

CBER Science Symposium

**New Efforts in  
Counter-Bioterrorism**

Anthony S. Fauci, M.D.  
September 23, 2002

**Warfare  
Terrorism  
Biowarfare  
Bioterrorism**

## **Biowarfare versus Bioterrorism**

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- The civilian population is significantly more diverse than the military with regard to age and health.
- Military plans for attacks emphasize vaccine prevention. Civilian attacks will be sudden and unexpected, requiring rapid diagnostics and antimicrobial treatments.
- Potential agents of bioterrorism in civilian settings are more numerous than potential military biological weapons.

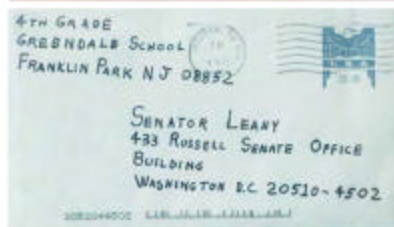
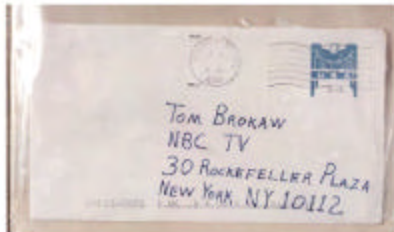
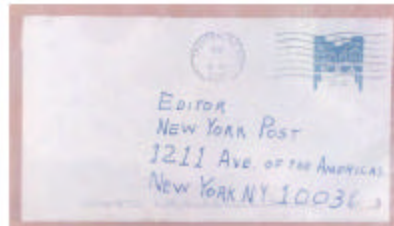
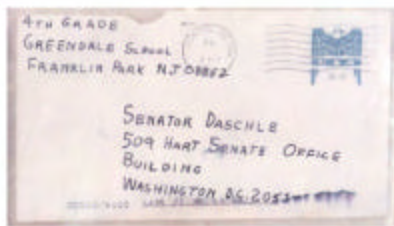
## **Selected Events in the History of Biowarfare and Bioterrorism**

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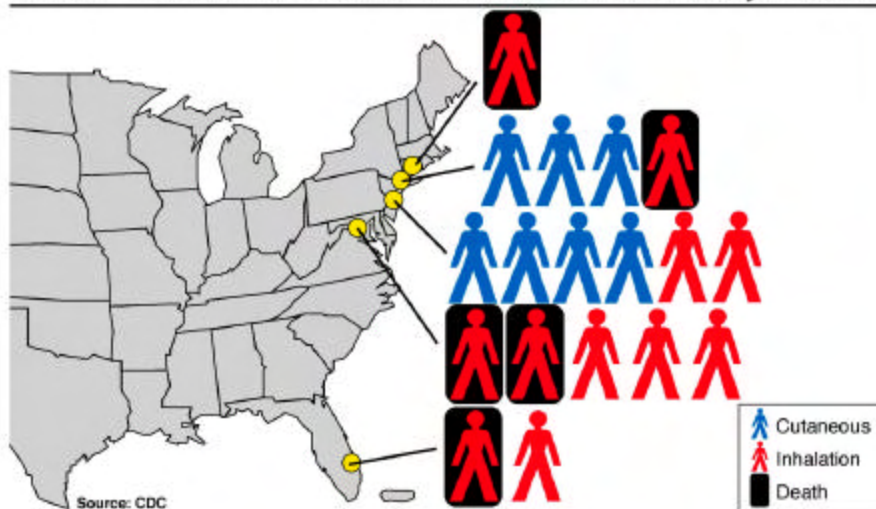
- 1346- Mongols catapult corpses contaminated with plague over the walls into Kaffa
- 1347 (In Crimea), forcing besieged Genoans to flee
- 1710 - Russian troops allegedly use plague-infected corpses against Swedes
- 1767 - The British give smallpox-contaminated blankets to hostile Indian tribes during the French and Indian Wars
- 1916- German agents use anthrax and the equine disease glanders to infect livestock
- 1918 and feed for export to Allied forces
- 1937 - Japan begins its offensive biological weapons program (Unit 731). Over the course of the program, at least 10,000 prisoners are killed in Japanese experiments
- 1940 - The Japanese drop rice and wheat mixed with plague-carrying fleas over China and Manchuria
- 1969 - President Nixon announces unilateral dismantlement of the U.S. offensive BW program
- 1972 - BWC opened for signature; ratified by U.S. in 1975
- 1979 - Outbreak of pulmonary anthrax in Sverdlosk, Soviet Union
- 1984 - *Salmonella* contamination of salad bars in Oregon by Rajneesh cult
- 2001 - Anthrax attacks in eastern United States

