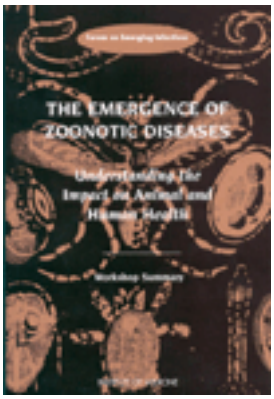

The Emergence of Zoonotic Diseases: Understanding the Impact on Animal and Human Health - Workshop Summary

Tom Burroughs, Stacey Knobler, and Joshua Lederberg, Editors, Forum on Emerging Infections

ISBN: 0-309-50869-X, 176 pages, 6 x 9, (2002)

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Understanding the Impact on Animal and Human Health

Workshop Summary

Tom Burroughs, Stacey Knobler, and Joshua Lederberg, *Editors*

Forum on Emerging Infections

Board on Global Health

INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C.

NATIONAL ACADEMY PRESS • 2101 Constitution Avenue, N.W. • Washington, DC 20418

NOTICE: The project that is the subject of this workshop summary was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

Support for this project was provided by the U.S. Department of Health and Human Services' National Institutes of Health, Centers for Disease Control and Prevention, and Food and Drug Administration; U.S. Department of Defense; U.S. Department of State; U.S. Department of Veterans Affairs; Abbott Laboratories; American Society for Microbiology; Bristol-Myers Squibb Company; Burroughs Wellcome Fund; Eli Lilly & Company; Glaxo Wellcome; F. Hoffmann-La Roche AG; Pfizer, Inc.; SmithKline Beecham Corporation; and Wyeth-Ayerst Laboratories. The views presented in this report are those of the Institute of Medicine Forum on Emerging Infections and are not necessarily those of the funding agencies.

This report is based on the proceedings of a workshop that was sponsored by the Forum on Emerging Infections. It is prepared in the form of a workshop summary by and in the name of the editors, with the assistance of staff and consultants, as an individually authored document. Sections of the workshop summary not specifically attributed to an individual reflect the views of the editors and not those of the Forum on Emerging Infections. The content of those sections is based on the presentations and the discussions that took place during the workshop.

Library of Congress Cataloging-in-Publication Data

The emergence of zoonotic diseases : understanding the impact on animal and human health : workshop summary / Tom Burroughs, Stacey Knobler, and Joshua Lederberg, editors ; Forum on Emerging Infections, Board on Global Health, Institute of Medicine.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-309-08327-3 (pbk.)
1. Zoonoses--Congresses.
[DNLM: 1. Zoonoses--epidemiology--Congresses. 2. Communicable Diseases, Emerging--Congresses. WC 950 E53 2002] I. Burroughs, Tom. II. Knobler, Stacey. III. Lederberg, Joshua. IV. Institute of Medicine (U.S.). Forum on Emerging Infections.
RA639 .E46 2002
614.5'6--dc21

2002002392

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Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

COVER: The background for the cover of this workshop summary is a photograph of a batik designed and printed specifically for the Malaysian Society of Parasitology and Tropical Medicine. The print contains drawings of various parasites and insects; it is used with the kind permission of the society.

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Willing is not enough; we must do."
—Goethe

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MARC RUBIN, Vice President of Infectious Diseases Therapeutic Development Group, Glaxo Wellcome, Research Triangle Park, North Carolina
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C. DOUGLAS WEBB, Senior Medical Director, Bristol-Myers Squibb Company, Princeton, New Jersey
CATHERINE WOTEKI, Undersecretary for Food Safety, U.S. Department of Agriculture, Washington, D.C.

Liaisons to the Forum

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NANCY CARTER-FOSTER, Director, Program for Emerging Infections and HIV/AIDS, U.S. Department of State, Washington, D.C.
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EDWARD McSWEEGAN, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
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GARY ROSELLE, Program Director for Infectious Diseases, VA Central Office, Veterans Health Administration, Department of Veterans Affairs, Washington, D.C.

