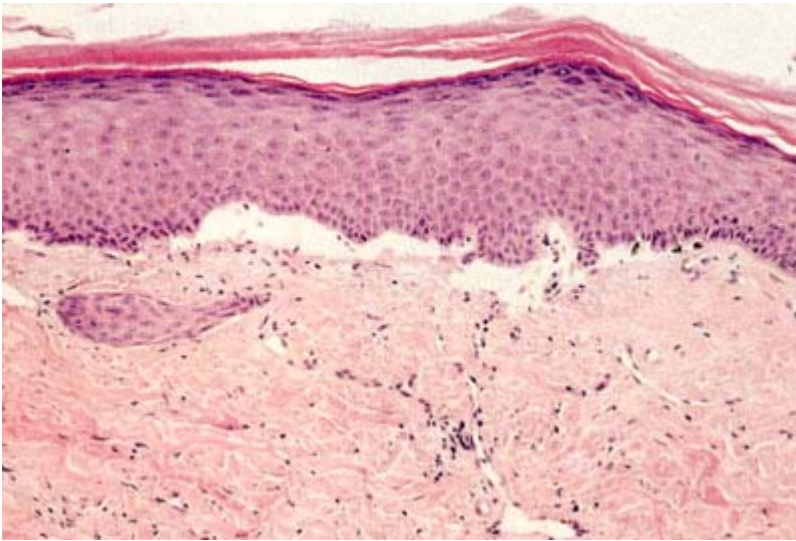
This description is based on biopsies taken from patients C1 and C2 11 days after exposure to the chemical agent. Biopsies taken in other patients, however, indicate that these histological findings are representative of clinically similar lesions.

A biopsy taken from an erythematous zone ([figure III-12](#)) indicates that the epidermis was still present with intact stratum corneum, granulosum and spinosum. The stratum spinosum was edematous. The basal layer was normal except for some irregular cells with pyknotic nuclei. Some dendritic melanocytes were present between the basal cells. This epidermal layer was loosened from the dermis, showing the subbasal cleavage plane where the epidermolysis occurred. The superficial dermis showed a decreased number of histiocytes and fibroblasts, and discrete necrosis with normal capillaries, collagen fibres and fibroblasts. Sweat glands and the middle and deep dermis were normal.

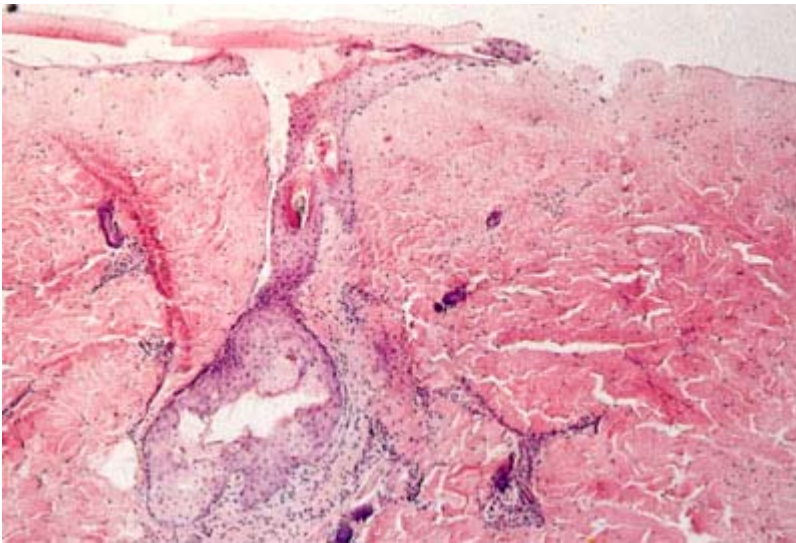
A second biopsy taken from an erosive zone ([figure III-13](#)) indicates that the epidermis was not present, the upper dermis showed necrosis; cell infiltrates can be seen in the middle and lower dermis. A hair follicle was partially detached from the surrounding dermis. At some places capillary thrombosis was seen (not shown in this picture). It is possible that the direct effect of mustard gas on the healing capillary cells, resulting in capillary thrombosis, contributed to the depth of the lesion (Vogt et al. 1984).

Electron microscopy showed inter- and intracellular epidermal edema ([figure III-14](#)), diminution of the number of tonofibrils, loosening of the desmosomes, mitochondria¹ destruction in the basal cells, absence of the basal membrane in several locations, subbasal cleavage, loss of structure in the dermis and hyperactive endoplasmatic reticulum in the fibroblasts ([figure III-15](#)). No striking abnormalities of the melanocytes were observed nor was there any special distribution of melanin.

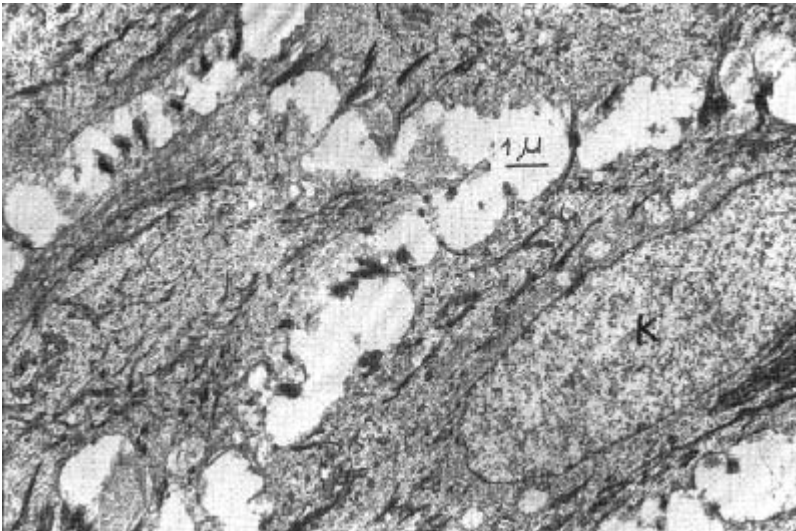
*Figure III-12 :
Erythematous lesion : early
epidermolysis, edema
present in stratum
spinosum. Biopsy taken 11
days after exposure to the
chemical agent (x180).
Hematoxylin-eosin. Patient
C2.*



*Figure III-13 :
Erosive lesion, upper
dermis : cell infiltrates and
necrosis, a hair follicle
became partially detached
from the surrounding
dermis. Biopsy taken 11
days after exposure to the
chemical agent (x180).
Hematoxylin-eosin. Patient
C1.*



*Figure III-14 :
Electronmicroscopy : intra-
and extracellular edema,
K : keratinocyte. Patient
C2.*



*Figure III-15 :
Electronmicroscopy : basal
membrane (BM), basal cell
(B), mitochondria (M),
fibroblast (F). For
explanations see text.
Patient C2.*



4. TOXICOLOGICAL ANALYSIS

4.1. METHODOLOGICAL ASPECTS

A series of toxicological analyses on blood and urine samples was offered as a screening service by the Laboratory of Analytical Toxicology, School of Pharmacy, University of Ghent, Ghent, Belgium. Analyses were performed for several or most of the patients of groups C, D, E, K, L, N and P and for several other groups not discussed in this report (Heyndrickx, 1986). The methodology used has been described in the proceedings of two meetings organized by that laboratory (Heyndrickx and Van Den Heede, 1986; Heyndrickx et al., 1984a; 1984b).

Other laboratories repeated some of these investigations using more elaborate and refined procedures.

In the Prins Maurits Laboratory TNO, Rijswijk, The Netherlands, sulfur mustard and its main metabolite, thiodiglycol, were determined in urine using a technique based on the conversion of thiodiglycol into mustard with concentrated HCl. Deuterated thiodiglycol was added as internal standard, and the quantitative analysis was performed by a gas chromatography-mass spectrometry (GC-MS) analysis of the head space. The detection limit of the method is 1 ng/ml using 10 ml of urine (Wills et al. 1985; 1988).

A different analytical procedure for detection and identification was followed at the Laboratory of the NBC Department of the Technical Division of the Belgian Army, Vilvoorde, Belgium. After treatment with HCl to liberate thiodiglycol from its conjugated form, cleaning on Seppak C18, and evaporation to dryness, thiodiglycol was derivatized with pentafluoropropionic acid anhydride and analyzed by GC-MS. The detection limit of this method is 1 μg/ml.

The Institut für Medizinische Mikrobiologie, Infektions-und Seuchenmedizin of the Ludwig-Maximilians-Universität of München, München, Federal Republic of Germany (FRG) (Prof. Dr. B. Gedek), performed analyses for mycotoxins. Three methods were used starting with a cleaned and concentrated methanol extract of blood and urine. The first physicochemical method was based on N-methyl(bis) trifluoroacetamide derivatization and MS identification with a positive ionization. The second was a GC procedure using a flame ionization detector. The third method was a biological test in which the extract was applied to the skin of a guinea pig and the skin was examined for cellular necrosis, the dermatotoxic effect of mycotoxins. The detection limit of the combined methods was 10 ng/ml.

A similar derivatization and MS identification technique was applied at the Bundesanstalt für Fleischforschung, Kulmbach, FRG (Prof. Dr. L. Leistner) (Hofmann et al., 1984).

Mycotoxin analysis was also performed at the Chemical Defence Establishment, Porton, UK, using heptafluorobutryl derivatization and detection by GS-MS with selected ion monitoring and an electron impact ionization detector, with a detection limit of 1-5 ng/ml (Black et al., 1986).

4.2. ANALYTICAL RESULTS

4.2.1. Sulfhemoglobinemia

Negative in all blood samples.

4.2.2. Blood cyanide, plasma and urinary thiocyanate

The range of normal blood cyanide concentration was 0 to 10 $\mu\text{g}\%$ ($0-10 \times 10^{-5} \text{ g/dm}^3$). Results are not available for group C. Normal values were obtained in patients of groups K, L and P (total of 14 patients). Slightly increased values were obtained in the three patients of group E (20, 14 and 28 $\mu\text{g}\%$) and in four of the twelve patients of group D (D1, 14; D2, 16.5; D4, 39; and D5, 13.5 $\mu\text{g}\%$). The significance of these small increases is not clear. The nerve agent tabun, which has also been used in that conflict, contains cyanide but these patients showed no history or clinical signs of anticholinesterase poisoning. Moreover thiocyanate, the cyanide metabolite in mammals, was at normal levels in plasma and urine.

4.2.3. Blood arsenic

Normal blood arsenic concentrations were lower than 4 $\mu\text{g}\%$ ($<4 \times 10^{-5} \text{ g/dm}^3$). All results for groups C, D, E, K, L and P (total of 34 patients) were lower than 4 $\mu\text{g}\%$, except for patient D11 who had a value of 7.5 $\mu\text{g}\%$ upon arrival. Arsenic is one of the constituents of the vesicant lewisite. One slightly increased value of arsenic, however, is not enough to implicate lewisite as the causal agent in these patients. Analysis of samples from group A and P (total of 11 patients) at FOA 4 (Sweden) also revealed normal values.

4.2.4. Methemoglobin

Physiological concentrations of methemoglobin are 1 to 2 % of the total hemoglobin concentration. The clinical sign cyanosis occurs for values above 15 % (Hall et al., 1986). Patients of groups D, E, K, L and P (total of 29 patients) gave normal values with a maximum of 2.6 % in patient L3. Some higher values were reported for the patients of group C (5 patients), from 8.1 to 10.5 %. These values returned to within normal limits when the analysis was repeated the next and following days, so their significance is not clear.

4.2.5. Serum cholinesterase activity

According to the method followed in the screening laboratory, normal values are between + or -10 around a mean of 50; units were not given. Serum cholinesterase activity was rather variable in these patients. In group L (4 patients) the deviation from normal was between -8 and -13, in group E (3 patients) it was between -1 and -5; one of the 6 patients of group P was reported to show an inhibition of -16. In group C (5 patients) inhibitions of -4 but also increased activities up to +29 were reported; in group D all eleven patients were within -8 to +7 from normal, except D12 who showed an inhibition of -17. Of the four patients of group K patient K5 showed an inhibition of -25.

In patients of group N, serum cholinesterase activity was determined at the local laboratory. Among the 8 available data 4 were within normal limits, i.e. + or -33 % among the mean value; for the others inhibitions between -40 and -65 % from the mean normal value were found.

It has been argued by some that this evidence of butyrylcholinesterase inhibition is proof that these patients had been exposed to the nerve agent tabun. We do not support this

interpretation for the following reasons :

1. As already stated, these patients did not present a history or symptoms of acute poisoning by cholinesterase inhibitors. This is in accordance with the observations by the UN team of experts, who observed only a small number of casualties with signs of mild poisoning by a cholinesterase inhibitor, in contrast to the large number of vesicant casualties they witnessed. Moreover, these findings had no influence on the treatment applied in the European clinics (see chapter 4).
2. When butyrylcholinesterase activity was repeatedly measured in the same patients over many days, large fluctuations were observed; maximum inhibitions sometimes were obtained long after arrival, and did not have any clinical correlates. Examples are patient D7, +3 at arrival and -24 17 days later; and patient D5, -3 at arrival and -26 17 days later. These results raise questions about the reliability of the assay method used.
3. It is known that poisoning of rats with sulfur mustard produces up to 50 % inhibition of serum cholinesterase activity (Thompson, 1947; Vojvodic et al., 1985).

