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Over the past several years there has been an increasing awareness and interest by the medical community, the media, and government at all levels regarding the need to plan for and defend against biological weapons. This article offers an overview of various new and emerging natural biological threats.

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The threat of bioterrorism has led to increased concerns over the availability of biological select agents and toxins (BSAT). Congress has implemented several public laws that have led to the development of federal regulations by the Centers for Disease Control and Prevention (CDC) and the US Department of Agriculture. The CDC regulation 42 CFR 73 has a direct impact on all clinical laboratories that may at some time identify BSAT in a clinical specimen. The Department of Defense has imposed a more stringent layer of regulation called biological surety (biosurety) on top of the requirements of 42 CFR 73 for military laboratories that possess BSAT. However, 42 CFR 73 falls into the framework of biosurety. Both sets of regulations have four pillars (safety, physical security, agent accountability, and personnel reliability) that are built on a foundation of training and covered by a roof of management (operations and plans).

**Medical Strategies to Handle Mass Casualties  
from the Use of Biological Weapons**

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Kristi L. Koenig, Christopher A. Kahn, and Carl H. Schultz

This article reviews the definitions of biological weapons and mass casualties. In addition, it discusses the main operational and logistical issues of import in the medical management of mass casualties from the use of biological weapons. Strategies for medical management of specific biologic agents also are highlighted.

**Clinical and Pathologic Differential Diagnosis  
of Selected Potential Bioterrorism Agents of Interest  
to Pediatric Health Care Providers**

329

J. Thomas Stocker

The early recognition of potential bioterrorism agents has been of increasing concern in recent years. The Centers for Disease Control and Prevention has categorized and listed biological terrorism agents. Although any or all of the highest risk biological agents (including inhalation anthrax, pneumonic plague, smallpox, tularemia, botulism, and viral hemorrhagic fevers) can be seen in the pediatric patient, several agents might closely resemble—at least in their initial stages—some of the more common childhood illnesses. The awareness of these similarities and, more importantly, their differences, are critical for all health care professionals. Selected examples of some typical childhood illnesses are presented and then compared with three of the most virulent biological agents (smallpox, anthrax and plague) that might be used in a bioterrorism attack.

**Viral Hemorrhagic Fevers**

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Peter B. Jahrling, Aileen M. Marty, and Thomas W. Geisbert

A taxonomically diverse set of single-stranded ribonucleic acid (ssRNA) viruses from four diverse viral families *Arenaviridae*, *Bunyaviridae*, *Filoviridae*, and *Flaviviridae* cause an acute systemic febrile syndrome called viral hemorrhagic fever (VHF). The syndrome produces combinations of prostration, malaise, increased vascular permeability, and coagulation maladies. In severe illness, VHF may include generalized bleeding but the bleeding does not typically constitute a life-threatening loss of blood volume. To a certain extent, it is a sign of damage to the vascular endothelium and is an indicator of disease severity in specific target organs. Although the viruses that cause hemorrhagic fever (HF) can productively replicate in endothelial cells, much of the disease pathology including impairment to the vascular system is thought to result primarily from the release of a variety of mediators from virus-infected cells, such as monocytes and macrophages that subsequently alter vascular function and trigger the coagulation disorders that epitomize these infections. While significant progress has

been made over the last several years in dissecting out the molecular biology and pathogenesis of the HF viruses, there are currently no vaccines or drugs licensed available for most of the VHF.

### **Fungi as Bioweapons**

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Mary K. Klassen-Fischer

Fungi cause disease directly by infection or indirectly through mycotoxins. Fungi that are used as weapons might be targeted against humans, livestock, or crops. Humans and animals encounter fungi and mycotoxins through inhalation, ingestion, and contact with skin and mucous membranes. Effective fungal bioweapons would require the ability to cause significant destruction and a means of delivery to target populations or farms. Effective countermeasures against fungal bioweapons would be able to prevent or treat this damage. This article describes several potential biological warfare or bioterrorism fungal species and mycotoxins in regard to their biology, epidemiology, potential for weaponization, and the clinical features, prevention, and treatment of the diseases that they cause.

