Chapter 5

CUTANEOUS REACTIONS TO NUCLEAR, BIOLOGICAL, AND CHEMICAL WARFARE

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INTRODUCTION

Throughout the history of warfare, adversaries have continually utilized new technology in an attempt to gain the advantage. In recent history, a great deal of effort has been centered on the development of nuclear, biological, and chemical weapons by many countries in pursuit of this goal. Although in the United States the military has been aware of the situation, the military medical community has been slow to react to these threats. Consequently, research and development of new and more effective drugs, therapeutic approaches, and prophylaxis for nuclear, biological, and chemical (NBC) casualties have not received adequate attention.

This problem persists in the field of dermatology. Although basic research has suggested many potential therapies for the treatment of NBC casualties, the application of these findings in the development and fielding of treatments for NBC casualties on the battlefield has been slow in developing. It is incumbent on all military physicians, including dermatologists, to become aware of the NBC threat, to know how NBC weapons induce pathology, and to utilize current and potential therapies to treat NBC casualties.

Clearly, many new developments in medicine can be applied to improve the standard NBC treatment regimens now in place; but to reach this objective, physicians must have a clear understanding of the effects of NBC weapons at the clinical and physiological levels and how these weapons may by used in future wars.

To this end, a brief discussion of the tactics of NBC warfare is presented, the clinical data compiled over the last 80 years on the effects of NBC weapons are summarized, and the most recent cases of mustard gas use from the Iran-Iraq War are discussed. Standard NBC therapies that have been developed during the two world wars are recounted and new therapeutic regimens based on more recent research are detailed.

HISTORY

Some weapons not only inflict casualties but manage to strike considerable fear in the enemy. It is this unique blend of real and perceived danger that makes nuclear, biological, and chemical weapons so appealing for nations and groups to acquire.

Nuclear Warfare

The history of nuclear warfare encompasses a fairly short time, dating back to the bombing of Nagasaki and Hiroshima in 1945. Despite the brevity of the nuclear era, it has been an extraordinary time when the way nations have had to deal with each other both politically and militarily has changed dramatically. This situation is due to the magnitude of destructive power that nuclear weapons possess. The threat of the destruction of global civilization has given the leaders of the nuclear nations pause when contemplating future conflicts.

The destructive physical power of the atomic bomb in the form of thermal and blast energy was acutely apparent after the atom bombs were dropped on Japan, but the lingering effects of radiation were not fully realized until weeks and months after the bombing.

That radiation could cause tissue damage has been known since Roentgen discovered X rays in 1896. Shortly after the discovery, Thomas Edison noted that his assistant, Clarence Dally, who had been working with X rays, developed an acute inflammation of his hands followed by scaling, blistering, ulceration, and eventual malignancy. This type of effect became apparent in the aftermath of the bombing of Hiroshima. Dr. Michihiko Achiya published her diary elucidating those times.[1] Some of the excerpts from her diary clearly describe the evolution of radiation symptoms and the constellation of signs associated with radiation poisoning. The following excerpt describes the thermal effects of a nuclear explosion as related by Dr. Tabuchi:

> "It was a horrible sight," said Dr. Tabuchi. "Hundreds of injured people who were trying to escape to the hills passed our house. The sight of them was almost unbearable. Their faces and hands were burnt and swollen; and great sheets of skin had peeled away from their tissues to hang down like rags on a scarecrow. They moved like a line of ants. All through the night, they went past our house, but this morning they had stopped. I found them lying on both sides of the road so thick that it was impossible to pass without stepping on them.

> "The sight of the soldiers, though, was more dreadful than the dead people floating down the river...they had no faces! Their eyes, nose and mouths had been burned away, and it looked like their ears had melted off. It was hard to tell front from back. One soldier, whose features had been destroyed and was left with his white teeth sticking out, asked me for some water, but I didn't have any. I clasped my hands and prayed for him. He didn't say anything more. His plea for water must have been his last words. The way they were burned, I wonder if they didn't have their coats off when the bomb exploded."[1(p15)]

Dr. Achiya noted the following long-term effects of radiation poisoning in her notes:

> Another observation was that the severity of gastrointestinal symptoms appeared to bear no relation to the extent of burns and other injuries. Many patients with severe wounds recovered rapidly whereas there were patients with the symptoms described who did not appear to be injured at all but who, nevertheless, died. Among those who died, many had a bloody diarrhea similar to that seen in dysentery, and others had bloody urine or sputum. Severe uterine hemorrhage, which at first we mistook for derangements of menstruation, was common among the women. Some, who lingered as long as a week, died with stomatitis or gangrenous tonsillitis. Now, with the death curve rising again, stomatitis appeared and with it petechiae. The occurrence of petechiae followed the same pattern we had observed in patients with gastrointestinal symptoms. They bore no relationship to the type or severity of injury, and those who appeared to be uninjured and had even felt well enough to help in the care of other patients were beginning to show these blood spots beneath the skin. We had several instances of presumably healthy people who developed petechiae and died before persons who were obviously critically ill. You can understand what an ominous portent the development of petechiae had for us.[1(pp97–98)]

The events of the nuclear holocaust in Japan have led the leaders of the nations with nuclear capability to avoid the use of nuclear weapons. However, as more nations develop the technological capability to construct nuclear devices, the threat of a repeat of the devastation of Hiroshima becomes more likely. Therefore, medical officers must be prepared to treat the casualties of nuclear warfare.

Biological Warfare

The use of biological weapons in warfare is not a recent development. In the 14th century, at the siege of the fortress of Kaffa by the Tartars, corpses infected with plague were catapulted into the fort to infect its occupants.[2] There are several reports of American Indians receiving articles contaminated with smallpox given to them in an attempt to infect the Indians with smallpox. The British troops under the orders of Amherst supplied the Amerindians with smallpox-infested blankets.[3] During World War I, it is believed that attempts were made to produce an epidemic of plague in the city of Petrograd. Also, anthrax and glanders are believed to have been used in World War I, primarily directed at infecting horses. These latter efforts involved the use of scientific discoveries (ie, the discovery of pure cultures and infection chains) and the application of these recent scientific discoveries for warfare. During World War II, the Japanese are believed to have organized industrial production of disease pathogens and carriers. Our own involvement in the research and development of biological weapons began in 1941.[4]

In April 1979, Sverdlovsk, a small village in the Soviet Union, was decimated by an anthrax epidemic in which many of the people of the town died of a pneumonic form of anthrax.[5,6] Although the Soviet government vehemently denied the charge that this tragedy was caused by a biological warfare–agent accident, it is unlikely that an epidemic of pneumonic anthrax could have been caused by any other circumstance.

Historical accounts also exist concerning the pathology caused by the by-products of microbes. The effects of fungal toxins have been known for centuries even though the cause was not. The earliest mention is on an Assyrian tablet dated from 600 BC, which refers to a noxious pustule in the ear of grains. The tablet probably refers to the infection of rye grains by the fungus *Claviceps purpurea* (Figure 5-1), which produces ergot alkaloids, the causative agents in ergotism.[7,8] During the Middle Ages, large epidemics of hallucinations, delirium, convulsions, and severe limb ischemia leading to dry gangrene and autoamputation were attributed to the ingestion of rye contaminated with ergot fungus (*Claviceps purpurea*).[8] One of the most vivid presentations of this malady is by Hieronymos Bosch in his painting *The Last Judgment*. In Figure 5-2, a detailed area of the painting, the signs and symptoms associated with ergot poisoning are shown.

During the latter part of World War II, the Soviets experienced an outbreak of human alimentary aleukia that caused numerous fatalities.[9] The outbreak was attributed to a fungal contamination of

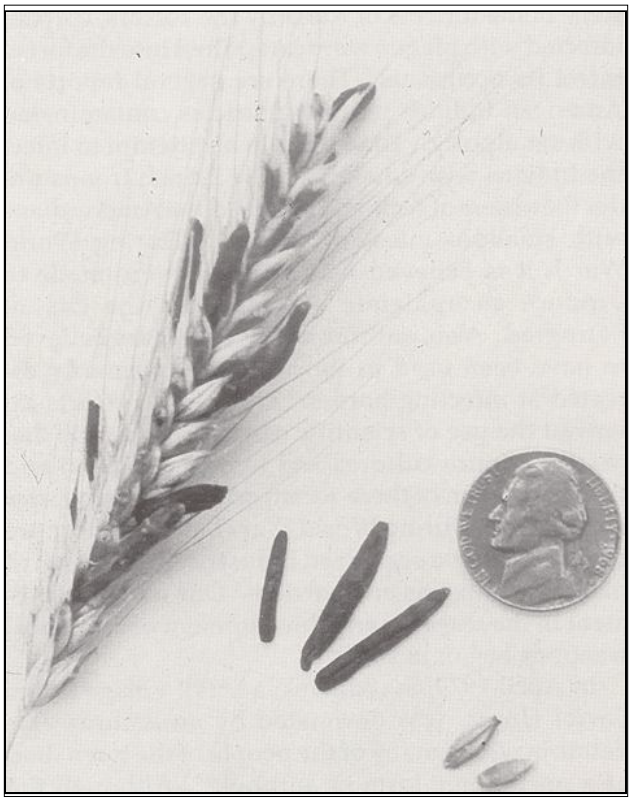


Fig. 5-1. (left) Rye grain infected with *Claviceps purpurea*, a fungus that produces ergot alkaloids. The darkening of the grains is characteristic of the infection. Photograph: Courtesy of Dr. Werner Schreiber, Nuremberg, Germany.

Fig. 5-2. (below) Detail of Hieronymus Bosch's *The Last Judgment* depicting the signs and symptoms of ergot poisoning. The painful paresthesias are represented by the "frying" extremities in the pan, the man roasting on the spit, and the webbed feet of the figure in the lower left corner. The cutaneous manifestations of blackened ischemic extremities and ascites are depicted in the figure in the upper right. Photograph: Courtesy of Akademie der bildenden Kunste, Vienna, Austria.

grains (corn, barley) by fungi that produce trichothecene mycotoxins. The lethality of these fungal toxins apparently impressed the Soviets because they incorporated trichothecenes into weapons. The subsequent use of trichothecene by the Russians in Afghanistan and Southeast Asia was supported by several reports that there have been chemical attacks on individuals in those areas, with resultant symptoms suggestive of trichothecene poisoning.[10,11] Although the validity of the findings has been questioned, the discovery of Soviet gas masks in Afghanistan, contaminated with fungal toxins, is strong supportive evidence that these agents have been used by the Soviets.[12]

Chemical Warfare

Since the first employment of mustard and chlorine gases in World War I, the use of chemical weapons has been sporadic. This restraint has been based in part on a fear engendered in world leaders by the effectiveness with which chemical weapons were used in that war. Due to the infrequency of chemical warfare in the last 75 years, the belief prevails that chemical weapons are a recent invention; however, the use of chemical weapons to gain advantage in war dates back to the Peloponnesian War in 428 BC. In this incident, which was the first recorded use of chemical weapons, the Spartans started a fire with sulfur-saturated wood under the walls of a city defended by the Athenians. Chronicles of ancient history also record that the Greeks used pots filled with a mixture of sulfur, pitch, tow, and resins; the pots were ignited and hurled into towns, producing suffocating smoke and fire.[13]

Despite protests by the clergy and others, the production of more effective weapons based on the technology of the day continued. An example of this was the crossbow. In 1139, Pope Innocent III and the Ecumenical Council to the Lateran expressed horror at its lethality in battle and banned its use (except against non-Christians) under penalty of excommunication.[13] Although the Pope had far-reaching influence at that time, the use of the crossbow in war became standard and widespread. Its use ebbed only when the more effective bow and arrow was demonstrated to possess a more rapid rate of fire in battle.

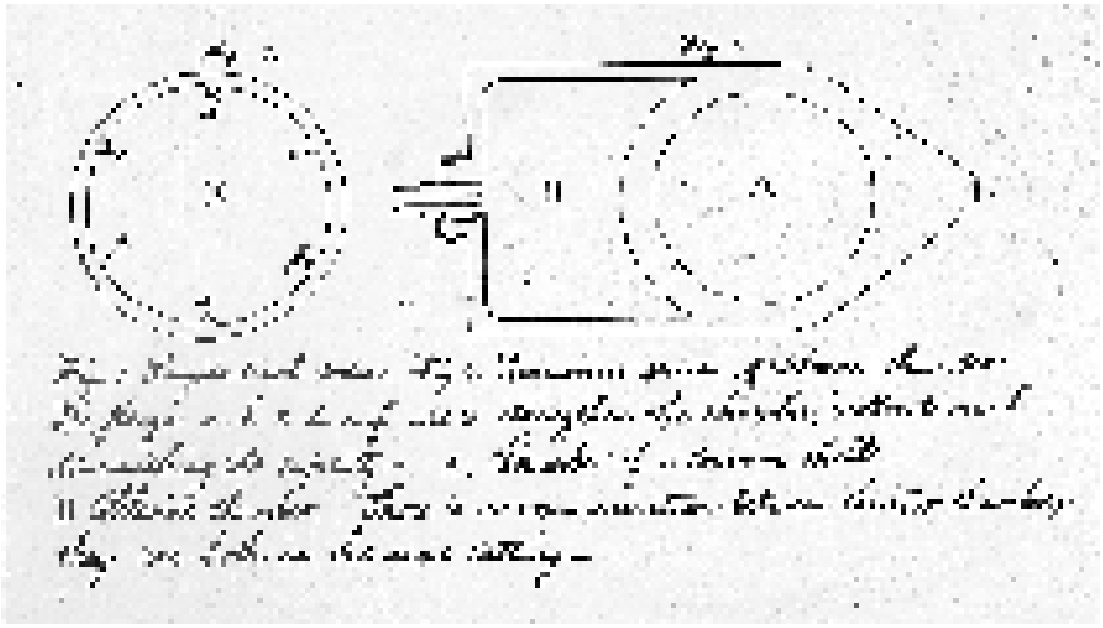
Attempts to introduce new and more effective weapons to gain advantage in battle continued into the 19th century. For example, the use of chlorine gas in warfare was not a German invention but one of an American named John W. Doughty. And chlorine might have been used in the U.S. Civil War if the War Department of 1862 had followed up on a suggestion of Doughty's that was contained in a letter with an illustration (Figure 5-3). This document is now kept in the Old Records division of the Adjutant General's Office in the Archives Building, Washington, D.C. The letter clearly predicted the details of the use of chlorine gas by the Germans in World War I.[14] The War Department concluded that there was no merit in Mr. Doughty's invention.

Efforts to prevent the use of certain weapons continued in the 19th century when the Hague Conference of 1899 was convened. At that time, a resolution was being contemplated (later rejected) that would ban the use of poisonous gases in war. The United States' representative, Admiral Mahan, was opposed to such a ban and stated:

> The reproach of cruelty and perfidy, addressed against those supposed (gas) shells, was equally uttered formerly against firearms and torpedoes, both of which are now employed without scruple …It was illogical, and not demonstrably humane, to be tender about asphyxiating men with gas when all were prepared to admit that it was allowable to blow the bottom out of an ironclad at midnight, throwing four or five hundred men into the sea, to be choked by water with scarcely the remotest chance to escape.[15(p686)]

Since then, the United States has continued to have an ambiguous position on the use of chemical warfare. This position was demonstrated by the United States' refusal to ratify the Geneva Gas Protocol in 1926.[16] In 1972, the Biological and Toxin Weapons Convention was written to supplement the Geneva Protocol, and it was signed by 103 nations including the United States.[10] However, this treaty does not limit research in the defense of biological warfare.

During World War I, a stalemate existed on Germany's Western Front between the allied forces of Britain and France, and the Germans. To break this stalemate, the Germans actively searched for a new weapon that could enhance their ability to wage effective maneuvers on the battlefield and break through the entrenched allied positions. Alerted to the possibilities of gas warfare by their scientists, they enlisted the help of two eminent German chemists, Professor Walther Nernst[14] and L. F. Haber. With their guidance, the Germans delivered the first gas attack of modern times near a small village in Belgium called Ypres. On April 22, 1915, late in the afternoon, they released large amounts of chlorine gas, the same chemical as that



Hon. Edwin M. Stanton
Secretary of War

Sir

The above is a representation of a projectile which I have devised to be used as a means for routing an *entrenched* enemy. Believing it to be new and valuable, I send the War Department a brief description: Chlorine is a gas so irritating in its effects upon the respiratory organs, that a small quantity diffused in the atmosphere, produces incessant & uncontrollably violent coughing. It is 2 ½ times heavier than the atmosphere, and when subjected to a pressure of 60 pounds to the inch, it is condensed into a liquid, its volume being reduced many hundred times. A shell holding two or three quarts, would therefore contain many cubic feet of the gas.

If the shell should explode over the heads of the enemy, the gas would, by its great specific gravity, rapidly fall to the ground: the men could not dodge it, and their first intimation of its presence would be by its inhalation, which would most effectually disqualify every man for service that was within the circle of its influence; rendering the disarming and capturing of them as certain as though both their legs were broken.

To silence an enemy's guns or drive him from his entrenchments, it would be only necessary to explode the shells over his head or on his windward side. If exploded in rapid succession over or within a fort, evacuation or surrender could not be delayed beyond fifteen minutes. Casemates and bomb-proofs would not protect the men.

This kind of shell would, I think, in the present advanced state of military engineering, be a very efficient means for warding off the attacks of iron-clad vessels and *steam rams*; for, as to the steam ram, a ten inch gun that would carry a shell containing a gallon or two of the liquid, would with ordinary accuracy, be able at the distance of ¾ of a mile, to envelop him in an atmosphere that would cause his inmates to be more anxious about their own safety than about the destruction of their enemy.

It may be asked if the gas which drove the enemy from his guns, would not prevent the attacking party who used the gas from taking possession of the abandoned position. I answer it would not: for, this shell does not, like the Chinese stink-pots, deposit a material emitting a deleterious gas *lighter* than the atmosphere, but suddenly projects into the air a *free* gas much *heavier* than the atmosphere, which does its work as it descends to the earth, where it is soon absorbed.

Experiment alone can determine whether this shell has any practical merit. Possibly, I overrate its value; but it must not be forgotten, that while it does the work of an ordinary shell, it also carries with it a force against whose effect the most skillful military engineering can not possibly make any adequate provision.

As to the moral question involved in its introduction, I have, after watching the progress of events during the last eight months with reference to it, arrived at the somewhat paradoxical conclusion, that its introduction would very much lessen the sanguinary character of the battlefield, and at the same time render conflicts more decisive in their results.

If I have erred, I have, *at least* meant well.