4.2.6. Sulfur mustard in blood or urine

The screening laboratory reported positive urinary results (said to be in the ppb range) for patients C3, C5, D6, E2, N1 and N2 and a positive blood result for patient K3. Borderline positive urinary results were reported for patients D2 and D12. The other patients and those of groups L and P were negative. These positive urine findings were unexpected since sulfur mustard has not been found in the urine of experimental animals, but is excreted in the form of metabolites, the most important of which is thiodiglycol, unchanged or conjugated (Davison et al., 1961; Roberts and Warwick, 1963).

Using the procedure developed at TNO (The Netherlands) no sulfur mustard could be detected in the urine of patients of groups B, C, D and I, which were collected immediately upon arrival at the European hospital. Thiodiglycol, however, was present. The following urinary concentrations were found :

- Below 20 ng/ml : patients B4, C5, D8, I2, I4.
- Between 20 and 90 ng/ml : patients B2, B3, B5-B9, C1-C4, D1, D2, D5-D7, I3, I5.
- High values : 333 and 125 ng/ml in patients D3 and I1.

Obviously, the method followed in the Laboratory of Vilvoorde (Belgium), which was less sensitive, did not detect thiodiglycol in the urine of patients of group C. The TNO laboratory, however, also detected thiodiglycol in control urine samples from other patients treated in the same hospitals and from laboratory personnel, in concentrations of about 5 ng/ml. In two control samples concentrations of 20 and 50 ng/ml were found. Therefore, the detection of thiodiglycol in urine samples cannot be accepted as proof for mustard gas exposure. Concentrations higher than 20 ng/ml, however, if in agreement with the clinical picture, have a strong indicative value.

Positive urinary results for sulfur mustard were also reported by Vycudilik (1965; 1986). It remains, however, unclear whether these observations reflected the excretion of unchanged mustard or of thiodiglycol (Vycudilik, 1965; Wills et al., 1988).

4.2.7. Trichothecene mycotoxins in blood and urine

In 1984 the screening laboratory reported positive mycotoxin findings for two of the five patients of group C and in one of the twelve patients of group N, and in several other patients not included in this report. Patient C3 was reported to have 0.54 ppm of diacetoxyscirpenol (DAS) in his blood; and patient N1, 0.15 ppm of nivalenol. Patient C5 was reported to have a urinary excretion of 0.13 ppm of HT-2. A GC procedure without MS identification was used. Later the results became negative for these patients. Negative results were found for patients in groups D, E, L, and P (total of 25 patients).

The positive mycotoxin findings were unexpected and inconsistent with the observations of the UN team. Hence, other laboratories tried to confirm these analyses. Samples from groups A and P, analyzed at FOA 4 (Sweden), were negative. Samples from group C were processed by the Chemical Defence Establishment (UK), and samples of group N by the

Institut für Medizinische Mikrobiologie, Infektions und Seuchenmedizin and by the Bundesanstalt für Fleischforschung (both FRG). These laboratories came independently to the same conclusions. Urine samples of group C and blood and urine samples of group N contained substances that, after extraction and GC processing, showed retention times that were identical to those of some of the trichothecene standards. However by MS it was shown that they were not mycotoxins. The last laboratory mentioned obtained similar results in samples taken from patients not covered in this study.

5. DISCUSSION AND CONCLUSION

5.1. SYMPTOMATOLOGY OF MUSTARD GAS POISONING

The official conclusions of the three UN missions confirmed the accusations formulated by Iran that chemical warfare agents, among them the vesicant sulfur mustard, had been used in the Iran-Iraq conflict (see chapter II). The casualties brought to Europe and described in this report had clearly been exposed to this vesicant, as shown above by the clinical picture and the laboratory investigations.

The clinical picture is very similar to the descriptions of mustard lesions found in the literature.

The literature data can be divided broadly in two categories. The more recent publications, although based on the older descriptions, are dominated by observations of animals and men exposed under experimental conditions to small droplets of mustard. Older data from World War I, however, are mainly based on clinical observations of casualties exposed to liquid and vapour mustard, either under field conditions or through accidents in manufacturing plants. Some important differences exist between the older and the more recent sources, and some of the old observations have been omitted in the more recent literature.

More recent reviews describe sulfur mustard lesions as follows (Stade, 1964; Fischbeck, 1969; AMedP-6, 1973; Klimmek et al., 1983) :

1) Local effects as a result of direct contact :

The penetration of mustard through mucosa and skin is without symptoms, and symptoms and lesions develop insidiously after an interval of one to several hours, which depends on the intensity of the exposure.

Eye symptoms are : pain, photophobia, blepharospasm, lacrimation, conjunctivitis, corneal lesions, blistering of the eyelids and periocular mucous membranes, and predisposition to secondary infections with suppuration.

The cutaneous syndrome that follows the latent period can be divided into three sequential phases that are a function of the dose (AMedP-6, 1973) :

- Erythema with itching (latent period 4-8 hours).
- Formation of vesicles and blisters (after 12-48 hours), continuing for several days before reaching a maximum. They contain a clear and slightly yellow liquid and rupture spontaneously, leaving erosive lesions.
- Necrotic lesions, generally after blister disruption but also without previous blister development, penetrating into the epidermis and dermis, and very sensitive to secondary infection with suppuration.

The most sensitive areas are the face, armpits, genitals, neck, skin between the fingers, and nailbeds. The palm of the hand, sole of the foot and skin of the scalp are very resistant.

In contrast, others described the cutaneous lesions as different clinical syndromes, which can exist independently or consecutively (Stade, 1964; Fischbeck, 1969; Klimmek et al.,

1983) :

- The erythematous form.
- Superficial blistering.
- Deep blistering.
- The ulcero-necrotic form.

Lesions of the respiratory tract develop with a delay of 4-6 hours. Irritation and congestion are seen in the mucous membranes of the nasal cavity, throat, trachea and bronchi. Nasal secretions, burning pain in the throat, and hoarseness and aphonia also are observed. A dry cough gradually changes to one with abundant expectorations. Fragments of necrotic epithelium obstruct the lungs, with atelectasis, dyspnea and secondary bronchopneumonia.

Gastrointestinal symptoms include nausea and vomiting, pain, bloody diarrhea and prostration.

2) Systemic effects after absorption and distribution :

Mustard acts at different sites in the body as a radiomimetic. The resulting symptoms are : headache, nausea, vomiting, anorexia, epigastric pain, leukopenia, thrombocytopenia and anemia.

Very high doses produce CNS excitation and convulsions, followed by CNS depression. They also produce cardiac irregularities, atrial-ventricular block, and cardiac arrest.

In general this description is applicable to the Iranian casualties discussed in this report, with the exception of the high dose systemic effects on the CNS and heart. These symptoms were absent in these patients, who had already survived the acute poisoning for several days.

Some observations, however, were different from those described above, and some of them could be interpreted only after the older literature from World War I was consulted. Therefore, it is necessary to complete our descriptions of sulfur mustard poisoning with clinical syndromes which are the result of exposure in battlefield conditions rather than in laboratory conditions.

The first discrepancy lies in the patient, accounts (see chapter II) that immediately or briefly after exposure they experienced a burning sensation in the eyes, a sensation of suffocation and loss of consciousness. The older publications do not mention these phenomena, a fact which might suggest, at first glance, an exposure to other vesicants, such as nitrogen mustard (2,2'.2"-tri(chloro-ethyl) amine; HN3), lewisite (2-chlorovinyl-dichloroarsine), or phosgene oxime (dichloroformoxime), for which the symptom-free interval is much shorter or absent (AMedP-6, 1973).

No traces, however, of these agents or their metabolites have been detected in environmental or ammunition samples from Iran (see chapter II), or in the toxicological analysis of biological fluids from the victims (see section III.4.2.), whereas sulfur mustard was detected in environmental and ammunition samples and its metabolite thiodiglycol in urine of casualties. Therefore, I suggest that some of the initial irritation symptoms should be ascribed to the combined effects of the explosion at short distance, and to the cloud produced at that moment consisting of a mixture of agent and dust. This means that early irritation should not automatically indicate an exposure to a substance such as lewisite.

A second aspect of the patients' accounts, the appearance of the first skin lesions when evacuees took their first shower and changed clothes, is probably best explained by the approximately equal durations of the symptom free-interval and the evacuation delay. It is interesting that the coincidence between showering and appearance of lesions was described after World War I (Vedder, 1925) and that, in 1918, Teulières even advised against bathing mustard victims since « the gas seems to operate only in the presence of water » (see Warthin and Weller, 1919).

Another important difference between our observations for the Iranian casualties and the more recent sulfur mustard literature is the absence in the latter of a prominent clinical picture in the Iranian casualties : darkening of the epidermis, followed by desquamation or exfoliation over areas of variable size. This process, which was exacerbated by pressure and friction, left areas with lesions of different degrees of severity. This syndrome is clearly described in the literature of World War I (Warthin and Weller, 1919; Reed, 1920; Vedder, 1925; Warthin, 1926), and of World War II (Alexander, 1947; Goodman and Gilman, 1941).

In 1917 Giraud (see Warthin and Weller, 1919) described late-developing burns in soldiers exposed in the field. These lesions were characterized by erythematous plaques resembling sunburn. The central portion desquamated after a time, leaving a slightly weeping surface without blister formation.

Warthin and Weller (1919; Warthin 1926) also described a similar picture in seven factory workers who were accidentally exposed to high mustard vapour concentrations while protected by gas masks. The lesions were erythematous plaques that did not vesiculate but did turn brown and even black, followed by desquamation or exfoliation of the superficial or whole epidermis in scales or flakes (Nikolsky's sign) over large areas, e.g., the whole back, leaving underneath regenerating epidermis or skin lesions of different degrees of severity.

Reed (1920) described a combination of severe conjunctivitis, skin exfoliation, and exfoliation in the nasopharynx after controlled exposure of humans to mustard vapour.

Von den Velden (1922) added a syndrome characterized by pigmentation and exfoliation to the four syndromes mentioned above.

Vedder (1925) wrote :

« After the second day, if blisters do not form, the deep red erythema gives place to a copperish, lavender or brownish color which finally becomes a dark or black pigmentation. When this pigmentation occurs it persists for several weeks, or until complete exfoliation of the epidermis. »

In 1947, Alexander gave an account of the accident at the harbour of Bari, where a large number of soldiers had been exposed to oil contaminated by mustard. He described a similar syndrome.

It thus appears that these dark exfoliative lesions, which are present after the exposure of large areas of skin to mustard dispersed under field conditions, in high vapour concentrations or dissolved in oil, are not observed in experimental exposures of human skin to small droplets of mustard. Therefore, these lesions have been omitted in current day handbooks. It is necessary that they be included again in teaching the symptomatology of sulfur mustard poisoning. With very few exceptions, mustard casualties will be due to accidental exposure or to the use of this agent on the battlefield.

5.2. REPRESENTATIVENESS OF OUR PATIENT SAMPLE

The present work tries to give a careful description of sulfur mustard lesions in patients exposed on the battlefield. Since this report is based on a limited number of clinical observations, it is important to compare these patients to other casualties treated elsewhere in Europe or in Iran, and to determine whether they are representative of the population of mustard gas casualties in Iran.

Several case reports about Iranian patients, some of whom are included in the patient sample in this report, have been published in the literature and in the UN reports (Balali and Navaein, 1986; Balali et al., 1986; De Keyser et al., 1986; Helm, 1985; Heyndrickx, 1986; Kaspar et al., 1985; Mandl and Freilinger, 1984; Pauser et al., 1984; United Nations, 1984; 1986; 1987). Through personal contacts I obtained additional information about

patients not included in this study (Helm and Maynard, personal communications). These sources of information are the basis for the following comparison.

In Iran about 1200 chemical casualties had been treated up to the time of the second UN mission in 1986. It is not known how many of these were mustard gas victims, although it may be assumed that they constituted the majority of these patients. The UN missions examined 41 patients and 6 corpses in 1984, 806 patients and 23 corpses in 1986, and 54 patients and 1 corpse in 1987. From these observations they gave brief descriptions of 116 patients with eye and/or skin lesions compatible with vesicant exposure. An additional 233 consecutive cases were described by Balali and Navaein (1986).

The general clinical description is similar to the clinical picture of the patients described in this report; in particular, the pigmented exfoliative syndrome is frequently mentioned. Table III-3 compares some of the clinical findings observed in these patient samples, as deduced from these different sources.

TABLE III-3 : Some comparisons between Iranian patients described in the literature and those discussed in this report. The total number of patients and the percentages of reported lesions are given. Airway lesions were counted whenever a respiratory symptom was mentioned.