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FRED TENOVER, Chief, Nosocomial Pathogens Laboratory Branch, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Staff

JONATHAN DAVIS, Senior Program Officer (until May 2001)
STACEY KNOBLER, Director, Forum on Emerging Infections
MARJAN NAJAFI, Research Associate
LAURIE SPINELLI, Project Assistant

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Bernadette Dunham, American Veterinary Medical Association, Washington, DC
Rosemary Humes, Association of Public Health Laboratories, Washington, DC
Arnold Weinberg, Harvard Medical School, Boston, MA

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Melvin Worth, National Academy of Sciences. Appointed by the National Research Council, he was

responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Preface

The Forum on Emerging Infections was created in 1996 in response to a request from the Centers for Disease Control and Prevention and the National Institutes of Health. The goal of the Forum is to provide structured opportunities for representatives from academia, industry, professional and interest groups, and government* to examine and discuss scientific and policy issues that are of shared interest and that are specifically related to research and prevention, detection, and management of emerging infectious diseases. In accomplishing this task, the Forum provides the opportunity to foster the exchange of information and ideas, identify areas in need of greater attention, clarify policy issues by enhancing knowledge and identifying points of agreement, and inform decision makers about science and policy issues. The Forum seeks to illuminate issues rather than resolve them directly; hence, it does not provide advice or recommendations on any specific policy initiative pending before any agency or organization. Its strengths are the diversity of its membership and the contributions of individual members expressed throughout the activities of the Forum.

*Representatives of federal agencies serve in an *ex officio* capacity. An *ex officio* member of a group is one who is a member automatically by virtue of holding a particular office or membership in another body.

ABOUT THE WORKSHOP

As defined by the World Health Organization, zoonoses are "those diseases and infections which are naturally transmitted between vertebrate animals and man, with or without an arthropod intermediate." Outbreaks of zoonotic diseases emerge either by apparently new agents or by known microorganisms that appear in areas or species in which the disease was previously unknown. New animal diseases with an unknown host spectrum are also included in this definition. The specific causes of such diseases are varied and include complex interactions at the molecular level as well as more large-scale social and ecological dynamics affecting the growth and movement of populations and changes in the environment. Additional factors such as climate, technology, land use, and human behavior can converge in a manner favorable to the emergence of zoonotic diseases.

Zoonotic diseases represent one of the leading causes of illness and death from infectious disease. Worldwide, zoonotic diseases have a negative impact on commerce, travel, and economies. In most developing countries, zoonotic diseases are of major public health significance and contribute to an already overly burdened public health system. In industrialized nations, zoonotic diseases are of particular concern for at-risk groups such as the elderly, children, pregnant women, and immunocompromised individuals. The potential use of zoonotic pathogens as bioterrorism agents should be considered as well.

In an effort to increase knowledge and understanding of zoonotic diseases with current and probable future public health significance, the Institute of Medicine's Forum on Emerging Infections hosted a 2-day workshop on June 7–8, 2000. The workshop, titled *The Emergence of Zoonotic Diseases*, explored the forces that drive zoonotic diseases to prominence and sought to identify more broad-based strategies and research programs that are needed to respond to these diseases. The goals of the workshop were to evaluate (1) the relative importance of zoonotic diseases against the overall backdrop of emerging infections, (2) the state of our understanding of zoonotic diseases, and (3) surveillance and response strategies to detect, prevent, and mitigate the impact of zoonotic diseases on human health. Issues pertaining to these three thematic areas were addressed through invited presentations and subsequent discussions, which highlighted the ongoing programs and actions being taken and identified the most important needs in this vital area. The agenda of the workshop appears in Appendix B.