Source: Monterey Institute of International Studies

## Bioterrorism: Letters Containing Anthrax



## Confirmed Anthrax Cases Associated with Bioterrorism: United States, 2001



## **Impact of 2001 Anthrax Attacks**

- 22 cases (18 confirmed); 5 deaths
- 30,000+ people received antibiotics
- 10,000+ people were recommended to receive antibiotics for at least 60 days
- Psychological impact
- Societal disruption -- Congress, postal system, etc.

## **The Anthrax Attacks of 2001**



**Biological  
Impact**



**Fear and  
Disruption**



**BIOHAZARD**

THE CHILLING TRUE STORY OF THE LARGEST COVERT BIOLOGICAL WEAPONS PROGRAM IN THE WORLD—TOLD FROM INSIDE—BY THE MAN WHO RAN IT

**KEN ALIBEK**  
WITH STEPHEN HANDELMAN

**BIOHAZARD**

THE CHILLING TRUE STORY OF THE LARGEST COVERT BIOLOGICAL WEAPONS PROGRAM IN THE WORLD—TOLD FROM INSIDE—BY THE MAN WHO RAN IT

*“Over a twenty-year period that began, ironically, with Moscow’s endorsement of the Biological Weapons Convention in 1972, the Soviet Union built the largest and most advanced biological warfare establishment in the world. . . . through our covert program, we stockpiled hundreds of tons of anthrax and dozens of tons of plague and smallpox near Moscow and other Russian cities for use against the United States and its Western allies.”*

**Science**

August 16, 2002

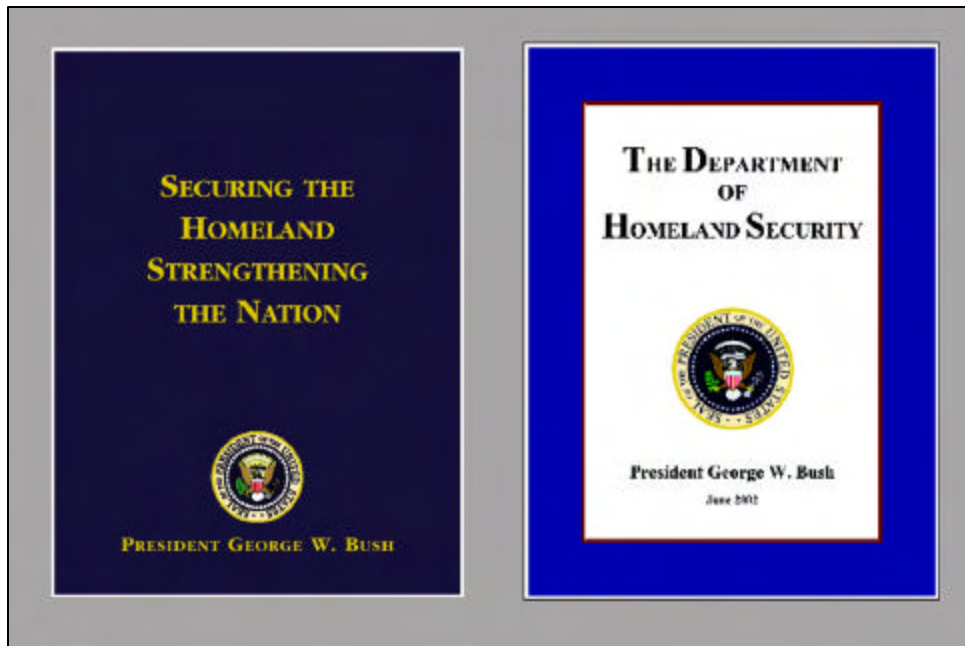
**Peering Into the Shadows: Iraq’s Bioweapons Program**

**IRAQI BIOLOGICAL AGENTS**

Agent	Summary
Botulinum toxin	19,000 liters concentrated (10,000 into munitions)
Anthrax	8500 liters (6500 into munitions)
Aflatoxin	2390 liters concentrated (1590 into munitions)
Wheat smut	Considerable quantities
Perfringens toxin	340 liters concentrated
Ricin	Trials failed
Trichothecene mycotoxins (such as T-2 and DAS)	Research
Enterovirus 70	Research
Rotavirus	Research
Camelpox virus	Research

