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Norton Zinder, The Rockefeller University

Peter Zuber, Oregon Health and Science University

David Zusman, University of California, Berkeley

[758]

[On February 28, 2005, when this letter was released, there were 758 signers, including the president-elect and seven past presidents of the American Society for Microbiology. A current complete list of signers is available at [http://waksman.rutgers.edu/NIH-MBC\\_BM/current/](http://waksman.rutgers.edu/NIH-MBC_BM/current/).]

cc:

Dr. Anthony Fauci, Director, National Institute for Allergy and Infectious Diseases

Dr. Jeremy Berg, Director, National Institute for General Medical Sciences

The Hon. Arlen Specter, Chair, Senate Appropriations Committee

Subcommittee on Labor, Health and Human Services and Education

The Hon. Daniel K. Inouye, Ranking Member, Senate Appropriations Committee

Subcommittee on Labor, Health and Human Services and Education

The Hon. Ralph Regula, Chair, House Appropriation Committee  
Subcommittee on Labor, Health and Human Services, Education, and Related Agencies  
The Hon. David R. Obey, Ranking Member, House Appropriation Committee  
Subcommittee on Labor, Health and Human Services, Education, and Related Agencies  
Dr. Shirley Jackson, President, American Association for the Advancement of Science  
Dr. Paul Kincade, President, Federation of American Societies for Experimental Biology  
Dr. James Tiedje, President, American Society for Microbiology  
Dr. Judith Bond, President, American Society for Biochemistry and Molecular Biology  
Dr. William Carroll, President American Chemical Society  
Dr. Stephen Harvey, President, Biophysical Society  
Dr. Walter Stamm, Infectious Diseases Society of America  
*Science*

## Appendix 1:

### Public-health relevance of prioritized bioweapons agents

[data for 1996-2003; <http://www.cdc.gov/mmwr/PDF/wk/mm4553.pdf>;  
<http://www.cdc.gov/mmwr/PDF/wk/mm4654.pdf>; <http://www.cdc.gov/mmwr/PDF/wk/mm4753.pdf>;  
<http://www.cdc.gov/mmwr/PDF/wk/mm4853.pdf>; <http://www.cdc.gov/mmwr/PDF/wk/mm4953.pdf>;  
<http://www.cdc.gov/mmwr/PDF/wk/mm5053.pdf>; <http://www.cdc.gov/mmwr/PDF/wk/mm5153.pdf>;  
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5330a6.htm>]

tularemia:

average US cases/year: 122

average US deaths/year: 0

anthrax:

average US cases/year: 3\* (includes 22 bioterrorism-related cases in 2001)

average US deaths/year: 1\* (includes 5 bioterrorism-related deaths in 2001)

plague:

average US cases/year: 5

average US deaths/year: 0

glanders:

average US cases/year: 0

average US deaths/year: 0

melioidosis:

average US cases/year: 0

average US deaths/year: 0

brucellosis:

average US cases/year: 103

average US deaths/year: 0

For comparison, US cases/year for diseases caused by other pathogenic microorganisms are as follows  
[data for 1996-2003; sources as above]:

tuberculosis: 17,403

salmonellosis: 42,457

shigellosis: 22,567

borreliosis: 17,642

legionellosis: 1,334

ehrlichiosis: 591

pertussis: 8,252

syphilis: 38,007

gonorrhea: 346,765

chlamydia: 685,508

meningococcal infection: 2,290

streptococcal infection, invasive: 4,371

streptococcal infection, invasive, drug-resistant *S. pneumoniae*: 3,083

## Appendix 2:

### Increase in number of grants for research on prioritized bioweapons agents

<http://crisp.cit.nih.gov/>

number of new and competing-continuation grants awarded under NIAID and referencing agents that cause tularemia, anthrax, plague, glanders, melioidosis, and brucellosis (*Francisella tularensis*, *Bacillus anthracis*, *Yersinia pestis*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Brucella melitensis*)

1996-2000: 33

2001-Jan 2005: 497 (133 in Jan 2005)

change: 1500% increase

number of new and competing-continuation grants awarded under NIAID and referencing agent that causes tularemia