ORGANIZATION OF WORKSHOP SUMMARY

This workshop summary report is prepared for the Forum membership in the name of the editors, with the assistance of staff and consultants, as an

individually authored document. Sections of the workshop summary not specifically attributed to an individual reflect the views of the editors and not those of the Forum on Emerging Infections' sponsors, or the Insitute of Medicine. The contents of the unattributed sections are based on the presentations and discussions that took place during the workshop.

The workshop summary is organized within chapters as a topic-by-topic description of the presentations and discussions. Its purpose is to present lessons from relevant experience, delineate a range of pivotal issues and their respective problems, and put forth some potential responses as described by the workshop participants. The Summary and Assessment chapter discusses the core messages that emerged from the speakers' presentations and the ensuing discussions.

Although this workshop summary provides an account of the individual presentations, it also reflects an important aspect of the Forum philosophy. The workshop functions as a dialogue among representatives from different sectors and presents their beliefs on which areas may merit further attention. However, the reader should be aware that the material presented here expresses the views and opinions of those participating in the workshop and not the deliberations of a formally constituted Institute of Medicine study committee. These proceedings summarize only what participants stated in the workshop and are not intended to be an exhaustive exploration of the subject matter.

ACKNOWLEDGMENTS

The Forum on Emerging Infections and the Institute of Medicine (IOM) wish to express their warmest appreciation to the individuals and organizations who gave valuable time to provide information and advice to the Forum through participation in the workshop.

The Forum is indebted to the IOM staff who contributed during the course of the workshop and the production of this workshop summary. On behalf of the Forum, I gratefully acknowledge the efforts led by Stacey Knobler and Jonathan Davis, who dedicated much effort and time to developing this workshop's agenda and for their thoughtful and insightful approach and skill in translating the workshop proceedings and discussion into this workshop summary. I would also like to thank the following IOM staff for their valuable contributions to this activity: Tom Burroughs, Marjan Najafi, Laurie Spinelli, Judith Bale, Katherine Oberholtzer, Paige Baldwin, and Jennifer Otten.

Finally, the Forum also thanks sponsors that supported this activity. Financial support for this project was provided by the U.S. Department of Health and Human Services' National Institutes of Health, Centers for Disease Control and Prevention, and the Food and Drug Administration;

U.S. Department of Defense; U.S. Department of State; U.S. Department of Veterans Affairs; Abbott Laboratories; American Society for Microbiology; Bristol-Myers Squibb Company; Burroughs Wellcome Fund; Eli Lilly & Company; Glaxo Wellcome; F. Hoffmann-La Roche AG; Pfizer; SmithKline Beecham Corporation; and Wyeth-Ayerst Laboratories. The views presented in this workshop summary are those of the editors and workshop participants and are not necessarily those of the funding organizations.

Joshua Lederberg, Chair
Forum on Emerging Infections

1

Introduction

"The significance of zoonoses in the emergence of human infections cannot be overstated."

—Institute of Medicine,
Emerging Infections: Microbial Threats to Health in the United States,
1992

A PERSPECTIVE ON EMERGING ZOONOSES

Frederick A. Murphy, D.V.M., Ph.D.

Professor of Virology, School of Veterinary Medicine
University of California, Davis

Since the publication in 1992 of the Institute of Medicine report *Emerging Infections: Microbial Threats to Health in the United States*, the concept of new and emerging diseases has changed as different people have influenced priorities. The balance seen in the original report has been skewed several times, not so much in the name of research needs or prevention and control priorities but in the name of funding the "home turf" of the agencies involved. Within this changing scene, where are the zoonoses, the diseases transmitted from animals to humans? The answer differs according to whether one addresses the question from the perspective of the animal disease community or the human disease community.

For some zoonotic infectious agents, general oversight and control responsibility has largely been in the hands of people associated with animal health and agriculture. These agents include those that cause substantial morbidity or mortality (or diagnostic difficulty) in livestock or poultry; certain classic agents, such as *Mycobacterium bovis* and *Brucella abortus*; and the bacteria of concern in preharvest food safety. Although a number

of these agents can be considered as emergent, many people from this community have not actively embraced the emerging disease concept.