Source: Science 2002; 297: 1110

# **The U.S. Government Response to the Threat of Bioterrorism**



## **NIH BSL-3/4 Pre-Clinical and Clinical Research Facilities, Fort Detrick**

**Occupancy** **TBD**

**Size** 120,000 gsf

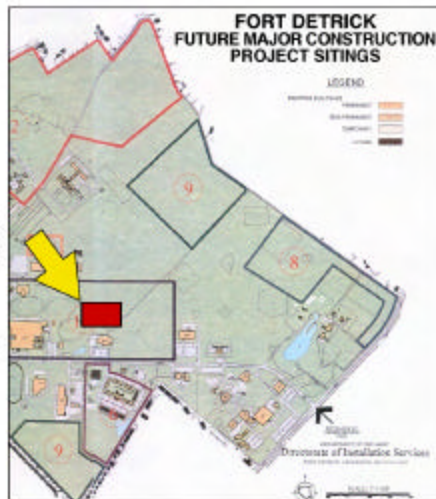
**Cost Design/Construction** \$105 M

### **Research Areas**

Anthrax, poxviruses, viral hemorrhagic fevers, drug-resistant bacterial infections


### **Features**

BSL-4 lab and animal facility with clinical capability



## **Biodefense Research: The Microbes**

- Expanded research into the microbial physiology, ecology and molecular pathogenesis of potential bioterror agents
- Genomic sequencing of potential bioterror agents, and genomic, proteomic and structural analyses of these agents
- Development of animal models to study potential bioterror agents

<p>November 8, 2001</p> <h1>nature</h1>	<p>nature <b>scienceupdate</b></p>
<p><b>Identification of the cellular receptor for anthrax toxin</b></p> <p>Kenneth A. Bradley, Jeremy Mogeridge, Michael Mourez, R. John Collier and John A. T. Young</p>	<p>24 January 2002</p>
<p><b>Crystal structure of the anthrax lethal factor</b></p> <p>Andrew D. Pannifer, Thiang Yian Wong, Robert Schwarzenbacher, Martin Renatus, Carlo Petosa, Jadwiga Bienkowska, D. Borden Lacyk, R. John Collier, Sukjoon Park, Stephen H. Leppla, Philip Hanna and Robert C. Liddington</p>	
	<p><b>Third anthrax toxin revealed</b></p>
	<p><i>Scientists now know structure of all three anthrax toxins.</i></p>

<p>nature <b>medicine</b></p>	<p><b>Molecular Cell</b></p>
<p>August 2000</p>	<p>August 2002</p>
<p><b>Identification of the Ebola virus glycoprotein as the main viral determinant of vascular cell cytotoxicity and injury</b></p> <p>Zhi-yong Yang, Henricus J. Duckers, Nancy J. Sullivan, Anthony Sanchez, Elizabeth G. Nabel &amp; Gary J. Nabel</p>	<p><b>The Assembly of Ebola Virus Nucleocapsid Requires Virion-Associated Proteins 35 and 24 and Posttranslational Modification of Nucleoprotein</b></p>
<p>Cytotoxicity of Ebola virus glycoprotein Blocking heme import in malaria Telomerase in mice and man</p>	<p>Yue Huang, Ling Xu, Yongnian Sun, and Gary J. Nabel</p>



## Genomic Sequencing of Potential Bioterror Agents: Selected Examples

Agent	Disease or toxin	Status
<i>Bacillus anthracis</i>	Anthrax	Complete, multiple strains
<i>Brucella suis</i>	Brucellosis	Complete
<i>Burkholderia mallei</i>	Glanders	Gap closure underway
<i>Clostridium perfringens</i>	Epsilon toxin	Gap closure underway
<i>Coxiella burnetii</i>	Q fever	Complete
<i>Cryptosporidium parvum</i>	Food- and water-borne diseases	Gap closure underway
<i>Rickettsia typhi</i>	Typhus	In progress
<i>Staphylococcus aureus</i>	Enterotoxin B	Complete
<i>Yersinia pestis</i>	Plague	Complete
<i>Variola major</i>	Smallpox	Complete sequence for some strains
<i>Vibrio cholerae</i>	Cholera	Complete