Yours,
Respectfully,
John W. Doughty

April 5th, 1862, 419 Eighth Avenue, New York

Fig. 5-3. Reproduction of original drawing by John W. Doughty, showing the chlorine gas weapon he proposed in 1862. Redrawn by Karen Wyatt, Medical Illustrator, Fitzsimons Army Medical Center, Aurora, Colorado. Letter reprinted from the Old Records division of the Adjutant General's Office in the Archives Building, Washington, D.C.

mentioned in John Doughty's letter almost half a century before. The yellow-green gas drifted toward the entrenched British soldiers and, being heavier than air, filled all the low-lying areas including the trenches where the British soldiers had taken refuge against a preceding bombardment. The cloud engulfed the 15,000 soldiers. After 15 minutes the attack was over; it had caused total chaos and perhaps 5,000 deaths (the exact number remains controversial).[17] The desired effect occurred and the British line was broken; however, the Germans did not take advantage of the situation and eventually were pushed back. The birth of modern chemical warfare had occurred and the use of the weapon that could "shoot around corners" had begun.

Although the German potential for waging chemical warfare was known to the U.S. forces in Europe, the full impact of these new weapons was not realized until Ypres. This battle, with its resultant casualties, arrested the American Expeditionary Forces' attention and forced the U.S. Army quickly to develop a chemical capability of its own. An excerpt from a 1918 army technical report titled *History of the First Gas Regiment*[18] is indicative of the prevailing doctrine of that era:

> It is impossible to conclude otherwise than that gas warfare is an extremely effective agent...However [as] much [as] the elimination of gas in the future as an agent in warfare might be desired, to make its elimination a certainty is impossible, for it is reasonable to suppose that a nation that would violate its treaties would not be scrupulous about the use of weapons to obtain its ends.
>
> Had Germany waited until she had sufficient chlorine and was ready to gas the whole British and French Armies upon every suitable front, she could have won the war in one gas attack. She erred vitally in trying gas on a small scale.[18(p57)]

After World War I, concerns persisted about the use of chemicals in future wars and, although no chemical warfare occurred in World War II, the history of that era is replete with isolated anecdotes in which one country used chemical weapons against another. Italy utilized a mustard agent against Ethiopia in 1935.[16] In 1941, the Japanese employed mustard gas against the Chinese at Ichang. A little-known incident in the northern Italian port city of Bari resulted in the only gas casualties in the European theater during World War II. The USS *John Harvey*, a supply ship carrying mustard gas munitions anchored in the harbor, was attacked by the Germans and destroyed. The contamination of the waters and surrounding area resulted in over 600 casualties.[19] Although many feared the use of chemicals in World War II and Germany had the ability to deploy both blistering and nerve agents, they were not used. This outcome may have been due to a combination of factors including the fact that the Allied Forces had the capability to retaliate in kind. Hitler's reluctance to use chemicals may have also been due to his own personal aversion to chemical weapons based on his experience of being gassed in World War I. In *Mein Kampf*, he relates his experience from 1918:

> ...the English gas attack on the southern front before Ypres burst loose; they used yellow-cross gas (mustard gas), whose effects were still unknown to us as far as personal experience was concerned. In this same night I myself was to become acquainted with it. On a hill south of Wervick, we came on the evening of October 13 into several hours of drumfire with gas shells which continued all night more or less violently. As early as midnight a number of us passed out, a few of our comrades forever. Toward morning I, too, was seized with pain which grew worse with every quarter hour, and at seven in the morning I stumbled and tottered back with burning eyes. A few hours later my eyes had turned into glowing coals; it had grown dark around me.[20(pp201–202)]

In 1967, reports surfaced that Egypt had used a form of mustard gas against Yemen.[16] During the 1980s, reports from Vietnam and Afghanistan have pointed toward the use of chemical weapons in conflicts in those areas. Most recently, the use of vesicants (blistering agents, eg, mustard gas) and nerve gas by Iraq against its own Kurdish population and against the Iranians in the Iran-Iraq War has focused our attention on the likelihood that U.S. forces will face adversaries who are able and willing to use chemical weapons on the battlefield.

In 1987, the Vesicant Workshop was held at The Johns Hopkins University Applied Physics Laboratory under the sponsorship of the U.S. Army Medical Research and Development Command. In his keynote address, General Richard T. Travis noted that the workshop was being held

> because of the use of sulfur mustard by Iraq in the Gulf War and the subsequent recognition of the availability and effectiveness of vesicant agents on the battlefield....Mustard's threat is critical, partly because it incapacitates so many more combatants than it kills and partly because it is so easily prepared from commercially available chemicals. Recently, a Belgian company was alleged to have exported 500 tons of thiodiglycol to Iraq in 1983. This chemical, when combined with hydrochloric acid, produces mustard in excellent yield. Clearly,

the synthesis of sulfur mustard is within the capability of any third world country.[10(p645)]

Despite the naysayers who deny the possibility of chemical warfare in future wars, an increasing body of evidence, especially that gleaned from the Iran-Iraq War, cannot be ignored and strongly suggests that chemicals will be used.

In his book titled *The Reformation of War*, General J. F. C. Fuller describes the ideal weapon:

1. Its production should not detrimentally affect prosperity.
2. It should be simple to manufacture in peace or war.
3. Its nature should be unknown to the enemy.
4. It should be capable of incapacitating without killing, and the incapacity should not be permanent.
5. It should permit of a defense against it being well-known in advance and prepared for by the side using it.
6. It should inflict no permanent damage upon property.[14(p10)]

These characteristics fit chemical agents precisely, and mustard in particular. In today's world, one could conclude that the ideal weapon, especially for countries without a nuclear capability, is a chemical agent.

NUCLEAR WARFARE

The types of casualties produced by a nuclear explosion depend on where the explosion occurs but are always due to one of three effects: blast injuries (direct and indirect), thermal burns, and radiation injuries. Thermal and blast energy account for 80% of the energy released by an atomic bomb (Figure 5-4). A discussion of blast injuries is beyond the scope of this chapter; therefore, we will limit the review to the dermatologic aspects of thermal burns and radiation injuries.

Thermal and Radiation Effects

Thermal burns can be caused directly by the initial flash of the thermonuclear explosion or by fires that are secondary to the explosion. The flash burns, which are caused by radiant or infrared energy from the initial fireball, occur on unprotected skin or skin under a light garment. Figures 5-5 and 5-6 illustrate the effect of garment protection from the thermal effects of the initial blast.

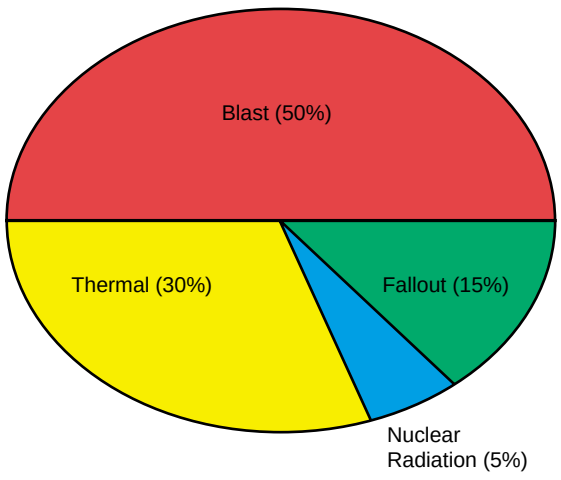


Fig. 5-4. Partition of energy of a nuclear air blast. Note that the majority of energy from a nuclear device is blast and thermal energy, the same energy released from a conventional bomb. Fallout and nuclear energy account for only 20%.

The treatment of thermal burns and blast injuries is greatly complicated by the effects of ionizing radiation. This radiation occurs in the form of neutrons, X rays, beta particles (electrons), and gamma radiation produced within the first minutes of the nuclear fireball, and alpha, beta, and gamma radiation from the residual fallout. The charged alpha and beta particles can only penetrate the skin layers, causing an initial erythema that can progress to superficial and deep ulcers (Figure 5-7). Such an occurrence took place in 1946 during the Bikini BRAVO shot, in which many Marshall Islanders were exposed to fallout from the large amount of coral picked up in the blast. The fallout in the form of lime "snowflakes" fell on 239 islanders, causing an initial burning and itching during the first 2 days, followed by epilation and a "wet" superficial ulceration that occurred 2 to 3 weeks after the exposure.[21] Conversely, gamma rays, X rays, and neutrons, all of which have no charge, penetrate deeply into the body and can cause severe damage to vital tissues, especially those such as the hematopoietic tissue with a high rate of cell division. The loss of significant numbers of bone marrow cells can lead to an immunosuppressed state in which the casualty is highly susceptible to bacterial infections. In addition, the epidermal healing process can be delayed by the same mechanism, leading to a protracted recovery period.

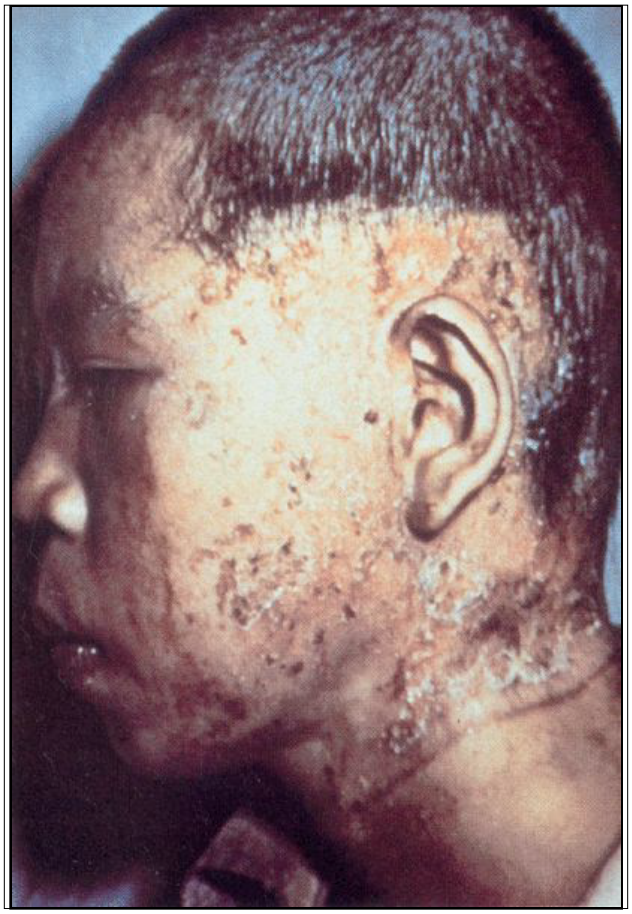
The effects of radiation on the human body fall into several different categories dependent on ra-

Fig. 5-5. A Japanese nuclear casualty with thermal burns caused by the initial fireball. Note the lack of burns on the upper scalp and forehead (**a**) secondary to the protective effect of the cap (**b**). Photograph: Courtesy of the Defense Nuclear Agency, Washington, D.C.

diation dose (Figure 5-8).[22] At doses greater than 100 to 150 rads, patients typically develop the radiation hematopoietic syndrome, which, after a latent period of 2 to 3 weeks, is manifested by bone marrow suppression, cutaneous and internal hemorrhage, and immunosuppression. Between 400 and 1,000 rads, the gastrointestinal syndrome occurs. This syndrome consists of edema, pseudomembrane formation in the gastrointestinal tract, and submucosal hemorrhage in the bowel and is accompanied by prolonged nausea, vomiting, watery diarrhea, shock, and death. Above 1,000 to 2,000 rads, casualties are likely to develop the cardiovascular/central nervous system (CNS) syndrome, which is invariably fatal. In this syndrome, CNS symptoms can occur within minutes, culminating in confusion, prostration, seizures, and coma. Patients with this syndrome typically die in shock or secondary to CNS complications.

With doses of less than 100 rads, the skin is essentially unaffected. At doses of 100 to 200 rads, a transitory erythema can occur within minutes and last 2 to 3 days.[23] This erythema is thought to be caused by vascular dilation secondary to the release of histamine and other vasoactive peptides. Then a deeper erythema develops around day 7 and lasts through day 14. The subsequent scaling, suggestive of a sunburn and hyperpigmentation, appears 14 to 21 days after radiation exposure in many cases. Doses of 200 to 1,000 rads typically produce epilation at approximately 1 to 3 weeks that at the lower doses (100–300 rads) is transient, and at doses greater than 700 rads is permanent.[24] The onset of epilation can be an indicator of radiation dose because higher doses induce earlier epilation.[25] In the 700-rad range, the number of casualties will be significant.

In case reports in which patients received high doses of radiation (4,000–8,000 rads), patients describe an acute burning sensation of their skin. In addition, if the patients survive over several days,



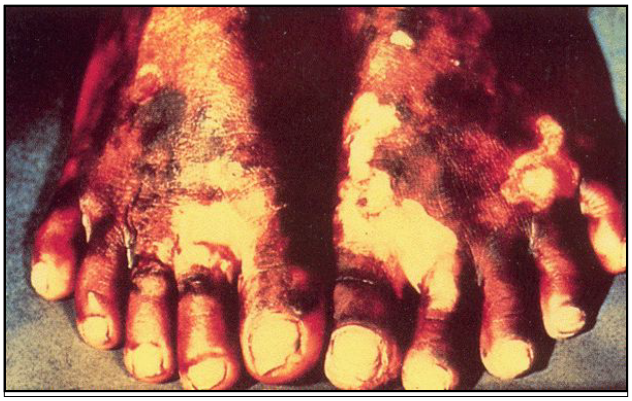
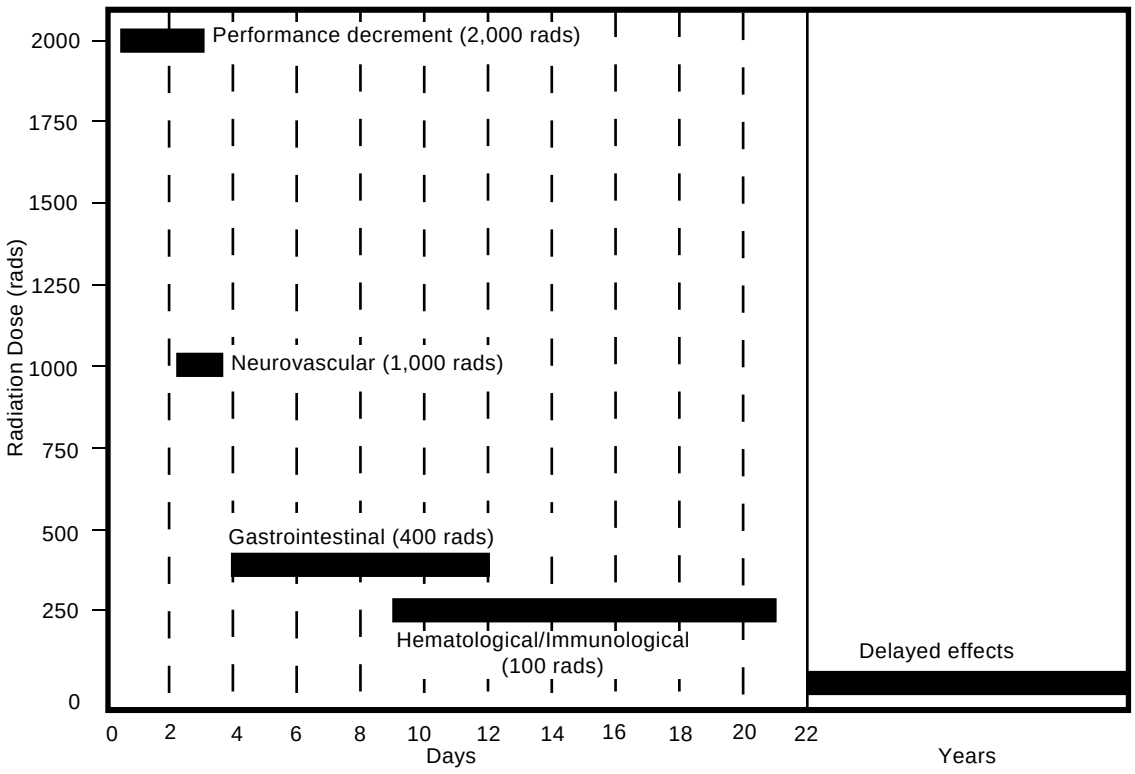


Fig. 5-6. (left) A pattern burn in a Japanese nuclear casualty caused by headgear protection at the time of the atomic bomb fireball. Photograph: Courtesy of the Defense Nuclear Agency, Washington, D.C.

Fig. 5-7. (above) Superficial radiation burns caused by beta radiation from nuclear fallout. Photograph: Courtesy of the Defense Nuclear Agency, Washington, D.C.

Fig. 5-8. (below) The effects of acute radiation exposure. Adapted from Walker RI, Cerveny TJ, Young RW. Acute radiation syndrome in humans. In: Walker RI, Cerveny TJ, eds. *Medical Consequences of Nuclear Warfare*. Part I, Vol2. In: *Textbook of Military Medicine*. Washington, DC: Office of The Surgeon General, US Department of the Army; 1989: 21.



vascular damage in the cutaneous tissues can result in diffuse bullae formation over the exposed skin surfaces (Figures 5-9 and 5-10).[26] The histological picture of skin exposed to high doses of radiation consists of keratinocyte damage with pyknotic nuclei, severe dermal edema, and subepidermal vesicle formation.[23] With higher doses, endothelial cell swelling, intravascular thrombi, and fibrosis can be seen.[23]

Skin manifestations that occur over weeks to months, in addition to those noted above, include[25]

- late erythema that occurs after 6 to 8 months and is associated with vasculitis, edema, and pain;
- moist desquamation that is usually manifest at the 3-week period with doses of 1,200 to 2,000 rads; and
- necrosis with onset at a few weeks to months, accompanied by fibrosis, atrophy, and vascular proliferation (Figures 5-11 and 5-12); necrosis occurs at doses of greater than 2,500 rads.

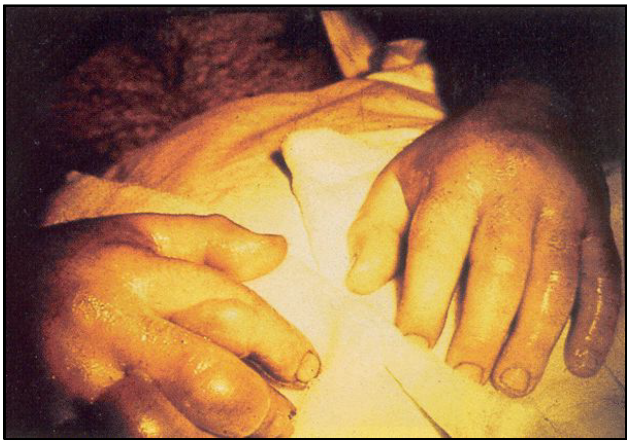


Fig. 5-10. Bullae on the hands of an individual involved in a nuclear incident in which he received a 1,000-rad dose. The patient developed a cardiovascular/central nervous system radiation syndrome secondary to the exposure, and he subsequently died. Photograph: Courtesy of the Defense Nuclear Agency, Washington, D.C.

