

Cutaneous Manifestations of Biological Warfare and Related Threat Agents

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The specter of biological warfare (BW) looms large in the minds of many Americans. The US government has required that emergency response teams in more than 100 American cities be trained by the year 2001 to recognize and contain a BW attack. The US military is requiring active duty soldiers to receive immunization against anthrax. Dermatologists need not feel helpless in the face of a potential BW attack. Many potential agents have cutaneous manifestations that the trained eye of a dermatologist can recognize. Through early recognition of a BW attack, dermatologists can aid public health authorities in diagnosing the cause so that preventive and containment measures can be instituted to mitigate morbidity and mortality. This article reviews bacterial, viral, and toxin threat agents and emphasizes those that would have cutaneous manifestations following an aerosol attack. We conclude with clues that can help one recognize a biological attack.

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The threats posed by biological weapons have gained increasing attention recently. Biological weapons have been discussed in the US Congress and in the medical literature, and they have been the subject of frequent commentaries.¹ The mention of biological warfare (BW) often elicits a sense of deadly mystery as summarized by a Russian journalist: "I have been gathering information on bacteriological weapons for several years. Out of all the means of mass destruction, this kind can be considered as the most mysterious."²

This article attempts to eliminate some of the mystery by discussing the background of biological weapons and by reviewing agents that cause cutaneous disease (**Table 1**). Dermatologists could play a critical role in recognizing an epidemic exanthem. Their prompt diagnosis could lead to early treatment that could mitigate the effects of a BW attack.

In 1970, the World Health Organization predicted that a city of 500 000

people would be devastated following an aerosol release of 50 kg of BW agent if deployed under ideal meteorological conditions (**Table 2**).³ In 1997, the economic impact of a bioterrorist aerosol attack on a city of 100 000 was estimated at \$477 million for brucellosis to more than \$26 billion for anthrax.⁴

One hundred forty nations have ratified the 1972 Biological Weapons Convention. Signatories agreed to never develop, produce, stockpile, acquire, or retain BW agents or the means to deliver them.⁵ Despite this convention, BW has continued to cast its dark shadow. In 1978, Bulgarian dissident Georgi Markov was assassinated in London, England, by secret agents using an "umbrella gun" that shot a ricin-containing pellet into his thigh.⁶ At least 66 people died of inhalational anthrax when an aerosol of *Bacillus anthracis* spores was accidentally released from a BW research facility in Sverdlovsk (now Ekaterinburg), Russia, in 1979.⁷

By 1991, the Iraqi regime had weaponized anthrax, botulinum toxin, and aflatoxin. Fortunately, these were not used during the Persian Gulf War.⁸ Controversies regarding possible continued Iraqi offensive BW research and development have

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Table 1. Potential BW Threat Agents With Their Natural Reservoirs, Likely Route of Exposure as a BW Agent, Incubation Period, Effects, and Cutaneous Findings*

Agent Class	Natural Reservoir	Likely BW Route	Incubation, d	Personnel Effect	Skin Findings	Prevention	Treatment
Bacterial							
<u>Anthrax</u> (<i>Bacillus anthracis</i>)	Soil, cattle, sheep, horses	R	1-6	L	E	C, V	1
Brucellosis (<i>Brucella</i> species)	Goats, swine	R, P	5-60	I	...	C	1
Cholera (<i>Vibrio cholerae</i>)	Contaminated water or food	G	1-5	I, L	...	C, V, X	1
Melioidosis (<i>Burkholderia pseudomallei</i>)	Soil	R	Weeks to years	I, L	E, BW	C	1
Plague (<i>Yersinia pestis</i>)	Fleas	R	2-6	L	E, BW	C	1
Q fever (<i>Coxiella burnetii</i>)	Sheep, cattle, goats	R	10-40	I	...	C, X	1
<u>Tularemia</u> (<i>Francisella tularensis</i>)	Deerflies, mosquitoes, ticks	R	2-10	L	E	C, X	1
Toxins							
Botulinum (<i>Clostridium botulinum</i>)	Soil	R	1-5	L	...	X	3
Trichothecene mycotoxins (various molds)	Soil	R, G, D	Minutes to hours	L	BW
Ricin	<i>Ricinus communis</i> (castor plant) seeds	R, G, P	4-6 h	L
<i>Staphylococcus</i> enterotoxin B	Contaminated food	R, G	1-6 h	I
Viral							
Argentine HF (junin virus)	Rodents	R	7-14	I	E, BW	...	2
Bolivian HF (machupo virus)	Rodents	R	7-14	I	E, BW	...	2
Congo-Crimean HF	Ticks	R	3-12	L	E, BW	...	2
Ebola HF	Unknown	R	3-16	L	E, BW
Hantaviruses	Rodents	R	9-35	I, L	E, BW	X	2
Lassa HF	Rodents	R	5-16	I, L	E, BW	...	2
Marburg HF	Unknown	R	3-16	L	E, BW
Rift Valley fever	Mosquitoes	R	2-5	L	...	X	...
Smallpox (variola major and minor)	Human (eradicated)	R	7-17	L	E, BW	V	...
Venezuelan equine encephalitis	Mosquitoes	R	2-6	I	...	X	...

*This is not to be construed as an official threat list. Diseases in **boldface** cause cutaneous findings if disease is contracted from aerosol exposure. Underlined diseases cause cutaneous manifestations in endemic disease but not in aerosol-generated disease. BW indicates biological warfare; R, respiratory; I, incapacitating; L, lethal; E, endemic disease; C, chemoprophylaxis; V, licensed vaccine; 1, antibiotics; P, percutaneous; G, gastrointestinal; D, dermal; X, investigational vaccine; 3, antiserum; HF, hemorrhagic fever; 2, investigational antiviral agents; and ellipses, not applicable.