1. This report.
2. United Nations, 1984.
3. United Nations, 1986.
4. United Nations, 1987.
5. Balali and Navaein, 1986.

TOTAL NUMBER	% CONJUNCTIVITIS	% CORNEAL DAMAGE	% SKIN LESIONS	% AIRWAY LESIONS
<i>Patients seen within 5 days after exposure</i>				
1. 23	87	65	100	65
2. 17	24	*	100	41
3. 11	36	*	82	36
4. 16	94	*	94	19
<i>Patients seen between 6 and 14 days after exposure</i>				
1. 38	84	50	100	76
2. 2	0	*	100	50
3. 20	95	*	100	65
4. 17	76	*	94	24
<i>Patients seen between 15 and 30 days after exposure</i>				
1. 4	75	25	100	50
2. 11	27	*	100	9
3. 9	78	*	100	44
4. 9	67	*	89	56
<i>Without information about the time interval</i>				
4. 3	0	*	33	100
<i>Patients seen within 5 days after exposure</i>				
5. 233	48	3	83	95

* Corneal lesions are not explicitly mentioned in the UN reports.

Besides the patients described in this report, about 107 other Iranian patients were hospitalized in European clinical centres in the same time period. As already mentioned, some case reports of these casualties have appeared in the literature, and information was gathered about other patients by personal communication. These information sources

clearly suggest that these patients were very similar to ours. In particular the severity of the poisoning was within the same range : the mortality in these 107 patients was 13 %, the same as the 14 % mortality in our patients (see table II-1 and chapter IV).

Finally, data of World War I show that 75 to 90 % of the mustard casualties developed eye lesions, and 10 % had corneal lesions which very rarely led to blindness (Vedder, 1925). Moreover, lethality caused by mustard in World War I is generally stated to have been around 2 % of the total number of casualties, and the same figure, 2 %, was mentioned in 1984 by Iranian physicians.

Therefore I conclude that the patients described in this report are representative of all the patients sent to European hospitals. Further, they showed a similar severity of poisoning as the victims described in the UN reports, but were likely among the more severely poisoned casualties that survived the immediate post-exposure period. It is reasonable that moderately to severely poisoned casualties were selected for examination by the UN experts and for secondary evacuation to Europe. Although I would have preferred to include more patients in this report, I believe that those described give a fair image of moderate to severe casualties after the use of sulfur mustard on the battlefield. The inclusion of all the European patients would not make this sample representative of all sulfur mustard casualties seen in Iran.

Table of Contents  **Next Chapter**

CHAPTER IV : TREATMENT PROCEDURES AND CLINICAL EVOLUTION

1. INTRODUCTION

On the basis of the background information, the medical history, the clinical observations at the time of admission, and the toxicological findings, I concluded (chapter III) that these casualties had been exposed to one chemical warfare agent, the vesicant mustard gas. This conclusion will be discussed again at the end of this chapter after further information about clinical course and autopsy findings has been given.

As already stated many uncertainties existed when the first patients arrived in Europe. This, together with a general lack of clinical experience, largely explains why several different treatment programs were applied. Moreover, a series of sophisticated techniques was available, e.g., for extracorporeal removal of chemical substances; these methods were applied in these cases without previous experimental testing.

Because of the complexity of the problems discussed in this chapter, several approaches were possible. I have chosen to describe separately the treatments for the different organ systems affected, and their healing processes, and to give an overall picture at the end. Whereas this approach has the advantage of linking the treatment to its healing effect, it has the disadvantage of neglecting the complex interplay of the different body systems during the healing process.

The overall treatment goals were as follows:

- To obtain the healing of the mucocutaneous lesions
- To avoid secondary infections, local and systemic, since they would interfere with the local healing process and be a serious threat for some of the patients that developed leukopenia
- To give general support, fluids, calories, oxygen and, if necessary, artificial ventilation and cardiovascular stabilization
- To eliminate the remaining poison from the body by applying artificial detoxification procedures. However, objective proof of the persistence of intact mustard gas in the living body and of its binding and removal by any chemical or physical means has not been provided.

2. MUCO-CUTANEOUS LESIONS AND TREATMENT PROCEDURES

2.1. TREATMENT OF THE EYE LESIONS

In nearly all cases of palpebral edema and erosions and of conjunctivitis, an antibiotic ointment was applied. It contained one of the following agents or a combination of them: tetracycline, chlortetracycline, oxytetracycline, chloramphenicol, gentamicin, neomycin, bacitracin and polymyxin B (groups A, B, C, D, E, I, K, L, N, P). In groups E, L and N the local steroid dexamethasone was added routinely.

When more severe lesions such as corneal erosions were present, atropine or homatropine (groups B, D, I and N) and penicillamine eyedrops (group D) were also used.

Patches were applied to the eyes of all patients of group K, and to the more severe cases in group D. In 1942, Hughes advised against closed eye treatment because of fear of adhesions.

2.2. TREATMENT OF THE SKIN LESIONS

2.2.1. Principles

Different local skin treatments were applied, but an initial classification can be made by identifying the goals for which they were used. The following goals were pursued : detoxification of possible remnants of the causal agent in the skin, disinfection of the skin lesions, protection against external noxious stimuli, promotion of healing and treatment of

pain or itching. Not all centres followed the same policy, as will be discussed in detail. Moreover, some systemic drugs were used in support of local treatment.

Detoxification :

In 1984 great emphasis was put on the possible persistence of the causal agent in the skin lesions. This issue is discussed in section IV.5. For this purpose chloramine was used, either as a solution of 0.2 or 0.3 % applied every two hours on wet dressings, or as a bath additive, 100 g to 600 l of water. This chloramine treatment is normally proposed for mustard lesions (Fischbeck, 1969).

Disinfection :

As in burn lesions, it was felt necessary to avoid any secondary infection; different means were used for that purpose. Chloramine has good disinfectant properties and was also used for that purpose. Because of its irritating properties, however, it was sometimes replaced by chlorhexidine hydrochloride (5 l of 5 % solution in a 500 l water bath). Povidone-iodine-containing soap was also used. A widely used << disinfectant >> was silver sulfadiazine cream. Other local disinfectants contained clioquinol, neomycin B, methyl violet, fuchsin, or resorcin.

Protection :

The application of wet dressings, washing or bathing, with or without the addition of disinfectants, facilitated cleaning of the lesions and removal of necrotic tissues.

After cleaning or disinfection the lesions were covered with dressings or left open to the ambient air. The last treatment generally was performed in a burn unit. In some cases the lesions were covered after bathing by protective creams containing different neutral or healing promoting substances, e.g., zinc oxide, panthenol and methyl salicylate. In some centres the healed skin lesions were further protected by ureum 5 % in cold cream (80 % lipid in an oil/water suspension).

2.2.2. Application

The aforementioned drugs were applied according to different treatment protocols :

- a. Wet chloramine dressings on all lesions, renewed every 4 hours. This allowed cleaning of the lesions and removal of dead tissue. This first treatment took between 2 and 6 days.

After this, silver sulfadiazine was applied on all lesions which were then covered by bandages. This treatment was continued till complete reepithelialization had occurred.

This scheme was followed for groups C and E.

- b. Similar treatment as in (a) but chloramine dressings were applied only to erosive lesions. Non-erosive lesions were treated throughout with silver sulfadiazine.

This scheme was followed for group D.

- c. Reserve of initial treatment in (b); chloramine was applied to non-erosive lesions and silver sulfadiazine to erosive lesions.

This scheme was followed for group K.

- d. Daily bathing of the patient in a chloramine-containing bath. After 3 days the chloramine was replaced by chlorhexidine hydrochloride.

After bathing the lesions were covered with a protective cream (zinc oxide/methyl salicylate), and left open to the ambient air.

This treatment was administered in a burn unit (group L).

- e. Wet isotonic saline compresses, sometimes with chlorhexidine added, applied on the erosive lesions and renewed every 2 to 3 hours in the first days.

Silver sulfadiazine on the non-erosive lesions.

Indifferent water-oil emulsions on desquamating superficial epidermal layers.

This treatment was followed for groups B and I.

- f. Washing of the deep lesions with povidone-iodine soap. Application of dressings, with adsorbent capacity, containing local disinfectant agents or neutral and healing-promoting agents.

Both treatments or only the second treatment were applied to patients of group N.

- g. Bathing of the patient every second day in tap water at 37°C, followed by open drying and the application of neutral protective dressings.

This treatment was administered in a burn unit (groups A and P).

In patients A4 and A5 Silver sulfadiazine was used from the second day on.

2.2.3. Healing process.

All lesions eventually healed. Reepithelialization proceeded to regeneration of full epidermis, generally with a very irregular pigmentation. In some cases scarring developed. It appears that the healing process and the final outcome were more dependent on the severity of the initial lesion than on the treatment applied. Therefore a description now follows of the healing process of the lesions described in chapter III.2 as observed in particular patients.

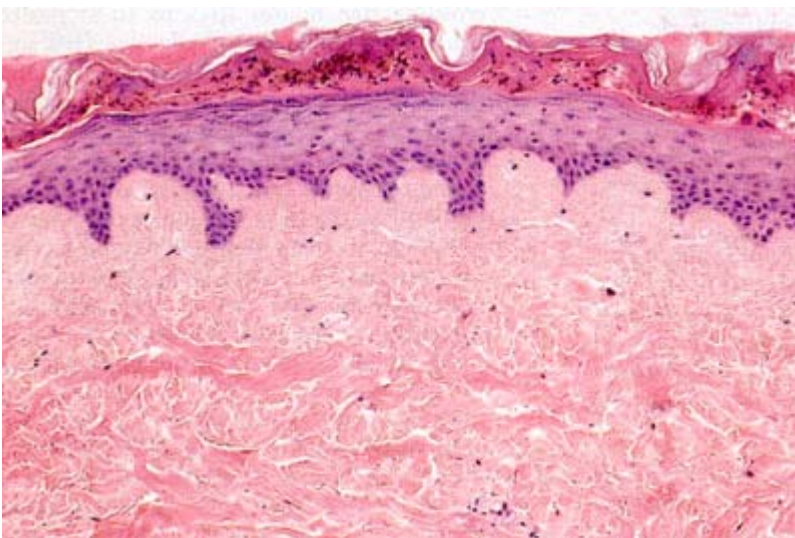
- The erythema observed on the 5th day after exposure (see [figure III-3](#)) gradually became gray-black at about the 15th day, desquamated and left a normal epidermis underneath ([figure IV-1](#)). A similar picture can be found in the Home Office Report of 1937. Histological examination showed that the upper necrotic epidermal layers desquamated when normal epidermis had regenerated underneath ([figure IV-2](#)). Some melanin, liberated from dead cells, precipitated in the lower part of the desquamating layer ([figure IV-3](#)), thereby contributing to the dark coloration of the skin. Part of the darkening is probably also produced by the epidermis which becomes necrotic and opaque before epidermolysis occurs.
- This irregular coloration, erosions, and scabs seen on the face (see [figure III-2](#)) completely healed but left some irregular pigmentation, as shown 28 days after exposure in [figure IV-4](#). This irregular pigmentation was a general characteristic of the healing process of different lesions.
- The pink surface appearing under the exfoliating epidermis (see [figure III-4](#)) healed rapidly from the skin adnexa, giving a dotted pigmented skin, as shown 15 days after exposure in patient D6 ([figure IV-5](#)). This patient also had shown an extensive exfoliation of the back on the 5th day.
- The yellow and white areas of deeper necrosis (see [figure III-4](#)) showed regeneration starting from the hair follicles and other skin adnexa ([figure IV-6](#)). This process is characterized by the development of small, red-brown epidermal spots that expand. This takes a rather long time, as shown in figures [IV-7](#) To [IV-10](#). They show the status of the lesions of the upper arm and shoulder region and of the back in patient C4 at 22 and 32 days after exposure. Epidermal regeneration in the belt region in patient D7 at 21 days after exposure is also shown ([figure IV-11](#)). As already mentioned, the irregular pattern of pigmentation is typical for this healing process.
- The large blisters and the underlying deep erosions (see figures [III-5](#) to [III-8](#)) healed from the surrounding epidermis. This surrounding epidermis developed a black coloration in some cases as shown on the hand of patient D7 on the 15th day ([figure IV-12](#)). In patient D4, slow ingrowth from the surrounding epidermis partially covered the lesion 49 days after exposure ([figure IV-13](#)). Full reepithelialization was obtained at about the 66th day, but beneath the thin,

transparent epithelium the dermal red vasculature could be seen ([figure IV-14](#)). At that time some limitation in the flexor movement of the fingers was observed; a local corticosteroid treatment was applied but it did not improve the situation. A similar reepithelialization is seen on the back of the left foot of patient D7 72 days after exposure ([figure IV-15](#)).

A different pattern of healing was observed on the hand of patient D7, which showed reepithelialization with no transparency 40 days after exposure ([figure IV-16](#)). A mixing of the two patterns is observed in [figure IV-17](#), which shows the healing of the smaller blisters on the right foot of patient D7 on the 66th day.

