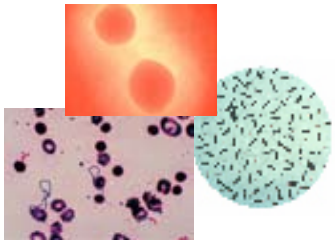
THE NATIONAL ACADEMIES

REPORT IN BRIEF

February 2007

Treating Infectious Diseases in a Microbial World



The vast majority of microorganisms do not cause disease. In fact, human evolution has occurred in the context of a world co-inhabited by thousands of types of microorganisms, and we couldn't survive without them. Although there is an acute need to pursue new drugs to fight emerging diseases and increasing antibiotic resistance, the proposed idea of developing a superdrug that kills all microorganisms is at best limited and at worst seriously flawed. Instead, more nuanced approaches should be pursued that seek to understand and mimic the complex relationships that keep human health and microbial communities in a healthy balance.

The emergence of new infectious diseases like SARS and West Nile virus, combined with the potential threat of bioterrorist attacks and growing antibiotic resistance among disease-causing bacteria, highlights an acute need for the development of new antimicrobial therapeutics to fight infectious agents. One might wish to identify one solution to all microbial threats to human health—a single "gorillacillin" drug that can protect against any infectious agent. But this type of antimicrobial superdrug could counteract the ancient and complex relationship between microorganisms and human health, in which microorganisms also contribute to protection against infection and maintenance of human health. Therefore, it is important to recognize the potential for finding novel ways to fight infectious diseases through a deeper understanding of the natural interactions between the human body and the microorganisms that dominate our world. To that end, possible antimicrobial therapies include those that are directed against the pathogenic microorganisms and those that are designed to boost the immune responses in the patient. These two approaches provide complementary and overlapping strategies in the treatment of infectious diseases.

MICROBES IN THE HEALTHY HUMAN BODY*

Microbes found in	
Ear (outer)	*Aspergillus* (fungus)
Skin	*Candida* (fungus)
Small intestine	*Clostridium*
Intestines	*Escherichia coli*
Vagina	*Gardnerella vaginalis*
Stomach	*Lactobacillus*
Urethra	*Mycobacterium*
Nose	*Staphylococcus aureus*
Mouth	*Streptococcus salivarius*
Large intestine	*Trichomonas hominis* (protozoa)

Bad guys? Not necessarily. Thousands of microbial species are found in the human body. The microorganisms listed in this table (and pictured above) are a sample of the species present in the healthy human body, most of which do not harm and, in fact, can benefit human health under some conditions. It is important to explore how the natural interactions between microorganisms and our bodies can help us find new ways to treat infectious diseases. (Table courtesy of NIH)

Living in a microbial world

Research in fields as diverse as evolutionary biology, bacteriology, ecology, immunology and developmental biology has led to a growing realization that humans exist as part of an environment full of mi-

croorganisms, the vast majority of which do not cause disease and many of which actually benefit human health. In fact, every human body contains many more bacterial cells than human cells. The microorganisms that overwhelmingly dominate our world have been evolving, coexisting, and competing with each other for millions of years. Humans have learned to take advantage of this long history: for example, most of the antimicrobial agents that have revolutionized the treatment of infectious diseases in the past several decades are derived from bacterial products that have been used by bacteria in their interactions with each other for millions of years. However, the ability of bacteria to develop resistance to antimicrobial agents is also an ancient evolutionary skill—one that presents a serious and growing threat to human health.

All humans live in intimate community with thousands of microbial species—on our skins and in our guts and oral cavities—and these microorganisms affect human health in many positive ways from development, to nutrition, to lowered susceptibility to disease. The human immune system has evolved in the midst of this microbe-dominated world, developing highly nuanced and carefully regulated responses to the myriad microorganisms it encounters.