### **Biologic Toxins: Bacterial and Marine Toxins**

397

Matthew Salzman, James M. Madsen,  
and Michael I. Greenberg

The term toxin refers in a specific way to a toxic substance of biologic origin; that is, a true toxin is a poison produced by a living organism. The purpose of this article is to review some of the most potentially dangerous toxins of concern today. Mechanisms of action, routes of exposure, diagnostic tools, and treatment recommendations are addressed. In addition, current therapeutic uses for certain toxins are discussed.

### **Bioregulators as Prototypic Nontraditional Threat Agents**

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Elliott Kagan

Bioregulators are naturally occurring organic compounds that regulate a multitude of biologic processes. Under natural circumstances, bioregulators are synthesized in minute quantities in a variety of living organisms and are essential for physiologic homeostasis. In the wrong hands, these compounds have the capability to be used as nontraditional threat agents that are covered by the prohibitions of the Chemical Weapons Convention and the Biological and Toxin Weapons Convention. Unlike traditional biowarfare/bioterrorism agents that have a latency period of hours to days, the onset of action of bioregulators may occur within minutes after host exposure. Concerns regarding the potential misuse of bioregulators for nefarious purposes relate to the ability of these nontraditional agents to induce profound physiologic effects.

**Clinicopathologic Aspects of Animal and Zoonotic Diseases of Bioterrorism**

445

Marc E. Mattix, David H. Zeman, Robert Moeller, Carney Jackson, and Thomas Larsen

We live in an era of emerging infectious diseases and the threat of bioterrorism. Most of the infectious agents of modern concern, from plague to avian influenza H5N1, are zoonotic diseases: infectious agents that reside in quiet animal reservoir cycles that are transmitted occasionally to humans. The public health, health care, and veterinary communities have an enormous challenge in the early recognition, reporting, treatment, and prevention of zoonotic diseases. An intimate understanding of the natural ecology, geographic distribution, clinical signs, lesions, and diagnosis of these diseases is essential for the early recognition and control of these diseases.

**Modulating Radiation Resistance: Insights Based on Defenses Against Reactive Oxygen Species in the Radioresistant Bacterium *Deinococcus radiodurans***

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Michael J. Daly

The classical dogma of radiation biology asserts that the cytotoxic effects of ionizing radiation (IR) are principally the result of DNA damage. Yet many organisms that encode a complement of DNA repair functions are killed by IR doses that cause little DNA damage. Instead, proteins likely are the first major class of molecules damaged by IR. This article presents a new perspective on extreme IR resistance in the eubacterium *Deinococcus radiodurans*, reevaluates the role of superoxide ( $O_2^{\bullet-}$ ) ions in IR toxicity, and speculates on potential strategies for controlling resistance in prokaryotes and eukaryotes based on scavenging IR-induced  $O_2^{\bullet-}$ .

**Immunologic Aspects of Select Agents**

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Florence M. Rollwagen

We are on the cusp of exciting new developments in vaccine biology. The use of DNA constructs allows virtually unlimited access to previously inaccessible organisms. Next-generation adjuvants will boost innate and acquired immunity, and will provide protection from infection with any potential biowarfare organism. We are limited only by our imaginations in the construction of a protective armamentarium.

**Anatomic Laboratory and Forensic Aspects of Biological Threat Agents**

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Aileen M. Marty

Anatomic pathology of surgical and cytologic samples and forensic autopsies is a critical component of our defense against biological

terrorism. In many instances, rapid, valuable diagnosis may be obtained by the proper immediate use of the anatomic pathology laboratory. Included in this field is the work of medical examiners and coroners, who are essential public health partners for terrorism preparedness and response. The investigation of sudden, suspicious, violent, unattended, and unexplained deaths may provide the first clue to a deliberate biological attack. Medicolegal autopsies are essential to making organism-specific diagnoses in deaths caused by biological terrorism.

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