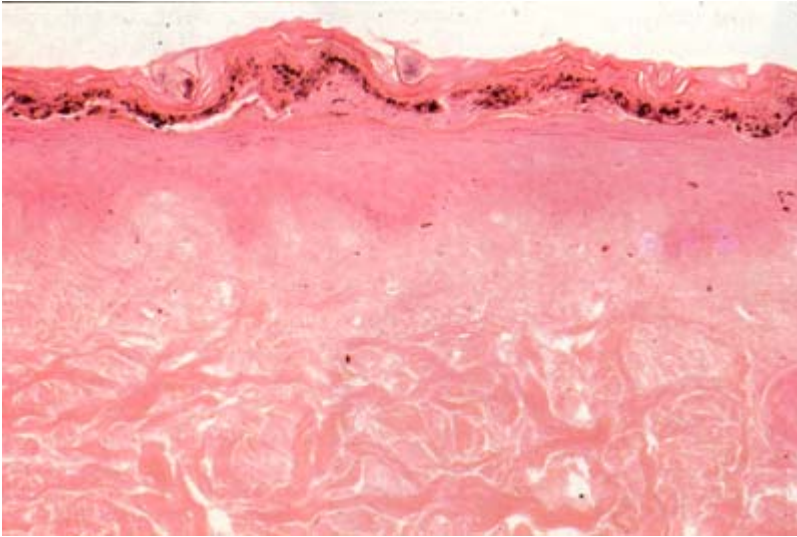


*Figure IV-1 :
Blackening of the skin and
desquamation of the
superficial layers, 15 days
after exposure. Patient D2.*



*Figure IV-2 :
Desquamation of the upper
necrotic epidermal layers,
with regeneration of the
underlying epidermal layers
(x180). Hematoxylin-eosin.
Patient D4.*

*Figure IV-3 :
Melanin dispersed in the
lower layers of the
desquamating epidermis.
At this stage no melanin is
seen in the regenerating
epidermal layers (x180).
Melanin coloration
according to Fontana.
Patient D4.*



*Figure IV-4 :
Healed skin of the face
with irregular
pigmentation, 28 days
after exposure. Patient D4.*



*Figure IV-5 :
Dotted pigmentation on the
healed skin of the back, 15
days after exposure.
Patient D6.*



*Figure IV-6 :
Regeneration of the
epidermis starting from the
hair follicles and skin
adnexa. Patient C1.*



*Figure IV-7 :
Regeneration of the
epidermis from the hair
follicles at 22 days after
exposure on the back and
shoulders of patient C4.*



*Figure IV-8 :
Regeneration of the
epidermis from the hair
follicles at 22 days after
exposure on the upper arm
of patient C4.*



*Figure IV-9 :
Nearly full epidermal
regeneration 32 days after
exposure on back and
shoulders of patient C4.
Note the irregular
pigmentation.*



*Figure IV-10 :
Still incomplete epidermal
regeneration 32 days after
exposure of the upper
arms of patient C4.*



*Figure IV-11 :
Epidermal regeneration of
the belt region, 21 days
after exposure. Patient D7.*



*Figure IV-12 :
Blackening of the skin
surrounding a deep erosive
lesion of the hand, 15 days
after exposure. Patient D7.*



*Figure IV-13 :
Partial reepithelialization of
a deep erosive lesion of the
hand, 49 days after
exposure. Patient D4.*



*Figure IV-14 :
Full reepithelialization of a
deep erosive lesion of the
hand, 66 days after
exposure. Patient D4. Note
the difference from figure
IV-16.*



*Figure IV-15 :
Full reepithelialization of a
deep erosive lesion of the
foot, 72 days after
exposure. Patient D7. Note
the similarity with figure
IV-14.*



*Figure IV-16 :
Full reepithelialization of a
deep erosive lesion of the
hand, 40 days after
exposure. Patient D7. Note
the difference from figures
IV-14 and IV-15.*



*Figure IV-17 :
Full reepithelialization of a
deep erosive lesion of the
foot, 66 days after
exposure. Patient D7.*



*Figure IV-18 :
Secondary blistering, 39
days after exposure.
Patient D5.*



2.2.4. Local complications

The skin lesions were rather painful, and during the healing process severe itching generally developed. Pain and itching were frequently most severe and most persistent at the genital region, particularly the scrotum. In some cases this was treated by local application of xylocaine gel (patients A1 , D1 and D8), a combination of xylocaine and prilocaine (groups A and P), or a local corticosteroid, flumethasone (groups L and N) or triamcinolone (group N). The local use of corticosteroids is advised by Fischbeck (1969), and has also been used by others (Kaspar et al., 1985). However, in animal experiments corticosteroids were shown not to have any effect on healing, although they diminished the initial edema (Vogt et al., 1984).

In nearly all cases systemic analgesics and antihistaminics were required to control pain and itching. The analgesics used were paracetamol (groups B, I and P), pethidine (group A), tilidine and fentanyl with droperidol (groups C, D, and E), pentazocine (groups D and E), pentazocine and diazepam (group N), morphine (group K) and noramidopyrine (group L). Morphine was administered as a continuous infusion. The antihistaminics were clemastine (group A), and dimethindene maleate (groups C, D and L), sometimes in combination with promethazine (group D). In groups B and I the hypno-sedative antihistaminic hydroxyzine was used.

These subjective complaints regularly remained present until the time of discharge from the hospital.

A peculiar phenomenon which developed in some deeper skin lesions during healing was the appearance of secondary blisters ([figure IV-18](#)). This was interpreted either as a mechanically induced lesion of the newly formed epidermis covering an incompletely healed dermis, or as an allergic reaction to silver sulfadiazine. Local treatment with a corticosteroid was without effect.

2.3. TREATMENT OF THE MUCOSAL AIRWAY LESIONS

The mucosal airway lesions, as observed by laryngobronchoscopy, were described in section III.2.1.4. They were classified as (necrotic) pharyngitis and laryngitis, bronchitis and bronchiolitis.

The following treatment procedures can be considered local therapies to clear the airways and improve mucosal healing.

In group D great emphasis was placed on kinesitherapy with tapotement and passive drainage of the secretions. This physical treatment was also used in other groups.

In groups K and L acetylcysteine was used as an aerosol primarily for its mucolytic properties. It was thought that it would also bind sulfur mustard if any remained. As already stated, no objective evidence exists for this hypothesis (see section IV.5).

Patients of group N received a corticosteroid spray. Patients N3, N1 and N10, however, had to be tracheotomized 5, 6 and 8 days later, respectively, because of the development of pharyngeal obstruction by pseudomembranes. They also received bronchial lavage with panthenol and a corticosteroid.

Patient N11 suddenly died of tracheal obstruction caused by pseudomembranes, and respiratory and cardiac arrest. Intubation and reanimation were unsuccessful.

In patient A5 a bronchial lavage was applied during bronchoscopy.

In patient K2 mechanical cleaning of the airways via a rigid bronchoscope, was applied. The third day after admission loosened mucosal pieces were removed but the result was not very satisfactory. One day later a purulent bronchitis was found, which was still present after 4 days.

In some cases systemic drugs were added to the therapeutic drug regime : the bronchodilators aminophylline (patient C1), diprophylline (patients L3 and L4), theophylline (patients B6, B8 and B9), fenoterol hydrobromide (patients K2 and K5) and terbutaline (patients B6 and B8), and the antitussive dextromethorphan and the expectorant ammonium chloride (patient C5).

The healing time of the upper and lower airways could be judged directly in some patients in whom the bronchoscopic examination was repeated at several times during hospitalization. In patient K2 the airways were cleared 15 days after the mechanical cleaning, i.e., 23 days after exposure and the mucosal lesions were cicatrized. The oropharyngeal lesions in group N healed by about 30 to 40 days after exposure. The deep bronchial lesions in this group healed within 20 to 50 days after exposure. The tracheostomies in patients N1 and N10, however, produced tracheal strictures when healed.

Indirect indicators for the anatomical and functional recovery of the airway mucosa were the quantity and quality of the expectorations. Expectorations and coughing remained present for a rather long time, and several patients still complained of them at the time of discharge from the hospital.

Intimately linked to the healing process of the bronchial mucosal lesions was the occurrence of lung infections, which had direct repercussions both on ventilation and oxygenation and on final recovery of ventilatory function. These aspects are discussed in section IV.3.2.2., on systemic infections and artificial ventilation.

2.4. RECOVERY AND SITUATION AT THE TIME OF DISCHARGE

Eyes :

Eye treatment lasted between 3 and 28 days, after which complete healing was obtained in most cases, although there was still some photophobia at the time of discharge from the hospital. In four cases keratitis punctata, i.e., the presence of small epithelial defects of the cornea, was diagnosed clinically and confirmed by slit-lamp biomicroscopy after hospital stays of 21 (patient N5), 28 (patient N4), 66 (patient D2) and 71 (patient D7) days. Patients N6-N10 still had some infiltration of the corneal epithelium, at the level of the eyelid cleft, when they left the hospital 46 to 60 days after exposure. Patient N2 had a temporal symblepharon at the right eye.

This clinical course is in agreement with previous observations : healing times of 2 weeks for mild conjunctivitis, 4-5 weeks for severe conjunctivitis, and 2-3 months for corneal

lesions (Reed, 1920; Hughes, 1942; Alexander, 1947).

Skin :

The descriptions given above are representative for the clinical course of patients of the different groups, and for the condition of the skin lesions at the time of discharge. Indeed, recovery of the skin lesions was the major determinant of the duration of the hospital stay. As can be deduced from the above descriptions, full reepithelialization was obtained, generally with an irregular pattern of pigmentation, some itching and, in a few cases, scarring with retraction and limitation of movement. Patient N2, for example, had a large area of retracting scarring peri-orally, limiting the opening of the mouth.

Table IV-1 lists in more detail the time required for healing of the superficial and deep lesions in the different patient groups. In presenting this table, it is not my purpose to make any inter-group comparisons or to relate the healing time to the treatment applied. This information about the approximate duration of the healing process could be of interest for planning purposes. It might be also of interest to compare this table with the total duration of hospitalization given in table II-1.

TABLE IV-1 : Number of days since exposure within which superficial or deep skin lesions healed in all (surviving) patients of the different groups.

GROUP	SKIN LESIONS	
	SUPERFICIAL	DEEP
A	14	
B	14	40
C	16	34
D	17	65
E		35
I	14	40
K		50
L		20
N	20	
P	<28	>65

Airways :

Because of the interaction between the local mustard lesions and the secondary infections, the final ventilatory condition of the patients at the time of discharge is discussed in section IV.3.3.

3. ANTIBIOTICS : LEUKOPENIA AND SYSTEMIC INFECTIONS

Table IV-2 lists the patients from the different groups who developed leukopenia and/or systemic infections, i.e., septicemia, bronchitis or bronchopneumonia (see sections IV.3.1 and IV.3.2 for further explanations).

TABLE IV-2 : Occurrence of leukopenia and/or systemic infections requiring systemic antibiotic therapy.

PATIENT	LEUKOPENIA	SEPTICEMIA	LUNG PATHOLOGY	DEATH
A1	+	+		

A2	+	+		+
A3	+	+	+	+
A5	+	+	++	+
B3		+		
B4	+			
B5		+	++	+
B6	+	+		
B8	+	+	+	
B9	+	+	+	
C1	+	+	++	+
C2		+	+	
C3		+		
C4	+	+	+	
C5		+	+	
D2			+	
D3	+	+	++	+
D4	+	+	++	
D5	+		+	
D6	+			
D7	+	+		
D12	+			
E1		+		
E2	+	+		
E3			+	
I1	+	+		
I2		+		
I3	+			
I4	+	+		
I5	+		+	
K1	+	+	++	+
K2		+	+	
K3			+	
K5		+	+	
L3			+	
L4			+	
N1		+	+	
N3		+	+	
N4	+	+		
N5		+		
N6		+		
N11	+	+		+
N12	+	+		
P2	+	+	++	+
P3	+			
P4	+			
P5	+			

3.1. LEUKOPENIA

Leukopenia occurred in 29 of the 65 mustard casualties. In two patients, D3 and K1, it was accompanied by total bone marrow aplasia. Both patients died and no recovery of white cell number was seen. Bone marrow biopsy was also performed in patients A1, C1, C2 and C4; it revealed a normocellular marrow and a slightly maturation disturbed granulocytopenia, with relative lymphopenia. Bone marrow examinations in patients of group N showed similar observations with a slight hyperplastic erythropoiesis and relative pigment deficiency, which was interpreted as a reaction to the toxic and infectious insults.

It seems that two opposing phenomena occur simultaneously, a reactive leukocytosis and a direct bone marrow depression. This might explain that in several patients the white cell count remained within normal limits or increased only slightly, despite secondary infections, and that in patients I3, I4 and I5 a biphasic leukopenia was observed. Another sign of a reactive bone marrow was the thrombocytosis that was normally seen during the recovery period.

Table IV-3 gives the time course and the degree of leukopenia.

In 9 other patients an isolated lymphopenia was observed (B2, B3 and B5, C2, I2, K2, K3, K5, N5).

Prophylactic, selective gut decontamination was applied in all patients of groups B and I.

Selective gut decontamination using oral antibiotics, in combination with systemic antibiotics, was started in patients A2, A3, P3, and in patients of group D at the time the leukopenia was observed. Patients D6 and D12 were exceptions, the first because his clinical condition was rather good, and the second because the leukopenia that had been detected in Iran, was no longer present at the time of hospitalization in Europe. In most cases leukopenia was accompanied by a systemic infection.

TABLE IV-3 : Occurrence and time course of leukopenia. Number of days since exposure to the chemical agent : d1, the first time the number of leucocytes dropped below 4000/ μ l; d2, time of minimum; d3, recovery > 4000; n : lowest number reached (/ μ l).