Table 2. Estimated Casualties for a Hypothetical Biological Warfare Attack on a City of 500 000*

Agent	Downwind Reach, km	No. Dead	No. Incapacitated
Rift Valley fever	1	400	35 000
Tick-borne encephalitis	1	9500	35 000
Typhus	5	19 000	85 000
Brucellosis	10	500	100 000
Q fever	>20	150	125 000
Tularemia	>20	30 000	125 000
Anthrax	>20	95 000	125 000

*This model assumes that 50 kg of agent is deployed from an aircraft along a 2-km line upwind of the city.³

continued as the regime has alternately resisted and permitted the operations of the United Nations weapons inspection teams to verify compliance with United Nations Security Council Resolution 687 that mandates the dismantling of the Iraqi offensive BW program.

By 1995, at least 17 countries (including several signatories of the 1972 Biological Weapons Convention) had been identified as nations harboring biological weapons according to sources cited by the Office of Technology Assessment and at US Senate committee hearings.⁹ They

included Iran, Iraq, Libya, Syria, North Korea, Taiwan, Israel, Egypt, Vietnam, Laos, Cuba, Bulgaria, India, South Korea, South Africa, China, and Russia. Clearly, BW remains a credible threat to our military, as it was during the Persian Gulf War.¹⁰ In addition, nonstate-sponsored terrorist organizations pose BW threats. In 1995, the Aum Shinrikyo cult, who released sarin nerve gas in a Japanese subway, was found to possess a rudimentary biological weapons program that included cultures of the etiologic agents of anthrax, botulism, and Q fever.¹¹ The vulnerability of civilian populations to biological attack was illustrated by the successful use of *Salmonella typhimurium* to poison salad bars and cause 351 cases of gastroenteritis in Oregon by the Rajneeshee cult in 1984.¹¹ Terrorist use of BW agents could kill many people to create an unparalleled medical, political, and social crisis. We must prepare for a new age of terrorism.^{1,10,12} Civilian health care providers must know how to recognize a BW attack in the event of the use of BW agents on civilian populations.¹

THE THREAT OF BW

Biological warfare agents can cause large numbers of casualties with minimal logistical requirements. Perpetra-

tors can escape long before BW agents incubate and cause casualties. Weapons are easy and relatively inexpensive to produce and can be used to selectively target humans, animals, or plants.

Agents can be easily procured from the environment, universities, biological supply houses, and clinical specimens.¹⁰ Common fermentation techniques used for producing antibiotics, vaccines, foods, and beverages can be adapted to grow large quantities of biological agents. Simple aerosol-generating devices mounted on planes or trucks, like those used for crop dusting, can be adapted to generate 1- to 5- μ m particles ideal for lodging in alveoli.¹³ Such aerosols would be undetectable by our senses, and an attack might not be noted until people became ill. Panic could result as medical capabilities become quickly overwhelmed. Aerosolization of biological agents often results in different clinical features of disease than those observed following natural infection. For instance, anthrax is usually a cutaneous disease in nature, but a rapidly fatal hemorrhagic mediastinitis ensues after inhaling spores.

Biological attacks could be attempted by contaminating water supplies, although modern water purification and the dilution effects of large water volumes would negate the effectiveness of such an attack.¹ While intact skin provides a barrier to most BW agents, the trichothecene mycotoxins can penetrate the skin and cause systemic effects.¹⁰ Ingestion and cutaneous penetration are currently considered as unimportant potential routes of exposure.¹⁰ Agents could be dispersed by releasing them in their natural arthropod vectors. Person-to-person aerosol transmission of several agents (notably plague and smallpox) could perpetuate an epidemic. Last, nosocomial transmission could also cause casualties following exposure to contaminated blood, body fluids, or respiratory secretions.

INHALED AGENTS CAUSING CUTANEOUS MANIFESTATIONS

Melioidosis: *Burkholderia* (formerly *Pseudomonas*) *pseudomallei*

Burkholderia (formerly *Pseudomonas*) *pseudomallei* is a gram-negative bacillus that is often isolated from soil and causes epizootics in sheep, goats, swine, horses, and seals.¹⁴⁻¹⁷ Humans most commonly contract disease via inoculation of cutaneous abrasions with contaminated soil. Ingestion and inhalation of bacilli may also cause clinical infection. Melioidosis is endemic to Southeast Asia and northern Australia where it often causes septicemia and death.^{14,18}

Clinical Features.—Melioidosis most commonly presents as an acute pulmonary infection, but it may also present as an acute, localized skin infection, septicemia, or a chronic disease with disseminated internal abscesses. Inhaled organisms would commonly cause a mild bronchitis, but it could lead to severe, necrotizing pneumonia, septicemia (with a 90% case-fatality rate), and death.¹⁹ Pulmonary infection could also lead to a chronic disease with clinical and radiographic features indistin-

guishable from tuberculosis. Metastatic infection can involve numerous internal organs, and the disease can remain latent for years.¹⁶

The overall mortality rate remains near 40%, despite antibiotic therapy. Before the antibiotic era, 95% of patients died.

Cutaneous Manifestations.—Severe urticaria may accompany pulmonary melioidosis.²⁰ Flushing, cyanosis, and a pustular eruption may develop during septicemia. Patients often present with pustules and cutaneous abscesses associated with lymphangitis, cellulitis, or regional lymphadenitis.¹⁶ Draining sinuses from lymph nodes or bone may develop. Abscesses may ulcerate and, rarely, ecthyma-gangrenosumlike lesions form.