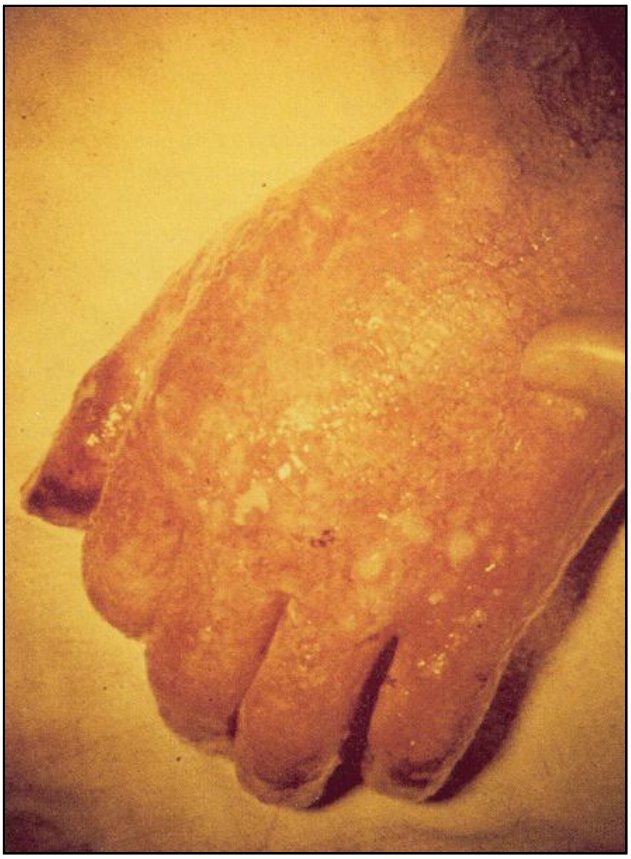


Fig. 5-9. Bullae on the hands of a Los Alamos nuclear accident victim 24 days after exposure. Photograph: Courtesy of the Defense Nuclear Agency, Washington, D.C.

The systemic effects of ionizing radiation can also manifest cutaneously. At doses of greater than 100 rads, depletion of the platelets and their precursors can cause cutaneous petechiae and hemorrhage. Bone marrow damage can also cause immunosuppression, which could lead to increased skin infections.

The patient who survives the acute phase of radiation exposure is at increased risk for chronic radiation dermatitis and cutaneous neoplasms (delayed effects).

Therapy of Cutaneous Radiation Injury

Participation of dermatologists in the treatment of thermal injuries after a strategic nuclear encounter will be, of necessity, significant. Overwhelming numbers of casualties will quickly saturate the capabilities of surgical personnel, leaving others to care for the burn victims who do not need intensive surgical or burn care. Dermatologists, with their broad experience in and knowledge of skin pathophysiology, will be uniquely qualified to care for this type of casualty.

Treatment for the cutaneous effects of ionizing radiation remains largely symptomatic. The initial step in caring for these patients is decontamination. Fallout particles can cause superficial burns to the

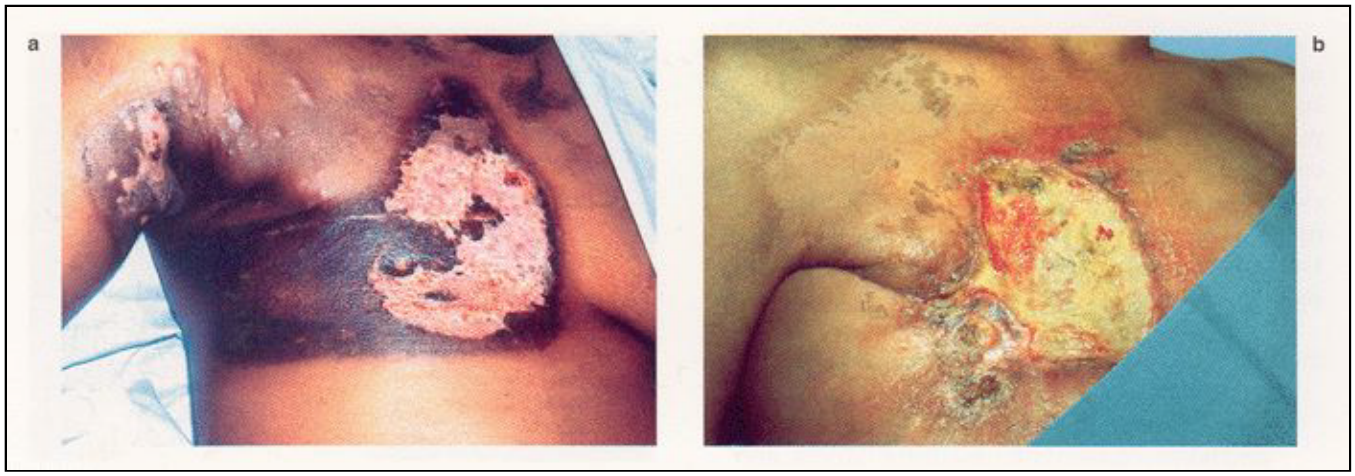


Fig. 5-11. Two cases of chronic radiation necrosis, ulceration, and scarring secondary to radiation therapy for breast cancer.

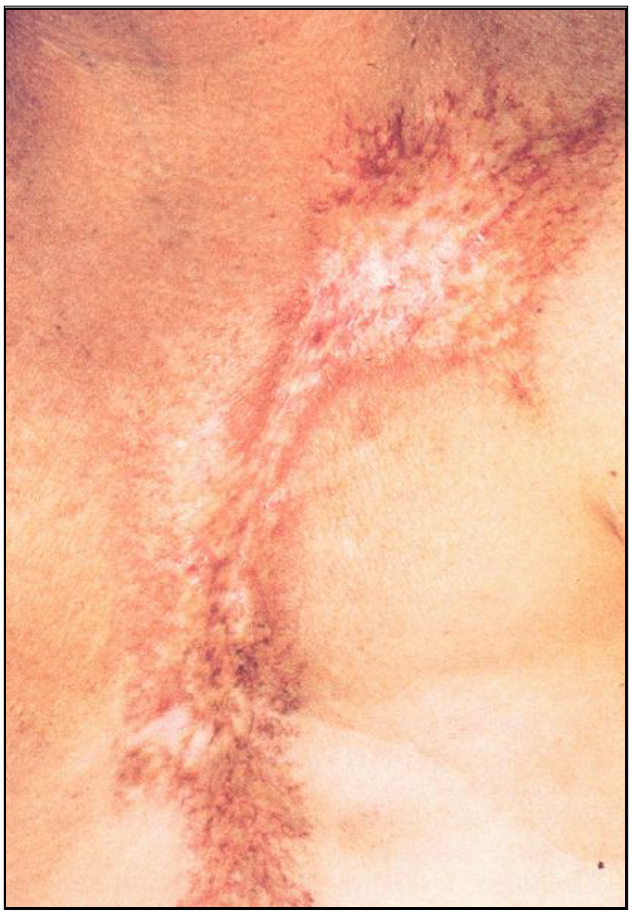


Fig. 5-12. Chronic telangiectasia, scarring, and pigmentary changes of the skin following radiation therapy.

skin but pose a relatively minimal risk for systemic problems. Of importance to medical personnel is the fact that patient contamination poses little risk to them and should not hinder appropriate lifesaving measures in an emergent situation.[27]

After decontamination, care of acute radiation injuries should consist of gentle cleansing and washing of denuded blisters and superficial and deep ulcerations. As with burns, frequent changes of sterile dressings and silver sulfadiazine and mafenide antibiotic creams are useful in the inhibition of local bacterial infections. Careful monitoring for signs of local and systemic infections is paramount because these patients are often immunosuppressed and are at increased risk for the development of infection.

Because of the damage to the mucosal barrier of the gastrointestinal tract secondary to the radiation, these patients are particularly susceptible to enteric pathogens. For this reason, it has been recommended that nonabsorbable antibiotics be given to decrease the intestinal flora.[24] In addition, fevers of unknown origin should be treated immediately with broad-spectrum antibiotics that cover Entero- bacteriaceae and *Bacteroides fragilis*. In radiation patients who exhibit an increased potential for Gram-negative organisms as well as avascular ulcerations, ciprofloxacin offers coverage for cutaneous infections with many Gram-negative organisms including *Enterobacter* and *Pseudomonas* species, and moderate coverage for *Staphylococcus* species, especially those that are methicillin resistant.[28]

Hydrogel and hydrocolloid gel dressings such as Vigilon (manufactured by C.R. Bard, Inc., Murray Hill, N.J.) and DuoDERM (manufactured by ConvaTec, Princeton, N.J.) may decrease wound

discomfort and wound healing time in radiation ulcers and should be considered, if available.[29]

Surgical treatment of chronic, painful nonhealing ulcers is often necessary in patients exposed to radiation doses greater than 1,000 rads. Surgical debridement of necrotic tissue, early treatment of cutaneous infections, and grafting are essential to ensure optimal healing.[30] Because the ulcer base often has a compromised blood supply secondary to vascular damage, the use of pedicled flaps that have an intrinsic blood supply may offer an improved recovery (lower graft-failure rate).[31]

Over the past decade, there has been increased study of drugs with an apparent systemic radioprotective effect. Animal studies of sulfhydryl drugs such as cysteamine (MEA) have demonstrated that both systemic and topically applied sulfhydryl drugs exert a significant radioprotective effect (taken either prophylactically or shortly after exposure) for acute and late sequelae of radiation exposure.[32] Histological examination of the animals receiving MEA at the time of irradiation demonstrated that fewer vascular abnormalities existed than in nonprotected animals. This finding suggests that both acute and late skin changes may be, in part, due to vascular damage. A study of radiation therapy patients who received the hemorrheologic drug pentoxifylline demonstrated significantly shortened healing time of skin ulcerations and duration of pain.[33] This study also suggests that drugs that act to maintain blood flow to irradiated skin help the healing process.

Another drug found to exert a protective effect on animal tissue is cuprozinc-superoxide dismutase (CSD).[34] Treatment with CSD reduces the bone marrow cell toxicity from irradiation in mice by a factor of two. The exact mechanism by which CSD protects the cell is unclear, but studies have demonstrated that it inhibits the action of poly(ADP [adenosine diphosphate]-ribose) synthetase, which is activated by DNA strand breaks.[35,36] Poly(ADP-ribose) synthetase, when upregulated by breaks in the DNA, depletes the cellular NAD (nicotinamide adenine dinucleotide) and thereby deprives the cell of substrates to produce ATP (adenosine triphosphate), which is necessary for cell function.[36] Further studies of CSD will be needed to determine its efficacy in humans. Other researchers have used cytokines to stimulate bone marrow precursors in radiation syndrome patients. Interleukin- (IL) 1, alone and in combination with tumor necrosis factor, IL-6, and colony stimulating factors, has promoted recovery in irradiated mice.[37] In eight patients with bone marrow failure due to cesium 137 exposure, the use of granulocyte-macrophage stimulating factor resulted in a prompt increase in bone marrow granulocytes.[38] Other drugs that are available and may have some beneficial effect on the course of radiation-induced skin injuries include the antioxidants such as ascorbic acid, α-tocopherol, and butylated hydroxyanisole (BHA).[39]

Late Sequelae of Radiation Exposure

Radiodermatitis and an increased propensity for cutaneous neoplasms are the late sequelae of radiation exposure. The onset of radiodermatitis is dependent on several variables including type of radiation, total dose, duration of dose, and density of radiation. Most of the clinical experience with the cutaneous effects of radiation has been with patients who have received radiation therapy. Patients who have received fractionated radiation therapy in the 4,000 to 6,000 rad range experience an acute erythema, blistering, necrosis, and sloughing of tissue, leaving an ulcer that heals slowly or is nonhealing (see Figure 5-11).[23] Fractionization of the radiation dose allows for high doses of radiation to be given with minimal skin damage; therefore, one high-dose exposure can cause significantly more skin damage than a higher dose that is fractionated. Case studies of radiation accident victims, which report that blistering and ulcer formation can occur with as little as 1,000 rads, support this contention.[24] The ulcerations heal with mottled hyper- and hypopigmentation, atrophic scarring, dermal fibrosis, and telangiectasia (see Figure 5-12).[23] Histologically, chronic radiation damage resembles severely actinically damaged skin, with epidermal hyperkeratosis, keratinocyte atypia, and elastotic changes in the dermis. In addition, there are dermal vessel changes with thickened walls and thromboses. The appendages, especially sebaceous glands and hair follicles, which are fairly sensitive to ionizing radiation, are often absent.[40] Skin cancers arising in radiation dermatitis include both squamous cell and basal cell carcinomas. These tumors tend to be more aggressive than tumors arising from skin not affected by ionizing radiation.[40]

The therapy of chronic radiation sequelae of the skin is largely palliative. The treatment of chronic ulcerations due to ionizing radiation is excision and graft placement.[30] The vascular changes of vessel wall thickening and thrombosis secondary to ionizing radiation exposure often lead to ischemia, poor healing, and increased chance of infection. Cell culture studies of fibroblasts exposed to ionizing radiation have demonstrated that irradiated fibroblasts have a

significantly prolonged generation time when compared to normal fibroblasts.[41] Therefore, it is important to remove all ischemic, necrotic, and infected tissue, including the ulcer bed and the surrounding affected epidermis, to obtain viable margins in which to place a graft.[30] The best graft is that of a pedicled flap from a site distant from the affected area to ensure viability of tissue, or musculocutaneous or muscle flaps with their own blood supply to increase vascularity in the damaged area.[31]

Other problems attendant with skin radiation injuries, especially those with large areas of cutaneous involvement, are severe pain, hepatorenal failure, and encephalopathic coma. These problems were especially prevalent during the Chernobyl nuclear reactor disaster in 1986.[42] Therapy for these patients consists of plasmapheresis for the hepatorenal failure and analgesics including antiinflammatory drugs and narcotics for the pain.

BIOLOGICAL WARFARE

Biological weapons, perhaps the most feared tools of war, are potentially much more destructive than any other nonnuclear munitions.[43] In a U.S. Army manual prepared for Operation Desert Shield, biological warfare was defined as "the use of microorganisms or toxins derived from living organisms to produce death or disease in humans, animals, or plants."[44(p74)] Some authorities have broadened the concept of biological warfare to include herbicides, defoliants, and other biologically active substances. Others define biological warfare more narrowly and exclude toxins because they are active outside their organism of origin. Two international agreements relate to the use of biological weapons in war: one that prohibits first use of chemical and bacteriological weapons in war (1925 Geneva Protocol) and another that prohibits the development, production, and stockpiling of biological and toxin weapons (Biological and Toxin Weapons Convention of 1972).[45] Despite these international agreements and widespread moral disapproval of the use of biological weapons, they have existed for many years, and there is continued evidence of development and production of biological weapons by the former Soviet Union and other countries.

A number of features make biological weapons attractive.

- Compared to other types of munitions, production costs are low.
- International monitoring of production is difficult.
- They are well suited for secret warfare operations.
- They are selective in their effects on the enemy: while biological weapons preserve industrial complexes, supply routes, and other military facilities, enemy personnel are either incapacitated or killed.
- Specific agents can be selected to achieve a high fatality rate, or to cause a high morbidity rate with a relatively low fatality rate, depending on the military objectives.
- Biological weapons may be used for both strategic and tactical objectives.

A number of criteria are used to select specific agents for use in biological warfare. One characteristic that makes an agent particularly attractive as a biological weapon is its ability to be aerosolized, especially if a particle size of 1.0 to 5.0 μm can be achieved. At this size, the agent generally is invisible and can also reach the lower parts of the respiratory tract (small bronchi, bronchioli, and alveoli). Resistance to environmental conditions, such as sun, heat, or cold, as well as to usual disinfectant agents, is also a desired characteristic. Preferred agents are highly virulent and able to produce severe illness, and are resistant to the usual chemotherapeutic agents. For production purposes, the ability to propagate the agent easily and to preserve it, particularly by lyophilization, is desired. Lastly, agents that produce atypical biological actions, particularly in the form in which they are delivered militarily (eg, anthrax by aerosolization) lead to difficulty in differential diagnosis and thus are also desirable. Agents currently believed to be fully developed as biological weapons that produce some dermatologic signs or symptoms include anthrax, tularemia, plague, hemorrhagic fevers, botulism, and mycotoxins.

Anthrax

Anthrax is caused by *Bacillus anthracis*, a large Gram-positive rod, either aerobic or anaerobic, that is nonhemolytic, encapsulated, and capable of forming spores. The toxin produced by *B anthracis* is

complex and includes three separate soluble proteins called protective antigen, edema factor, and lethal factor. All three have been purified, characterized, and their structural genes cloned and sequenced. A fragment of protective antigen binds to the membrane of target cells and serves as a specific receptor for edema factor or lethal factor, allowing entry of either factor by receptor-mediated endocytosis. Edema factor is a calmodulin-dependent adenylate cyclase, expressed only in target cells that provide the required calmodulin activator and ATP substrate, which is converted to cyclic AMP (adenosine monophosphate). The biological effects of edema factor, edema and inhibition of phagocytosis by polymorphonuclear leukocytes, are believed to be due to the actions of cyclic AMP in the intoxicated cells. The mechanism of action of lethal factor is unknown.[46] The usual source of human disease from *B anthracis* is contact with infected animals or contaminated animal products, usually manifested initially by cutaneous lesions. When used as a biological warfare weapon, the method of delivery would most likely be via aerosol, producing inhalation anthrax, a rare form of the naturally occurring disease, with a mortality rate approaching 100%. The skin and the gastrointestinal tract are other possible portals of entry when *B anthracis* is used as a biological weapon.

Cutaneous Findings

When the skin is the portal of entry, the characteristic finding in anthrax is a macule that progresses through papular, vesicular, or pustular stages leading to an ulcer with a blackened, necrotic eschar and surrounding, nonpitting, gelatinous, and painless edema (Figures 5-13 and 5-14). The lesion usually occurs on an exposed surface. Satellite vesicles may surround the lesion. Painful regional lymphadenitis is common. Pruritus may be an early symptom; however, advanced lesions are often asymptomatic.

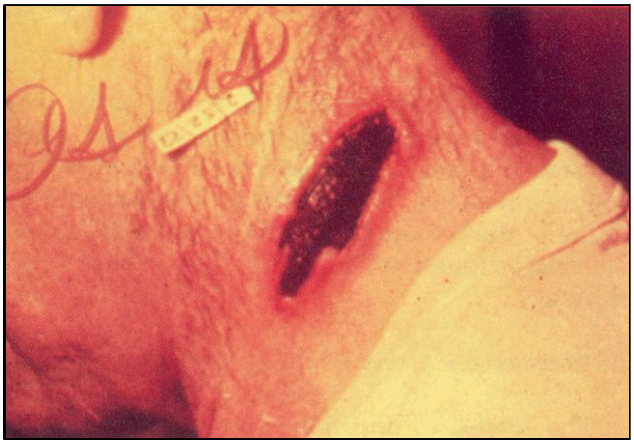


Fig. 5-13. Large necrotic lesion of cutaneous anthrax. Photograph: Courtesy of Armed Forces Institute of Pathology, Washington, D.C.