In such a microbial world, the idea of developing a "gorillacillin" to eliminate all disease-causing microorganisms becomes hopelessly complicated. How would such a drug distinguish microbial friend from foe? How would it outwit the varied defense tactics developed over millions of years by thousands of microorganisms? Would this "gorrillacillin" improve or diminish the performance of the highly complicated human immune system? How long would it remain effective before harmful microorganisms evolve resistance to it? These questions are daunting, even discouraging. At the same time, antibiotics have saved millions of lives and interventions exploiting the human immune system—especially immunization—have vastly reduced human vulnerability to infectious disease. If "gorillacillin" is an unrealistic—perhaps even an undesirable—goal, it is nevertheless clear that effective antimicrobial therapeutics have been and can again be developed.

Antibiotic	Year Deployed	Resistance observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosprins	1960s	late1960s

Disease-causing bacteria can quickly evolve resistance to antibiotics. The problem of antibiotic resistance highlights the need for developing new ways of fighting infectious disease. (Table provided by Steve Palumbi, Stanford University.)

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Identifying new ways of fighting disease

At the request of the National Institute of Allergy and Infectious Diseases, two committees established by the National Academies organized workshops to help generate ideas for innovative research approaches to the development of antimicrobial therapeutics. One workshop focused on potential new classes of antibiotics, while the other explored the possibility of treating infectious diseases by affecting the response of the immune system.

The road from a brilliant idea to a clinically available treatment is long and full of pitfalls. Differing approaches to antibiotic use in different countries, declining investment in antimicrobials by large pharmaceutical companies, increasing costs of clinical trials, and complicated regulatory and legal environments are just a few of the obstacles to bringing new compounds from the laboratory to the clinic. Interesting and important as these issues are, the workshops were not designed to address them—rather they focused on the scientific possibilities. Readers interested in the non-scientific aspects of drug development are referred to related reports from the National Academies and other sources.[1]

At each workshop, participants considered the current state of knowledge, identified approaches that have been successful in the past, and brainstormed about ways in which new areas of research could revolutionize the treatment of infectious disease. The recommendations put forward by each committee emerged independently from their respective workshop discussions.

[1]Related publications from the National Academies are available at www.nap.edu. The interested reader is also referred to Infectious Diseases Society of America, *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates…A Public Health Crisis Brews* (http://www.idsociety.org/badbugsnodrugs).

Short-term gains: improving current approaches

Some of the committees' recommendations reflect ways in which current approaches to developing antibiotics and ways of influencing the immune system's response to pathogens could be improved. Implementation of recommendations of this type is most likely to provide improved therapeutics in the short term. For example,

- Many successful antibiotics have been discovered by studying natural products. The emerging field of metagenomics offers the possibility of discovering gene products with antibiotic activity without having to culture individual organisms.

Metagenomics: an emerging field in which the power of genomic analysis is applied to entire communities of microorganisms, bypassing the need to isolate and culture individual bacterial community members.

- Generating slight chemical variations of compounds with promising activity frequently results in more effective drugs; new chemical synthesis approaches that allow the rapid synthesis of more varied structures could speed this process.

"Click chemistry": a method of synthetically building new compounds by joining small units together. This technique represents one approach to the rapid synthesis of promising antimicrobial compounds.

- Immunization, both passive and active, has been hugely successful, but could be improved with enhanced understanding of exactly how different antibodies function and how they interact with the innate immune system (the non-specific or general immune system).

Long-term gains: basic research and novel approaches

Other recommendations reflect the committees' judgments as to which areas of basic research are most likely to lead to genuinely novel approaches to infectious disease treatment. Because the outcome of such basic research is difficult to predict, these approaches might be labeled "high-risk," but have the potential also to yield great reward in the long term.

