Introduction

Hidden Costs of Biodefense Research

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Infectious diseases have threatened human civilization for more than 2000 yr. Hippocrates seems to have been the first observer to record an influenza pandemic in 412 B.C. (UW-Madison 2004). In addition, a major plague epidemic likely occurred in Egypt in 540, and then spread to Europe and Asia in the 14th century (Smith 1996-1997). The latter, known as the "Black Death," devastated the peoples of the Old World on multiple occasions and is an oft-cited example of infectious disease. More insidious and equally profound in contemporary times has been the steady increase of human immunodeficiency virus, which now infects 38 million people, with 5 million new cases per year worldwide, and has caused 20 million deaths since its first diagnosis (UN AIDS 2004). Malaria afflicts 300 million people globally, with 1 to 1.5 million deaths annually (WHO 2004). Yet these statistics pale in comparison with tuberculosis, from which one third of the world population is infected, with 2 to 3 million deaths annually, and antibiotic-resistant tuberculosis is on the increase (WHO 2004). The influenza pandemic of 1918 occurred on a global scale and resulted in 40 million deaths. It was the most devastating epidemic in world history, and the origin of the 1918 virus remains undetermined. What is known is that epidemics of influenza occur annually, and the likelihood of another pandemic is certain (Reid and Taubenberger 2003). Recent outbreaks of severe acute respiratory syndrome (SARS[1]) elicit concern that a similar event might occur with this newly emergent zoonotic coronavirus. Of the last 12 emerging infectious diseases, 11 have been zoonotic, or transmitted from animals to people (F. A. Murphy, University of California-Davis, personal communication, 2004). Increasing populations, poverty, politics, religious zealotry, despair, travel, environmental degradation, intensive farming, and many other factors are creating a virtual "witches brew" of opportunity for emerging and re-emerging pathogens.

Iatrogenic introduction (a.k.a. bioterrorism) is simply another means of transmission and spread of infectious agents, which, in the current political climate, evokes considerable fear among the populace. Through the dark side of the human condition, pathogens can now be elegantly engineered genetically, although in many cases, this process is not necessary because relatively primitive means can be used to utilize them for malicious intent. Bioterrorism, which was on the agenda of the cold war for decades, has taken on totally new dimensions with the realization that the geopolitics of detente between super powers can no longer contain the possibility of a bioterrorist event from happening. The US anthrax scare showed us that a simple anonymous postal envelope can serve as a fomite of terror. Remarkably, 22 cases and five deaths from anthrax, which are certainly not trivial, have effectively terrorized the politics of research in the United States, and in many ways have overshadowed the much more sobering but paradoxically accepted terror of AIDs, tuberculosis, malaria, influenza, and emerging and re-emerging infectious diseases.

The National Institutes of Health (NIH[1]), which was established in 1949, has been an American success story. It fostered innovative research and individual initiative within the scientific community, which in turn created a vital biomedical research infrastructure for academia, including robust scientific environments for training the next generation of scientists in hypothesis-driven research. The system allowed funding of a broad range of subjects, with peer review and funding based on merit and relatively unencumbered by politics. This broad base of science fostered interdisciplinary discovery as research results were openly published in peer-reviewed journals. Advances in one field often fostered advances in others. Congress recognized the enormous impact of NIH-funded research on both the economy and the health of the nation, with unprecedented bipartisan support that resulted in doubling of the NIH budget over the last 5 yr. This investment has ended, and the modest increases that are projected for the NIH budget cannot keep pace with increasing costs of performing science, sustaining excellence, and solving complex diseases that require basic research.

Those days are indeed over, and they ended even more abruptly after September 11, 2001. Almost immediately, $1.7 billion became available for biodefense research. The

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[1]Abbreviations used in this Introduction: BSL, biosafety level; NIH, National Institutes of Health; SARS, severe acute respiratory syndrome.