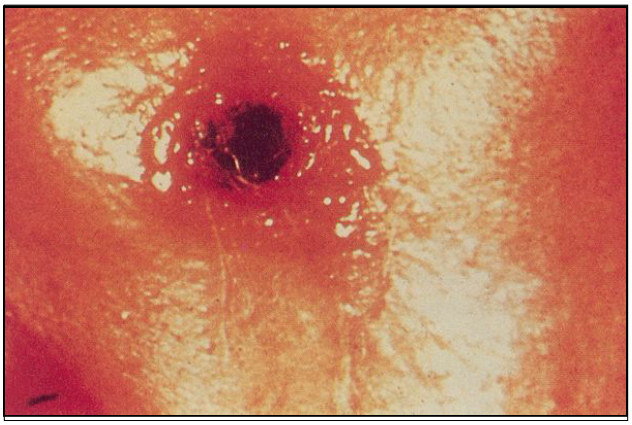


Fig. 5-14. Cutaneous anthrax. Photograph: Courtesy of Armed Forces Institute of Pathology, Washington, D.C.

Other Clinical Findings

The majority of patients with cutaneous anthrax do not have systemic symptoms; however, severe edema and septic shock may occur. Anthrax meningitis occurs rarely. If it is acquired via the gastrointestinal tract, symptoms include abdominal pain, enteritis, ascites, bloody diarrhea, fever, and nausea and vomiting. Usually, mesenteric adenitis is present. Oropharyngeal anthrax is associated with fever, sore throat, dysphagia, and, occasionally, respiratory distress. The most severe form of anthrax is acquired via inhalation, with fulminant pneumonitis and hemorrhagic mediastinitis the characteristic features.

Diagnosis

Gram's stains or cultures from cutaneous anthrax lesions usually yield *B anthracis*. Blood, pleural fluid, and cerebrospinal fluid may also be positive using routine culture techniques. Impression smears of mediastinal lymph nodes and spleen as well as smears from pleural and cerebrospinal fluid should be positive by Gram's or Giemsa stains. Direct fluorescent antibody staining of tissues is

available. Lastly, anthrax toxin may be detected in the blood by immunoassays.

Treatment

Penicillin G, 2 million units every 6 hours until edema subsides, followed by a 7- to 10-day course of oral penicillin is the recommended therapy for cutaneous anthrax, with erythromycin, tetracycline, or even chloramphenicol used in adults unable to take penicillin. For gastrointestinal or inhalation anthrax, high-dose penicillin G, 2 million units every 2 hours, is recommended. Specific therapy recommended in a primer developed for medical personnel involved in Operation Desert Shield includes ciprofloxacin 1,000 mg initially, followed by 750 mg by mouth twice daily, or intravenous doxycycline, 200 mg initially, followed by 100 mg every 12 hours. The duration of these regimens should be dictated by symptoms. Supportive therapy for shock and respiratory compromise may also be needed.

Prophylaxis

A vaccine consisting of purified protective antigen has been developed, with limited data from human studies suggesting that protection against both cutaneous and inhalation anthrax occurs with doses given at 0, 2, and 4 weeks, and then at 6, 12, and 18 months. Animal studies suggest that good protection lasting 2 years may be afforded after just two doses, 10 to 16 days apart.[44] Live, attenuated spore vaccines are used for both animals and humans in the former Soviet Union.

Prophylaxis with antibiotics, specifically ciprofloxacin (500 mg by mouth twice daily) or doxycycline (100 mg by mouth twice daily), has been suggested if information is received that a biological weapon attack is imminent.[44]

Military Significance

Anthrax has many characteristics that make it a good choice as a biological weapon. It can be produced very quickly in almost unlimited quantities, and it produces a spore form that is highly resistant to heat, disinfectants, sunlight, and other environmental factors. It can be delivered in wet or dry form and produces an aerosol of optimum size. Although high numbers of spores are required to kill 50% of exposed individuals (the LD_{50} [median lethal dose] is between 8,000 and 10,000), such doses would not be difficult to deliver using currently available techniques.[45] An outbreak of anthrax in the Soviet Union city of Sverdlovsk in April 1979 is regarded by the United States as an accidental release of dry anthrax spores, presumably from an explosion within the Microbiology and Virology Institute, a military facility. Although the official Soviet explanation for this incident was that anthrax-contaminated meat was the cause of the outbreak, an analysis by the United States suggests this incident was the result of an accident within a biological warfare facility.[45]

Tularemia

Tularemia is caused by *Franciscella tularensis*, a small, Gram-negative, pleomorphic, bipolar rod. Under ordinary conditions, the disease is acquired by contact with infected animals or via an insect vector. Delivery by aerosol would be the likely method for tularemia used as a biological weapon, causing typhoidal tularemia. For a further discussion of tularemia, see Chapter 13, Bacterial Skin Diseases.

Plague

Plague is caused by *Yersinia pestis*, a Gram-negative bacillus with pleomorphic or coccoid variants. The disease is usually acquired by skin inoculation via a flea bite or through direct animal contact. When used as a weapon of biological warfare, an aerosol would most likely be the method used. For a detailed discussion of plague, see Chapter 13, Bacterial Skin Diseases.

Hemorrhagic Fevers

Hemorrhagic fevers include a number of viral infections, such as the Marburg virus and Lassa and Ebola fevers. All the viruses in this group are highly infectious. The clinical picture is similar for many of these diseases. A more complete discussion can be found in Chapter 10, Viral Hemorrhagic Fevers.

Cutaneous and Other Clinical Findings

The cutaneous eruptions seen with the hemorrhagic fevers have been described as maculopapular in nature, becoming petechial with time. A generalized erythema may be present (Figure 5-15). Extensive purpura may develop (Figure 5-16).

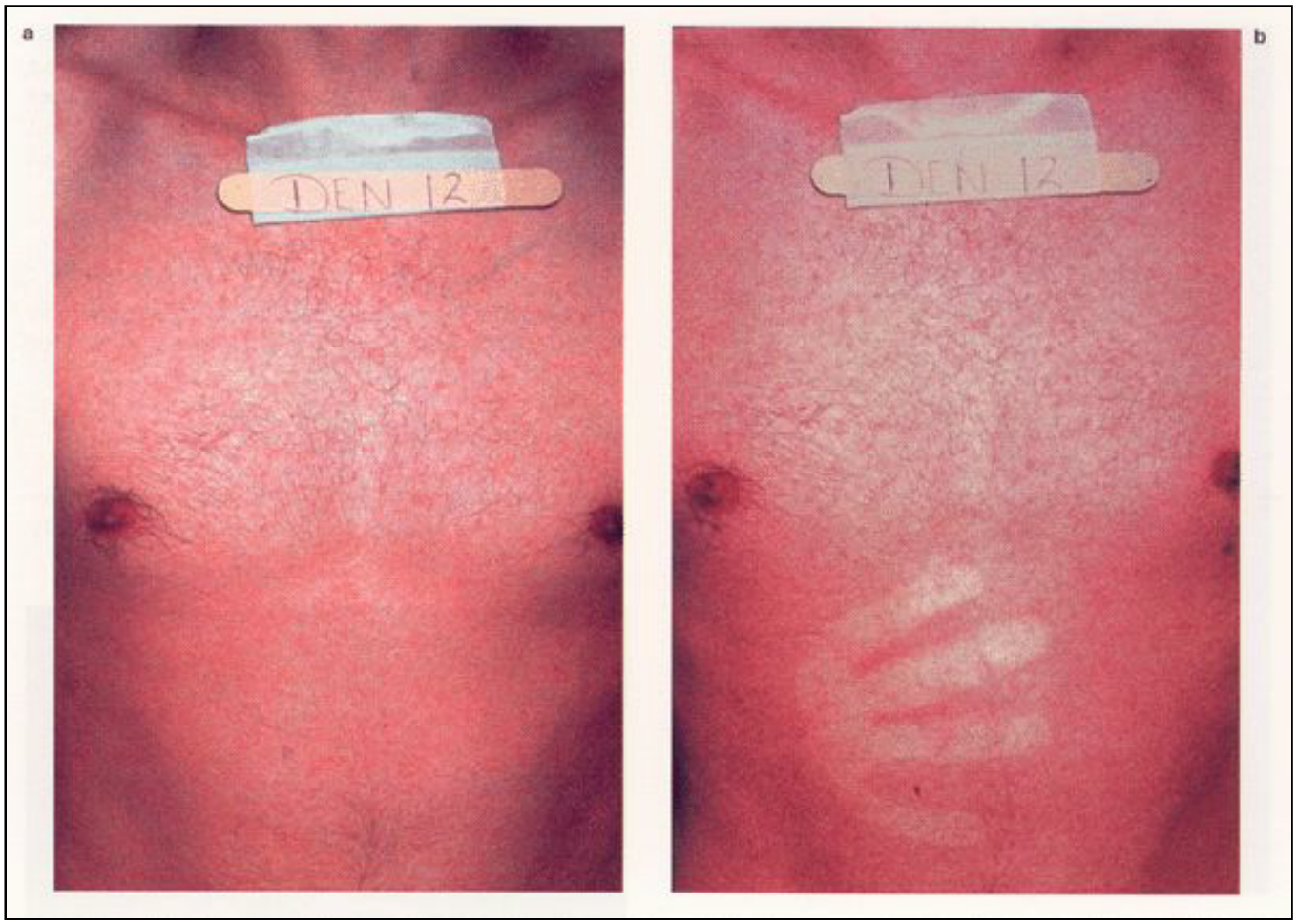


Fig. 5-15. (**a**) The scarlatiniform eruption and (**b**) the characteristic blanching that occur in the scarlatiniform type of dengue fever. Photograph: Courtesy of U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Md.

Mucous membranes may be involved, with blisters leading to ulcerations as well as petechiae and hemorrhages (Figures 5-17 and 5-18). Conjunctivitis may also be seen.

Hemorrhagic fevers usually begin with a flulike syndrome following a 3- to 10-day incubation period. Deterioration often occurs about the third day after symptoms begin, with high fever, weakness, nausea, vomiting, diarrhea, headache, chest pain, joint pains, and an eruption. Bleeding may be a significant problem, and death secondary to shock may occur in as many as 50% of patients.[47]

Diagnosis

Definitive diagnosis of hemorrhagic fevers may be difficult; however, the virus may be identified using electron microscopy or fluorescent microscopy on peripheral blood or cell cultures. Serologic tests by enzyme-linked immunosorbent assay (ELISA) or hemagglutination are available in some cases. Clinical criteria for dengue hemorrhagic fever have been established by the World Health Organization.

Treatment

Currently, treatment of hemorrhagic fevers consists of symptomatic support. Control of hemorrhagic diathesis and fluid and electrolyte management are particularly important. Use of convalescent serum has been helpful in isolated cases but would not be practical for mass casualties. Ribavirin might be useful in the treatment of viral hemorrhagic fevers, including Crimean-Congo hemorrhagic fever. The dose of ribavirin recommended is 400 mg by mouth every 4 hours for 24 hours, then 400 mg by mouth every 8 hours for 7 to 10 days or, if given intravenously, a 2-g loading dose, then 1 g every 8 hours for 4 days, then 500 mg every 8 hours for 6

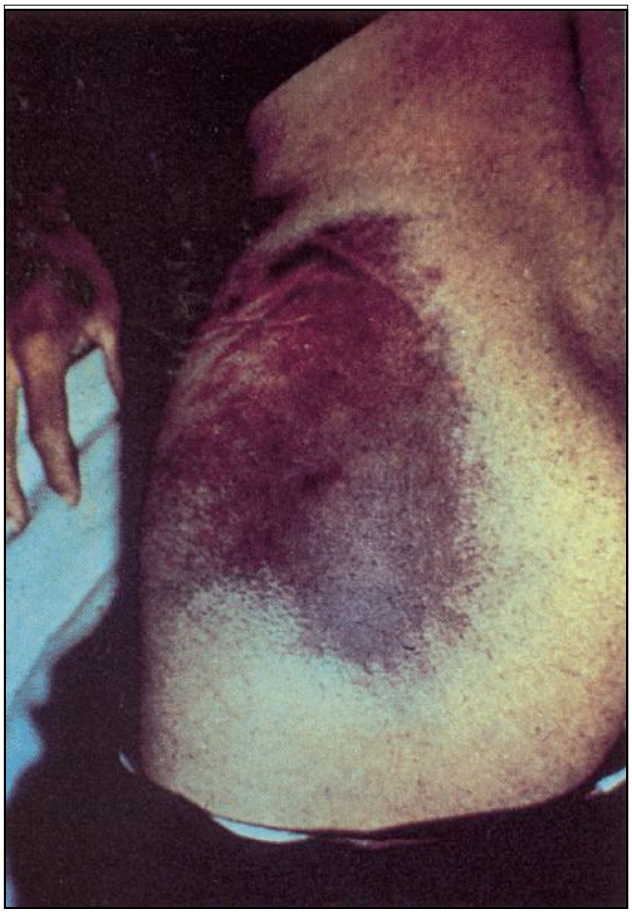


Fig. 5-16. Large purpuric lesion in a hemorrhagic fever patient. Photograph: Courtesy of U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Md.

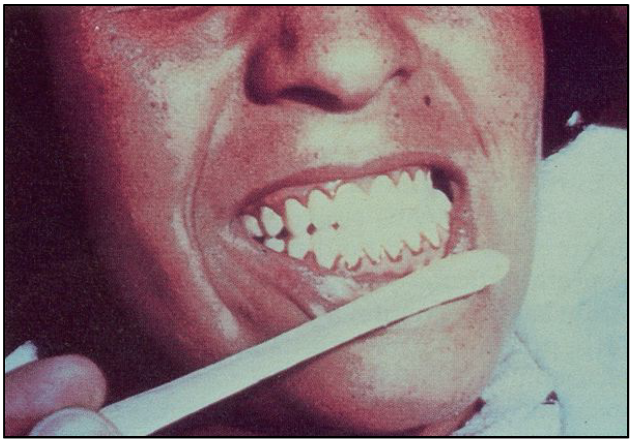


Fig. 5-17. Gingival petechiae characteristically seen in cases of Argentine and Bolivian hemorrhagic fever. Photograph: Courtesy of U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Md.

days. When given intravenously, ribavirin should be diluted in saline or 5% dextrose in water and should be administered over 15 to 20 minutes. Strict isolation of affected individuals is mandatory and should include contact, body fluids, blood, and respiratory isolation.[44]

Prophylaxis

A number of vaccines for the hemorrhagic fevers have been studied, with none currently licensed for use in humans.

Military Significance

The hemorrhagic fevers fulfill many of the criteria for effective biological agents including stability

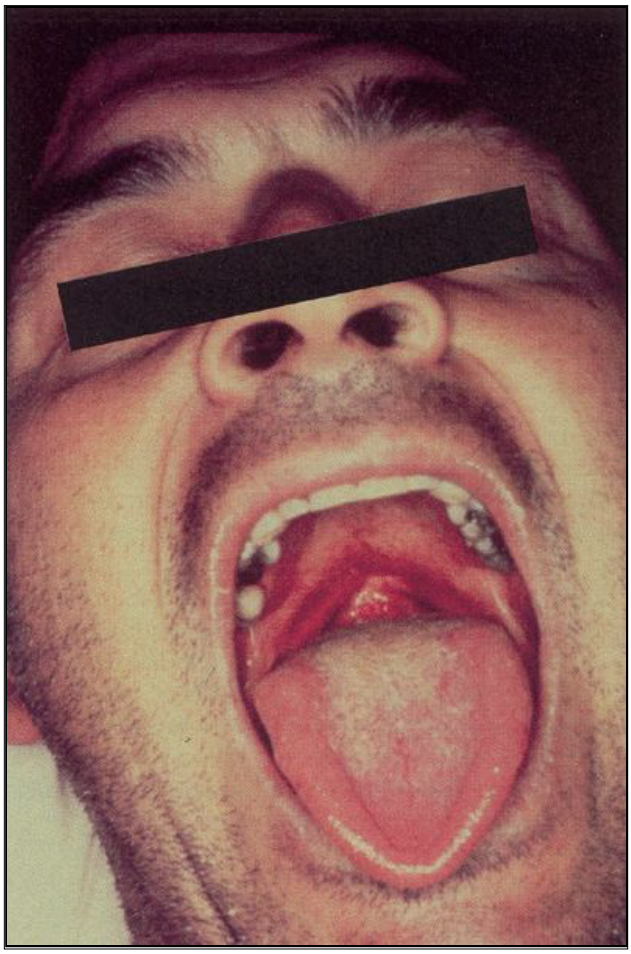


Fig. 5-18. The characteristic petechial lesions of the soft palate, which are seen in several hemorrhagic fevers. Photograph: Courtesy of U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Md.

in aerosol form, high virulence and the ability to produce severe illness, and the absence of specific prophylactic measures or specific treatments for the disease produced.

Botulism

Botulism refers to the disease produced by the potent neurotoxins of the organism *Clostridium botulinum*. *C botulinum* is a Gram-positive, incompletely aerobic, spore-forming bacillus. Its neurotoxins are large proteins of molecular weight approximately 150,000 daltons, and are identified by their antigenic specificities as types A, B, C, D, E, F, and G. Their toxic effects are due to inhibition of acetylcholine release from cholinergic terminals at the motor end plate.[48] Human disease occurs after ingestion of preformed toxin (food poisoning), by enteric production and subsequent absorption of toxin (infant botulism, shaky foal disease, adult sudden death), or via absorption from infected wounds. It is speculated that the most likely method of delivering botulism via weapons would be by aerosolization of alpha toxin, a highly toxic phospholipase C.

Cutaneous and Other Clinical Findings

Dry mucous membranes, with extreme dryness of the mouth, perhaps with crusting, are the only mucocutaneous findings in clostridial food poisoning; dilated pupils and a clear sensorium are seen; gastrointestinal symptoms are variable. Sensory functions are intact, but cranial nerve weakness and descending peripheral motor weakness progressing to paralysis occurs, which may result in respiratory failure. In infant botulism, feeding problems from cranial nerve weakness, altered cry, hypotonia, poor head control, and constipation are seen. Wound botulism results in disease similar to that seen in clostridial food poisoning. No information is available on the precise toxic effects of inhalation botulism; however, it is presumed to result in a serious pulmonary insult, with associated vascular leak, hemolysis, thrombocytopenia, and liver damage.[44]

Diagnosis

The clostridial enterotoxin can be detected in fecal samples, vomitus, or gastric fluid from individuals with clostridial food poisoning. An animal bioassay is available for detection of toxin in serum but may be falsely negative.

Treatment

In addition to supportive care for cranial nerve paralysis, respiratory failure, and autonomic dysfunction, an equine antitoxin is available, and a human pentavalent antitoxin is being tested in the treatment of botulism.[44] Attempts to remove remaining toxin from the gastrointestinal tract may be helpful, as well as antibiotics.