PATIENT	d1	d2	d3	n
A1	13	15	19	900
A2	*	11	—	0
A3	11	14	16	100
A5	*	9	—	200
B4	13	14	17	1800
B6	9	11	13	1000
B8	10	10	11	2600
B9	9	9	11	1400
C1	13	14	—	200
C4	*	10	11	3200
D3	*	6	—	0
D4	8	9	11	1500
D5	7	9	21	400
D6	13	13	15	3700
D7	8	9	15	1200
D12**	9	11	15	1400
E2	10	11	17	1000
I1**	2	3	4	2000

I3	4	5	12	2100
	20	25	31	1600
I4	14	14	15	3000
	16	16	17	2100
I5	11	12	14	1400
	18	18	20	2000
K1	6	9	—	100
N4	*	*	<21	800
N11	6	6	—	200
N12	8	8	11	3700
P2	*	+	—	+
P3	*	+	+	+
P4	*	+	+	+
P5	*	14	<20	3000

* present at time of admission

** observations found in the Iranian clinical file

— lethal outcome without recovery of leukopenia. Patients A2, A3, A5, C1, D3, K1, N11, and P2 died

+ data unknown.

The following oral drugs at appropriate doses were used in different combinations : colimycin sulfate, neomycin sulfate, amphotericin B, sulfamethoxazole and trimethoprim, nystatin, and miconazole nitrate.

In some cases blood or white cell transfusions were performed.

Data for other patient groups are shown for comparison (table IV-4).

TABLE IV-4 : Percentages of leukopenia and isolated lymphocytopenia reported in other patient groups.

GROUP	LEUKOPENIA	LYMPHOCYTOPENIA
UN mission 1984	23 %	7 %
UN mission 1986	8 %	
UN mission 1987	2 %	
Balali and Navaein 1986	1.5 %	
Mandl and Freilinger 1984	100 %	

Our figures of 45 % and 14 % are rather high, but it is quite certain that, at least in the UN reports, all cases were not reported. Indeed the UN inspections did not follow the patients in time. The comparative data confirm, however, that our sample represents more serious cases.

It is of interest that older observations report that leukocyte counts started to drop on the third to fourth day after exposure (Alexander, 1947) and that a minimum was obtained at 9 days (Krumbhaar, 1919; Krumbhaar and Krumbhaar, 1919). Alexander (1947) further states that cell counts of $100/\mu 1$ or below were recorded and that all patients with

extremely low leukocyte counts died. In our series also, all patients who had minimum counts of 200 cell/ μ l or less died.

3.2. SYSTEMIC INFECTIONS

The most important systemic infections were septicemia, secondary infection of the upper and lower airways and bronchopneumonia.

3.2.1. Septicemia

Septicemia was a rather serious complication for these potentially immunocompromised patients. Its time course and bacteriological findings are listed in table IV-5. In this context septicemia is defined as a clinical episode characterized by an acute temperature peak, shivering, a small decrease in blood pressure and tachycardia. If the repercussion on the cardiovascular system was important, i.e. a profound fall in blood pressure, increase in central venous pressure and oliguria or anuria, the diagnosis of septicemic shock was made. For both episodes the time interval when it occurred is indicated as number of days since exposure to the chemical agent. The bacteriological analysis of the blood sampled at the time of these episodes is given. Asterisks denote results that were obtained on at least two occasions. When tables IV-3 and IV-5 (to IV-8) are compared it becomes clear that the systemic infections were not necessarily concomitant with leukopenia and bone marrow depression. The possibility that the septicemia in some patients was correlated with the application of hemoperfusion is discussed in section IV.5.2.

Some patients showed a good general clinical condition despite a positive hemoculture (table IV-6). These positive cultures may have been produced by contamination of samples by skin organisms.

All patients with septicemia received adequate antibiotic support. As soon as possible, the choice of antibiotic was based on the antibiogram determined in the bacteriological laboratory. The choice of the antibiotics was also determined by the results of sputum analysis since several of these patients also had lung complications (see tables IV-7 and IV-8).

Cardiovascular shock was treated according to the procedure normally used in the hospital, using cautious fluid replacement, intravenous dopamine and/or noradrenaline, and high dose corticosteroids. In patient B8 the shock was due to bleeding from a gastric ulcer.

Patient A2 developed cardiac arrest during an infusion of white cells. He was resuscitated but died in cardiovascular shock one day later. This patient was ventilated because of respiratory insufficiency without clear pulmonary pathology.

Patients A3, A5, C1, D3, K1 and P2 also died in cardiovascular shock, but they had developed a manifest lung pathology. Patient N11 died in cardiac arrest because of acute tracheal obstruction by pseudomembranes. Patient B5, who was ventilated for a long period, suddenly died, probably because of a pulmonary emboly. These patients are described further in the next section.

TABLE IV-5 : Septicemia, characteristics.

d1-d2 : start and end of septicemic symptoms (see text).

CV shock : occurrence of severe cardiovascular repercussions, with start and end.

Hemoculture : laboratory result.

PATIENT	TIME COURSE d1-d2	CV SHOCK (TIME COURSE)	HEMOCULTURE
A1	13-19		<i>Staphylococcus aureus</i> <i>Pseudomonas</i>
A2	10-12	11-12	negative
A3	12-16	13-16	Gram (+) and (-) rods

A5	9-13	10-13	Gram (-) cocci negative*
B3	9		<i>Staphylococcus aureus</i> Diphtheroid rods
B5	15-19		<i>Staphylococcus aureus</i> *
B6	11-18		<i>Staphylococcus</i> <i>epidermidis</i> * Enterococcus
B8	24-27	24	Propionibacterium
B9	10-16		<i>Staphylococcus aureus</i> * <i>Enterobacter cloacae</i>
C1	11-15	14-15	<i>Serratia liquefaciens</i> <i>Staphylococcus aureus</i> * <i>Pseudomonas</i> <i>aeruginosa</i> *
C2	13-19		<i>Staphylococcus aureus</i> * <i>Serratia liquefaciens</i>
C3	10-19	14-15	<i>Staphylococcus aureus</i> * <i>Serratia liquefaciens</i> * Streptococcus D* <i>Klebsiella pneumoniae</i> <i>Escherichia coli</i>
C4	10-17	14	<i>Staphylococcus</i> <i>epidermidis</i> * <i>Staphylococcus aureus</i> Streptococcus D* Enterococci
C5	14-21		<i>Serratia liquefaciens</i> Aspergillus
D3	5-6	6	not done
D4	7		Streptococcus D Lance
D7	9		negative
E1	10-13		<i>Staphylococcus aureus</i> * <i>Streptococcus fecalis</i> *
E2	11-13	11-13	negative
I1	12-14		<i>Staphylococcus aureus</i>
I2	9-13	8	negative
I4	14-15		negative
K1	11-12	12	<i>Pseudomonas</i> <i>aeruginosa</i>
K2	5		<i>Staphylococcus albus</i>
K5	16-17		<i>Klebsiella pneumoniae</i>
N1	11-16		<i>Staphylococcus aureus</i> *
N3	9-11		<i>Staphylococcus aureus</i> Enterococci <i>Acinetobacter</i> <i>calcoaceticus</i>
N4	21-24		<i>Staphylococcus albus</i>
N5	12-15		negative
N6	4-8		not done
N11	6-7	7	negative
N12	5-11		not done

* Obtained on 2 or more separate occasions.

TABLE IV-6 : Bacteriemia, characteristics.
d1-d2 : start and end of positive hemocultures.
Hemoculture : laboratory result.

PATIENT	d1-d2	HEMOCULTURE
B2	7-13	<i>Staphylococcus epidermidis</i> * Enterococcus
B4	13-18	<i>Staphylococcus aureus</i> *
B8**	13-15	<i>Staphylococcus epidermidis</i>

* Obtained on 2 or more separate occasions.

** Different episode from that in table IV-5.

TABLE IV-7 : Bronchopneumonia, time course and bacteriological findings (patients not receiving artificial ventilation).
d1-d2 : start and end of lung infection.

PATIENT	TIME COURSE d1-d2	SPUTUM CULTURE
B8	7-30	<i>Staphylococcus aureus</i> <i>Haemophilus influenza</i>
B9	12-14	<i>Staphylococcus aureus</i>
C2	19	<i>Klebsiella pneumonia</i>
C4	10-22	mixed flora
C5	10-15	mixed flora
D2	5-9	<i>Haemophilus influenza</i> Aspergillus
D5	9-19	mixed flora
E3	10-15	<i>Haemophilus influenza</i> <i>Streptococcus pneumoniae</i> a-hemolytic streptococcus Neisseria
I5	13-15	<i>Haemophilus influenza</i>
K2	5-14	<i>Haemophilus influenza</i>
K3	5-14	<i>Haemophilus influenza</i>
K5	16-28	<i>Haemophilus influenza</i>
L3	6-12	Hemolytic streptococci <i>Staphylococcus epidermidis</i> <i>Streptococcus viridans</i>
L4	9-11	<i>Pseudomonas aeruginosa</i>

3.2.2. Lung pathology

A first series of patients showed minor respiratory symptoms at the time of admission (see chapter III). They had an uncomplicated recovery and needed no systemic antibiotic treatment.

A second series, at first glance similar to the previous one at the time of admission, developed secondary lung lesions of different degrees of severity during hospitalization. The mustard-induced bronchitis and bronchiolitis became complicated by secondary infection, characterized by coughing, expectorations, auscultatory symptoms, chest X-ray abnormalities, low normal PO₂, and positive sputum cultures. Table IV-7 lists the bronchopneumonic complications with their time course expressed as number of days since exposure to the chemical agent. For several patients this was part of the general systemic lesions they developed (see table IV-2). It is possible that the rigid bronchoscopy and mechanical cleaning performed in patient K2 (see section IV.2.3) facilitated the appearance

of an infection in this patient.

As already stated above, antibiotic treatment was administered; the choice of the antibiotic was guided as soon as possible by the antibiogram. Several of these patients received supplementary oxygen via nose catheter. All patients recovered. One patient, E3, suddenly developed a spontaneous pneumothorax on the 12th day; with proper treatment the lung was fully expanded again the 15th day.

A third series of patients developed lung lesions serious enough to produce ventilatory insufficiency requiring artificial ventilation (table IV-8).

Patients A3, A5, D4 and P2 were ventilated shortly after admission because they developed a bronchopneumonia serious enough to impede gas exchange. As already mentioned, patients A3 and A5 also developed septicemia and cardiovascular shock, and eventually died despite the intensive care they received. Patient P2 showed increasing airway resistance during ventilation which could not be overcome by technical means. He died in cardiac arrest. Patient D4 received ventilatory support and systemic antibiotics during two weeks, and he recovered.

Patient C1 showed moderate lung lesions, similar to the second group described here, which, together with the other systemic effects, justified systemic antibiotic therapy. As a result of the leukopenia and sepsis, however, his cardiovascular condition deteriorated with the development of adult respiratory distress syndrome (ARDS). This was characterized by increasing PCO₂ and decreasing PO₂, necessitating artificial ventilation (7-8 l of air/min) with supplementary O₂ (5 l/min) and positive end-expiratory pressure (PEEP). As a result of this he developed a pneumothorax. Despite intensive treatment he died on the 15th day.

Patient B5 developed a severe bronchiolitis obliterans, diagnosed on the basis of a relatively larger increase in PCO₂ than decrease in PO₂. He had to be ventilated because of exhaustion after a period of spontaneous hyperventilation. The ventilation parameters needed, including PEEP, amplified the already existing hyperinflation, provoking multiple large bullae visible on chest X-ray. The clinical course was complicated by the occurrence of several pneumothoraxes, both sequential and simultaneous. Because of the existence of interpleural adhesions, sometimes several pleural drains had to be installed simultaneously. When his clinical condition eventually improved, and a progressive withdrawal from the respirator was planned, he suddenly died, probably because of pulmonary embolism.

TABLE IV-8 : Lung infections in patients requiring artificial ventilation; time course and bacteriological findings.

d1-d2 : start and end of the infection.

d3-d4 : start and end of the ventilatory support.

PATIENT	TIME COURSE		SPUTUM CULTURE
	d1-d2	d3-d4	
A3	11-16	12-16	
A5	** -13	9-13	
B5	13-19 25-185	30-185	<i>Staphylococcus aureus</i> <i>Haemophilus influenza</i> <i>Haemophilus hemogl. phi.</i> <i>Pseudomonas</i> <i>Acinobacter anitratum</i>
C1	10-15	14-15	<i>Staphylococcus aureus</i>
D3	** -6	5-6	not available
D4	7-18	7-18	<i>Haemophilus influenza</i>
K1	** -12	5-12	<i>Staphylococcus aureus</i> <i>Haemophilus influenza</i> <i>Pseudomonas aeruginosa</i>

P2	**--+	+	<i>Staphylococcus aureus*</i>
* Obtained on 2 or more separate occasions	** Lesion already existing at the time of admission	+ Data unknown.	