## Biodefense Research: Immunology/Host Response

- Innate immunity
- Adaptive immunity
- Mechanistic studies of response to vaccines
- Passive immunotherapy
- Mapping of protective epitopes for microbes and their toxins

## **Biodefense Vaccine Research: Goals**

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- **Protect all groups of civilians**
- **Develop improved vaccines against microbes for which vaccines currently exist**
- **Develop new/novel vaccines against microbes for which none currently exist**



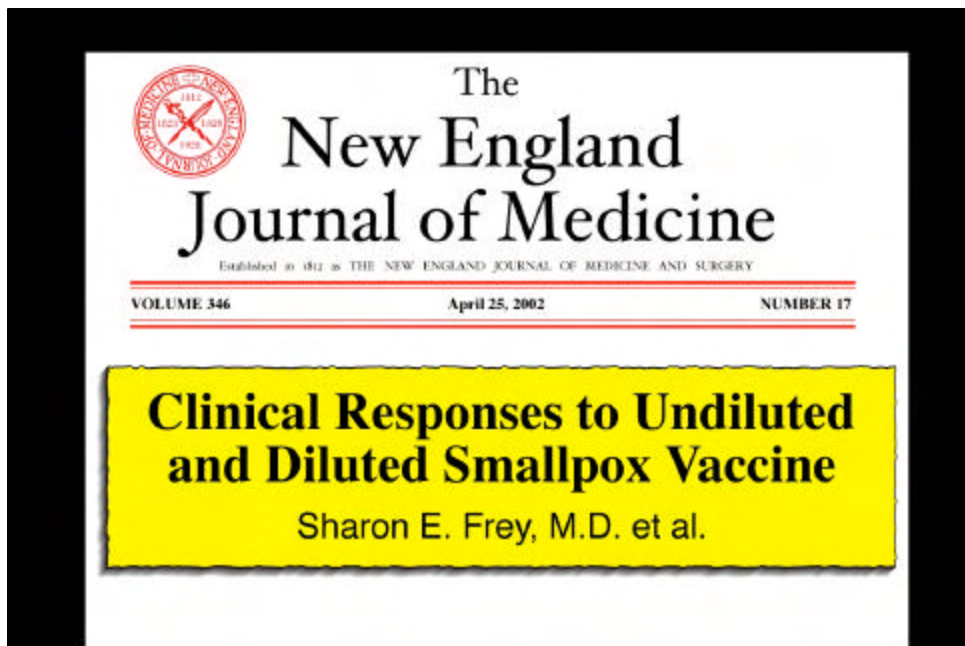
### THE WALL STREET JOURNAL

October 19, 2001

## **Search for Better Anthrax Vaccine Expands**

*Clinical Trials Are Expected*

By LAURA JOHANNES and LAURIE MCGINLEY  
Staff Reporters of THE WALL STREET JOURNAL

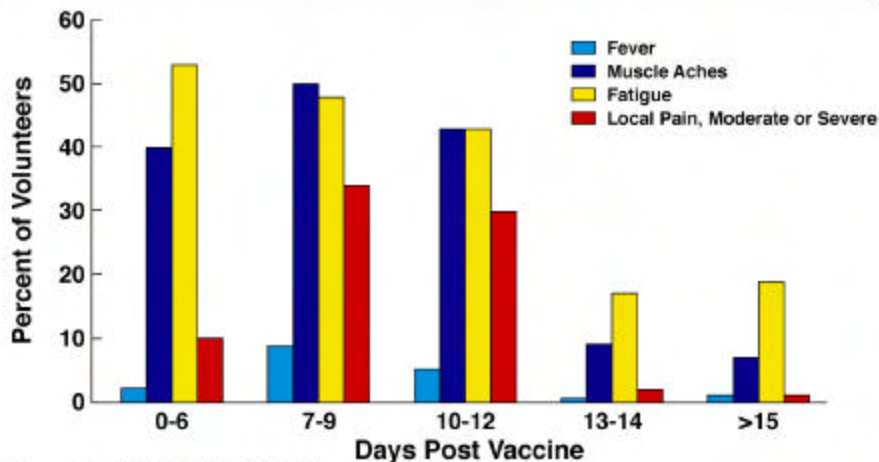


## Rate of Success\* of Initial and Repeated Vaccination with Dryvax

Vaccine	No. of Subjects	Initial Vaccination Successful	Initial or Subsequent Vaccination Successful
Undiluted	106	97.2%	97.2%
1:5 dilution	234	99.1%	100.0%
1:10 dilution	340	97.1%	98.8%