BW Considerations.—*Burkholderia pseudomallei* would most likely be delivered as an aerosol. The lack of a vaccine and its high mortality despite treatment could make it a plausible BW agent. Acute pneumonia could be confused with plague given the similar appearance of stained organisms, while a diffuse, pustular eruption could be mistaken for varicella or smallpox.

Plague: *Yersinia Pestis*

Because of its high mortality (approximately 200 million deaths throughout history), *Y pestis* has been studied as a possible BW agent.^{10,21} In nature, mammals of at least 73 genera and some 30 species of fleas serve as reservoirs.²² Humans contract disease from flea bites, and less commonly from mammalian hosts or other humans via respiratory droplet transmission.²¹ Between 1980 and 1994, 18 739 cases worldwide resulted in more than 1800 deaths.²³

Clinical Features.—After an incubation period of 2 to 6 days, bubonic plague acutely causes fever and prostration associated with painful lymphadenitis in the nodal basin draining the site of the flea bite.^{24,25} Buboes (painful, inflammatory, and necrotic lymph nodes) may point and drain spontaneously.²⁴ Less than 10% of patients complain of a prior flea bite.²⁶ Untreated, bubonic plague progresses to septicemic plague within 2 to 6 days.²⁷ Patients exhibit shock, ecchymoses, and small artery thromboses resulting in digital gangrene (**Figure 1**).^{27,28} Both septicemic and pneumonic forms of plague can occur primarily, without antecedent bubonic disease, or, secondarily, due to dissemination of bubonic disease.²⁸⁻³¹ Abdominal pain is the only presenting symptom more common in septicemic plague than in bubonic plague.³¹

The case-fatality rate of untreated bubonic plague is approximately 60%, but less than 5% with antibiotic therapy.^{26,32} The case-fatality rate for untreated septicemic and pneumonic plague approaches 100%.²⁶

The currently licensed, inactivated, whole-cell vaccine prevents bubonic plague. However, animal challenge studies³³⁻³⁵ suggest that it does not reliably protect against primary pneumonic plague, and thus it would not be helpful in a BW context. Candidate live-attenuated vaccines are no more immunogenic than the



Figure 1. Septicemic plague. Acral necrosis of nose, lips, and fingers and residual ecchymoses over both forearms in a patient recovering from bubonic plague that disseminated to blood and lungs. At one time, the patient's entire body was ecchymotic.¹¹⁴ (Photograph courtesy of Dr Jack Polard.)

killed vaccine, and they may revert to virulent, wild-type bacteria.³⁶

Cutaneous Manifestations.—Patients with terminal pneumonic and septicemic plague would develop livid cyanosis and large ecchymoses (Figure 1).^{28,31} The petechiae and ecchymoses can mimic meningococemia.^{28,37} Dark areas of cyanosis, ecchymoses, or acral necrosis probably gave rise to the Medieval epithet, “the Black Death.”¹¹ Rose-colored purpuric lesions gave rise to the nursery rhyme “Ring around the rosy.”^{38,39} The “pocket full of posies” referred to the sweet-smelling flowers carried into the homes of the sick, in an effort to ward off the stench and transmission of disease. “Ashes, ashes” referred to impending mortality (ashes to ashes, dust to dust) or, alternatively, “A-choo, a-choo” referred to the sneeze of pneumonic plague. “All fall down” referred to the terminal event—death.

Rare cases of ecthyma gangrenosumlike lesions and carbuncles due to *Y pestis* have been reported.^{24,37} Pharyngitis associated with cervical lymphadenopathy has been reported in contacts of patients with bubonic plague.⁴⁰

BW Considerations.—The Japanese allegedly tested plague as a BW agent in China during World War II.⁴¹ Human fleas (*Pulex irritans*) were bred and infected with *Y pestis*. Infected fleas were released into several Chinese cities where small epidemics of bubonic plague en-

sued. Normally, animal hosts die in epizootics before humans are infected, but in these cases, humans died of plague before animals did.⁴¹

Plague would likely be released as an aerosol during a modern BW attack and could generate many cases of highly lethal and contagious pneumonia. Bubonic plague would not ensue after aerosol release, but it could occur after transmission by fleas. The possibility of rapid death combined with potential person-to-person transmission (in contrast to anthrax) makes plague an ominous BW threat. The United States studied *Y pestis* as an offensive weapon in the 1950s.¹⁰ Other countries are suspected of weaponizing plague.¹⁰

Toxin Threat: Trichothecene Mycotoxins

Trichothecene mycotoxins (“yellow rain”) are the only potential BW toxins with cutaneous activity and manifestations.⁴² Mycotoxins are a diverse group of small-molecular-weight compounds mainly produced by fungi of 5 genera: *Alternaria*, *Aspergillus*, *Claviceps*, *Fusarium*, and *Penicillium*.⁴³ Toxic levels may develop in moldy grains. If eaten or inhaled, such grain may cause human or animal disease.^{43,44}

Clinical Features.—Alimentary toxic aleukia, reported in Russia since the 19th century, is thought to result from ingesting mycotoxins while eating foods prepared from moldy grain. Symptoms and signs include vomiting, diarrhea, skin inflammation, leukopenia, and hemorrhage.^{10,43}

More recently, trichothecene mycotoxins are thought to have caused fatal pulmonary hemorrhage in Cleveland, Ohio, area infants.⁴⁴ In all cases, the fungus *Stachybotrys atra* was found growing in water-saturated cellulose in the walls of poorly maintained homes. In one area of Cleveland, mycotoxins may have accounted for 5% of cases of sudden infant death syndrome between 1993 and 1995.^{45,46}