Patients D3 and K1 needed ventilation and systemic antibiotics from the time of admission because they developed ARDS, with increasing PCO₂ and decreasing PO₂, despite ventilation with large volumes of air and oxygen and of PEEP (20-30 cm H₂O). Patient D3 was ventilated under heavy sedation with fentanyl and pancuronium. A general deterioration of his clinical condition, with agranulocytosis, septicemia and ventilatory problems, led to a rapid lethal outcome. Patient K1 was ventilated for four days, after which spontaneous ventilation was tried since he struggled against the ventilator, but cardiac arrest followed. Cardiac resuscitation was successful but artificial ventilation had to be continued, and the patient eventually died in septic shock.

On the basis of antibiotic sensitivity of the organisms identified by blood culture and sputum analyses, antibiotics belonging to the following groups were applied in the different patients described above : penicillins, carboxypenicillins, aminopenicillins, cephalosporins, aminosides, tetracyclines, sulfamides and trimethoprim and vancomycin.

A brief comparison with other patient groups shows a 34 % occurrence of moderate to severe lung complications in our group, but of only 1.2 % in the series of Balali and Navaein (1986), indicating again that the more severe cases were sent to Europe. Lung complications were reported in 24 % of a group of 692 casualties observed for 4 months during World War I (Vedder, 1925). Finally, besides case B5, another casualty brought to Europe, but not included in this study, had to be ventilated and died 168 days after exposure (Helm, personal communication).

3.3. RECOVERY AND SITUATION AT THE TIME OF DISCHARGE

As already mentioned most patients recovered, with the exception of one with acute airway obstruction (N11), one with septicemia and shock (A2), two with lung pathology (B5, P2), and five with lung pathology, septicemia and shock (A3, A5, C1, D3 and K1). With the exception of patient B5, they all showed a severe leukopenia, indicating the primary importance of the lung effects and the systemic effects in mustard poisoning.

Table IV-3 shows that recovery from leukopenia was rather rapid. With appropriate antibiotic treatment the systemic infections were cured in an acceptable time in the surviving patients, as indicated in tables IV-5 and IV-7.

Some of patients discussed in table IV-7 still experienced some coughing and expectoration at discharge from the hospital, but were without chest X-ray abnormalities.

As stated in the discussion of the skin lesions, it is impossible to relate the final outcome to the treatment applied. The groups are too small to make any inter-group comparison possible. It is impossible to determine from this sample of casualties whether the prophylactic use of antibiotics and systemic corticosteroids (Fischbeck, 1969), or of systemic antihistamines and corticosteroids (Vojvodic et al., 1985), had a beneficial effect.

Lung function tests were performed in patients of groups E, K and N. Patient E1 and patients of group N, who remained without lung complications, showed a completely normal picture.

Of the patients with lung complications, K2 and K5 showed an obstructive syndrome. The lung function results obtained in patients E2 and E3 were hard to interpret, which might be due to faulty execution of the test because of language problems.

4. GENERAL TREATMENT, COMBINED INJURIES AND GENERAL CLINICAL EVOLUTION

4.1. NONSPECIFIC GENERAL SUPPORTIVE THERAPY

General supportive treatment was determined both by the condition of the patient and the clinical service to which he was admitted.

Patients of groups C, K, E and N were first admitted to an intensive care unit and received almost routinely the following general therapy :

- Prophylaxis against stress ulcer using H₂ antihistaminics, cimetidine or ranitidine, or local protection with Mg and Al salts.
- Prophylaxis against deep venous thrombosis with subcutaneous heparin.
- General support using high doses of vitamins C, B₁₂ and folic acid.
- General protection against tissue damage, usually with a single injection of 2 g of methylprednisolone.

Patients of groups B and I, also admitted to an intensive care unit, were treated symptomatically. Some of them received magnesium oxide as a prophylaxis for gastric ulcers.

Patients of groups A, L and P were admitted to a burn unit. They received high doses of vitamins as a general supportive treatment. Cimetidine was given to patient L4.

Patients of group D, who were admitted to a dermatological ward, did not routinely receive general supportive therapy. However, some of these patients received supportive therapy when, because of deterioration of their clinical condition, they were transferred to the intensive care unit (D4) or to the burn unit (D5, D7).

Ascaris lumbricoides was detected in some of the patients of groups B and D : they received a three day treatment with mebendazole.

4.2. INTRAVENOUS FLUIDS AND ORAL FEEDING

In groups A, C, D, K, L and P the policy was to provide an intravenous catheter to allow gradual rehydration, the administration of intravenous drugs, the administration of albumin solutions in the case of hypoalbuminemia, and the administration of blood or white cells if needed. Except for those who were ventilated, all other patients were orally fed.

Patients of group B, I and N first received complete parenteral feeding, followed as soon as possible by oral feeding.

In group E it was initially thought that hyperalimentation, together with fluid replacement calculated, as in classical burn therapy, from the area of the skin lesions, would be beneficial to the patients. A subclavian catheter was therefore inserted. After a few days, however, hypervolemia developed. The diuretic furosemide was given and the amount of intravenous fluid was limited.

4.3. COMBINED INJURIES

It is remarkable that very few patients had conventional war wounds in addition to the vesicant lesions. Indeed, in our series only patients D3 and D10 showed an additional lesion, respectively large penetrating wounds in the left leg and left upper arm, and a metallic fragment in the distal phalanx of one of the fingers of the right hand. Patient D3 died too soon to evaluate the healing of these wounds, whereas in the clinical files of patient D10 no further information was found about his finger wound. Therefore, the possible interference of the alkylating sulfur mustard with wound healing cannot be evaluated.

Further, it is impossible to decide whether this absence of combined injuries is due to

selection bias in sending preferentially pure mustard gas casualties to Europe, or whether this chemical warfare agent had been used mainly without concomitant conventional weapons.

4.4. RECOVERY AND GENERAL CONDITION AT THE TIME OF DISCHARGE

The recovery of the general clinical condition is the sum of the healing of the individual systems, and of their repercussion on the general well-being of the patient.

The healing of these individual systems, i.e., eyes, skin, airway mucosa, bone marrow, and systemic infections with septicemia and lung lesions, has been described in detail in this chapter. Some remaining lesions were present in some patients at the time of discharge, especially skin abnormalities and an obstructive airway syndrome with some coughing and clear expectorations. Nevertheless, almost all patients were in good general health at the time of discharge and return to their country. As an almost general rule it can be said that the duration of the hospital stay was mainly determined by the healing time of the skin lesions. Table II-1 gives the total duration of hospitalization for individual patients.

As far as the fatalities are concerned, more information about the autopsy findings is given in section IV.6.

It would be of interest to follow these patients over the years, to relate their subsequent medical history to the degree of poisoning. This was impossible for us because of the return home of our patients. A more general follow-up has been started by Balali (1986a), who described the following medical problems over 2 years in 236 mustard victims :

- 78 % showed complications of the respiratory tract, mainly chronic bronchitis and asthma-like symptoms.
- 45 % showed CNS complications, mainly neurosis, depression, and personality disorders.
- 41 % showed skin abnormalities, mainly abnormal pigmentations.
- 36 % showed eye abnormalities, mainly chronic conjunctivitis; 2 patients showed blindness.
- 33 % showed allergic reactions, mainly pruritus.
- 23 % showed gastrointestinal dysfunctions.
- 14 % showed a loss of libido.

5. QUESTIONS ABOUT THE PERSISTENCE OF MUSTARD GAS AND THE USEFULNESS OF LOCAL AND SYSTEMIC DETOXIFICATION PROCEDURES AT THE TIME OF ADMISSION IN THE EUROPEAN CLINICS

5.1. POSSIBLE PERSISTENCE OF MUSTARD GAS ON OR INSIDE THE CASUALTY

No detection devices for residual chemical contamination were used when the patients described in this report arrived at the different airports or hospitals. In 1986, however, patients arriving at London airport were monitored by the British Health Authority using the Chemical Agent Monitor (CAM, CDE Porton), a preselected selective ion detector instrument. The same device was also used by the UN team at their second and third missions to Iran. In 5 patients, on a total of 48 examined (mustard casualties and others), positive readings were obtained when the device operated in the H mode (i.e. selective for mustard gas). No positive readings were obtained in the nerve agent mode. These patients arrived approximately 6 to 8 days after exposure to the chemical agent. The vapour concentration detected is quantitatively expressed as 1 to 8 bars; 8 bars correspond approximately to 10 mg/m³ of mustard gas (De Bisschop, personal communication). A 3 to 8 bars reading was obtained over the bandages, the hair and the skin. In one patient, who showed a 8 bars positive reading over the back, no apparent skin lesions were present. No positive readings were obtained on accompanying personnel or in the cabin atmosphere.

These findings would strengthen the fear for the persistence of mustard gas on the skin or clothing of the victim, even several days after contamination. It is, however, quite certain

that, within the prevailing working conditions, these observations were not clinically important. The readings were obtained nearly at the skin surface, and not in the surrounding atmosphere, and the corresponding vapour concentrations were too low to produce any skin lesion by contact or any eye lesion by short time exposure.

Indeed, a major argument against the danger of this kind of potential contact is that no single case of secondary contamination, and subsequent development of lesions, has been documented in flight attendants or in European hospital personnel who were involved in the handling and treatment of these casualties. Even handling of the bandages and touching of the skin of the CAM positive patients did not provoke any skin lesion.

Because of the absence of back lesions on the patient whose back gave a positive reading, it can even be questioned whether the CAM detected residual vapour of an originally high mustard contamination of the skin. The possibility exists that some substance, interfering with the detection method, had contaminated the patients later on. A definite identification of the origin of the positive signal has not been obtained, but it remains interesting that at least in one case positive confirmation was obtained for a mustard gas like compound by a Residual Vapour Detector Kit (CDE, Porton).

A second important question regards the questionable persistence of mustard, in the skin and systemically, in the casualty several days after the exposure.

Eighty percent of a small amount of liquid sulfur mustard applied on human skin evaporates, 10 % of the penetrating fraction is fixated throughout the skin tissues, and 90 % is absorbed systemically (Renshaw, 1946). Because of its poor water solubility the circulating mustard concentrations are probably very low. Circulating mustard reacts irreversibly with rapidly multiplying tissues and the remaining part probably distributes to fatty tissues. Animal experimental data showed that after percutaneous absorption, tissue levels of ³⁵S-labeled mustard became maximal in 2-6 hours and rapidly declined afterwards, with further slow decline of the remaining low level 24-72 hours after exposure (see Whitfield, 1987). ³⁵S-labeled mustard was used to measure the original compound and its metabolites. It can be shown that sulfur mustard circulating in the blood is rapidly metabolized, and appears in the urine under the form of thiodiglycol and conjugated metabolites. About 80 % of the radioactivity administered intraperitoneally is excreted via the urine in 2 days, and 90 % in 5 days (Roberts and Warwick, 1963). Although no firm data exist describing the toxicokinetics of sulfur mustard and of its metabolites in animal or man, it is highly probable that by several days after exposure, only an insignificant fraction of unmetabolized mustard is still present in the body.

With the exception of one laboratory, the overall toxicological analyses are compatible with this interpretation, finding no intact mustard in blood, urine, or skin fragments at the time of admission, but detecting higher than normal concentrations of thiodiglycol in the urine of these casualties (section III.4.2.6).

The unexpected finding of intact sulfur mustard in post mortem samples of one patient, reported long after death, is discussed in the section on autopsy findings (section IV.6).

These contradictory findings and opinions clearly influenced the clinical approach to these patients, leading in some groups to the use of local and systemic detoxification techniques which were completely avoided in other groups. It must be added that, besides the fear of remaining mustard gas, the presence and persistence of mycotoxins was evoked as an argument for applying systemic detoxification techniques. The reasons why we do not accept these positive mycotoxin findings are explained in section 111.4.2.7.

5.2. THE APPLICATION OF LOCAL AND SYSTEMIC DETOXIFICATION PROCEDURES AT THE TIME OF SECONDARY ADMISSION

The local use of chloramine on the skin and the inhalation of acetylcysteine at the time of the secondary admission, i.e., in the European hospitals, have been described above.

Acetylcysteine, 150 mg every 3 hours (groups C, K, L and N), and sodium thiosulfate, 250 to 500 ml of a 10 % solution (groups E and N), were also administered systemically via an intravenous catheter. This was done on the theoretical basis that these agents would bind and inactivate persisting sulfur mustard in the body. Several sulfur containing compounds, e.g. dithiocarbamates, cysteine, cysteamine and thiosulfate, have indeed been shown to protect experimental animals against sulfur mustard, but the timing of their administration is rather critical: They have to be administered before or shortly after mustard exposure (see Whitfield, 1987).

There is no objective evidence that any of these substances did indeed bind to remaining mustard in the skin or in the body of our patients, or that they increased the excretion of the toxicant from the body. Furthermore the different treatment groups are too small, and too many differences existed among the individual patients, to judge from the healing of the lesions and the recovery of the casualties whether these measures had any benefit.

Another procedure that was applied, e.g., in patients of groups C and N, was the oral administration of activated charcoal followed by the laxative magnesium sulfate or lactulose. It was thought that this procedure would have a systemic effect, i.e., would extract the toxic substance from the body via the gastrointestinal system. It was not demonstrated whether this actually occurred. From animal experiments we know that only 10 % of absorbed ³⁵S-mustard is excreted via the feces, nearly all of it in the first 24 hours (see Whitfield, 1987). Therefore the usefulness of this procedure is not proven.