President's "Project Bioshield" will provide $6 billion over the next decade, but it is anticipated that the Department of Health and Human Services will invest nearly $15 billion in biodefense from FY2001 to 2005, and the total spending for all government agencies (e.g., Homeland Security, Defense, Agriculture, National Science Foundation) will exceed $22 billion (Schuler 2004). It was inevitable that some of the funding would not be additive to the current NIH budget but rather, taken from existing programs. The NIH budget is no longer increasing at its former rate, during that doubling phase, and therefore must absorb those losses in addition to the demands placed on it by biodefense. The National Institute of Allergy and Infectious Diseases program priorities are emphasizing biodefense, thus diverting funds from other areas of infectious disease research. Funding has been taken from traditional infectious disease programs, with nuances like "recycling," which means projects that are approved for funding are now being truncated by 6 mo, creating considerable angst in the scientific community (Birmingham 2003).

Perhaps the highest cost to science has been the major shift in NIH philosophy from funding basic biomedical research, an approach that has been seminal to discovery, to supporting much more politically directed and applied research on select agents, with emphasis on "deliverables" (vaccines and therapeutics), an approach that is new to NIH. These revolutionary changes are changing the face of academia and science in the United States, and they will have a profound impact on the future of science. These efforts are requiring considerable investment in infrastructure, such as the national network of eight Regional Centers of Excellence for Biodefense and Emerging Infectious Disease Research, nine Regional Biocontainment Laboratories for biosafety level (BSL[1])2-3 containment, and two National Biocontainment Laboratories for BSL2-4 containment. Meanwhile, the nation's biomedical research infrastructure is stressed, and support is diminished for animal facility renovation or construction—especially for rodents and nonhuman primates—at a time when animal-related research has increased significantly. Furthermore, emphasis in biodefense research will place additional strains on animal resources because much of the work will require animal-related research.

The hidden costs in this scenario are the incredibly burdensome costs of regulation, inspection, biosafety, waste management, record keeping, and bureaucracy, all of which translates directly into less available funding for science or infrastructure. The various new regulations that pertain to biodefense research are discussed in this issue of *ILAR Journal* by Drs. Gonder (2005) and Jaax (2005). These restrictions are so onerous that a recent international group of scientists urged the US government not to place SARS on the "select agent" list because that course of action would stifle research progress and hurt, rather than help, public health (Enserink 2004). Animal-related research is also affected by all of these factors, as well as by diversion of much needed support to improve laboratory animal health and welfare. In times of financial austerity, animal health and welfare programs, let alone animal-related infrastructure and resources, are vulnerable at a time when they are most needed.

This issue focuses on infectious disease research in the age of biodefense, but emphasizes, wherever possible, issues of relevance to research animals. Dr. Gonder (2005) provides an overview of select agent regulations. Dr. Jaax (2005) discusses the administrative issues. Drs. Patterson and Carrion (2005) emphasize the demand that will be placed on primate resources, with a descriptive list of select agents that will likely require additional nonhuman primates and primate-related resources that simply do not exist. Drs. Frasier and Talka (2005) discuss considerations for facility design, and Dr. Copps (2005) addresses aspects that pertain to infectious disease containment when working with animals. Two of the articles describe relatively unique challenges that may be faced by animal programs: Drs. Brown and Abee (2005) discuss issues relevant to work with prion agents, and Dr. Scott (2005) provides an overview of containment for arthropod vectors. Dr. Fell and colleague Bailey (2005) coauthor a commentary on the experience of an academic institution with public concerns and dissent, describing how institutional responsibility for animal-related research influenced that debate. At the end of the issue, Dr. Kelly (2005) offers a challenge to the veterinary profession, discusses why veterinarians are needed in infectious disease research, and notes the lack of manpower that exists in the profession to meet these needs. His focus is on agricultural issues, but veterinarians are equally needed to support biomedical research, as recently emphasized in the National Research Council report *National Need and Priorities for Veterinarians in Biomedical Research* (NRC 2004).

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