Prophylaxis

A pentavalent toxoid of *C botulinum* types A, B, C, D, and E is currently being tested. This toxoid is not yet available for general prophylactic use.[44]

Military Significance

Botulinum toxins are dangerous as biological warfare agents because they produce illness with a high mortality rate. The toxins are readily available and are relatively stable, resisting degradation by acid and proteolytic enzymes, and requiring heating to 100°C for 10 minutes for inactivation. They can be delivered in aerosol form. In addition to being highly lethal, those individuals who survive botulism intoxication often require several weeks of convalescence; thus, effects on troop strength are potentially very serious.

Mycotoxins

Mycotoxins are toxins produced by many strains of fungi that grow on food products and produce toxic effects in animals and people exposed to them. Mass outbreaks of disease in animals caused by moldy foods have been documented in animals and humans. The only human outbreak with extensive documentation occurred in the USSR during the later years of World War II, producing a syndrome termed alimentary toxic aleukia, a panleukopenia.[49] Interest in mycotoxins has increased in recent years due to reports of their use as biological warfare agents in various regions of the world, including Southeast Asia and Afghanistan.[50–54] Trichothecene mycotoxins are a family of sesquiterpenes, all derived from a trichothecene ring system (Figure 5-19). They are insoluble in water, but can be solubilized in lipids, propylene glycol, and dimethyl sulfoxide (DMSO). They are produced by many species of molds in the genera *Fusarium*, *Myrothecium*, *Trichothecium*, *Trichoderma*, and *Cephalosporium*. They produce a wide range of toxic effects in ani-

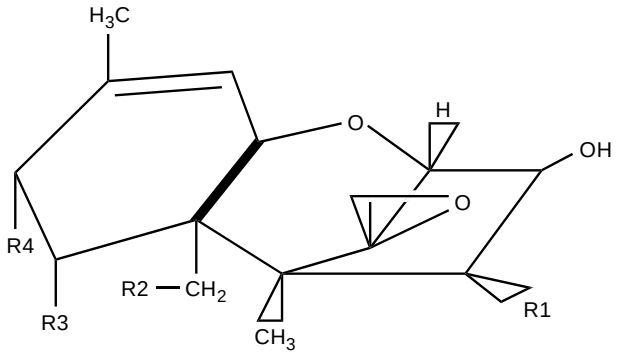


Fig. 5-19. Diagram of the basic trichothecene ring.

mals, depending on dose, specific metabolites present, and even the particular combinations of toxins present.[55] The biochemical changes leading to cell death induced by the toxins are not completely known; however, it has been shown that protein synthesis is impaired at the initiation, elongation, and termination phases, and marked polysomal disaggregation is evident.[49,56] It is believed that trichothecene mycotoxins are very potent inhibitors of protein synthesis in eukaryotic cells.[56] The most toxic trichothecene toxin identified is called T-2 toxin. Others include deoxynivalenol (DON, also called vomitoxin), diacetoxyscirpenol (DAS), and zearalenone. Most of the information that follows is derived from the study of the T-2 toxin.

Cutaneous Findings

Exposure to trichothecene toxins often causes prominent cutaneous findings. Erythema, which may be generalized, occurs within minutes to hours of exposure. It may be accompanied by itching, burning, tingling, or even painful sensations. Evanescent "scattered red spots" have also been reported. Blisters, which may be large, and red papules have also been described. A Red Cross physician described erythematous 5- to 10-mm papules with fine vesicles that developed 6 to 24 hours after exposure as characteristic lesions. The lesions later become black and crusted. When blisters erode or form ulcers, prolonged healing, up to several months, may be noted. In severe cases, large sheets of skin were shed. Alopecia has also been reported, along with necrotic oral ulcers.[57]

Other Clinical Findings

Severe systemic symptoms, sometimes resulting in death, have been reported from presumed trichothecene toxin exposure. Extensive bleeding, acute leukopenia, septicemia, and bone marrow function failure may all be seen. Based on evaluation and questioning of presumed victims of trichothecene toxin exposures in Cambodia, Laos, and Afghanistan, the clinical signs and symptoms of trichothecene toxicosis are believed to occur in four stages[56,57]:

1. The initial findings consist of a burning sensation of the skin and mucous membranes, headache, dizziness, weakness, abdominal pain, vomiting and diarrhea, fever, sweating, tachycardia, and cyanosis. This stage may last up to 9 days.
2. Next, from 2 to 4 weeks following exposure, anemia, leukopenia, granulocytopenia, thrombocytopenia, and lymphocytosis are seen, along with symptoms of headache, fatigue, vertigo, and the clinical finding of petechiae.
3. The third stage is not well characterized as to duration and may result in death. Petechiae, focal necrotic lesions, ulcerative pharyngitis, gastrointestinal and mucosal hemorrhage, lymphadenopathy, and progression of hematological abnormalities occur.
4. Lastly, resolution of hemorrhage and necrotic lesions may occur, with slow improvement of hematological abnormalities, and a prolonged risk of infectious complications.

Diagnosis

The diagnosis of mycotoxin-related disease will be a challenge for medical personnel. The specific signs and symptoms that result from exposure depend on a large number of variables including the specific mycotoxin or mycotoxins involved, the method of delivery, the dose received, the specific vehicle used, the portal of entry into the body, climatic conditions, the use of protective gear, and the nutritional status and general health of the casualty. Because of the large number of variables determining the clinical presentation, the spectrum of disease resulting from exposure to mycotoxins will likely be very broad. Differential diagnosis should include exposure to other toxins, such as the vomiting agents (adamsite, diphenylchloroarsine), mustards, Lewisite, phosgene oxime, and nerve agents.[57] The vomiting agents have a shorter duration of action, about 30 minutes, compared to 1 to 2

days for mycotoxins, and also generally cause less severe vomiting. Mustard agents produce symptoms that are not quite as delayed as with mycotoxins, and less often cause burning, dysesthesias, generalized erythema, or hemorrhagic lesions. Healing following mustard exposure is delayed even longer than that seen after mycotoxin injury. Lastly, mustard generally does not cause hemoptysis, hematemesis, or toxic pulmonary edema. Lewisite may cause many signs and symptoms similar to mycotoxins; however, they occur much sooner, usually within a few minutes of exposure. In addition, hematemesis and other hemorrhagic signs and symptoms are more often seen with mycotoxin exposure than with Lewisite. Phosgene oxime causes immediate effects on the skin and eye, and also causes less hemorrhage than the mycotoxins. With nerve agents, miosis, severe bronchoconstriction, wheezing, hypersecretion, and polyuria are prominent, and skin changes are not seen. Pulmonary edema, massive hemoptysis, and hematemesis are not sequelae of nerve agents.

Although optimal field detection of mycotoxins is not yet available, a number of detection methods have been developed or are under study including radioimmunoassay in biological fluids, gas chromatograph mass spectrometry, polarography, thin-layer chromatography, gas–liquid chromatography, high-performance liquid chromatography, infrared spectroscopy, and nuclear magnetic resonance spectroscopy. The most promising area of development of detection methods is in the use of immune-based systems such as monoclonal antibodies.[57]

Treatment

Immediate treatment of mycotoxin exposure should include lavage of eyes and skin with any nontoxic liquid. Absorption from the skin is slow; therefore, thorough cleansing with soap and water is very important in limiting the amount of systemic toxin exposure. Wounds should be irrigated with saline or other solutions, blotted with sterile dressings, then managed like other wounds. The U.S. Army's M258 kit, which is used in mustard decontamination, has been found to be unsatisfactory for decontaminating mycotoxins from the skin. Personnel performing the decontamination should wear eye and skin protection. Contaminated water should be considered toxic. Instruments that become contaminated must be handled carefully, because even autoclaving may not eliminate the mycotoxins. If heavy exposure is suspected, stripping of the stratum corneum from the hands and face with tape may remove a reservoir of mycotoxin, as significant binding to the stratum corneum may occur.

In addition to skin, the bowel may serve as a reservoir for mycotoxins. Toxin is excreted in the bile and subsequently reabsorbed. Emesis is often associated with mycotoxin exposure and probably eliminates some toxin. Activated charcoal, bentonite powder, and cholestyramine given orally may be used to bind the toxin and remove it from the gastrointestinal tract. Once in the circulation, mycotoxins are excreted primarily in urine, so one might consider dialysis or hemoperfusion; however, such treatments have not been adequately studied and may even be contraindicated if coagulopathy or hypotension is present.

Systemic steroids and vitamins A, C, and E are mycotoxin treatments supported by animal studies. If significant skin exposure has occurred, consideration of therapy with microsomal enzyme inducers such as phenobarbital may be reasonable, as this treatment may speed clearance of toxin that is being slowly absorbed.[57]

Prophylaxis

Standard protective clothing and chemical warfare masks are believed to provide some protection from mycotoxins.[57] In addition, a variety of drugs have been proposed as possible pretreatments for mycotoxin exposure. A number of compounds have been studied in animal models; however, no single pretreatment is known to prevent disease from mycotoxins without causing side effects. Drugs that are proposed as possibly useful include microsomal enzyme-inducing compounds such as phenobarbital; free-radical protectants or antioxidants such as vitamins A, C, and E; membrane-stabilizing drugs such as the systemic steroids; detoxifying compounds such as the thiazolidines; and antimuscarinic drugs such as atropine. In addition, maintaining normal stores of intracellular glutathione may be an important protective measure and could be accomplished by adequate nutrition, avoidance of alcohol, tobacco, and drugs, and possibly by dietary supplementation with D-L methionine.[57] The decision to pretreat troops, and the specific agents employed, will need to be carefully considered in view of the possible adverse effects caused by pretreatment.

Military Significance

Characteristics of trichothecenes that make them good candidates for biological warfare agents

include their irritating and damaging effects on many organs vital to effective combat, such as the eyes, skin, upper and lower respiratory tracts, mouth, throat, and entire gastrointestinal tract. Effects are also seen in the peripheral and central nervous systems; skeletal and cardiac muscles; and the hematopoietic, clotting, and immune systems. In large doses, death may occur within minutes to hours, whereas smaller doses cause delayed death or incapacitation that may last for days to weeks. As adjuncts to more toxic agents, mycotoxins may irritate the skin enough to prevent wearing of protective gear.[57] Production of mycotoxins is relatively simple, and reports of mycotoxins found in high concentrations, along with man-made materials such as DMSO, suggest that the incorporation of trichothecenes into weapons has already been successful. It is believed that delivery can be accomplished by aircraft via spraying, dusting, rockets, or dropped exploding containers, as well as artillery and mortar rounds.[57] Trichothecenes are moderately potent, with nanogram levels causing skin erythema. Field detection is not yet reliable. In addition, mycotoxins are persistent, difficult to decontaminate, and have no specific treatment or prophylaxis. Thus, their potential use as biological weapons must be considered a serious threat.

CHEMICAL WARFARE

The technology for the development of chemical agents is readily available and the manufacture of these agents is relatively simple. Compounding the problem is the willingness of some countries with the technology to manufacture tactical weapons to supply other countries with the arms that are capable of delivering chemical weapons. Reports suggesting that Iraq has produced thousands of tons of sarin, tabun, and mustard gas demonstrate how real the problem has become.[58] Therefore, the likelihood is quite high that one will encounter the use of chemical weapons in future conflicts.

Chemical Warfare Doctrine and Weaponry

To understand the potential for chemical casualties in modern warfare, one needs to understand why chemicals might be used on the battlefield. Many think that the main purpose for using chemical warfare would be to inflict fatalities; however, close scrutiny of the chemical tactics and doctrine of the former Soviet Union suggests otherwise. Their goal in the use of chemical weapons was to degrade the enemy's combat effectiveness. This feat was accomplished through inflicting nonlethal casualties, denying key terrain, and necessitating the wearing of chemical protective clothing. To accomplish these goals, massive amounts of chemical agents have to be delivered, and it appears that the Soviets acquired both the necessary quantities of agent and the means with which to deliver it.

It is estimated that at one time Soviet chemical munitions consisted of 350,000 tons of various agents that composed up to 20% of the artillery munitions stockpile and 30% of the FROG and Scud rocket warheads.[59] Although this stockpile is now being rapidly destroyed, substantial amounts will remain, and the possibility that these weapons could fall into the hands of third-world nations or terrorists is strong. Additional means of chemical delivery include the multiple rocket launcher, mortars, aerial sprays, and bombs. In combination, these weapons would be used to degrade our ability to wage war. Figure 5-20 shows the various areas of the battlefield that would be subject to attack. Areas likely to receive persistent chemical agents would include key terrain, necessitating that those positions would either have to be evacuated or the troops in those areas would have to don chemical protective gear and lose a significant portion of their combat effectiveness. The former Soviet doctrine also required the chemical attack of rear areas in which command centers, hospitals, and logistical supply areas are located. This strategy would be well within the capabilities of Soviet-made weapons including the artillery (20-km range), FROG missiles (60-km range, 300-kg payload), the Scud missiles (280-km range, 1,000-kg payload),[15,16] and the FROGGER aircraft. Nearer the forward edge of the battle area, smaller weapons such as mortars could be used. In addition, the multiple rocket launchers of the Soviet Army have been noted for their capacity to deliver large quantities of chemical agents over a company-sized defensive area (Figure 5-21).[59,60] Intelligence estimates suggest that the main chemical threats developed by the former Soviet Union include mustard gas, cyanide gas, and various nerve agents.

Sulfur Mustard and Nitrogen Mustard

The mustard used in World War I, called sulfur mustard (H), Yperite, or LOST, has a chemical struc-

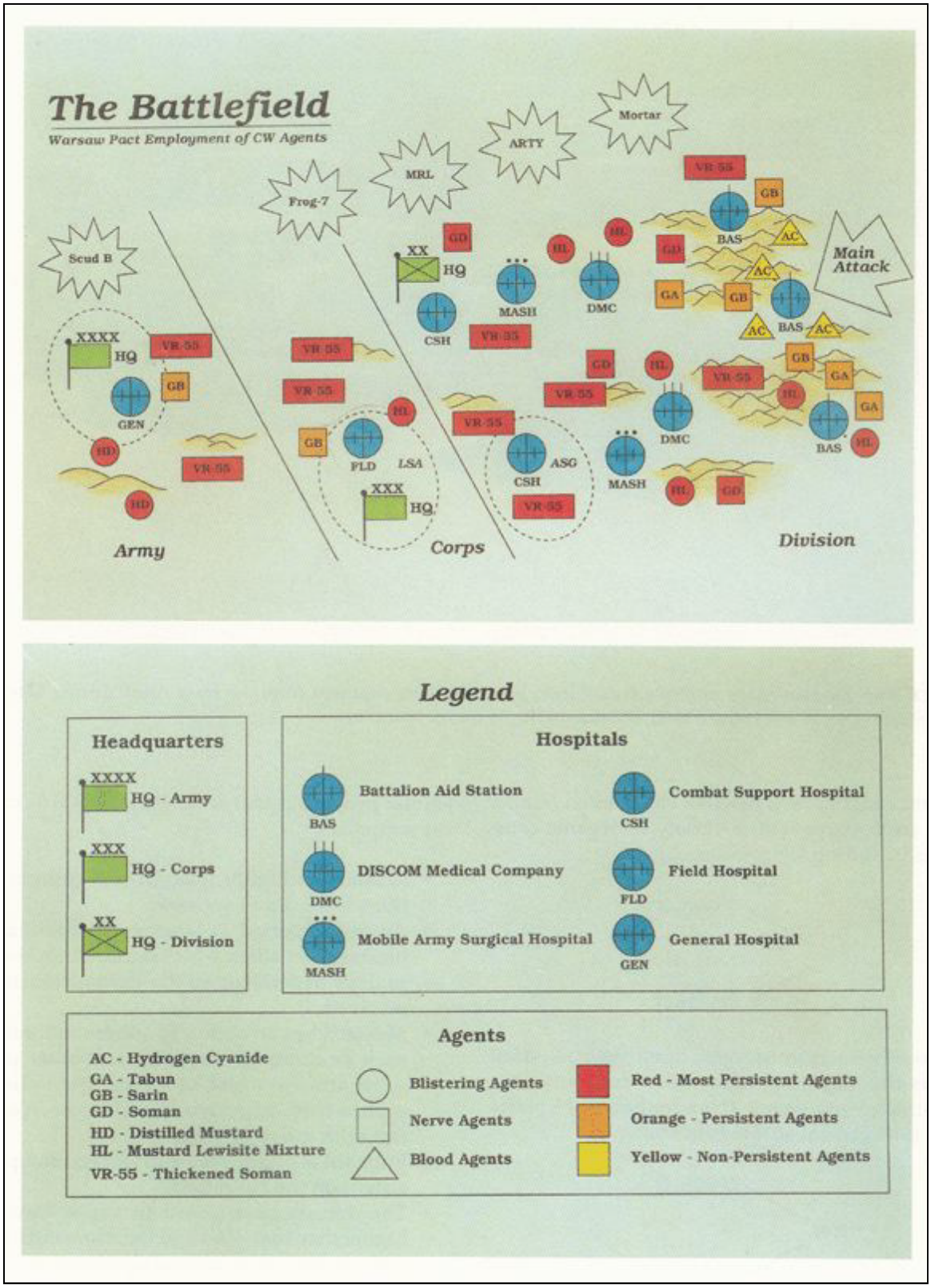
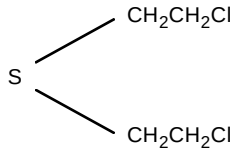


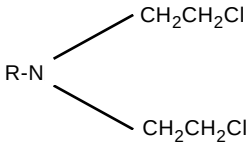
Fig. 5-20. A depiction of a chemical warfare attack based on Soviet tactics. Note the use of persistent agents such as mustard in rear areas where hospitals may be located. Reprinted from US Department of the Army. *Desert Storm*. Washington, DC: DA; 1992. DA PAM S-8.

Fig. 5-21. Two Russian-made multiple rocket launchers that were captured from the Iraqi Army during Operation Desert Storm. On the left is the BM-21 122-mm multiple rocket launcher.

ture that contains two reactive chloroethyl bonds, which are reactive with a variety of organic compounds including DNA molecules.[61]



Mechlorethamine, mustargen, or nitrogen mustard (NH) is the alkylating agent used currently as a chemotherapeutic agent. It is a congener of Yperite with a nitrogen substituted for sulfur.



Although nitrogen mustard is considered more toxic and less persistent than sulfur mustard, they have similar properties that make them useful as chemical weapons:

- Mustard is highly toxic in low concentrations to all organ systems.
- An initial period of latency is exhibited in mustard casualties, which can last from hours to days dependent on the dose of mustard received.
- Mustard has an ability to adhere to fomites such as clothing, weapons, and other personal articles, which can injure individuals such as medical personnel who come in contact with mustard casualties.
- Mustard is highly stable in storage and persistent on the battlefield.
- The density of mustard in vapor form is higher than that of air and therefore mustard will remain stationary and sink into trenches and other protective structures in the delivery area.
- Mustard can be delivered effectively with a variety of weapons.

- Production is simple and relatively inexpensive.
- Mustard casualties typically have a low mortality and a long recuperation, which can overwhelm the capacity of the medical treatment facilities all along the echelons of care.