\*Success was defined by vesicle formation 7-9 days after inoculation.  
Reference: Frey S et al. *NEJM* 2002; 346:1265

## Acute Viral Illness Associated with Vaccinia



Reference: Frey S et al. *NEJM* 2002; 346:1265



## **Smallpox Vaccine: Availability by Late 2002**

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	<u># of Doses</u>
■ 15.4 million doses of Dryvax diluted 1:5	77 million
■ Contracts for cell culture-derived vaccine	209 million
■ Vaccine from Aventis Pasteur Inc.	> 75 million
<b>Total</b>	<b>&gt; 363 million</b>

# **Formulation of Smallpox Vaccination Policy**

## Complications of Smallpox Vaccination United States, 1968

Vaccination Status	Estimated No. of Vaccinations	No. of Cases						Total
		Postvaccinial Encephalitis	Progressive Vaccinia	Eczema Vaccinatum	Generalized Vaccinia	Accidental Infection	Other	
Primary vaccination	5,594,00	16(4)	5(2)	58	131	142	66	<b>418</b>
Revaccination	8,574,00	0	6(2)	8	10	7	9	<b>40</b>
Contacts	-	0	0	60(1)	2	44	8	<b>114</b>
<b>Total</b>	<b>14,168,000</b>	<b>16(4)</b>	<b>11(4)</b>	<b>126(1)</b>	<b>143</b>	<b>193</b>	<b>83</b>	<b>572</b>

Source: JAMA 1999; 281:2127

A.S. Fauci, NIAID

## Eczema Vaccinatum in a Patient Vaccinated Against Smallpox

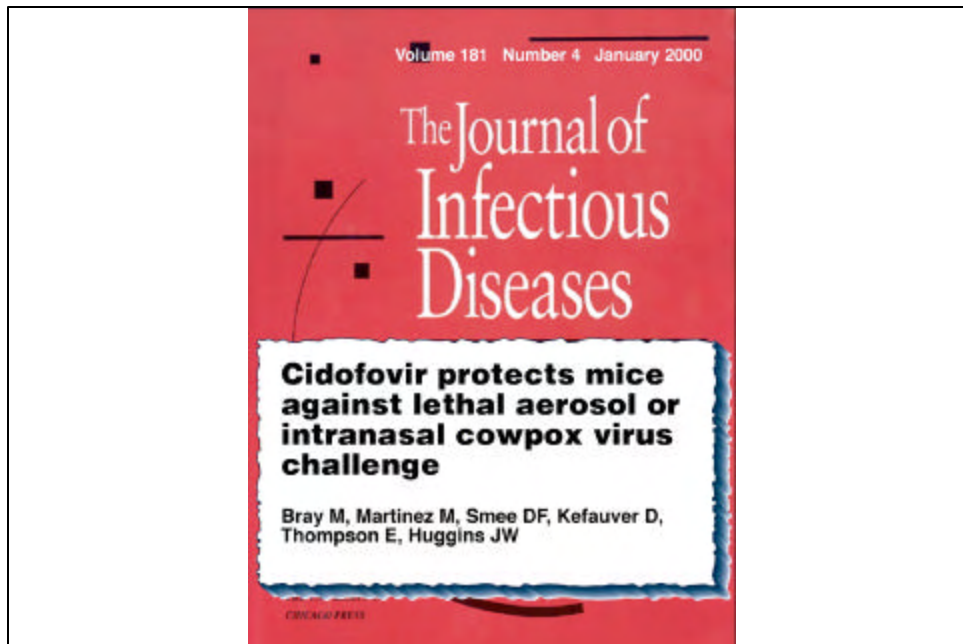


Source: NEJM 346:1287, 2002

## Biodefense Research: Therapeutics

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- Screening of existing antimicrobial agents for activity against potential agents of bioterrorism
- Development of therapeutic agents against new targets
- Development of therapies against drug-resistant microbes
- Development of broad-spectrum therapies





**Dominant-Negative Mutants of a Toxin Subunit: An Approach to Therapy of Anthrax**  
Bret R. Sellman, Michael Mourez, and R. John Collier