1996-2000: 3

2001-Jan 2005: 93 (19 in Jan of 2005)

change: 3100% increase

number of new and competing-continuation grants awarded under NIAID and referencing agent that causes anthrax

1996-2000: 7

2001-Jan 2005: 243 (76 in Jan 2005)

change: 3500% increase

number of new and competing-continuation grants awarded under NIAID and referencing agent that causes plague

1996-2000: 22

2001-Jan 2005: 129 (31 in Jan 2005)

change: 590% increase

number of new and competing-continuation grants awarded under NIAID and referencing agent that causes glanders

1996-2000: 1

2001-Jan 2005: 10 (3 in Jan 2005)

change: 1000% increase

number of new and competing-continuation grants awarded under NIAID and referencing agent that causes melioidosis

1996-2000: 0

2001-Jan 2005: 16 (3 in Jan 2005)

change: >1000% increase

number of new and competing-continuation grants awarded under NIAID and referencing agent that causes brucellosis

1996-2000: 0

2001-Jan 2005: 6 (1 in Jan 2005)

change: >1000% increase

**Appendix 3:**

**Decrease in number of grants for research on non-biodefense-related microbial physiology, genetics, and pathogenesis**

<http://crisp.cit.nih.gov/>

number of new and competing-continuation grants awarded under Microbial Physiology and Genetics Initial Review Group (MBC1, MBC2)

1996-2000: 490

2001-Jan 2005: 289

change: 41% decrease

number of new and competing-continuation grants awarded under Bacteriology and Mycology Initial Review Group (BM1, BM2)

1996-2000: 627

2001-Jan 2005: 457

change: 27% decrease

#### **Appendix 4: Research opportunities in basic microbial science**

NIH support for basic research on microorganisms has paid for itself many times over. Hundreds of pharmaceutical and biotechnology companies in the United States are exploiting discoveries from basic research on microorganisms that they could not have performed themselves. The significance of NIH support for this research is obvious: it has made the United States the world leader in the advancement and application of the biological sciences.

By allowing research funding on basic microbial genetics, physiology, and pathogenesis to decrease as a consequence of prioritization of research on bioweapons agents, the NIH and the United States risk losing research momentum and missing research opportunities. The funding decrease will hinder research progress, jeopardize research infrastructure, deny research training, and discourage research careers in basic microbial science. The threat to basic microbial science comes at a time when there are exceptional research opportunities and exceptional potential for breakthroughs. The following sections summarize some of these research opportunities and make policy recommendations:

**Development of new antibiotics.** The 2003 National Academy of Sciences report "Microbial Threats to Health" warned that "The world is facing an imminent crisis in the control of infectious diseases as the result of a gradual but steady increase in the resistance of a number of microbial agents to available therapeutic drugs," and recommended that "The U.S. Secretary of Health and Human Services should ensure the formulation and implementation of a national strategy for developing new antimicrobials" [<http://books.nap.edu/catalog/10636.html>].

These threats are posed by bacterial agents now established in human populations (Appendix 2). Tuberculosis is in global resurgence. The World Health Organization projects that there will be more than 10 million new cases of tuberculosis in 2005 and that there will be nearly 1 billion newly infected people by 2020, 200 million of whom will become seriously ill, and 35 million of whom will die [<http://www.who.int/infectious-disease-news/>]. Additional threats are posed by other bacterial agents, including the agents responsible for salmonellosis, shigellosis, borreliosis, legionellosis, ehrlichiosis, pertussis, syphilis, gonorrhea, chlamydia, meningococcal infections, and staphylococcal infections. For each of these agents, strains resistant to multiple current antibiotics have emerged, and strains resistant to all current antibiotics either have emerged or are expected soon to emerge.