Within the context of the many uncertainties that existed in the beginning with regard to the identity of the causal agent, the metal complexing agent Unithiol (Dimaval) has been used in some patients, a.o. in patients A1 and A3. This drug was without any effect on the clinical situation. It has also been used by others (Mandl and Freilinger, 1984; Kaspar et al., 1985).

Finally, in the patients of group C and in some patients of group N the extracorporeal detoxification procedure of hemoperfusion was applied. This was also performed in other patients not discussed in this survey (Pauser et al., 1984; Balali et al., 1986).

The following discussion is based on group C. The procedure requires a permanent entrance into the vascular system, e.g., via a catheter into the femoral vein, and perfuses the blood via a push-pull pump system over a column containing coated activated charcoal. The column used was ADSORBA 300C, and the flow rate was 100 ml/min. Before each session the patient received heparin, 5000 IU, intravenously. The hemoperfusion sessions started the day after arrival, i.e. 11 days after exposure, and were repeated every two days for a total of 6 sessions. Each session took 2 to 3 hours.

In group N a combined hemodialysis and hemoperfusion was applied, in sessions of 6 hours, for about 5 days.

Clinical efficiency

The efficiency of this procedure has to be judged on three different levels : first, the ability of the column to eliminate the toxic substance from the blood; second, the efficiency of eliminating the toxic substance from the body; and finally, the impact of this procedure on the recovery of the patient.

On all three levels the result is inconclusive. Indeed there is no analytical proof that mustard gas was circulating in the blood and that it was captured by the charcoal. This also implies that no information exists with regard to the decrease of the total body burden of sulfur mustard, provided that mustard was still present in the body. The laboratory that suggested these detoxification procedures did not provide the analytical results necessary to prove or disprove their efficacy. The same argument also applies to the hypothetical presence of mycotoxins in these casualties (see section III.4.2.7). Finally, it seems to me that from the clinical point of view there is no evidence that the hemoperfusion sessions accelerated the recovery of these patients. However, because of the small number of

patients treated in this way, and because of the large interindividual differences, clear differences in clinical outcome could hardly appear. My negative conclusion might, therefore, appear premature.

On the basis of this inconclusive evidence, I would like to conclude that the procedure was without therapeutic effect; it even produced several side effects (see below) that should be avoided in these immunocompromised patients (Rommès et al. 1986).

Deleterious effects

During the sessions shivering was observed in the 5 patients of group C. In patient C2 hemoptysis occurred during the fourth and fifth sessions, no further hemoperfusion was administered to him.

During the twelve day period when this procedure was performed, the patients showed abnormalities in blood coagulation tests at some time. Most prominent in group C were thrombocytopenia and prolongation of the thrombin time (TT); e.g., TT remained abnormal for the whole period in patient C2. Together with the occasional prolongation of the cephalin bentonite time, this prolonged TT was compatible with the administration of heparin. Of the 7 patients of group N (N1-N6, N9) who underwent hemoperfusion, patients N1 and N3 showed decreases of blood coagulation factors II, VII and X, and increases in factors VIII and IX. No blood coagulation disorders were observed in patients that were not treated with hemoperfusion, although patients N7 and N8 also showed increases of factors VIII and IX.

A second side effect, which seems obvious from the data in table IV-2, is the occurrence of septicemia in the 5 patients of group C and in 5 of the 7 hemoperfused patients of group N. Several of these patients had no leukopenia. In patients of group C septicemia occurred during the time period where hemoperfusion was applied and disappeared a short time after hemoperfusion was stopped. In patients N4 and N5 it appeared several days after the single hemoperfusion that was performed, and in patients N1, N3 and N6 it appeared near the end of the hemoperfusion series. Septicemia was much less frequent in groups D and L, in whom a conservative approach was taken. The frequency in groups A, E and K was intermediate. However, these patients were also treated in an intensive care unit with several permanent intravenous catheters. Indeed, it is probable that despite the application of aseptic techniques, the permanent presence of intravascular catheters constitutes a real danger for these immunocompromised patients. Special care was taken in groups B and I to minimize invasive techniques. Several patients, however, showed positive hemocultures, that were partially explained by contamination of the needle during puncture through the skin (see section IV.3.2.1).

5.3. CONCLUSION

It seems rather clear to me that, at this stage, no convincing argument can be made to support the presence of toxicologically relevant concentrations of sulfur mustard on the patient or circulating in the blood at the time of arrival at the European clinic, several days after exposure. Data on the application of external and internal detoxification methods remain therefore inconclusive. As far as hemoperfusion is concerned, in the absence of any proof of its effectiveness, it should be avoided because of the serious side effects it can produce.

6. PATHOLOGY

Pathological observations are available from patients A2, A3, C1, D3 and N11. These findings, although differing in detail from one patient to the next, are mutually compatible. The descriptions made from these patients are also compatible with postmortem findings or ex vivo histological observations made in other Iranian casualties (D'Halluin and Roels, 1984; Balali et al., 1986; Coppens et al., 1986; Maynard, personal communications).

Death was due to respiratory insufficiency and subsequent cardiovascular failure, with severe lesions of the airways and airway obstruction, purulent bronchitis and bronchopneumonia, and lung edema.

6.1. MACROSCOPIC OBSERVATIONS

Skin lesions

On external examination no damage was found in the haircovered parts of the head, but important lesions were found in the face, neck, back, thoracic and abdominal regions, upper extremities, legs, penis and scrotum. The following lesions were described : patches of partially hyperpigmented but loose epidermis that could be peeled off by pressing, areas of brownish-red to partly pink dermis, and epidermal regrowth with hyperpigmentation. Remains of blisters were seen. The face, neck, ears, hands, external genitalia and feet showed edema.

Respiratory tract

The following observations were made : necrotizing laryngitis, tracheitis, bronchitis and bronchiolitis; sloughing with free or partially free mucous membranes in the throat, trachea and bronchi; hyperemia and bleeding; purulent bronchitis and focal bronchopneumonia; and congestion and edema of the entire lungs.

Either no immunological response was seen or a fibrinoleukocytic inflammation was observed with beginning organization of the tract and scarring.

Other lesions

The following findings were also observed : significant vasodilation of the intestinal tract, with extravasation of blood in the small intestine and punctiform hemorrhages in the large intestine, steatosis and slight secondary siderosis of the liver, massive stasis and subcapsular liver hemorrhages, atrophy of the lymphoid tissue, depletion of the immunological system and bone marrow, acute tubular necrosis and interstitial edema and massive stasis in the kidneys, acute hypoxic myocardial damage, and sequelae of stress in the adrenals.

6.2. MICROSCOPIC OBSERVATIONS

Part of the macroscopically intact epidermis showed vacuolization of basal cells, intraepithelial vesicle formation in the stratum spinosum and stratum lucidum, hyalin inclusions in some cells all over the stratum Malpighii, and separation of the basal cell layer from the underlying dermis. The pigment present in the stratum corneum was negative for iron coloration. The dermis was hyperemic, but no inflammatory infiltrations were seen. The adnexa were normal.

The lesions with absence of epidermis showed a fibrin covering and presence of bacterial colonies. The venules and capillaries were dilated, especially around the adnexa and in the hypodermis. In some venules fibrin deposits were found. No lesions of arteries and arterioles were observed. The inflammatory infiltration was very limited.

The aplastic bone marrow showed focal hyalin cylinders from hemorrhages. The liver showed moderate round cell infiltration within portal regions. In the spleen small follicles of histiocytosis were seen.

6.3. COMMENTS

It is not the aim of this survey to give a detailed overview of the pathological findings, experimental and human, in mustard gas poisoning. Excellent reviews exist (Koch, 1921; Pappenheimer, 1926; Vedder, 1925; Warthin, 1926; Warthin and Weller, 1919). The

observations described above are compatible with mustard gas induced pathological changes, but some comparisons between our observations and data from the literature remain of interest.

In experimental exposure of human skin to liquid mustard or vapour, vesicle formation starts between the epidermis and the superficial dermis. Progressive changes are seen in the epidermis, leading to necrosis extending some distance into the dermis and reaching its maximum in 5 to 10 days. The latter might be explained in part by contraction and death of blood vessels, a nonhemorrhagic and nonthrombosing process, with resulting anemia. In the dermis persisting edema and hyperemia are observed, but very little leukocyte infiltration occurs. This picture is quite different from the coagulated, shrunken and cooked appearance of tissues and massive thrombosis in heat burns.

In clinical cases (Pappenheimer, 1926), however, it appears that intra-epidermic vesicle formation also occurs, with intracellular hydropic changes and intercellular fluid and subsequent necrosis of cells, whereas basal cells remain intact.

In our patients subepidermal cleavage has been described ([figure III-12](#)), but also an intraepidermal scission between an upper, necrotic and pigmented epidermal layer and the lower intact layers ([figures IV-2](#) and [IV-3](#)). It seems, however, rather difficult to decide a posteriori whether the ongoing recovery process, before total desquamation of the upper layers, started from the original basal layer that had remained intact or from surrounding basal layers that had proliferated under the lesioned epidermis.

As far as the hyperpigmentation is concerned, it was known that in very superficial lesions with only erythema, chromatophores become larger, increase in number and are heavily pigmented with melanin. They further develop large branches in the upper layers of the dermis and epidermis, distributing pigment into keratinocytes of the stratum Malpighii and the stratum corneum (Pappenheimer, 1926). It seems possible that the presence of melanin in the superficial desquamating layers, but not in the recovering epidermis ([figure IV-3](#)), indicates total loss of the original epidermis and ingrowth of nonirritated surrounding basal cell layers.

In contrast to the absence of thrombosis mentioned above, capillary thrombosis was seen in some biopsies (see section III.3). In the autopsies capillary fibrin deposits were seen. It is possible that the fibrin deposits had produced secondary thrombosis at some places.

The lesions of the respiratory tract were similar in nature to the skin lesions. The necrosis of the walls of the respiratory tract, with sloughing and the formation of mucosal casts obliterating the upper and lower airways, is very typical for the action of a vesicant. These lesions were accompanied by congestion, edema and increased mucus secretion. In severe cases secondary infection almost always occurred, producing purulent bronchitis, bronchiolitis and bronchopneumonia. Atelectatic zones alternated with emphysematous areas, and secondary hemorrhage occurred.

Small-cell infiltrations were seen, and fibroblast proliferation appeared to start the recovery process. Cicatricial contraction of trachea and larynx could result from healing of these airway lesions.

Direct application of mustard to the gastrointestinal mucosa, e.g., by means of contaminated food or saliva, produces lesions similar to those described above. But the symptoms seen in gassed casualties are probably of reflex origin, associated with lung irritation or shock, or due to emboli arising in the primary mustard lesions.

Drasch et al. (1986) reported the finding of unchanged mustard in rather high concentrations in tissues (up to 15 $\mu\text{g/g}$ in fat and 8 $\mu\text{g/g}$ in skin) and in blood (1 $\mu\text{g/ml}$) of a casualty that died 7 days after exposure. It should be stressed that even in this case, no mustard was detected in the urine. The biological samples had been stored for more than 1 year at -20°C before analysis; the detection limit was not given, and it is not possible to assess the significance of readings that differed from the blank. These positive findings are

in contrast with most experimental work, in which it was impossible to detect extractable mustard from tissues of animals exposed to mustard administered by different routes. Therefore, it seems important that these interesting findings be confirmed, if possible in a different casualty and a different laboratory. Toxicokinetic study of the fate of mustard in the mammalian body is also needed. In the meanwhile the significance of these positive results remains open for discussion.

If these results are confirmed, they indicate the preferential uptake of mustard in peripheral tissues, that is a large volume of distribution. For substances with a large volume of distribution, hemoperfusion is generally thought to be ineffective since it hardly decreases the total body burden of the toxic substance.

7. CONCLUSION

Treatment of these casualties was based on the following principles : avoidance of secondary infection, treatment of secondary infections when they occurred, general support, and the application of detoxification procedures.

Eye and skin lesions healed slowly and steadily, but some lesions remained. Airway lesions were frequently accompanied by secondary infections, which could aggravate an already existing ventilatory insufficiency. It is clear that the more extensive the lung lesions, the more compromised the general state of the patient. The need for artificial ventilation indicated a poor prognosis. The occurrence of leukopenia in several of these patients revealed the systemic absorption of mustard. Because of the reduced defense mechanism, septicemia was frequently observed.

The clinical course of the patients and the postmortem findings confirmed the conclusion of the previous chapter that these patients were mustard gas casualties. A detailed description of the clinical condition of the patients at the time of discharge from the European clinics is given in sections IV.2.4, IV.3.3 and IV.4.4.

Detoxification techniques, local and systemic, were applied. In the absence, however, of reliable laboratory data concerning the presence of unchanged mustard in or on the casualties, the therapeutic efficacy of these techniques remains unproven. In some cases the technique of hemoperfusion was probably harmful for the patient.