Cutaneous Manifestations.—At low doses (nanograms) most trichothecene mycotoxins, including T-2 mycotoxin, cause cutaneous erythema, edema, vesicles, bullae, and necrosis in guinea pigs. Maximal vesiculation occurs at 48 hours in guinea pigs.⁴² Similar findings have occurred in humans accidentally exposed to T-2 mycotoxins.⁴⁷⁻⁴⁹ T-2 mycotoxin is estimated to be 400 times more potent than mustards (alkylating agents) in producing skin injury in laboratory animals.⁵⁰ T-2 mycotoxins can be absorbed percutaneously, and they can cause death in animals with a median lethal dose of only 2 to 12 mg/kg compared with 37 mg/kg for lewisite and 4500 mg/kg for mustards.^{50,51}

BW Considerations.—The United States accused the Soviet Union and its proxies of using mycotoxins (yellow rain) as biological weapons in Afghanistan and Southeast Asia between 1974 and 1981.^{52,53} However, these accusations were never conclusively proven and they are regarded as controversial.¹⁰

Animal studies have suggested that aerosolized mycotoxins could be adapted for BW use. At microgram levels, trichothecene mycotoxins can induce tearing, eye pain,

conjunctivitis, and blurred vision lasting 8 to 14 days in humans exposed to aerosols containing T-2, HT-2, and/or anguidine.^{54,55} Higher doses (0.1-0.2 median lethal dose) induce emesis and diarrhea. Aerosols cause death in humans within minutes to hours by destroying alveoli.⁵⁶ The toxins kill rapidly proliferating tissues by inhibiting protein and RNA synthesis. They gain access to all rapidly proliferating tissues following cutaneous absorption.⁴² In one animal study,⁵⁷ washing the skin with soap and water within 4 to 6 hours of exposure removed 80% to 98% of T-2 mycotoxin and prevented cutaneous necrosis and death.

Poxviridae

The Orthopox genus of the *Poxviridae* family includes variola, the etiologic agent of smallpox, and a number of animal poxviruses that occasionally cause human disease.⁵⁸ This family also includes the molluscum contagiosum virus that is well known to all dermatologists. Thirty years ago, smallpox was endemic in 31 countries, resulting in 15 million illnesses and 2 million deaths annually. Fortunately, a 10-year World Health Organization program eradicated the disease as of October 1977.^{59,60} Unfortunately, smallpox still lingers as a potential BW threat.

Variola can remain viable for 1 year in dust and cloth.⁶¹ Person-to-person spread requires close contact, typically via a respiratory route.⁶² Only 30% of close contacts develop disease with infectivity peaking between days 4 and 6 of illness.⁶⁰

The closely related virus causing monkeypox was first identified in 1958 as a pathogen in cynomolgus monkeys; in 1971 it was first linked to human disease.^{63,64} Unlike smallpox, monkeypox is maintained in an animal reservoir, an arboreal squirrel of tropical rain forests in western and central Africa.⁶⁵ Person-to-person transmission by respiratory droplets has been documented.⁶³

Clinical Features and Cutaneous Manifestations.—

The clinical findings that follow pertain to smallpox unless otherwise stated. Following a 7- to 17-day incubation period, a flulike prodrome lasting 2 to 4 days ensues during which 10% of light-skinned patients exhibit an erythematous exanthem.⁶⁶ Most patients develop a buccal and pharyngeal enanthem that shed virus and enhance respiratory transmission.⁶⁷ Cutaneous lesions typically appear first on the face, then on the forearms and hands, and finally on the lower limbs and trunk within 1 week. Lesions favor ventral surfaces and begin as macules that progress to papules, vesicles, pustules (often umbilicated, like molluscum contagiosum lesions), and crusts. This synchronous progression of centrifugal lesions (**Figure 2**) results in crusts within 1 to 2 weeks. The deep crusts then detach after 2 to 4 weeks leaving depressed, hypopigmented scars.⁶⁸ Virus can be cultured from crusts throughout convalescence.⁶⁹ Survivors often remain disfigured or blinded for life.

Two different strains of variola are recognized.⁵⁹ The more virulent strain (*variola major*) caused death



Figure 2. “Ordinary” smallpox due to *variola minor* strain in an unvaccinated infant with (centrifugally distributed umbilicated pustules on day 7 of eruption. (Photograph courtesy of I. Arita.)¹¹⁵

in 20% to 50% of the unvaccinated. The less virulent strain (*variola minor*), also known as “alastrim,” led to death in less than 1% of unvaccinated patients.⁵⁹ Four clinical forms of smallpox were described: ordinary, flat, hemorrhagic, and modified.^{60,70} Either strain of variola could bring about any one of these clinical pictures.⁶⁰

Ordinary smallpox (as described in the first paragraph of this section) (Figure 2) presented in 80% of patients and led to death in 30% of unvaccinated and 3% of vaccinated individuals.^{60,70} When ordinary smallpox was caused by *variola minor*, illness was milder and lesions were more diminutive.⁶⁰

The most virulent form, hemorrhagic smallpox, accounted for 3% of infections and caused death in 99% of unvaccinated and 94% of vaccinated patients, usually before they developed typical pox lesions.⁷¹ Flat smallpox occurred in 4% of patients and caused severe systemic toxic effects during the slow evolution of macular, soft or velvety, focal skin lesions.^{60,70} Case-fatality rates were 66% among the vaccinated and 95% among the unvaccinated.^{60,70} Modified smallpox accounted for the remaining 13% of cases. It usually occurred among vaccinees and was composed of a mild prodrome, rapid development and crusting of lesions (by day 7), and frequent absence of a pustular stage. The extent of the eruption was not necessarily any different than in the other types.^{60,70} *Variola sine eruption* occurred in 30% to 50% of vaccinated contacts of patients with smallpox. While no cutaneous changes occurred, patients often developed conjunctivitis following a mild prodrome.