The mustards are colorless to light yellow viscous liquids that, in high concentrations, smell like garlic or fish. Hydrolysis of mustard, which renders it relatively nontoxic, occurs in water, albeit slowly over hours. The process of hydrolysis can be greatly accelerated by the addition of a strong base or acid; however, the reaction between mustard and concentrated acids can produce high amounts of heat and possibly fire. Therefore, dilute acid solutions should be used in mustard decontamination. Decontamination agents include sodium thiosulfate, chloramine, potassium permanganate, sodium bicarbonate, hypochlorite, hydrogen peroxide, sodium chlorate, super tropical bleach, sodium hydroxide, soap and water, and ammonia solutions. Absorbants that bind mustards include fuller's earth, activated charcoal, and other available absorbent powders including earth and flour. Mustards are soluble in organic solvents such as petroleum distillates and alcohols, and these agents may be used to assist in removal of mustards; however, care must be used to avoid increased skin absorption of mustards with these solvents.

Pathophysiology of Mustard Poisoning

Mustard is a local and pulmonary irritant and vesicant, and a systemic poison. Whether in gas or liquid form, mustard binds to tissue and reacts irreversibly within minutes or is taken into the circulation.[62] The action of mustard involves the release of alkylating chemical linkages that interfere with DNA synthesis by binding to the nucleotides within the DNA strands; this is the radiomimetic effect of mustard (ie, it mimics the effect of radiation in producing DNA molecule breaks).[61] This characteristic appears to result in the death of the cell. The exact mechanism is not understood but may involve the upregulation of cellular DNA repair enzymes, which decrease the intracellular stores of NAD that are normally used to produce ATP, the energy storage molecule of the cell.[63] The loss of ATP in the epidermal cells of the skin may also induce a hypoxemia-like state, which may result in oxygen radical formation and subsequent cell-structure damage from reaction with the free radicals.[64] Another mechanism of cell death has been postulated that involves the effect of mustard on the Ca^{2+} adenosinetriphosphatase (ATPase) in the cell membrane. The alkylation of the sulfhydryl groups in this enzyme leads to an increase in cytosolic calcium and cell death.[65] Direct DNA damage, inactivation of cellular enzymes such as pyruvate oxidase, increased cell-membrane permeability, and the resultant loss of the cell's ability to maintain the integrity of the cell membrane may all contribute to cell death. Despite the fact that the action of mustard at the molecular level is not completely understood, the knowledge already gained over the past 2 decades has led to new insights into potential therapeutic modalities for mustard casualties, which will be discussed later in this chapter.

At a cellular level, skin damage is related to the amount of exposure to mustard, either as a gas or a liquid. Although the fixation of mustard to the tissue occurs within several minutes, histological changes within the epidermis are not evident until 30 to 60 minutes after exposure and do not become fully manifest until 2 to 3 days after exposure. The earliest changes are in individual keratinocytes, which become pyknotic and dyskeratotic (Figure 5-22). In 24 hours, inspection reveals more keratinocytes that are dyskeratotic and swollen, invasion of inflammatory cells into the epidermis, and intra- and subepidermal vesicle formation as a result of widespread cellular edema and death. This process often occurs over 2 to 10 days and is slowly progressive. In the affected areas, at the height of the reaction, dermal vessels are contracted and necrotic. This feature probably contributes to the dermal edema and epidermal necrosis seen histologically during this period.[66,67] Typically, an absence of thrombi in vessels and a mild, mixed, perivascular infiltrate are found. Histological specimens taken from Iranian mustard casualties revealed that blister formation was intra-epidermal, with the periodic acid-Schiff– (PAS) positive basement membrane located on the floor of the vesicle (Figure 5-23).[68] A sparse, inflammatory infiltrate in the blister and upper dermis are present. The picture of a necrotic epidermis with minimal inflammation mimicked the histology of toxic epidermal necrolysis. When these blisters healed, the histological picture of the areas of dark pigmentation included increased amounts of melanin throughout the epidermis (especially along the basal layer) and in dermal macrophages and was consistent with postinflammatory hyperpigmentation (Figure 5 -24).[68]

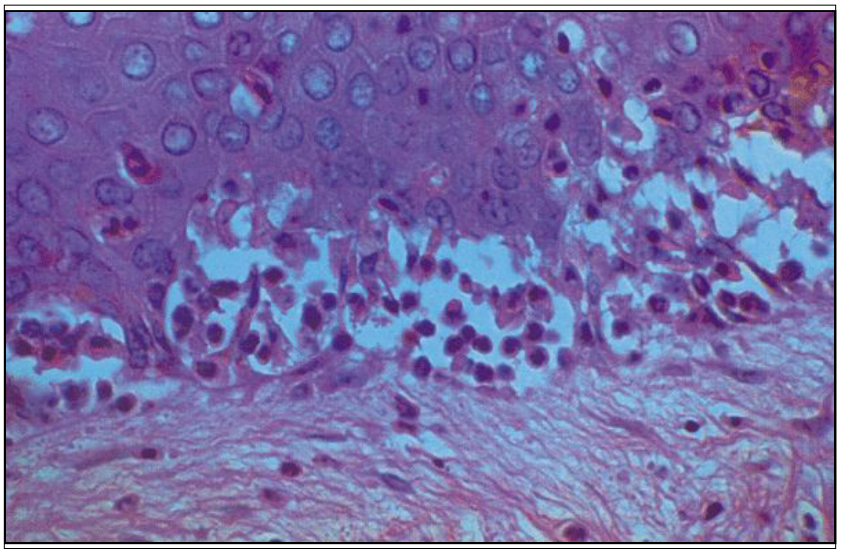


Fig. 5-22. Micrograph of a human skin graft on a nude mouse 24 hours after mustard exposure. Note the epidermal cell necrosis, infiltration of inflammatory cells, and incipient blister formation along the dermal– epidermal junction. Photograph: Courtesy of Dr. Bruno Papirmeister, Science Applications International Corporation, Joppa, Md.

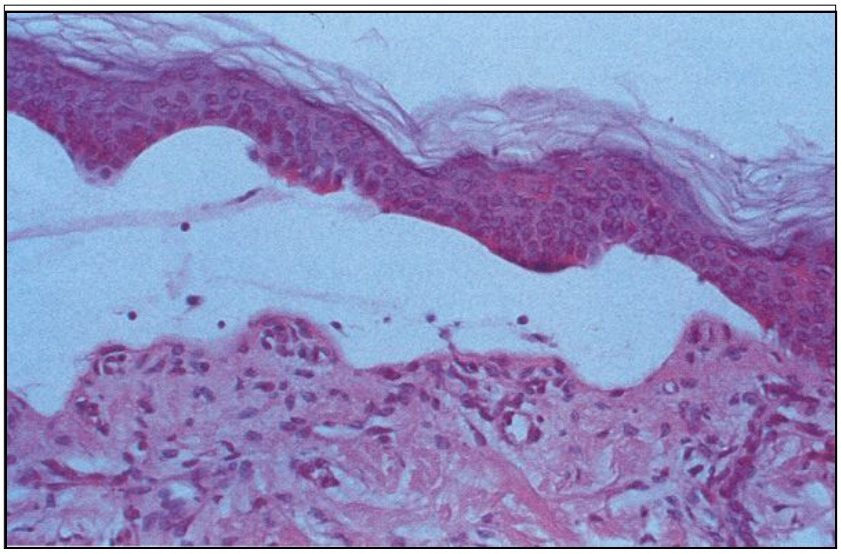


Fig. 5-23. Histological picture of a newly formed blister in an Iranian casualty exposed to mustard gas. The stain is periodic acid-Schiff (PAS); note that the PAS-positive basement membrane is at the floor of the blister. Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

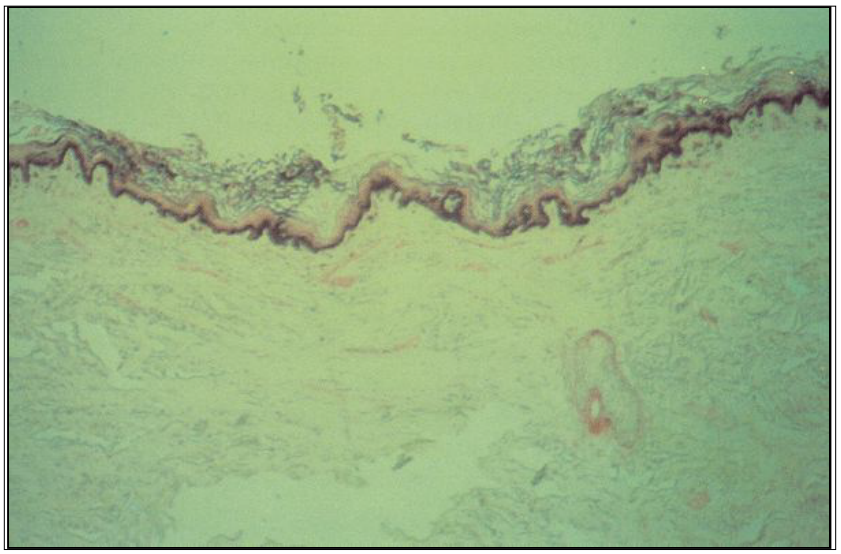


Fig. 5-24. Biopsy of an area of residual hyperpigmentation in a mustard casualty reveals increased melanin deposition along the basal cell layer of the epidermis (Fontana-Masson's stain). Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

Clinically, mustard blisters result in superficial ulcerations not unlike those that develop in chemical or thermal burns. Although the ulcers look like burns, reepithelialization and the propensity to infection are altered due to the radiomimetic effects of mustard. These effects include prolonged healing due to the suppression of cell division and systemic immunosuppression via immune cell damage and death.

Clinical Signs and Symptoms of Mustard Exposure

The experience with mustard poisoning in World War I until recently has been the chief source of information on the effects of mustard on human subjects. A classic description of the effects of mustard on an unprotected individual was provided in 1925:

> On exposure to the vapor or to a finely atomized spray of mustard, nothing is noticed at first except the faint though characteristic smell. After the lapse of several hours, usually four to six, the first symptoms appear. The systemic symptoms are intellectual dullness or stupidity, headache, oppression in the region of the stomach, nausea or vomiting, malaise and great languor and exhaustion. In many cases these symptoms may not be noticed, and the local symptoms first attract attention. The eyes begin to smart and water. There is a feeling of pressure or often of a foreign body, and photophobia, and when examined the conjunctiva is found to be reddened. The nose also runs with thin mucus as from a severe cold in the head, and sneezing is frequent. The throat feels dry and burning, the voice becomes hoarse, and a dry harsh cough develops. Inflammation of the skin now shows itself as a dusky red erythema of the face and neck which look as though they had been sunburned, but are almost painless. The inner surfaces of the thighs, the genitals, the buttocks, the armpits, and other covered portions of the body are similarly affected. Mustard affects more severely those parts of the body where the skin is tender and well supplied with sweat glands. Itching and burning of the skin may be spontaneous, or first noticed as the result of washing. Even these mild symptoms may be sufficiently irritating to cause sleeplessness. At the end of twenty-four hours a typical appearance is presented. The conjunctivitis has steadily increased in intensity, the vessels are deeply injected, and one of the main items of distress is caused by the pain in the eyes which may be very intense. The patient lies virtually blinded, with tears oozing from between bulging edematous eyelids, over his reddened and slightly blistered face, while there is a constant nasal discharge, and continuous harsh, hoarse coughing. Frontal headache is often associated with pain in the eyes and photophobia and blepharospasm is always marked. During the second day the burned areas of the skin generally develop into vesicles, and the scrotum and penis and other badly burned areas become swollen, edematous and painful to the touch. Bronchitis now sets in with abundant expectoration of mucus, in which there may later be found large actual sloughs from the inflamed tracheal lining. The temperature, pulse rate and respiration rate are all increased.
>
> These symptoms now increase in intensity for several days if the case has been severely burned. On the other hand, cases that have been only slightly poisoned may never proceed to the blister stage.[69(p327)]

Recent United Nations observers sent to Iran to evaluate chemical casualties have given descriptions of sulfur mustard victims that essentially mirror this description.[68] In the aftermath of a chemical attack on the Iranian towns of Oshnaviyeh and Abadan, the victims were described with initial symptoms of severe coughing, discharge from the nose and eyes, conjunctivitis (Figure 5-25), and skin irritation, all of which occurred from 20 minutes to several hours after the chemical exposure. The first skin symptom was often itching, and with heavy gas exposure was accompanied by nausea and vomiting. The skin then developed an erythema not

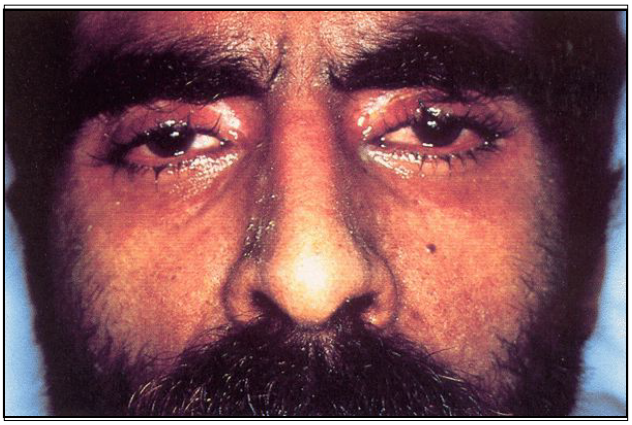


Fig. 5-25. Conjunctivitis in an Iranian soldier exposed to mustard. Although the skin is minimally affected, eye involvement is relatively severe. As demonstrated in this patient, the eyes are significantly more sensitive to the effects of mustard than the skin. Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

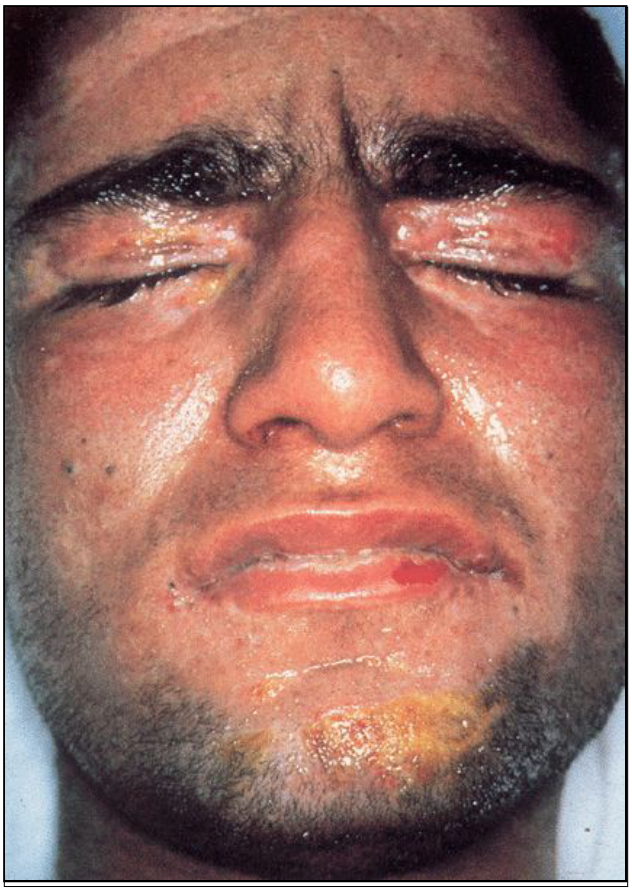


Fig. 5-26. Mild erythema with some mucosal involvement in an Iranian mustard casualty. Note the yellow crusting below the mouth, which is suggestive of a secondary bacterial infection. Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

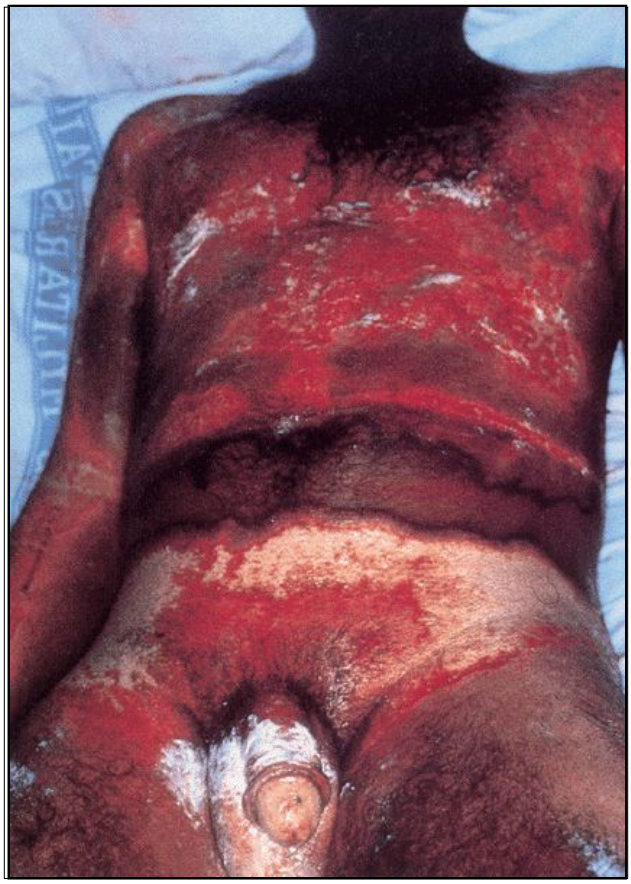


Fig. 5-28. Diffuse superficial ulcerations secondary to the rupture of bullae in an Iranian casualty of a mustard attack. Note the involvement of the inguinal area. Although this area was probably protected with at least two layers of clothing, the increased moisture in the area resulted in significant blistering. The characteristic hyperpigmentation seen in mustard casualties is apparent around this individual's waist and neck areas. Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

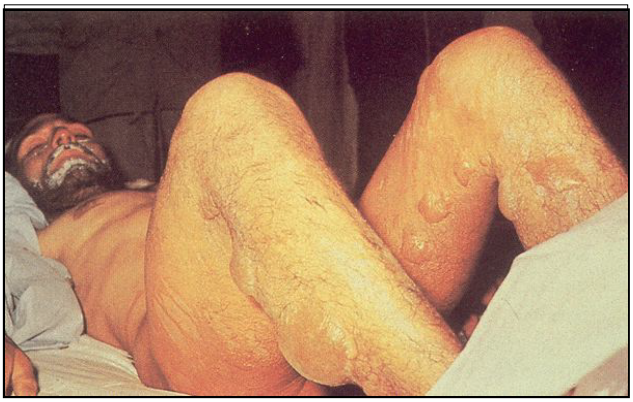


Fig. 5-27. Diffuse bullae in an Iranian mustard casualty. This type of blistering usually occurred in relatively heavy mustard exposures. The intensity of the blistering was usually greater in the intertriginous areas, where there was increased moisture. Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

unlike that seen with a moderate sunburn (Figure 5-26). After 1 to 4 days, blisters appeared on exposed areas of the extremities (Figure 5-27). In some patients, the blisters coalesced to form large bullae that broke, leaving large superficial ulcers that covered in excess of 85% of the surface area (Figure 5-28).[70,71] In patients in the Abadan attack, intertriginous areas such as the axillae and inguinal areas became intensely involved (Figures 5-29 and 5-30). The affected skin developed black and blue discoloration and became infected in many areas.[70] Other signs and symptoms included hemoptysis, bronchitis, pulmonary edema, severe leukopenia, thrombocytopenia, and pancytopenia. Death was usually a result of respiratory compromise, infection, fluid imbalance, or any combination.