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CHAPTER V : SUMMARY

Since 1984 chemical weapons, in particular the vesicant mustard gas and the nerve agent tabun, have been used on the battlefield in the Iran-Iraq conflict (United Nations, 1984; 1986; 1987). Most chemical casualties were mustard gas victims. Among those, about 172 patients were evacuated several days after exposure from Iranian medical facilities to West European hospitals in 1984, 1985 and 1986. Clinical files for 65 of these casualties have been studied in detail and are described in this survey. When comparing our data with other case reports from this conflict, published and unpublished, it appears that the patients transferred to Europe were selected from the moderate to severe cases of vesicant exposure observed in Iran.

MEDICAL HISTORY

Some information about exposure, initial symptomatology and treatment could be obtained from the patients. A more straightforward description, however, was available from a team of UN experts that visited Iran in 1984, 1986 and 1987. This description was complementary to the individual patient accounts.

The casualties had been exposed to exploding bombs that generated a cloud of dust and rain. The cloud showed different colours, grey, green-blue or orange, and had an odour of garlic or a pungent smell.

Shortly after exposure they experienced a burning sensation in the eyes and throat and difficulty in breathing. In the following 4 hours conjunctivitis, photophobia and palpebral edema developed. At about that time they were evacuated from the field, took a shower for decontamination and changed clothes. Further symptoms then gradually developed over the following days : itching, erythema, darkening of the skin, blister formation, erosions, and tracheitis and laryngitis.

As a local treatment, antiseptic solutions, ointments and creams were applied on the eyes and lesioned skin. Systemic treatment included bronchodilators, corticosteroids, mucolytics, expectorants and antibiotics. When necessary, oxygen was given or artificial ventilation was applied. Further treatment was symptomatic, maintaining water and electrolyte balance, giving a calorie-rich diet, and sometimes white cell transfusions to counteract leukopenia.

Secondary evacuation to European hospitals took place 5 days or more after exposure.

OBSERVATIONS AT THE TIME OF ADMISSION

The general description is based on patients that arrived within 5 days after being exposed to the chemical agent.

GENERAL CLINICAL CONDITION

These casualties were conscious and had blood pressure within normal limits but a variable degree of tachycardia, paralleled by a moderate increase in body temperature. Respiratory symptoms included sore throat, abundant white aqueous sputum, and coughing.

Chest X-rays revealed relatively few abnormalities. Several patients showed a moderate alkalosis, moderate decreases in plasma electrolytes, blood protein and albumin, small increases in the serum enzymes SGOT, SGPT, and LDH, and a high fibrinogen. Most showed low to normal PO₂ and normal PCO₂. In several patients leukocytosis was seen, but others showed leukopenia. Bacteriological investigations showed a large variety of bacteria on the skin lesions and throat and in sputum, both normal flora and pathogens possibly of hospital origin. In contrast to this rather benign general clinical picture, a few patients were severely ill with extensive lung lesions requiring artificial ventilation.

MUCOCUTANEOUS LESIONS

Eye lesions were blepharospasm, erosions and crustae on the eye lids, conjunctivitis and corneal lesions.

Skin lesions were erythema, areas of dark brown color with epidermolysis underneath which were areas of regenerating epithelium, and erosive lesions, erosions, and partially disrupted blisters. These lesions were rather painful. They were distributed all over the body, but moist places such as axillae, the genital region and groin were frequently involved. In most cases the deeper erosive lesions constituted only a small part of the total body surface affected.

Lesions of the upper airways were similar to the skin lesions, with laryngo-pharyngeal erythema, bleeding, purulent secretions and mucosal casts in the bronchi.

Other groups of patients, who arrived between 5 to 14 days or later after exposure, showed similar lesions. It seemed, however, that the general clinical condition and the mucocutaneous lesions became less severe with longer time after exposure, especially for the patients arriving more than 14 days after exposure.

DIAGNOSIS OF MUSTARD GAS POISONING

The medical history and clinical picture were compatible with the diagnosis of mustard gas poisoning as described in the literature. It appeared, however, that some of the clinical symptoms, especially the pigmented exfoliative form of skin lesion, with epidermolysis of the darkened epidermis, had received less attention in the more recent literature but were explicitly described in the literature from World War I and II.

The diagnosis was further compatible with the toxicological findings. Sulfur mustard had been detected on the Iranian battlefield in ground samples and in an unexploded bomb (see United Nations, 1984; 1986; 1987). Although a first report of unchanged mustard in blood and urine of some of the casualties could not be confirmed, increased amounts of thiodiglycol, a mustard metabolite, were found in the urine of several patients, pointing to mustard as the causal agent. No reliable proof of the presence of other chemical warfare agents in biological samples was provided.

LOCAL TREATMENT

Treatment of mucocutaneous lesions was based on the following principles : disinfection and avoidance of secondary local infections, and protection of the recovering epidermis. These objectives were obtained either by isolation and open treatment in a controlled environment, e.g., a burn centre, or by antiseptic creams or ointments, healing-promoting and protective substances, and bandages.

Healing of these lesions took 1 to 2 months and sometimes more, depending on the depth of the initial lesion. Local complications were pain and itching, hypo- and hyperpigmentation, scarring and the appearance of secondary blisters.

SYSTEMIC EFFECTS

LEUKOPENIA

Leukopenia was observed in 29 of our patients. This systemic mustard effect occurred between 5 and 20 days after exposure. In most cases a rapid recovery was seen, except for the very severe leukopenias (200 leukocytes or less/ μ l); these patients died. Selective gut decontamination was applied in these leukopenic patients.

SECONDARY INFECTIONS

Secondary infections were septicemia and bronchopneumonia. A conservative approach was followed, using systemic antibiotics but taking into account the general condition of the patient and the results of the bacteriological investigations. In some cases the severity of the airway lesions, the bronchopneumonic complications and the septicemia led to severe ventilatory insufficiency with cardiovascular depression and shock. Artificial ventilation using PEEP and cardiovascular support were required. One complication was the occurrence of a pneumothorax. All but one of the ventilated cases eventually died.

GENERAL TREATMENT

General treatment consisted of intravenous fluids and electrolytes, intravenous and oral feeding and symptomatic drug treatment. The choice of these « nonspecific » drugs was largely determined by the routine drug policy of the clinical service where the patients were hospitalized. Intensive care units used a large number of drugs; fewer were used in burn units and fewer in general or dermatological wards. It appeared that, except in special cases, these patients could be successfully treated in a normal ward. Isolation in a burn unit seems desirable, but is not indispensable.

DETOXIFICATION PROCEDURES

The following treatment procedures, aimed at binding and removal of hypothetical remaining mustard, were applied in some patients : local application of chloramine on the skin, inhalation of acetylcysteine, intravenous administration of acetylcysteine or sodium thiosulfate, and hemoperfusion. However, there are no theoretical arguments or clinical or analytical observations available to demonstrate the persistence of toxicologically relevant concentrations of unchanged mustard in these patients, or to demonstrate its inactivation and removal by these detoxification procedures.

FINAL OUTCOME

Eight patients died between 6 and 15 days after exposure. One patient died 185 days after exposure; he had been ventilated for an extended period because of severe bronchiolitis complicated by a series of more or less localized pneumothoraxes. Most patients returned to Iran in a fairly good condition after 2 to 10 weeks of treatment. Their lesions were nearly completely healed, although some lesions remained. The duration of hospitalization was determined mainly by the time needed for healing of the deeper skin lesions.

PATHOLOGY

The macroscopic and microscopic observations during autopsy of some of the deceased casualties confirmed the diagnosis of mustard gas poisoning. In particular, the sloughing of the mucosa of the upper and lower airways, the airway obstruction and secondary infection, together with the eye and skin lesions, characterized these patients as vesicant casualties (Warthin and Weller, 1919).

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S/16433, 26 March 1984.

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ANNEX

1. UNITED NATIONS, 1984

Report of the specialists appointed by the Secretary-General to investigate allegations by the Islamic Republic of Iran concerning the use of chemical weapons.

S/16433 26 March 1984.

VI. CONCLUSIONS

35. The following are our unanimous conclusions.
- a. Chemical weapons in the form of aerial bombs have been used in the areas inspected in Iran by the specialists as indicated above.
 - b. The types of chemical agents used were bis-(2-chlorethyl)-sulfide, also known as mustard gas, and ethyl N,N-dimethylphosphoramidocyanidate, a nerve agent known as Tabun.
36. The extent to which these chemical agents have been used could not be determined within the time and resources available to us.

2. UNITED NATIONS, 1986

Report of the mission dispatched by the Secretary-General to investigate allegations of the use of chemical weapons in the conflict between Iran and Iraq.

S/17911 12 March 1986.

VIII. SUMMARY AND CONCLUSIONS

55. At the specific request of the Secretary-General we visited Iran from 26 February 1986 to 3 March 1986 in order to conduct an investigation into the alleged use of chemical weapons in the Iran-Iraq conflict. Experience, knowledge and results obtained during two earlier investigations conducted in 1984 and 1985 were used to support the present investigation. Although we examined many casualties from the current conflict in the Al-Faw area, we did not visit this war zone. Casualties were seen at hospitals in Tehran and Ahvaz and a visit was made to sites in the area around Abadan.
56. Summary comments in relation to the present investigation are :
- (a) Detailed examination of Iranian casualties showed ocular lesions ranging from mild to severe conjunctivitis with intense palpebral edema, skin lesions including large vesicles filled with amber fluid, cutaneous separations, dark pigmentations and lesions approximating to second-degree burns. In some of the cases respiratory injuries and reduced leucocyte levels were found. The same features were found in other casualties which were cursorily examined as well as in corpses. All the lesions observed were caused, without any doubt, by mustard gas (yperite);
 - (b) Using a special instrument designed to detect chemical warfare agents, low concentrations of mustard gas vapour were detected in numerous craters at three sites around Abadan. Contaminated soil collected from a bomb crater (resulting from an attack the previous day on a field hospital) when analysed in laboratories in Europe was found to contain mustard gas. In addition, a hair sample collected from a victim after he had been attacked with chemical weapons was shown to contain mustard gas;
 - (c) Examination of metal components of aerial bombs, collected from bomb craters around Abadan, showed that the items had come from bombs that were similar to

those examined by the teams in 1984. (During the present mission we did not find nor were we shown any other type of chemical weapons, such as artillery shells).
(d) Significant new evidence was provided during interviews in Tehran of Iraqi casualties. They stated that their injuries had been caused by chemical bombs dropped by Iraqi aircraft during attacks on Iranian positions;
(e) Important new evidence was also provided by a captured Iraqi pilot. He confirmed that Iraqi aircraft had been used to attack Iranian positions with chemical bombs and that he had personally participated in two such « special missions ».

57. From the present investigation the following are our unanimous conclusions :

- (a) In areas around Abadab inspected by the mission, chemical weapons have been used against Iranian positions by Iraqi forces;
- (b) Based on medical examinations and testimony of Iranian and Iraq casualties evacuated from the Al-Faw area, chemical weapons were also used in that war zone by Iraqi forces;
- (c) From the evidence examined by the specialists the type of weapons used was aerial bombs;
- (d) The chemical used was mustard gas (yperite);
- (e) The extent to which mustard gas was used could not be determined within the time and resources available to us. However, from the over 700 casualties actually seen in Tehran and Ahvaz it is our impression that the use of chemical weapons in 1986 appears to be more extensive than in 1984.

58. After having conducted the examination of various sites, weapons components and numerous casualties in our investigations undertaken in 1984, 1985 and 1986 according to the guidelines given by the Secretary-General, together with circumstantial evidence, we unanimously conclude that :

- (a) On many occasions, Iraqi forces have used chemical weapons against Iranian forces;
- (b) The agent used has mainly been mustard gas although on some occasions nerve gas was also employed.

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VII. CONCLUSIONS

From the present investigation, the following are our unanimous conclusions :

- (a) In the areas around Khorramshahr, Iran inspected by the mission, chemical weapons have been used against Iranian positions by Iraqi forces. In addition to military personnel, civilians have also been injured in these attacks. The main chemical used was mustard gas (yperite), but nerve agents have probably been used on some occasions.
- (b) In the area around Baneth, Iran civilian as well as military personnel have also been injured by mustard gas, as evidenced by the medical examination of casualties and interviews with witnesses.
- (c) From the examination of weapon fragments found in the Khorramshahr area, chemical bombs similar to those used in 1984 and 1986 have again been used against Iranian forces. In addition, it is most likely that chemical rockets have also been used in this area.
- (d) In the areas around Basra, Iraq inspected by the mission, Iraqi forces have been

affected by mustard gas and a pulmonary irritant, possibly phosgene.

After having conducted the examination of various sites, weapon components and numerous casualties in our investigations undertaken in Iran in 1984, 1986 and 1987 and in Iraq in 1987, according to the guidelines given by the Secretary-General, together with circumstantial evidence, we unanimously conclude that :

- (a) The use of chemical weapons against Iranian forces by Iraqi forces continues. The weapons are aerial bombs and very probably rockets. The chemical agents used are mustard gas (yperite) and probably, on some occasions, nerve agents.
- (b) Civilians in Iran have also been injured by chemical weapons.
- (c) Iraqi military personnel, for the first time, have sustained injuries from chemical agents, which are mustard gas (yperite) and a pulmonary irritant, possibly phosgene.

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