Responsibility for some other zoonotic infectious agents has largely been in the hands of people associated with public health. These agents include rabies virus; numerous arthropodborne viruses, bacteria, and protozoa; several rodentborne viruses and bacteria; and primateborne pathogens. Obviously, quite a few of these agents are emergent and, under the emerging disease concept, much progress has been made. The cap on progress lies primarily in priority and funding decisions made high in the nation's public health bureaucracy.

There also are zoonotic infectious agents that seemingly have always been "in between," and these have often been the subject of foolish turf wars between government officials from the animal health and public health communities. These agents include new influenza viruses; *Salmonella enteriditis*; Listeria monocytogenes; and, most recently, the West Nile virus. Some progress is being made here, but usually only after contentious turf battles and other delays.

So, the concept of new and emerging zoonotic diseases has not been fully exploited in any of the communities dealing with zoonoses. This situation seems especially appalling given the fact that nearly all emergent disease episodes of the past 10 years have involved zoonotic infectious agents. These agents have included some that maintain an ongoing reservoir life cycle in animals or arthropods, without the permanent establishment of a new life cycle in humans, as well as some "species jumpers" that derive from an ancient reservoir life cycle in animals but have subsequently established a new life cycle in humans that no longer involves an animal reservoir. Given their troubling history, merely having to ask the question "Into which camp will the next important emergent zoonotic agent fall?" suggests that something is wrong.

Determinants in the Emergence of Zoonotic Disease Agents

Many different determinants contribute to the emergence of new zoonotic disease agents. Rarely do such determinants act alone. Given the complexity of their interactions, there likely is no way to predict when or where the next important new zoonotic pathogen will emerge. Consider zoonotic viruses. It has become fashionable to build so-called "predictive" models—this has been done for influenza viruses, for example—but it is likely that the next virus to emerge, influenza or otherwise, will not be as predicted. A danger, of course, is that in our enthusiasm for modeling, we may not recognize the significance of an emergence that does not match up with a favorite model. There also is a danger that too many researchers will

be sitting in front of computer screens, modeling, and too few people will be out in the field witnessing the next emergence.

Our understanding of the direction and rate of the evolution of viruses and their potential for emergence as pathogens follows upon spectacular achievements in viral genetics. We are on soundest footing when we consider the smallest variations between viruses—say, between strains. It is quite a different matter to consider variance and emergence in the context of the natural history of specific zoonotic pathogens, where key phenotypic characters, dominant selective forces, and the true essence of "fit" are much more complex and still quite mysterious.

To restate this point: in the Darwinian cause–effect equation, we understand the second term (the effects of mutation and selection) rather well, but we do not understand the first term (the causative forces driving selection) very well at all. We often describe the selective forces themselves in the most theoretical fashion. For example, we tend to portray the direction of evolution as toward commensalism, that is, a relationship between two kinds of organisms in which one obtains food or other benefits from the other without damaging or benefiting it. But this picture obviously fails when we face a new emergent zoonosis that brings untoward health effects. Again, the specific forces driving selection of particular viral variants in real-world settings are quite mysterious.

In considering the effects of mutation and selection on the evolution of zoonotic viral pathogens, successful variants appear to have evolved with particular characteristics. The pattern of these characteristics suggests that the variants most likely to emerge as new zoonotic threats are like their parents, but more so. They are the alpha children, but they are not, as often depicted in fiction, new "super-bugs," such as an Ebola virus variant that is transmitted as easily as influenza viruses.

From virus to virus, in keeping with diverse lifestyles in reservoir hosts and vectors, key advantageous characteristics are amazingly diverse and sometimes seemingly contradictory. We often explain the advantage to the virus in each situation in simplistic ways. For example, most virulent alphaviruses spread by mosquitoes produce very high viremia levels, or viral load levels, in their reservoir vertebrate hosts, so as to better assure transmission to the next feeding mosquito. Thus, we say that high vertebrate host viremia represents a key evolutionary advantage. But many virulent, successful flaviviruses produce low-level viremia, requiring exquisite susceptibility of those mosquitoes that serve as their vectors. So, what characteristic of a variant flavivirus might make us worry most in regard to potential for emergence?