The course of the signs and symptoms of mustard exposure depends on dose, type of exposure (liquid versus vapor), individual susceptibility, and other variables such as protective equipment worn and decontamination measures. Therefore, symptoms ranging from mild, transient, respiratory symptoms to severe, widespread, systemic involvement can be seen in the casualties from a single gas attack.

The clinical course of skin signs and symptoms of mustard poisoning can be divided into five phases: the latent phase, erythema phase, blistering phase, necrosis phase, and healing phase. In cases of mild exposure to vaporized mustard (concentrations around 1 μL/L), often the course consists only of the latent and erythema phases without the blistering and necrosis phases. In moderate-to-severe exposures to high concentrations of gas or to liquid mustard (concentrations above 10 μL/L), all phases occur and often at an accelerated pace. In mild exposures, the latent skin phase, in which no symptoms occur, may last up to 24 to 48 hours; but in heavy exposures, skin symptoms such as itching, burning, and erythema have been noted in as short a time as 5 minutes. Although there can be variability in the clinical course, Table 5-1 summarizes the chronology of the different phases of the acute signs and symptoms of mustard poisoning utilizing clinical data from several sources, including case histories of some Iranian mustard casualties reported by the World Health Organization.[70–73] Skin lesions

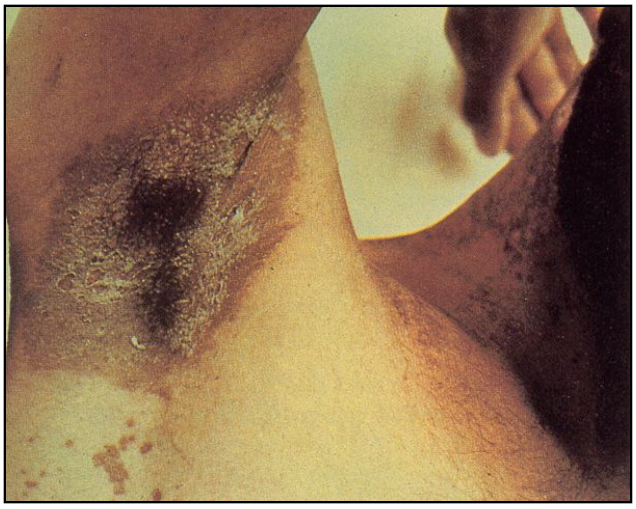


Fig. 5-29. Intertriginous (axillary) accentuation of blistering in an Iraqi mustard casualty. Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

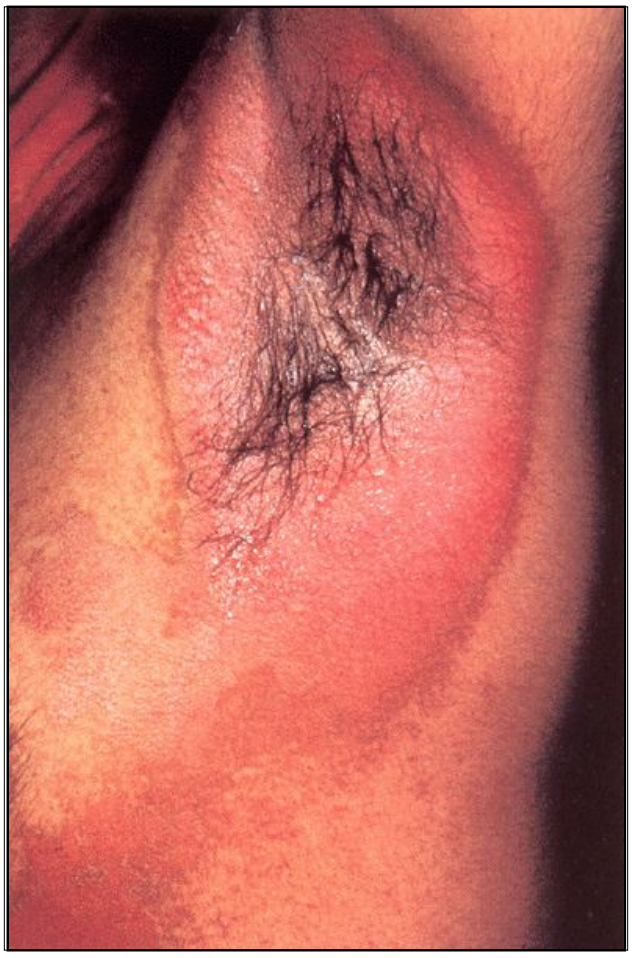


Fig. 5-30. Axillary accentuation of skin blistering and erosion in an Iraqi vesicant casualty. Photograph: Courtesy of Dr. U. Imobersteg, United Nations Observation Team, Gunten, Switzerland.

TABLE 5-1

SKIN MANIFESTATIONS OF MUSTARD TOXICITY

Phase	Time of Onset (range)	Skin Signs and Symptoms	Associated Systemic Symptoms
Latent	0–6 h (0–24 h)	Itching; exposed area can be dry and pale	Nausea and vomiting (early onset: 19–20 min)
Erythema	6–48 h (1 h–5 d)	Itching, burning, edema, cyanosis (no progression to blisters in mild cases)	Nausea and vomiting
Blistering (usually occurs only with relatively high doses of mustard)	6–48 h	Increased itching, pain; blisters usually at periphery of erythema; maximal expression at day 3–4: ulceration with trauma, infection development in area	
Necrosis	1–2 d	Upper dermis with necrosis of vessels; severe pain associated	Increased incidence of infection; leukopenia at day 7–10
Healing	2–8 wk	Superficial blisters with ulceration will heal in 2 wk without scarring; deep ulcers heal with scarring in 4–8 wk or remain as indolent ulcers. Post-inflammatory hyperpigmentation common in both	

Data source: US Department of the Army. *Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries*. Washington, DC: DA; 1974. Army TM 8-285: 2–7.

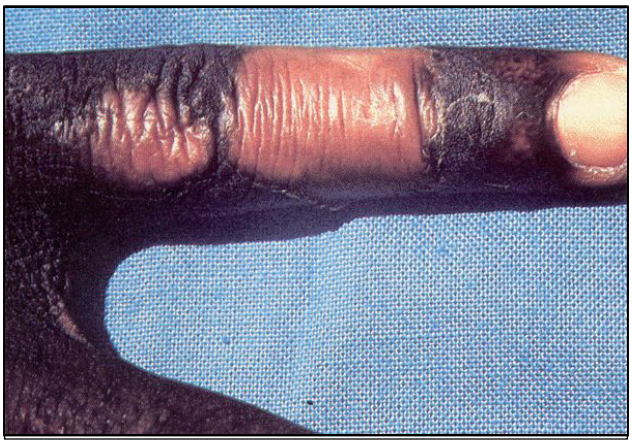


Fig. 5-31. Minimal residual hypopigmentation in an area exposed to a small amount of distilled mustard.

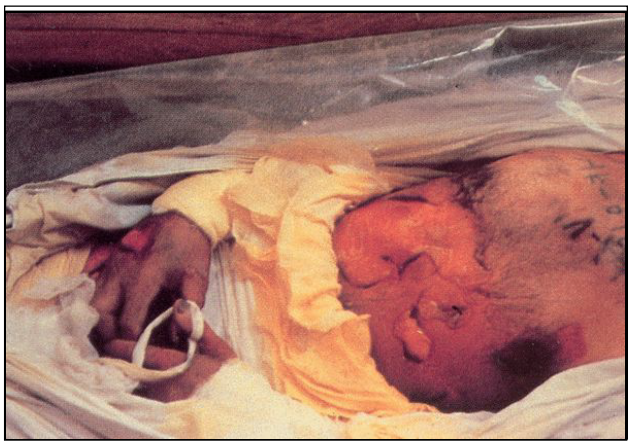


Fig. 5-32. Iranian mustard fatality. Note the large area of involvement with the characteristic blistering and skin darkening. Photograph: Courtesy of Dr. Peter Dunn, Materials Research Laboratory, Victoria, Australia.

may vary in the severity of tissue damage and course of healing according to the amount of mustard absorbed at the site. A mild exposure to sulfur mustard at a testing facility resulted in a superficial blister that healed with mild hypopigmentation within 2 weeks (Figure 5-31). At the opposite end of the spectrum are the mustard casualties who received a heavy mustard exposure and percutaneous absorption, which led to necrosis of the epidermis and dermis over large areas (Figure 5-32). The

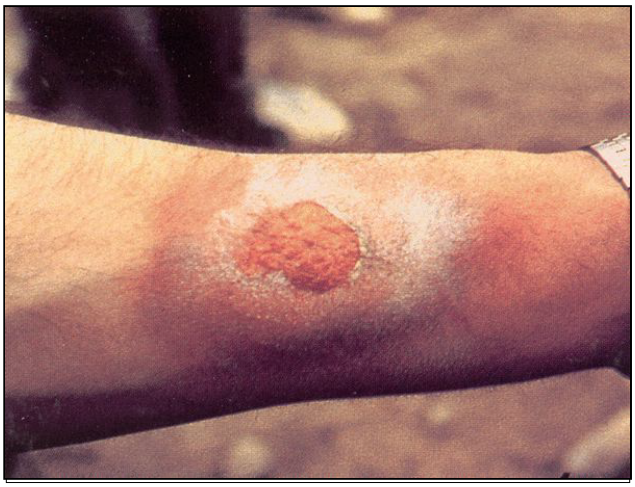


Fig. 5-33. A localized mustard lesion. In this lesion, a gradation of skin damage is apparent in a targetlike pattern. In the central area, blistering and superficial ulceration occurred. Surrounding the area of most intense exposure is an area of intact necrotic skin and peripherally, an area of skin darkening. Photograph: Courtesy of Dr. Peter Dunn, Materials Research Laboratory, Victoria, Australia.

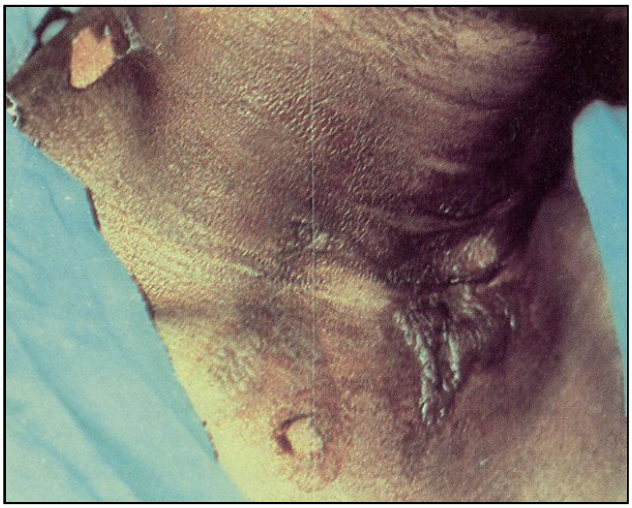


Fig. 5-34. Residual hyperpigmentation in the healing phase of a mustard lesion. Typically, the hyperpigmentation would be greatest in the areas of highest mustard exposure. Photograph: Courtesy of Dr. U. Imobersteg, United Nations Observation Team, Gunten, Switzerland.

TABLE 5-2

HEALING TIME OF MUSTARD BURNS OF THE SKIN

Type of Burn	Days	Weeks
Erythema	3–7	—
Facial blisters	5–8	—
Pinpoint blisters	—	1–2
Large nonfacial blisters	—	2–4
Feet and genital blisters	—	4–6
Mustard burns with coagulation necrosis	—	6–8

Adapted from McNamara BP. *Medical Aspects of Chemical Warfare*. Alexandria, Va: Defense Technical Information Center; 1960. Report AD 240713: 18.

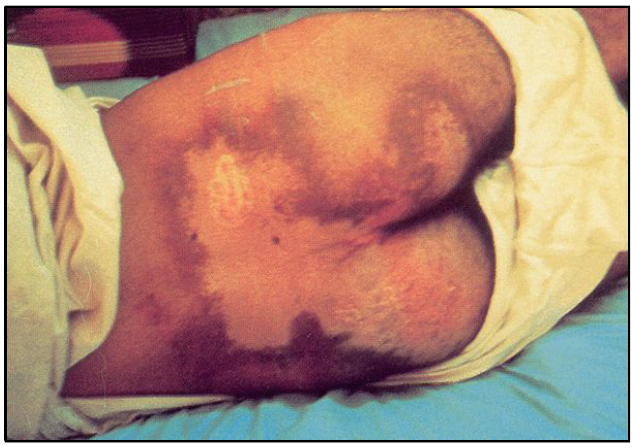


Fig. 5-35. Another example of hyperpigmentation in a mustard lesion. The mechanism of the hyperpigmentation as shown here is probable postinflammatory deposition of melanin in the dermis and is directly related to the severity of the primary lesion. Photograph: Courtesy of Dr. Peter Dunn, Materials Research Laboratory, Victoria, Australia.

dose–response relationship of skin damage and mustard dose is clearly demonstrated in Figure 5-33. In this mustard patient, an isolated exposure to mustard produced a graded response, from severe necrosis of the skin in the central area of greatest mustard concentration to a mild erythema in the areas of lesser mustard concentration at the periphery of the lesion. The dose of mustard also has a significant effect on the healing time (Table 5-2).[74] As the blistered areas heal, characteristically a dark

red-brown hyperpigmentation occurs at the periphery of the lesion (Figures 5-34 and 5-35).

Many organ systems are affected by mustard poisoning. Because the mucosal surfaces are exposed in the cornea and the lining of the upper airways, the eyes and respiratory tract are the most frequently involved organ systems. Eye injuries range from conjunctivitis in mild exposures to corneal damage, scarring, and iritis in severe exposures (Figure 5-36). Respiratory compromise occurs in vapor exposures. Mustard gas in concentrations less than that which can be detected by smell can cause significant upper airway signs and symptoms if inhaled over a several-day period. Respiratory injuries range from mild inflammation of the upper airway to bronchopneumonia, pulmonary edema, and, in severe exposures, adult respiratory distress syndrome. The onset of mustard poisoning symptoms in the skin, respiratory system, and eye often occur concurrently, beginning within the first several hours after exposure and peaking within the first 72 hours. As with skin symptoms, an early onset of eye and pulmonary symptoms suggests a worse prognosis. Table 5-3 shows the relative frequency of the various signs and symptoms of Iranian mustard casualties.

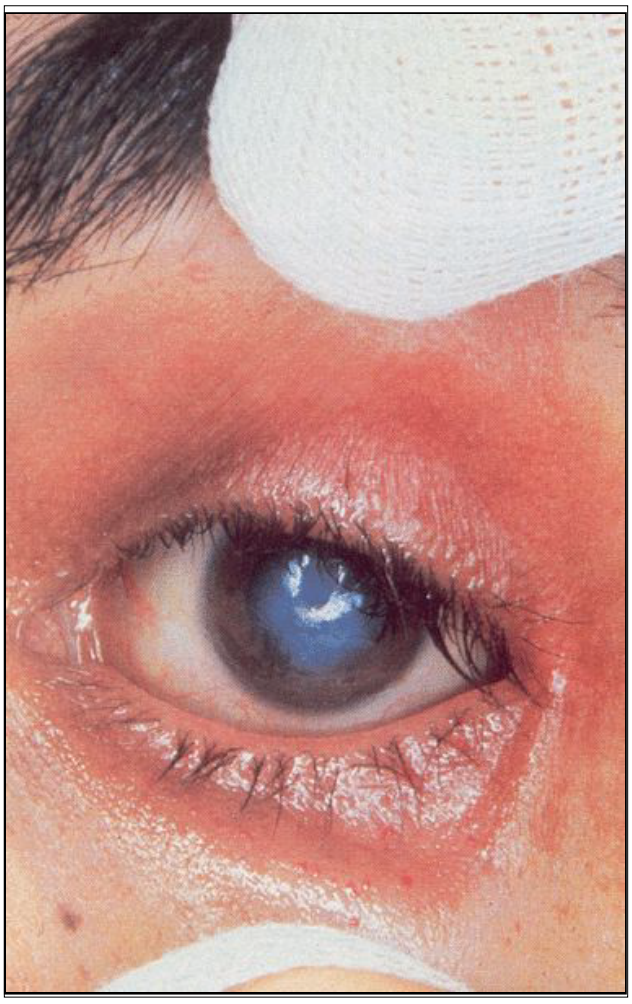


Fig. 5-36. Residual corneal opacity secondary to mustard exposure. Photograph: Courtesy of Dr. Luis Requena, Universidad Autónoma de Madrid, Madrid, Spain.

Absorption of mustard through epithelial surfaces or ingestion of mustard via contaminated food or water can lead to hematopoietic, neurological, and gastrointestinal involvement. When ingested, mustard can cause acute nausea and vomiting. Later symptoms include oral and esophageal pain and desquamation, abdominal pain, hemorrhage, diarrhea, and prolonged anorexia. These symptoms can interfere with the maintenance of adequate hydration and electrolyte balance in patients who may already have difficulties secondary to compromise of the skin barrier.

Neurological involvement can produce nystagmus, decreased motor activity, disturbed consciousness, anxiety, hearing loss, motor paralysis, and coma.[61,66] Case reports of acute and delayed (3 mo after mustard administration) neurotoxicity from nitrogen mustard (mechlorethamine) describe mental confusion, ataxia, amnesia, headache, hyperreflexia, and localizing CNS signs as additional symptoms occurring after mustard therapy.[75,76] In both cases, an increased ventricular pressure was noted, and measures taken to decrease the intraventricular pressure resulted in clinical resolution of the symptoms. These symptoms may be misdiagnosed as nerve agent poisoning if the physician is unaware of the CNS effects of mustard poisoning.

Mustard toxicity to the hematopoietic system can result in myelosuppression within 7 to 15 days after exposure.[61] The resultant drop in leukocyte and platelet counts can lead to increased susceptibility to infection and bleeding during this period. The implications for therapy during bone marrow suppression are significant. An immunocompromised patient with large areas of denuded epidermis is at great risk for sepsis and must be followed closely and treated when evidence of infection is discovered.