Figure 3. Boy with monkeypox in Democratic Republic of the Congo in 1996. Note the centrifugal distribution, as was typical for smallpox. (Photograph courtesy of William Clemm).

The cause of such cases was confirmed by serologic studies.⁶⁰

The main differential diagnosis of smallpox is monkeypox.¹⁰ Patients with monkeypox develop fever, respiratory symptoms, and synchronized lesions just like patients with smallpox (**Figure 3**). Patients with monkeypox seem more prone to develop inguinal and cervical lymphadenopathy and appear to have a lower mortality rate (3%-10%).^{59,63} Pneumonia secondary to monkeypox has a 50% mortality rate.⁵⁵ A search for monkeypox in the Democratic Republic of the Congo (formerly Zaire) in February 1997 found 92 cases among 4000 inhabitants of 12 villages yielding an attack rate of 2%.⁶³ Of these, 18% had smallpox vaccination scars. Vaccinia seems to provide some cross-protection against monkeypox.⁶³ Person-to-person transmission has been documented.⁶³

BW Considerations.—Smallpox has been eradicated, but at least 2 sites, the Centers for Disease Control and Prevention in Atlanta, Ga, and the Russian State Research Center of Virology and Biotechnology in Koltsovo still maintain viable variola. The extent of clandestine stockpiles remains a matter of debate and concern.¹⁰ The World Health Organization has recommended the destruction of remaining stocks by June 30, 1999.⁷² If variola were released by an enemy or by terrorists, morbidity and mortality could be devastating. Its person-to-person communicability, high mortality, and stability make variola a significant potential BW threat. In addition, animal poxviruses that are virulent to humans (eg, monkeypox) or recombinant poxviruses could be developed as BW weapons.¹⁰ While approximately 20 million doses of smallpox vaccine are stored worldwide, the vaccine is gradually losing potency, and the number of smallpox-naïve individuals continues to increase as vaccination has virtually ceased.⁷³

Hemorrhagic Fever Viruses

Viral hemorrhagic fever (VHF) denotes a clinical syndrome that includes fever, malaise, myalgias, hemorrhage, and sometimes hypotension, shock, and death. The hemorrhagic fever viruses belong to 4 families of

lipid-enveloped viruses with single-stranded RNA genomes.⁷⁴ Animal reservoirs have been identified for 3 of these families (*Arenaviridae*, *Bunyaviridae*, and *Flaviviridae*); however, the reservoirs for the *Filoviridae* are unknown.⁷⁵⁻⁷⁸

Transmission may occur via arthropod vectors or from inhalation of aerosolized rodent excreta. Person-to-person spread often occurs via direct contact with blood and bodily fluids.^{79,80} All hemorrhagic fever viruses except dengue can be transmitted via aerosol.¹⁰ Four VHFs carry a high risk of nosocomial transmission and are quarantinable: Lassa fever, Congo-Crimean hemorrhagic fever, Ebola fever, and Marburg disease.⁷⁴

While epidemiological studies have not implicated respiratory transmission of VHFs among humans, such transmission has occurred among non-human primates.^{79,81} Furthermore, subclinical human infections due to a filovirus virulent for monkeys (Ebola-Reston) occurred after respiratory exposure to infected animals.⁷⁹

Clinical Features.—Viral hemorrhagic fevers present as acute febrile illnesses with nonspecific constitutional symptoms including fever, headache, sore throat, malaise, myalgia, nausea, and vomiting. Initial signs include flushing, conjunctival injection, periorbital edema, petechiae, and hypotension. Disease may progress to prostration, shock, hemorrhage, and organ system failure. Sequelae of infections include alopecia, Beau lines, and deafness (Lassa and Ebola fevers), retinitis (Rift Valley fever, Kyasanur Forest disease), uveitis (Rift Valley fever, Marburg disease), encephalitis (Argentine hemorrhagic fever, Bolivian hemorrhagic fever, Rift Valley fever, Kyasanur Forest disease, and Omsk hemorrhagic fever), pericarditis (Lassa fever), and renal insufficiency (hemorrhagic fever with renal syndrome).⁷⁴

Cutaneous Manifestations.—Hemorrhagic fevers produce a variety of cutaneous findings that are mostly due to vascular instability and bleeding abnormalities. All these diseases, except Rift Valley fever, may manifest flushing, petechiae, purpura, ecchymoses, and edema.

The Old World Arenavirus responsible for Lassa fever causes an extensive capillary leak syndrome without clotting abnormalities. Thus edema, without petechiae or hemorrhage, is most commonly seen.^{75,77,80} The South American Arenaviruses (Junin, Machupo, Sabia, and Guanarito) more commonly cause petechiae, purpura, ecchymoses, palatal hyperemia, and hemorrhage from mucosal surfaces.^{74,75}

The Bunyavirus causing Congo-Crimean hemorrhagic fever results in the most severe hemorrhagic complications among all VHFs (**Figure 4**).^{74,75} The hantaviruses of the *Bunyaviridae* cause hemorrhagic fever with renal syndrome. Around day 3, patients develop a petechial eruption on the neck, anterior and posterior axillary folds, arms, and thorax.^{82,83} A morbilliform eruption may also appear. A sunburn flush is commonly seen about the head, neck, and upper torso accompanied by facial edema.^{10,83} Dermatographism is often present, and



Figure 4. Ecchymoses encompassing left upper extremity 1 week after onset of Congo-Crimean hemorrhagic fever. Ecchymoses are often accompanied by hemorrhage in other locations: epistaxis, puncture sites, hematemesis, melena, and hematuria. No other hemorrhagic fever virus causes such severe bleeding abnormalities.¹¹⁶ (Photograph courtesy of Robert Swaneopoe, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.)