Particular viruses have evolved survival strategies to deal with the extremes in host population qualities. Of the viruses transmitted from human to human, most thrive either in the largest, densest populations or when

introduced into an isolated population whose members lack immunity to the particular virus. However, many of the zoonotic infectious agents survive where there are just enough susceptible reservoir hosts to sustain the transmission chain. It might seem that such transmission chains are fragile, subject to interruption by minimal human intervention, but in most cases this has not been the case. Mutation and selection work well in the circumstances of such "thready" transmission chains.

Most changes in reservoir host populations that affect zoonotic infectious agents are caused either directly or indirectly by human activities. The major such changes are the ever-increasing density of human populations, the increasing density of monotypic domestic animal populations, and the crowding of wildlife in limited areas. Other changes deriving from human activities serve to amplify the risk of the emergence of new zoonotic agents, for example, the increased mobility of humans regionally and globally, changes in the natural movement patterns of birds and animals, and increased transport of a variety of products that may help to distribute viruses, vectors, and exotic hosts. The burgeoning threat of bioterrorism and biowarfare adds yet another factor to the risk equation, and some observers argue that xenotransplantation (the transfer of organs or other tissues from animals to humans) presents yet another level of risk.

Given this key role of human activity in the emergence of zoonoses, the current focus of public attention on remote "econiches"—what might be called the "Ebola Mystique"—needs to be reexamined. Rather than seeing potential threats as being largely confined to exotic hosts in isolated regions, we should consider, for example, the reservoir host population represented by the cattle herd of the United Kingdom. In the 1980s, as dairy cattle were fed bovine offal in feed supplements, there followed an epidemic of bovine spongiform encephalopathy, commonly known as mad cow disease. More than 1 million cattle were infected. These cattle became the reservoir hosts for a new, emergent zoonosis: new variant Creutzfeldt-Jakob disease. In this case, no remote econiche was involved; rather, the threat emerged from less than exotic changes in common animal husbandry practices.

Toward an Ideal Prevention and Control System

Zoonotic diseases require rather different prevention and control strategies than diseases of etiologic agents employing only human-to-human transmission. For the latter, clinically based or laboratory-based surveillance provides the foundation for such intervention activities as vaccination. Prevention and control strategies for the zoonoses have come from amazingly diverse bases, usually stemming from individual scientists or groups of scientists who have devoted years to accumulating highly special-

ized knowledge and experience. In fact, the work of these scientists might best be described as basic research, that is, research that only secondarily seeks the means for disease control and prevention.

Rather than dwell on what is wrong with today's systems for studying, controlling, and preventing zoonotic diseases, it may be more beneficial to identify the elements of an ideal system. Ten such elements present themselves. In each case, the concept of new and emerging diseases can provide the impetus for moving ahead.

1. *Independent Scientific and Administrative Leadership*. Responsible administrative leaders in disease prevention and control institutions need to know a great deal about the zoonotic infectious agents themselves, their reservoir hosts, their ecology and natural history, and the systems used in the past for their control. Zoonotic diseases cannot be dealt with effectively when they are last on a list of administrative responsibilities. Looking back, we see that successes in dealing with major disease episodes came from multidisciplinary, collaborative groups. Leaders of these groups were world-class scientists, who were inclusive in their style. Can such teams be rebuilt within public and academic institutions? Of course. The next step will require new thinking at higher levels.

