Federal Funding for the Study of Antimicrobial Resistance in Nosocomial Pathogens: No ESKAPE

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(See the article by Peters et al., on pages 1087–93; the article by Dagan et al., on pages 1094–102; and the editorial commentary by Friedman and Whitney, on pages 1082–3.)

The discovery of potent and safe antimicrobial agents is arguably the single greatest health care advance in history. The availability of these agents rapidly reduced the morbidity and mortality associated with a host of formerly fatal diseases. In addition, the confidence that infections could be prevented or treated by antibiotics allowed major leaps forward in the treatment of noninfectious diseases, including serious heart disease, cancers, and organ failure requiring transplants. Medical care, as we now know it, could not exist without the availability of effective antibiotics.

The widespread use of antibiotics has been associated with what we now know to be the predictable emergence of resistance. Early confidence that infections would eventually be conquered has given way to a greater appreciation of the genetic flexibility of common human pathogens. Moreover, we have come to appreciate the role played by microorganisms in our homeostasis. Microorganisms are an intrinsic part of us, and we would do well to learn to live with them.

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Where we cannot live with them is in the hospital, because patients with compromised defenses are particularly vulnerable to bacterial diseases. Although many bacteria remain susceptible to most of our antimicrobial agents, a coterie has emerged that escape the lethal action of antibiotics. In hospitals in both the developed and the developing world, this small group—*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanni, Pseudomonas aeruginosa,* and *Enterobacter* species, hereafter referred to as "the ESKAPE bugs"—is the same.

The ESKAPE bugs are extraordinarily important, not only because they cause the lion's share of nosocomial infections but also because they represent paradigms of pathogenesis, transmission, and resistance. If we learn to control these microorganisms, our hospitals will be immeasurably safer, because the lessons learned could be applied to virtually any species that attempts to take their place. Unfortunately, the ESKAPE bugs are increasingly prevalent in our hospitals and increasingly resistant to many of our antimicrobial agents. In this issue of the *Journal,* Peters et al. [1] detail the research agenda of the National Institute of Allergy and Infectious Diseases (NIAID) for antimicrobial resistance. As the primary federal agency for conducting and supporting medical research, the National Institutes of Health (NIH) is the standard-bearer for the federal government's commitment to health research. NIAID manages most, but certainly not all, of the work performed by the NIH in the areas of antimicrobial resistance and infectious diseases. As such, the NIAID agenda defines the weight of federal government efforts in the area of infectious diseases. One need look no further than the pivotal role played by NIAID in the enormous success of the AIDS research effort over the past 2 decades to understand the profound impact this institute's agenda can have on the growth and success of individual research areas.

Peters et al. indicate that NIAID funding of antimicrobial research has grown considerably over the past decade, now totaling more than $800 million annually. In considering this very large number, it is important to realize that it represents NIAID's total commitment to all areas defined as being related to antimicrobial therapy. This category includes research on antibacterial, antifungal, antiparasitic, and antiviral therapies, whether related to the treatment of diseases or to their prevention through the use of vaccines. It is therefore difficult to get a firm grip on what level of support is devoted to antibacterial therapy and resistance, particularly in reference to the ESKAPE bugs.

Regarding research specific to issues involving antimicrobial resistance, Peters

et al. indicate that NIAID is currently spending more than $200 million. In considering this amount, it is important to recognize that it also includes support for research on resistance to antiviral (including HIV), antifungal, and antiparasitic (including antimalarial) agents. Within the bacterial category, research on resistance to drugs targeting *Mycobacterium tuberculosis* is included. It is not possible to tease from this analysis the level of commitment NIAID has made to the study of resistance in the ESKAPE bugs.