Figure 5. Flavivirus infection with dengue virus, a patient with morbilliform exanthem with characteristic islands of sparing. (Photograph courtesy of Duane Gubler, ScD.)

severe hemorrhages on oral and conjunctival mucosae may be seen.⁸³

The highly feared Filoviruses (*filo*, which is thread in Greek) Marburg and Ebola frequently exhibit characteristic exanthems noted best in light-skinned patients.^{76,78,84,85} Disease typically presents with an acute, flulike syndrome with soft-palate reddening spreading to the hard palate. The most reliable diagnostic sign is a nonpruritic, centripetal, pinhead-sized papular, erythematous eruption appearing between days 5 and 7.^{76,84,85} Sometimes, scrotal or labial erythema and dermatitis accompany this. After 24 hours, this eruption develops into large, well-demarcated, coalescent macules and papules that are sometimes hemorrhagic.^{75,76,84,85} In severe cases, a dark, livid erythema with or without cyanosis develops on the face, trunk, and extremities. Patients have expressionless, ghostlike faces. With progressive disease, hemorrhage exudes from mucous membranes, venipuncture sites, and body orifices. After 1 to 2 more weeks, desquamation of the palms, soles, dorsal feet, and extremities follows.^{75,76,84} Death occurs owing to a combination of hemorrhage, capillary leak, shock, and end-organ failure. The mortality rate for Marburg disease is 23% and for Ebola fever, 70%.^{75,78,86}

Dengue fever is the most common Flavivirus disease in the world and causes approximately 100 million annual cases of an erythematous exanthem with notable islands of sparing (**Figure 5**).⁷⁵ Infection due to 1 of the 4 serotypes grants lifelong immunity to that serotype only and predisposes one to develop dengue hemorrhagic fever or dengue shock syndrome following infection with a heterologous strain.⁸⁷ Only patients infected sequentially with different dengue serotypes will develop the life-threatening hemorrhagic fever or shock syndrome. This occurs in 1 million people annually resulting in approximately 100 000 deaths.⁷⁵ Typically, yellow fever's only cutaneous manifestation is jaundice. The tick-borne Flavivirus diseases (Omsk hemorrhagic fever and Kyasanur Forest disease) can

cause any of the hemorrhagic manifestations listed earlier.^{74,75}

BW Considerations.—Hemorrhagic fever viruses cause high morbidity and, in some cases, high mortality. Some replicate well enough in cell culture to permit weaponization. With the exception of dengue, all the hemorrhagic fever viruses are transmissible by aerosol, underscoring their possible role as BW agents.¹⁰ For example, Marburg virus can be stabilized in 10% glycerin so that viral inactivation occurs at a rate of 1.5% per minute instead of 11.5% per minute. This rate of inactivation is similar to that for influenza virus (1.9% per minute) that spreads naturally via aerosol.⁶¹

On a positive note, the susceptibility of Bunyaviruses to heat, drying, and UV light make them poor candidates as BW agents (Peter B. Jahrling, PhD, oral communication, May 1997). Hantaviruses replicate poorly in cell culture.¹⁰ The Flaviviruses are unlikely to be used since dengue is not infectious by aerosol and troops are routinely immunized for yellow fever.¹⁰ A live-attenuated junin vaccine provides protection against infection with both junin and machupo viruses.¹⁰ Investigational vaccines that include both a formalin-inactivated and live-attenuated vaccine protect against Rift Valley fever, and a vaccinia-vectored vaccine protects against Hanta virus.¹⁰

CUTANEOUS COMPLICATIONS OF BW PREVENTION

Strategies have been developed to prevent and treat the diseases that could develop after a BW attack. These include vaccines, antibiotic prophylaxis, and protective measures such as the use of gas masks (Table 1).¹⁰ Vaccinia, which would be used as a preventive measure if smallpox was released, causes a variety of cutaneous adverse effects in a small percentage of vaccinees.



Figure 6. *Vaccinia necrosum* (progressive vaccinia, *vaccinia gangrenosum*) represents progressive viral replication in an immunocompromised individual leading to inexorable tissue destruction.¹¹⁵ (Photograph courtesy of C. H. Kempe.)

Vaccinia

The Orthopox virus vaccinia, used as the first live vaccine, was essential for the global eradication of smallpox.^{60,88,89} Vaccinia has recently been studied as a vector for experimental recombinant vaccines.⁹⁰ Its origin is obscure. Vaccinia may have developed from an extinct animal poxvirus, such as horsepox, or it may represent a cowpox mutant that emerged during multiple human passages as vaccine was passed from arm-to-arm during the early vaccine era.⁹¹ Vaccinia has little virulence for immunocompetent humans and would not be an effective BW agent, but it could cause disease when used to prevent smallpox. Vaccinia can cause serious complications in those with impaired cellular immunity, widespread dermatitis, and exfoliative dermatoses.