2. *An Expanded Research Base*. The research base for many recently emergent pathogens and the diseases they cause is very small and very narrow. Because of funding priorities and biosafety constraints, few grants are awarded in these subjects. The large public institutions seem to be emphasizing molecular methods for agent identification and the descriptive epidemiology needed for control actions. The middle ground is at particular risk. The next step will require developing and implementing a new model for enlisting researchers and ensuring adequate public funding.

3. *A Proper Primary and Reference Laboratory Diagnostics System*. The World Health Organization's (WHO) network of arbovirus and rabies laboratories was exemplary at one time. Building a proper network today, however, must go farther. This effort must overcome old cultural differences between laboratories operated in the animal health sector, the public health sector, and the academic sector. The current system for West Nile virus testing punctuates the problem. In some laboratories, dead birds submitted for testing are subjected to full or modified necropsy, with all the delays and expenses pertaining. In some laboratories, there is a cap on the number of birds that can be submitted, and this cap is sometimes reached early in the year, thus preventing continued testing of newly found specimens. In some laboratories, test results are reported back only to the person submitting the specimen. Since the primary purpose of nearly all testing for West Nile virus is currently focused on providing early warning of the presence of virus in an area (the sentinel concept), anything other than

unlimited, ultra-rapid testing and proper reporting fails to meet the needs of disease control authorities. The laboratory system must match these needs. The model for such testing is not the traditional necropsy-based diagnostic system of many veterinary laboratories, nor the "kit-based" system of many primary care laboratories. Rather, the model should be the streamlined, rapid system of rabies laboratories. The next step in developing a proper network will require a cultural paradigm shift.

4. *Adequate Laboratory Facilities.* An expanded research base and a broadly based primary and reference laboratory diagnostics system must be supported by adequate laboratory facilities. This will mean expanding national Biosafety Level 3 and 4 laboratory facilities. These laboratories must operate multifaceted research programs, and they must be ready to deal with large episodes of disease. It also will mean constructing several small high-containment laboratories in academic institutions, yet plans for building such laboratories are going forward without specific federal commitment or funding. Needed, too, are facilities to meet such emergencies as bioterrorism threats. These facilities must be placed in various parts of the country, with coordination and training organized from a national center. The next step will require national leadership and new cooperation among diverse participants.

5. *Federal Interagency Communication, Cooperation, and Collaboration.* In 1995, when an epidemic of Venezuelan equine encephalitis occurred in South America, reaction in the United States should have been driven by the memory of the 1970–71 epidemic. At that time, as the virus eventually found its way into Texas, agricultural disease control authorities were prepared to start shooting and burying horses in a massive "sanitary rifle" campaign, while scientists from what is now the federal Centers for Disease Control and Prevention and from other health research units provided the virologic and epidemiologic base to override the strategy of agricultural authorities, and the United States Army provided its then-new TC83 vaccine. Conflict was rampant. But when the virus threatened in 1995, it was as if nothing had been learned. Neither agricultural, public health, nor defense agencies undertook much in the way of field investigation, and there was little real effort to develop an interagency action plan. If the epidemic had progressed, jumped north, would federal agencies have worked together? What would have been done? Did the agencies have the specialists necessary to deal with a major mosquitoborne disease emergence? The evidence suggests that answers would not have proved satisfactory. These questions are being asked again in regard to the West Nile virus emergence in the United States in 1999, and answers again are very slow in coming. Although the concept of new and emerging diseases provides the impetus to fix this, the next step seems lost under the usual barrage of interagency meetings, memos, reports, and press briefings.

6. *Federal–State Communication, Cooperation, and Collaboration.* Because state agencies that might be involved in emerging infectious disease episodes are so different from each other, there is no simple model for cooperation with federal agencies. Complicating matters, recent episodes have presented evidence of new turf tensions. The risk that this will get worse affects zoonotic disease episodes in particular, where laboratory and field activities resemble research projects and many different specialists must be involved. In several recent zoonotic episodes, however, scientists became competitive and insular, seeming to worry more about their publications than about the public's health. The time-honored public service tradition holds the key for remedying this situation. Bureaucratic barriers, such as shipping permits and laboratory inspections, must be penetrated; agencies and individual scientists must immediately share information and materials, such as reagents. The tradition of cooperation and service in the interests of public health must be learned by every young scientist—it is the key not to personal fame but to personal and institutional integrity. The next step in resolving turf and cultural issues will require high-level leadership.