The enormous importance of HIV, malarial parasites, and *M. tuberculosis* to public health around the world should never be doubted. However, antimicrobial resistance in these microorganisms is fundamentally different from that observed in the ESKAPE bugs. Resistance in the ESKAPE bugs is primarily (although no longer exclusively) associated with the nosocomial environment. Nosocomial transmission of HIV through transfusion or contaminated needles, of malaria through transfusion, or of tuberculosis through contaminated aerosols constitute only a very small minority of transmission events. It is also fair to say, given what we know about the mechanisms of antimicrobial resistance in HIV, *Plasmodium* species, and *M. tuberculosis,* that the lessons learned from their study are unlikely to have a major impact on our understanding of resistance in the ESKAPE bacteria, because of the abundance of plasmids, transposons, and frequent genetic exchanges that characterize the latter microorganisms. Moreover, the enormous importance of HIV, malaria, and tuberculosis worldwide has attracted the sustained interest and philanthropy of many other organizations. For example, the Bill and Melinda Gates Foundation lists as examples of grants given out $458 million for malaria research, $374 million for AIDS research, and $154.2 million for tuberculosis research [3]. The Wellcome Trust, for its part, acknowledges granting £150 million to malaria research over the past decade [4]. In an era of limited resources, it is critical that we assess the incremental value of NIAID dollars invested in these well-funded areas compared with other areas that are not the beneficiaries of commitments from foundations.

One need only survey our knowledge of some very basic questions regarding antibacterial therapy compared with to our knowledge of the use of anti-HIV drugs to realize that whatever quantity of NIAID dollars has been devoted to antibacterial research is not enough. For most bacterial infections, minimal lengths of treatment have never been defined. The benefit of antimicrobial therapy over placebo for many common infections (such as otitis media or sinusitis) remains murky. The use of combinations of antibiotics is widespread, without conclusive evidence of benefit in most circumstances. There are far more questions than answers about the utility of basic infection-control measures. Even if we had that information, there has been very little research into the best mechanisms for disseminating the knowledge in a way that will change physicians' practices. In each of these areas (optimal antimicrobial therapy, infection control, physician and patient behavior), our evidence-based knowledge in the area of HIV (accumulated for <3 decades) far outstrips our knowledge in the area of antibacterial therapy (around for nearly 8 decades).

The roots of this disappointing progress in our knowledge are not surprising. For decades many people believed that resistance was a problem for the pharmaceutical industry to solve. The fact that the pharmaceutical industry would not favor research on ways of minimizing antimicrobial use somehow escaped us. The regrettable recent departure of most big pharmaceutical companies from the area of antibacterial development has made it clear that a pharmaceutically sponsored solution was always a myth. It is also a fact that many different federal agencies (the NIH, the Centers for Disease Control and Prevention [CDC], the Department of Agriculture, the Food and Drug Administration, and the Department of Veterans Affairs) focused on the narrow strips of the issue perceived as being relevant to their missions. The result was that the big picture did not receive the attention it deserved. In an attempt to coordinate the activities of different agencies, the federal government in 1999 sponsored an interagency task force to create *A Public Health Action Plan to Combat Antimicrobial Resistance* [5]. The plan proposed 84 action items, 13 of which were accorded "high priority." Unfortunately, the funding that was authorized for the activities of the task force was never appropriated, and each agency was left to its own devices to make good on the action items with which they were charged. The task force recently held a second advisory meeting at which progress was assessed and goals updated. The results of that meeting should be available for comment in the *Federal Register* by the end of 2008.

Recognizing the importance of antimicrobial resistance to public health and the difficulty of coordinating federal efforts through different agencies, members of the House and Senate have introduced versions of the Strategies to Address Antimicrobial Resistance (STAAR) Act. This act would establish an Office of Antimicrobial Resistance in the Department of Health and Human Services, reauthorize the interagency task force, establish a public health antimicrobial advisory board, and charge the NIH, the CDC, and other agencies with developing a strategic plan for combating antimicrobial resistance. Also, the act would authorize the establishment of at least 10 Antimicrobial Resistance Clinical Research and Public Health Network sites, which would be geographically dispersed across the United States. The sites would monitor the emergence of resistant pathogens, study the epidemiology of these pathogens, evaluate the efficacy of interventions, and study problems associated with antimicrobial use. More than any other provision, the establishment of these centers would send a strong signal to the academic community that the federal agen-

cies plan to emphasize antibacterial research, bringing a much needed infusion of new investigators into this area.

For decades, the ESKAPE bugs have smoldered along, acquiring resistance and virulence determinants that have allowed them to affect seriously the way we practice medicine in the modern hospital. The individual studies cited by Peters et al. are encouraging examples indicating that NIAID recognizes the difficulties that these resistant pathogens create. To truly succeed, these studies need to be part of a much larger coordinated effort, one with considerably more resources devoted to it than at present.

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