Clinical Response to Vaccination.—Vaccine is administered percutaneously with a bifurcated needle. Primary vaccinees usually develop a 2- to 4-cm pustule surrounded by induration 6 to 8 days after vaccination. This is accompanied by low-grade fever and axillary lymphadenopathy that indicate viral replication.^{60,91} This *major* reaction was required to confer protective immunity and occurred in 95% of primary vaccinees. All other reactions were termed *equivocal*.⁹¹ The pustule would evolve into an ulcer with an overlying eschar that would eventually separate. This process became known as scarification because of the ensuing perma-

nent scar.⁹² Vaccination by intramuscular injection induces a 3-fold to 10-fold reduction in the immune response.⁹³ Vaccinia provided at least 3 years of protection against smallpox.⁹²

Cutaneous Complications of Vaccinia.—Cutaneous complications were at least 10 times more common in primary vaccinees than revaccinees. The most severe cutaneous complication, *vaccinia necrosum* (*vaccinia gangrenosum*, progressive vaccinia), occurred in 12.3 individuals per million primary vaccinees.⁹⁴ Vaccinees, usually with impaired cell-mediated immunity, developed relentlessly progressive pox lesions and metastatic lesions (**Figure 6**). Fatal cases demonstrated no evidence of immune response.

Eczema vaccinatum featured hundreds of pox lesions and occurred in patients with active atopic dermatitis who were either vaccinated or exposed to a recent vaccinee. Mortality was 10% to 14%.⁹⁴ Patients were treated with vaccinia immune globulin (0.6 mL/kg per day) until no new lesions appeared.⁹² Only 1.5 cases per million primary vaccinees were reported in the United States. This low rate is best explained by the fact that atopic dermatitis was identified as a contraindication to vaccination.⁹⁴

Accidental vaccinia infection occurred among 242 per million primary vaccinees by autoinoculation to another body site or to another individual via intimate contact.⁹⁴ Ocular vaccinia was one of the most morbid complications since it resulted in conjunctivitis, keratitis, or corneal perforation.^{91,94}

Generalized vaccinia presented as a vesicular eruption 1 to 2 weeks after primary vaccination. Afebrile and nontoxic-appearing patients developed many small vesicles on erythematous bases. This self-limited complication resolved in about 1 week in the 39 people per million primary vaccinees who contracted it.⁹⁴ Other patients developed erythematous urticarial eruptions that resembled enterovirus or roseola exanthems.⁹⁴

Other complications included the formation of melanoma or basal cell carcinomas in vaccination scars. Bullous erythema multiforme, overwhelming and fatal viremia in infants, and fetal vaccinia have also been reported after vaccinia inoculation.^{91,94}

AGENTS PRODUCING CUTANEOUS MANIFESTATIONS NATURALLY, BUT NOT AFTER INHALATION

Anthrax: *Bacillus anthracis*

Spores of the gram-positive bacterium *Bacillus anthracis* survive extremes of heat, cold, drying, and chemical disinfection, and in nature, they retain viability for years.^{15,95,96} Anthrax is endemic in western Asia (Afghanistan, Iran, and Turkey) and western Africa.⁹⁷ Disease is transmitted from infected animals or their products via skin abrasions in more than 90% of cases. Less commonly, ingestion or inhalation of spores transmits anthrax.^{95,98}

Clinical Features.—Approximately 95% of cases present as cutaneous disease. Gastrointestinal anthrax fol-

lows ingestion of poorly cooked meat obtained from infected livestock and results in mucosal ulcers that can perforate viscera to cause abdominal pain, diarrhea, and sepsis.⁹⁹

Inhalational anthrax, or wool-sorter's disease, is an extraordinarily rare form of anthrax; only 18 cases were reported in the United States between 1900 and 1980.⁹⁸ Inhaled spores germinate in hilar nodes and cause a deadly hemorrhagic mediastinitis, not a primary pneumonia. Inhalational anthrax would follow a biological attack using anthrax spores. The illness begins with a vague prodrome featuring low-grade fever, malaise, myalgias, and nonproductive cough with transient improvement in some patients after 2 to 4 days. This is followed by the acute phase, manifesting with abrupt onset of respiratory distress, shock, and death. Metastatic infection results in hemorrhagic meningitis in up to 50% of cases. Radiographic findings may include hilar adenopathy, a widened mediastinal shadow, and pleural effusions. Because the disease is difficult to diagnose in the early, treatable stages, it is almost uniformly fatal.^{98,100,101}

Cutaneous Manifestations.—Cutaneous disease begins as a small, painless, red macule that progresses to a papule that vesiculates, ruptures, ulcerates, and forms a classic 1- to 5-cm brown or black eschar surrounded by significant edema.^{100,102} This coal black eschar gave rise to the term *anthrax* that is derived from the Greek *anthrakos* meaning "coal."¹⁰³ Lesions usually appear within 2 weeks after handling sick animals or eating their meat; however, incubation periods of more than 8 weeks have been observed. Lesions are not purulent in the absence of superinfection, thus the term *malignant pustule* ascribed to this lesion is a misnomer.¹⁰⁰ Even with prompt antibiotic therapy, cutaneous lesions progress through the eschar phase. While 80% to 90% of lesions heal spontaneously, 10% to 20% of untreated patients develop malignant edema, septicemia, shock, renal failure, and death. In contrast to inhalational anthrax, fatalities due to cutaneous disease are uncommon with therapy.^{100,102,104,105}