7. *Government–Academic Communication, Cooperation, and Collaboration.* Interactions among federal and state government agencies and scientists and academic institutions and scientists also are marked by variations from institution to institution and person to person. Part of the complexity arises because relationships are not symmetrical: the world of the scientist in public service is a bit different from that of the academic researcher. The involvement of academic researchers with industrial partners adds to this asymmetry, as do the different traditions in the health sector versus the agricultural sector. For example, in the case of the West Nile virus, the seemingly simple matter of U.S. Department of Agriculture regulations for certifying outside laboratories to work on the virus and for shipping infectious materials seem to have caused friction and have become impediments to collaborative research. The next step in putting the public interest ahead of other motives will require bold action from institutional leaders.

8. *International Communication, Cooperation, and Collaboration.* This subject is much like the previous two, with variations from country to country, institution to institution, and person to person. Despite some problems, there have been many successes in international activities, often via WHO. But when circumstances have required the involvement of institutions outside the usual public health agency loop, such as agricultural agencies, there often have been difficulties. This was true when the West Nile virus emerged in the United States, when the Nipah virus emerged in Malaysia in 1999, when the H5N1 influenza virus emerged in Hong Kong in 1997, and when the Hendra virus emerged in Australia in 1994. In each

case, turf issues arose, and in some instances efforts to protect agricultural markets seemed more important than efforts to protect public health. We may have been lucky that these agents did not spread farther, but who is to say what the next zoonotic agent will be like? The next step in solving such turf issues will involve recognizing the primacy of prevention and control of human disease.

9. *A System for Organizing the Involved Professional Community.* Scientists interested in emerging zoonotic diseases represent diverse professional backgrounds and expertise and associate themselves with many different professional organizations. Thus, there has been no continuing venue for exchanging or integrating information and experiences. As the next step in building a better community, professional organizations should develop or help develop a unified, more comprehensive information and communications system, and they should establish a regular meeting venue, perhaps at the annual meeting of a larger organization with overlapping interests.

10. *A Strategic National Plan.* To integrate all of these "next steps," the zoonoses community, working in concert, must devise a comprehensive plan that addresses all aspects of this problem, including research needs and the needs of an effective system for disease prevention and control. As a model, the community might look to the Centers for Disease Control and Prevention's emerging disease plan. Strategic planning must not be biased by the most recent zoonotic disease episode, the West Nile virus. Although this virus might seem an ideal model, we would be better served by using a more complex model, one that would test all facets of candidate plans. The ultimate test of candidate plans is bovine spongiform encephalopathy and the resultant new variant Creutzfeldt-Jakob disease. Today, with the wisdom of hindsight, many observers note that the ministries of agriculture and health in the United Kingdom failed to react in a timely fashion and with proper scope and scale of actions to deal with what was clearly a great risk to public health. Every aspect of the ministries' disease prevention and control responsibilities has been called into question. This zoonosis also may be instructive in a larger sense, especially in its easy extension into the worlds of macroeconomics, international trade, national politics, and even regional governance.

Data clearly show that the concerned public wants more disease control and intervention actions, more of the medical research needed to support such actions, and more participation across the country. Numerous surveys of public opinion done by Research!America and other groups also show that the concerned public is willing to pay. Such public expectations can only be met by the speedy development of a coordinated national system for studying, controlling, and preventing zoonotic diseases. In addition, the U.S. system must be fully integrated into the nascent global public

health network targeted at emerging diseases, as well as with networks focused on threats posed by livestock animal diseases, crop plant diseases, and bioterrorism. The public would see such an overall system as having a high cost–benefit ratio and as offering a credible approach to solving several high-priority problems most efficiently.