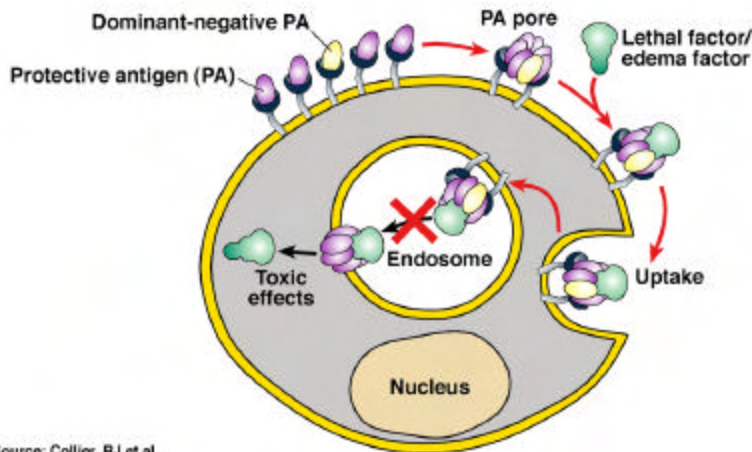


**Designing a polyvalent inhibitor of anthrax toxin**  
Michael Mourez, Ravi S. Kane, Jeremy Mogridge, Steve Metallo, Pascal Deschatelets, Bret R. Sellman, George M. Whitesides & R. John Collier





## Mutant Protein Blocks Anthrax Toxicity



Source: Collier, RJ et al.

22 August 2012 International weekly journal of science

# nature

www.nature.com/nature

## Defence against anthrax

A bacteriophage enzyme detects and kills *Bacillus anthracis* spores

### Heavy element chemistry

108 and counting

### Solar System

Lifting the smog on Titan

### Starburst neurons

How the eye detects motion

## A Bacteriolytic Agent That Detects and Kills *Bacillus anthracis*

Raymond Schuch, Daniel Nelson and Vincent A. Fischetti

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## **Biodefense Research: Diagnostics**

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### **Goals:**

- Identify cases in civilian settings
- Assist in case management
- Rapid, sensitive, easy to use



## **Biodefense Research: Challenges for the Future**

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- A culture of responsibility
- Classified research
- Restricted publication

# Newsday

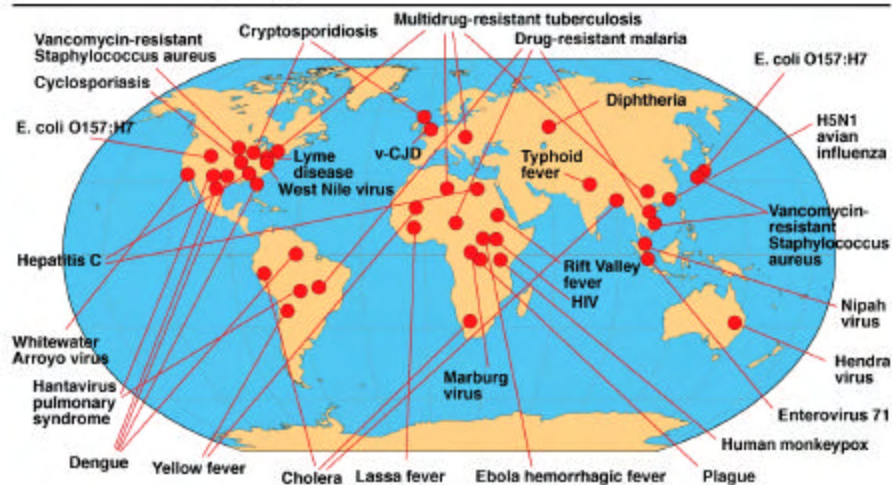
November 18, 2001

## The Worst Bioterrorist May Be Nature Itself

By Frederick M. Cohan

While we are under siege by microbes spread by terrorists, we face what is probably a worse threat from pathogens that we encounter naturally as part of our human ecology. This important fact is getting overlooked in the national panic over anthrax.

### Examples of Emerging and Re-Emerging Diseases



## Emerging Infectious Diseases: A Continuing Threat

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## Bioterrorism Information

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[www.bt.cdc.gov](http://www.bt.cdc.gov)

[www.niaid.nih.gov](http://www.niaid.nih.gov)