The synergistic effect of combined injuries in a casualty must also be considered when triaging and treating a patient. These patients typically have injuries secondary to conventional weapons such as shrapnel wounds in combination with an NBC injury such as mustard poisoning. Past experience

TABLE 5-3

FREQUENCY OF SIGNS AND SYMPTOMS IN 94 MUSTARD CASUALTIES DURING THE IRAN-IRAQ WAR

Signs and Symptoms by Organ System	Frequency (%)
Ophthalmic	
Conjunctivitis	94
Blurred Vision	80
Photophobia	72
Temporary blindness	4
Skin	
Erythema	86
Pigmentation	82
Blistering	69
Severe burning	12
Skin (scrotal)	
Erythema	25
Edema	21
Pain	18
Ulceration	10
Respiratory	
Coughing	86
Dyspnea	45
Wheezing	40
Rales	22

Adapted with permission from Balali M. Clinical and laboratory findings in Iranian fighters with chemical gas poisoning. *Arch Belg*. 1984(suppl):256.

with these casualties has revealed that the lethality and morbidity of the combination of injuries is higher than that expected from the added effects of either injury alone.

Arsenical Vesicants

Chlorovinyldichloroarsine, or Lewisite (L), is an arsenical vesicant. It is a colorless to brown liquid with a fruity to geranium-like odor, is more volatile than mustard, and is soluble in organic solvents. Lewisite is considered to be a lesser threat than mustard and will be described briefly.

Lewisite's mode of action in many ways appears to mimic that of mustard. It appears to bind to thiol (sulfhydryl) groups on enzymes, which results in decreased cell metabolism and death. Clinically, Lewisite skin injuries are similar to those caused by mustard gas (Exhibit 5-1). The main differences include an earlier onset of pain (occurring within minutes of exposure), a decreased incidence of skin infection, and a shortened healing time (2–3 wk). Like mustard compounds, Lewisite has an effect on multiple systems including the eye, respiratory tract, gastrointestinal tract, musculoskeletal system, nervous system, and the hematopoietic system, among others. Since Lewisite is an arsenical compound and some of its toxicity involves the arsenical group, Lewisite therapy includes the use of the chelator British anti-Lewisite (BAL). Topical application of BAL ointment within 5 minutes after exposure and intramuscular injection of a 10% solution at a dose of 0.025 mL/kg every 4 hours for a total of 4 to 6 injections may decrease some of the epidermal and systemic toxicity of Lewisite.

Management of Vesicant Injury

Management of blister agent casualties can be divided into several chronological phases: prophylaxis, decontamination, and treatment of lesions. Prophylaxis consists of the use of protective clothing, avoidance of contaminated areas, and destruction of the enemy's chemical capability. Because these prophylactic measures can, at best, only minimize chemical casualties in a war rather than eliminate them, we must be prepared to decontaminate and treat vesicant injuries with all effective means at our disposal.

Decontamination

Protection for the medical personnel who are caring for blister agent casualties is perhaps the single most important aspect in mustard casualty treatment. Mustards are notorious for their persistence and ability to adhere to fomites. In 1956, an incident of mustard poisoning occurred in North Africa that illustrates the potential for symptomatic vesicant exposure of individuals including medical personnel, who are not exposed to the actual chemical attack but come in contact with contaminated casualties, their clothing, and other fomites. This incident involved three children who were playing with a mustard gas shell that exploded. During their transport to the hospital and the initial period of care, nine contacts including a physician, a nurse, and several medical assistants, experienced symptoms of mustard gas poisoning ranging from conjunctivitis to severe blistering, nausea, and vomiting.[77]

Once medical providers become blister agent casualties, they are unable to provide further care, producing a significant degradation of the medical

EXHIBIT 5-1

DIFFERENTIAL CHARACTERISTICS OF LEWISITE AND MUSTARD TOXICITY

1. Liquid Lewisite is absorbed into the skin more rapidly.
2. Erythema appears more rapidly with Lewisite and is intense red instead of pink.
3. The area between normal surrounding skin and affected skin is less well defined in Lewisite lesions. The demarcation becomes clear after 2 to 3 days. The areas of injured skin of mustard lesions are well defined from the beginning.
4. Edema is much more pronounced with Lewisite.
5. Instead of the single, large blister produced by Lewisite, mustards create tiny blisters at the periphery of the injury ("pearl necklace") that later join to form large blisters.
6. Maximum development of inflammatory reaction occurs earlier with Lewisite than with mustards.
7. A Lewisite ulcer is bright red with a multitude of hemorrhages at the base. The base of a mustard ulcer is gray and has a single hemorrhage that is usually superficial.
8. Secondary infections are rare with Lewisite and frequent with mustard.
9. Pigmentation is less frequent with Lewisite-induced lesions than with mustard-induced lesions.
10. Wounds contaminated with Lewisite change color sharply and more rapidly than those contaminated with mustards; the tissues may show gray-black spots with a silver sheen that later turn red-brown. Wounds contaminated with Lewisite will give off the characteristic odor of geranium for 8 hours or longer.
11. Wounds contaminated with Lewisite present additional problems and increased risk of systemic effects. The casualty notices sharp pain in the wound out of proportion to the trauma.
12. Coagulation is poor and bleeding can become life-threatening with Lewisite injuries. The edges of the wound may turn pale yellow and, after a period of erythema (18–24 h), inflammatory blisters develop in the adjacent skin.

Adapted from Augerson WS, Sivak A, Marley WS. Chemical casualty treatment protocol development—treatment approaches. In: *Lewisite*. Vol 3. Air Force Chemical Defense Report. AD-B112 916, September 1986: 1–55.

unit's ability to sustain its mission. Therefore, it is necessary to ensure that affected soldiers are decontaminated before medical treatment. In emergent cases, soldiers may be treated before decontamination by personnel wearing appropriate protective gear. However, chemical protective gear worn by the patient or the physician poses a significant obstacle in the evaluation and treatment of the patient.[78]

Decontamination of mustard casualties and fomites exposed to mustard can be accomplished by absorption and deactivation of the chemicals. The U.S. Army's M13 decontamination kit contains dusting pads of fuller's earth, which absorbs liquid mustard, and chloramide powder, which inactivates mustard. The army's newer M258 skin decontaminating kit contains solutions of chloramide and a mixture of ethanol, phenol, and sodium hydroxide to inactivate mustard compounds. In the absence of standard decontaminating kits, other decontaminants can be used. For example, washing repeatedly with soap and warm water can inactivate large quantities of mustard on the skin. If water is not available, mechanical scraping and application of absorbents such as activated charcoal or grain flours can be used to decontaminate the skin. Strong basic solutions such as ammonia and lye, or chlorinated acids such as sodium hypochlorite (household bleach), may be used to decontaminate fomites.

Conventional Therapy

Conventional therapy for mustard wounds consists of symptomatic care (burn care) of the lesions

and their attendant symptoms. Patients with areas of involvement less than 20% of the total body surface are unlikely to develop significant complications secondary to fluid and electrolyte imbalances[79] and can be treated in a nonacute care setting. Dermatologists are uniquely qualified to care for this group of patients.

After thoroughly decontaminating and cleansing the involved areas, topical care is initiated. Application of anti-infectious creams such as Sulfamylon (mafenide acetate, manufactured by Sanofi Winthrop, New York, N.Y.) or Silvadene (silver sulfadiazine, manufactured by Marion Merrell Dow, Kansas City, Mo.) inhibits bacterial colonization and infection of the denuded skin and should be routinely used in mustard casualties with blisters and superficial ulcers. Use of antibacterial ointments and creams such as Neosporin (polymyxin B sulfate, bacitracin zinc, and neomycin, manufactured by Burroughs Wellcome, Research Triangle Park, N.C.) and bacitracin also are useful in protecting blister wounds and promoting reepithelialization.[80] The new biosynthetic dressings such as hydrogel and hydrocolloid gel accelerate reepithelialization, induce faster healing, reduce wound contamination, and decrease pain.[81] They also absorb fluid (sera) from the occluded area into their biosynthetic matrix, and this action may allow binding and inactivation of any free mustard compounds from the wound. Constant vigilance of the denuded areas to monitor for early signs of bacterial infection is of paramount importance. Daily debridement and cleansing of the wounds is necessary to avoid undue risk of developing infection.

Symptoms related to skin injury by sulfur mustard include pain and itching. Symptomatic therapy for the itching includes potent antihistamines such as Atarax (hydroxyzine hydrochloride, manufactured by Roerig, New York, N.Y.) and Sinequan (doxepin hydrochloride, manufactured by Roerig, New York, N.Y.). Topical steroids may help in areas of severe itching resistant to antihistamines, but caution should be used since steroids may slow healing. In addition to standard analgesics such as codeine, nonsteroidal antiinflammatory drugs (NSAIDs) such as Clinoral (sulindec, manufactured by Merck and Co., West Point, Pa.) and Naprosyn (naproxen, manufactured by Syntex, Humacao, P.R.) help relieve pain and may reduce inflammation. Because NSAIDs can adversely affect renal function, careful consideration should be given before utilizing them in blister patients, who are susceptible to fluid and electrolyte imbalances.

Potential New Therapies

Research into new treatments for mustard gas injury has focused on two areas: deactivating the compounds before they can cause significant damage and reducing the mustard's deleterious effects. Both approaches require rapid application for best results.

Inactivation of Mustard Compounds. Because mustard reacts with tissue within minutes of exposure, specific therapy designed to inactivate the chemical or to slow its rate of absorption must be initiated within minutes to be maximally effective. Most casualties, however, appear to continue to absorb free, nonfixed mustard compounds from their skin surface or from mustard-contaminated fomites, so therapy specifically used to inactivate mustard externally or internally may be useful long after the initial mustard exposure.

Studies have shown that thiols or compounds containing sulfhydryl groups decrease the toxic effects of mustard.[82,83] Their action, in part, appears to be mediated through the direct inactivation of mustard compounds. The list of the thiols that have been used is long but only a few thiol compounds are readily available currently. A thiol compound that has been used orally in the past to treat acetominophen toxicity is Mucomyst (acetylcysteine, manufactured by Apothecon, Princeton, N.J.). That regimen includes an oral loading dose of 140 mg/kg followed by doses of 40 mg/kg every 4 hours for a total of 17 doses. The drug is relatively innocuous, with side effects including nausea, vomiting, and, rarely, urticaria. Another thiol that is available for parenteral use is sodium thiosulfate. Currently, it is used to treat cyanide poisoning. Dosage is 50 mL of a 25% solution (12.5 g) given intravenously over 10 minutes. At this dose, the only significant side effect is that of hypovolemia secondary to an osmotic diuresis caused by the drug.

Theoretically, thiols could also be used topically in wounds and areas where routine decontamination may be contraindicated. The only drawback to these drugs is that they do not react with mustard already bound to tissue; therefore, their ideal use would be as a pretreatment. Studies have shown that thiols have a systemic protective effect even when given up to 15 minutes after exposure.[83] Research in Germany in 1950 utilized iontophoresis of a cysteine hydrochloride solution on human subjects exposed to varying amounts of sulfur mustard.[84] The results demonstrated that the therapy, which was begun after erythema developed, re-

sulted in significant amelioration in the clinical course of blister formation and healing.

Other substances that could inactivate mustard compounds when applied topically include albumin, collagen, powdered milk, gel or collagen dressings, and activated charcoal slurry, all of which have an affinity for mustard agents and will bind and inactivate them.[66]

Reduction of Untoward Reactions to Mustard. Two therapies greatly reduce the effects of mustard compounds on the skin[62]: cooling the skin and using trichloroacetic acid crystals to prevent desiccation. Cooling the skin with ice bags appears to inhibit vesication of mustard-exposed skin. The physiology of the inhibition of mustard toxicity with cooling is unknown but may be related to decreased transport through the skin and into the bloodstream, or a decrease in the rate of mustard reaction with substrates within the tissue at lower temperatures. The application of trichloroacetic acid crystals after the erythema of mustard exposure develops prevents vesication. Dermatologists routinely use 20% to 50% solutions for cosmetic peels without complication; however, trichloroacetic acid at 50% concentrations and above can cause significant dermal scarring[85] and the medical officer should use great caution in considering this therapy in a soldier who already has significant compromise to the integrity of the epidermis.

Other readily available drugs that have been reported to ameliorate the toxic effects of mustards on the skin by interfering with primary mustard reactions at the molecular level include vitamin E (antioxidants), Mandelamine (methenamine mandelate, manufactured by Parke-Davis, Morris Plains, N.J.), and niacin.[66]

Treatment of Complications

Complications from exposure to mustard compounds arise from (*a*) systemic toxicity of the absorbed mustard and (*b*) direct insult to the epidermal barrier. Damage to the epidermal barrier results in increased fluid loss from the body and electrolyte imbalance. With areas of involvement greater than 20%, the casualty must be evacuated to a hospital capable of treating burn patients, if possible. If the area of epidermal barrier loss is less than 20%, the patient can be managed in a nonacute care setting.[79] However, the patient must be carefully monitored to avoid the complications of hypovolemia and electrolyte imbalance. Another complication associated with epidermal barrier loss in mustard casualties is the increased incidence of cutaneous and systemic infection. Therefore, mustard casualties must be monitored closely for signs and symptoms of infection. If an infection is suspected, blood and the appropriate tissue cultures must be obtained and the patient placed on antibiotics. Typically, two of the most common pathogens in burn patients are *Staphylococcus aureus* and *Pseudomonas aeruginosa*; therefore, broad-spectrum antibiotics should be used. The patients should not be placed on prophylactic systemic antibiotics because this only results in the colonization of the wounds with drug-resistant organisms.

The suppressive effect of mustard on the immune system can increase the likelihood of cutaneous and systemic sepsis. Leukopenia secondary to mustard exposure typically is the greatest approximately 7 to 10 days after mustard exposure. At this time, the patients are most likely to become septic, and close monitoring during this period is paramount.

As noted earlier, mustard patients usually develop symptoms concurrently in several organ systems after exposure. When the skin is involved in mustard toxicity, the eyes, respiratory system, gastrointestinal system, hematopoietic system, heart, and central nervous system can also be affected. Although treatment of the effects of mustard on these systems is beyond the scope of this chapter, the same basic principles of skin therapy can be applied to the treatment of mustard toxicity in these systems. A good review of the treatment of mustard casualties is available elsewhere.[66]

When triaging and treating chemical casualties, the synergistic effect on the morbidity and mortality of casualties with injuries that involve a combination of conventional and NBC injuries must be kept in mind.

Halogenated Oximes

Phosgene oxime (CX) is a colorless liquid or solid (melting point 40°C) that has an intense, disagreeable odor. It belongs to a class of chemical agents called urticants or nettle gases. It should not be confused with phosgene (CG), which is primarily a choking agent and exerts its effects mainly in the upper airways and lung. Phosgene oxime's primary sites of action are the skin, eyes, and upper respiratory system. In these areas, it is extremely irritating to the epidermal and mucosal tissues.[86] Its mechanism of action is not completely understood, but studies suggest that it is an alkylating agent and

its toxicity is mediated via binding to sulfhydryl and NH_2 groups. The action on the skin, like Lewisite, is immediate, with development of irritation and burning suggestive of the reaction to stinging nettle. With the characteristic pain that is felt almost immediately with exposure, a white area surrounded by erythema develops. An urticaria-like edema ensues within the first hour, followed by blistering after 24 hours. The skin can become necrotic, and healing may take up to 3 months.[86,87] Specific treatment consists of immediate decontamination with copious amounts of water and any mild base (buffer) such as sodium bicarbonate solution. After initial therapy, symptomatic burn therapy is indicated.

Nerve Agents and Cyanides

Although nerve agents (tabun [GA], sarin [GB], soman [GD], and VX) and the cyanides (hydrogen cyanide [AC] and cyanogen chloride [CK]) are considered threat agents by the allied forces, their cutaneous effects are minimal and will be described briefly.

The cutaneous effects of nerve agents are mostly limited to the areas of exposure. In these areas, nerve agent casualties may develop increased sweating secondary to the muscarinic-like effect of the agents on eccrine sweat gland innervation.[86] The muscarinic effects of nerve agents on the erector pili muscles may cause contraction and the development of "goose-bumps" on exposed areas. Fasciculations of the striated muscle underlying the exposed area can occur as a result of the nicotinic-like effects of the absorbed nerve agents. Tabun and sarin have caused a cyanotic redness and edema of the skin, respectively.[66]

Treatment of nerve agents consists of the administration of atropine to inhibit the muscarinic effects of the agent, and pralidoxime chloride (2-PAM) to reactivate acetylcholinesterase.

The cyanides (blood agents) act by inactivating cytochrome oxidase, which prevents the cells from utilizing oxygen. They are acutely lethal, causing apnea, convulsions, and death within minutes. Because the cells cannot utilize oxygen, the blood remains oxygenated and the mucosal membranes and skin of a blood agent casualty appear dark red. Although this sign is nonspecific, it is very suggestive of cyanide poisoning in the context of convulsions and acute loss of consciousness. Acutely, the only effective therapy is amyl nitrite inhalation, which generates methemoglobin, which, in turn, binds cyanide. After an intravenous line is established, sodium thiosulfate can be given. Sodium thiosulfate reacts with cyanide to form thiocyanate, which can be excreted by the kidneys.

SUMMARY

The threat of chemical warfare today is real and medical officers must be prepared to treat chemical casualties if the need arises. In the past, this area has been neglected; however, the possibility that U.S. military forces could sustain a substantial number of nuclear, biological, and chemical (NBC) casualties in future conflicts is very high. Therefore, it is incumbent on us, as physicians, to ensure that we are capable of rendering the best care possible.

In preparation for cutaneous lesions found in NBC casualties, medical personnel should understand some fundamental principles that have been noted in this chapter:

- Basic supportive measures for NBC casualties are based on the same medical principles, such as wound and burn care, that are already contained in the present literature and known to most physicians.
- There is an overriding need to protect medical personnel in an NBC environment to ensure they do not become casualties and thus severely hinder the medical team's capabilities.
- Although supportive care of NBC casualties requires no NBC training, specific therapy with NBC antidotes and decontamination of patients requires specialized knowledge gained only through extensive review of medical literature or through attendance of military medical NBC courses. Therefore, military physicians should actively prepare for the possibility that they may treat NBC casualties by reading the NBC literature and attending NBC training courses.
- If placed in a situation with an NBC threat such as that of the Persian Gulf War, the medical officer should immediately evaluate the preparedness of his medical unit to treat casualties. This evaluation should include the availability of specific NBC antidotes such as sodium thiosulfate for cyanide

poisoning, NBC protective gear for the medical personnel, and decontamination supplies and equipment for area and patient decontamination.
- Triage procedures will be complicated by NBC casualties. Medical officers should be capable of triage and treatment of combined injuries, in which patients have conventional wounds such as blast injury in addition to exposure to chemical or biological agents. Often these patients would be treatable if they had only one type of injury but would be expectant (ie, seriously injured or with poor chance of survival) with the combination of injuries.
- NBC doctrine often targets rear areas, where hospitals and other medical facilities are located. Therefore, medical officers should be aware of the enemy's NBC doctrine and should be prepared for movement and decontamination of medical facilities if the threat is high.

Future wars involving NBC undoubtedly will be very different from those since World War I. However, if physicians, nurses, and other medical personnel are prepared and cognizant of the threat, the impact of an enemy NBC offensive on the combat effectiveness of U.S. forces will be minimized.

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