There is an urgent need to characterize existing antibiotic targets, to locate new antibiotic targets, and to develop new antibiotics, before strains resistant to all current antibiotics become widespread. Current research is providing new insights about the structures and mechanisms of the molecular machines that are targets and resistance determinants of current antibiotics--including DNA polymerases, RNA polymerases, ribosomes, topoisomerases, and efflux pumps--in order to enable rational design of new antibiotics effective against bacterial strains resistant to current antibiotics. Other current research is exploiting newly available genome sequences, and newly developed genomics and proteomics technologies, in order to identify novel targets for antibiotics. These lines of research, which impact both on public health and on biodefense, must be accelerated.

**Systems microbiology.** Basic microbial science is primed for a period of revolutionary advances, made possible by newly available genome sequences (full genome sequences for more than one hundred microbial species, and full genome sequences for multiple strains of several microbial species); newly developed and increasingly automated microarray technologies for analysis of microbial nucleic acids and proteins; newly developed mass-spectrometry technologies for analysis of microbial proteins, lipids, carbohydrates, and metabolites; and newly developed imaging technologies for analysis of microbial cell structure and cell dynamics.

The ability to observe, quantitatively define, quantitatively simulate, and rationally manipulate, the complete gene-expression patterns and molecular-interaction networks of a microbe has created an entirely new scientific discipline: "systems microbiology." Systems microbiology has exceptionally high potential for impact both on public health and on biodefense. Systems microbiology may allow creation of "reporter" microbes that inexpensively detect diseased human cells, and may allow creation of "factory" microbes that inexpensively make complex pharmaceuticals. Systems microbiology also may offer a critical testing ground for the broader development of systems approaches to molecular medicine. All living organisms, including humans, depend on the same types of complex, interconnected, and overlapping biomolecular networks found in microbes. Understanding biomolecular networks will be a monumental challenge and will require an unprecedented integration of biological, analytical, and computational approaches. Without question, this challenge could most readily, and most rapidly, be addressed in microbial systems.

Realizing these opportunities will require building an infrastructure and training enterprise that develops and makes available the tools of systems microbiology. It also will require a renewed effort to understand the individual genes, enzymes, and regulators--many still incompletely understood or wholly unknown--that are the building blocks of microbial systems.

**Model microorganisms.** Studies on simple, well characterized, experimentally tractable, model microorganisms underpin our understanding of complex biological systems. Past studies on model microorganisms led to the development of recombinant DNA technology, spawned the biotechnology industry, and provided the tools and materials to sequence the human genome, to define structures of proteins in the human proteome, and to create transgenic organisms. Today, researchers are using model microorganisms to design new regulatory circuits for cells and to study properties of these regulatory circuits, such as intrinsic noise and robustness; this research will provide a foundation for understanding gene regulation in all living organisms, including humans. In addition, today, researchers are using model microorganisms to understand microbial biofilms and intercellular communication within microbial populations; this research will yield a better understanding of the molecular basis of disease, and provide routes to disease prevention and control.

Analysis of model microorganisms is cost-effective and rapid. Advances in understanding or manipulation of model microorganisms often immediately can be applied to understanding, prevention, and control of diseases caused by less well characterized, less experimentally tractable, microorganisms, such as the prioritized bioweapons agents. By comparison, analysis, from scratch, in relatively poorly characterized microorganisms, with relatively poorly developed experimental tools--as with much research on the prioritized bioweapons agents--is much less cost-effective, much less rapid, and much less likely to succeed

**Policy recommendations.** These, and other, research opportunities in basic microbial science could be addressed by any or all of the following actions: (1) creation of new NIH initiatives for research on basic microbial science; (2) broadening of the NIH definition of biodefense, to include not only research on prioritized bioweapons-agents but also research on basic microbial science, and (3) consolidation of study sections for research on prioritized bioweapons-agents with study sections for research on basic microbial science, thereby ensuring a uniform standard of evaluation and merit in study sections. These actions would improve the quality of the NIH extramural grant portfolio, would increase NIH positive impact on science, would increase NIH positive impact on public health, and, indeed, would increase NIH positive impact on biodefense. We recommend that the NIH implement these actions. We further recommend that, as a first step, the NIH establish a committee of eminent microbiologists to plan and coordinate implementation of these actions.