- Current antibiotic development concentrates on targets that are essential for bacterial metabolism; research into how bacteria communicate with each other may allow the development of drugs that confuse, rather than kill, bacteria. Such drugs might be less likely to provoke resistance, because bacteria with the ability to resist such drugs would not necessarily be any more likely to survive than non-resistant bacteria.
- The human immune system is constantly interacting with the thousands of bacterial species naturally living within the human body; understanding how these bacteria communicate with the immune system and how the immune system singles out harmful microorganisms could lead to drugs that help the bacteria in our bodies outcompete pathogens.
- Once considered primitive, the innate immune system (the non-specific or general immune system) is increasingly regarded as highly complex, regulated and intimately intertwined with the acquired (specific or targeted) immune system and the nervous system. Understanding innate immune system regulatory pathways and active molecules may lead to drugs that are effective against a wide array of infectious agents.
- Development of techniques that affect the response of the immune system must be conducted carefully to avoid unintended harmful effects of artificially boosting natural immune responses. Overstimulation of the immune system can disrupt natural balances and present a danger to the host.

Improving diagnostic tools

Both workshops highlighted the value of improved diagnostics and recommended new approaches to identifying disease-causing agents.

- Rapid diagnostic tools to allow identification of disease-causing microorganisms would make it possible for physicians to reduce the use of broad-spectrum antibiotics and to encourage the use and development of narrowly-targeted therapeutics.
- Diagnostic profiles that describe the immune status of the patient could make it possible to predict how effective different treatments will be and to target drugs that affect the response of the immune system to the right patients at the right time.

Addressing challenges of clinical development

Both workshops identified imperfections in many of the techniques currently used to evaluate antimicrobial compounds. For example, testing antimicrobial compounds against microorganisms grown under ideal laboratory conditions does not reflect the reality of pathogens competing against the natural microbiota in human tissue under pressure from the immune system. Participants also identified

the challenges in developing and validating animal models for studying diseases. It is also difficult to design and evaluate clinical trials of drugs that are designed to affect the response of the immune system—compounds that affect the highly complex and individually variable immune system because such "personalized" therapies do not easily fit within the traditional model of drug development and testing.

Conclusions

Many of the most effective solutions will require the integration of antimicrobials and approaches that influence the response of the immune system. For example, many immune-system affecting drugs may not be able to cure disease directly, but could be effective in combination with traditional antimicrobials. Similarly, it is possible that researchers could develop antibiotics that would be selectively activated through interaction with the compounds used by the immune system to signal damage. Future discussions of infectious disease treatments that target the disease-causing agent and enhance the immune response at the same time could generate even more promising ideas.

The committees' recommendations address new approaches to fighting disease from a variety of angles, from improved diagnostics to greater utilization of the natural immune system to development and testing of antibiotics. New technological advances such as high-throughput screening and innovative chemistry techniques can allow rapid generation and testing of multiple variants of promising antimicrobial compounds. Emerging areas of research such as metagenomics offer insights into a variety of microbial communities previously inaccessible to medical research. Basic research in areas such as bacterial communication and the workings of the natural immune system can provide the basis for novel approaches to fighting pathogens.

The incredible array of microorganisms that is found in every corner of our world—including inside the human body—offers a huge potential for developing ways to use beneficial microorganisms and the long history of microbial evolution to our advantage in treating infectious diseases. By exploring the complex relationships between human health and microorganisms, we can hope to discover new approaches that avoid the pitfalls of traditional approaches to fighting infection by killing all microbes, such as antibiotic resistance. A deeper understanding of the microbial communities within our bodies and in our environment would aid in many aspects of treatment, from diagnosis to disease management to cure and recovery.

Committee on New Directions in the Study of Antimicrobial Therapeutics: New Classes of Antimicrobials

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Committee on New Directions in the Study of Antimicrobial Therapeutics: Immunomodulation

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This report brief was prepared by the National Research Council based on the committees' report. For more information, contact the Board on Life Sciences at bls@nas.edu or visit http://nationalacademies.org/bls. *Treating Infectious Disesases in a Microbial World: Report of Two Workshops on Novel Antimicrobial Therapeutics* is available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; www.nap.edu. Support for this publication was provided by the Presidents' Circle Communications Initiative of the National Academies.