BW Considerations.—In a BW attack, anthrax spores would most likely be disseminated as an aerosol. In April and May 1979, at least 66 people died during an epidemic of inhalational anthrax in Sverdlovsk (now Ekaterinburg), Russia, following the accidental release of aerosolized spores.⁷ It has been estimated that the release of less than 1 g of spores caused the outbreak.^{7,98} All 42 victims undergoing autopsy demonstrated hemorrhagic mediastinitis.¹⁰⁶ This accident demonstrated the silent and deadly nature of an aerosol BW attack. Anthrax spores were weaponized by Japan, the United Kingdom, and the United States in the 1940s, 1950s, and 1960s before their offensive BW programs were terminated.¹⁰ Iraq admitted to a United Nations inspection team in 1995 that it had weaponized anthrax.¹⁰⁷

A Food and Drug Administration–licensed vaccine has proven safe and effective in preventing anthrax among textile workers, veterinarians, and laboratory workers at risk. The toxoid vaccine also protects non-

human primates against aerosol challenge with anthrax spores.¹⁰⁸

Tularemia: *Francisella tularensis*

Francisella tularensis is a gram-negative, pleomorphic coccobacillus maintained in numerous mammalian reservoirs and spread by dozens of biting and blood-sucking arthropods. Skin or mucous membranes serve as the portal of entry for arthropod bites or abrasions. As few as 10 organisms are necessary to cause cutaneous or pulmonary infection.^{109,110}

Clinical Features.—Each of 6 possible clinical forms (ulceroglandular, glandular, oculoglandular, gastrointestinal, typhoidal, and pulmonary) begins with the sudden onset of a flulike syndrome. An ulcer is commonly seen at a bite site, and the ulcer may persist for several months. Cutaneous multiplication of *F. tularensis* can allow organisms to spread to lymph nodes and then to the blood. Inhalation of organisms may result in typhoidal disease (septicemia) or a primary pneumonia. Pneumonic tularemia is the primary concern in a BW scenario. Patients complain of fever, cough, minimal or no sputum production, and pleuritic chest pain. Physical findings are variable, and they may include rales, pleural friction rubs, and signs of consolidation or effusions. Radiographic findings are also variable, and they may include infiltrates, cavitation, hilar adenopathy, and pleural effusions. The clinical course may be rapidly progressive and fulminant. While 4% of patients with the most common form, ulceroglandular tularemia, die if untreated, fully 35% die from typhoidal disease, and 30% to 60% succumb to the pulmonary form.¹⁰⁹ Mortality drops to 1% to 2.5% with appropriate treatment.¹¹¹

Cutaneous Manifestations.—A chancrelike ulcer with heaped-up borders forms at the site of bacterial inoculation in 60% of patients.¹¹² About 85% of patients develop tender lymphadenopathy¹¹² that sometimes presents as fluctuant buboes.¹¹³ Pharyngeal ulcers may accompany aerosol-induced disease.¹¹² A morbilliform eruption has been reported in a minority of patients with systemic disease.¹¹¹

BW Considerations.—Tularemia was weaponized by the United States in the 1950s and 1960s.¹⁰ Other countries may have weaponized tularemia for aerosol delivery.^{10,13} Both typhoidal and pulmonary tularemia can result from inhalation, and mucosal lesions could accompany inhalational disease. The rapid onset of action, nonspecific nature of complaints in those affected, and the difficulty in identifying and culturing the organism make it a potential threat agent.¹¹²

RECOGNIZING A BW ATTACK

Owing to the incubation periods of most BW agents, an enemy could complete a BW attack before health care providers and public health officials would be aware that an attack had occurred. Large and steadily increas-

ing numbers of casualties could present within a shorter period than during a natural epidemic. There could be large numbers of rapidly fatal cases with few specific signs and symptoms depending on the agent(s) used. Multiple diseases could present simultaneously. Vector-borne diseases could appear without natural outbreaks in animals. The disease(s) would typically be unusual for a given geographic area and attack a high proportion of those exposed. Because most agents would be delivered in aerosol clouds, patients could develop pulmonary disease caused by agents that usually do not involve the respiratory tract.^{3,10,13}

Unlike conventional, chemical, or nuclear warfare, BW attacks would generally allow time for an effective emergency response to save many lives.¹ Due to the vulnerability of the civilian population to a biological attack, civilian medical personnel need to be aware of how such an attack would present so that they could ameliorate its effects (Table 1). We cannot presume that such an attack would never happen.^{3,10,13} Fortunately, the US government is educating urban emergency response teams. The US Army Chemical and Biological Defense Command, supported by the US Army Medical Research Institute of Infectious Diseases and the US Army Medical Research Institute of Chemical Defense, in accord with the Nunn-Luger-Domenici legislation of 1996, is conducting training for emergency responders and caregivers in more than 100 cities over 5 years so that these responders can recognize and respond to a BW assault.

ROLE OF THE DERMATOLOGIST

The dermatologist need not feel helpless in the face of a BW terrorist attack. Indeed, he/she may be one of the most valuable assets who can use his/her highly trained clinical skills to diagnose the cause of an attack. The dermatologist should be aware of the ecchymotic and purpuric changes seen in septicemic plague and various hemorrhagic fevers. This article has also reviewed some of the distinctive findings of several threat agents, such as the significant edema of Lassa fever, the massive hemorrhage of Congo-Crimean hemorrhagic fever, the sunburn flush of hemorrhagic fever with renal syndrome, and the early centripetal, papular eruption of Ebola and Marburg hemorrhagic fevers. The dermatologist should be able to recognize smallpox or monkeypox and quickly differentiate it from the more common varicella. Many of these diseases can be treated to prevent death and disfigurement.

Prompt recognition of the dermatologic features of BW-associated diseases can lead to a more rapid mobilization of public health and medical assets, leading to implementation of vaccines, chemoprophylaxis, and appropriate therapy (Table 1). Thus, the effects of a potentially devastating epidemic could be mitigated.

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