2

The Importance of Zoonotic Diseases

PATHOGENESIS AND VIRULENCE OF ZOONOTIC INFECTIONS IN HUMANS

Robert E. Shope, M.D.

Professor of Pathology, Center for Tropical Diseases
University of Texas Medical Branch

The transmission of an infectious agent from an animal to a human being initiates a series of events that constitute the pathogenesis of the infection. Pathogenesis is the entry, primary replication, spread to target organs, and establishment of infection in the target organs. The process by which a pathogen replicates itself in the human host depends on cell-specific and organ-specific receptors, cell and tissue injury, and host immunity and other defense factors. The final outcome is either termination of infection, persistence and latency of infection, transmission to another host, or some combination of these. This series of events is not specific for zoonotic infections, except possibly that zoonotic agents are rarely sexually transmitted. The zoonoses, however, illustrate some of the more interesting and complex patterns that have evolved in nature.

Virulence can be defined as "the degree of pathogenicity of an infectious agent, indicated by case fatality rates and/or its ability to invade and damage tissues of the host." In many bacterial agents, virulence is mediated through a number of factors coded for by the genetic molecule DNA in a

chromosome, a bacteriophage, a plasmid, or some other unit. These virulence factors include:

Adherence. Some bacteria have specialized structures called pili that attach to the intestinal epithelium of the host and permit replication before the infecting cells are swept away.

Invasion. These factors permit bacteria to gain entry into the cell, where they replicate in a protected environment.

Capsules. Some bacteria, such as *Pneumococcus*, form an outer capsule of viscous polysaccharide gel that increases their virulence and resistance to phagocytosis and destruction.

Endotoxins. Gram-negative bacteria have an outer membrane that consists of lipopolysaccharides, or fat- and sugar-based compounds, that may damage or kill the host.

Exotoxins. These are proteins that are poisonous to cells and often have specific cell targets.

Siderophores. Some bacteria produce these iron-binding proteins that serve to increase virulence by consuming iron needed by eukaryotic cells, which are the type of nucleus-containing cells that comprise humans.

Viruses, with a rare exception, do not have bacterial-like virulence factors or toxins. Being intracellular, viruses disrupt the body's function either by direct destructive effect on target cells and organs or by inducing pathogenic host responses. The cell can be looked on as a factory. A virus may use up the cell's energy; shut off the synthesis of required materials; compete for the cell's ribosomes, which are necessary for building proteins; or compete for the cell's polymerases and inhibit its innate defense system. Some viruses have the capacity to integrate into the cell's genome and thus cause indirect damage, leading, for instance, to malignancy. As with bacterial virulence factors, the elements responsible for viral virulence affect both zoonotic and nonzoonotic agents equally.

Examples of Pathogenesis and Virulence in Zoonoses

Zoonotic diseases offer some interesting insights into pathogenesis and virulence, as well as to the links between them. Consider two examples, one a bacterium and the other a virus.

Anthrax

Anthrax is one of the more interesting zoonoses from the point of view of a link between pathogenesis and virulence. The virulence is directly related to the site of entry of the bacterium.

Bacillus anthracis is a gram-positive organism that infects cattle and

sheep. When dormant (not living in an animal host), the organism exists as a very hardy spore that resides in the soil. In a biological warfare experiment conducted during World War II, spores were exploded over the small Gruinard Island off the coast of Scotland. The spores remained viable in the soil for 44 years, until 1986, when formaldehyde treatment of the island finally made it habitable again.

The bacillus remains in the soil until consumed by sheep, cattle, or other animals that browse on grass and leaves. Such infection is especially common during dry periods, when animals frequently ingest soil as they eat plants down to the roots and as they drink from watering holes contaminated with spores carried by soil runoff. Nearly all warm-blooded animals are susceptible. Carcasses, when opened by vultures or carnivores, are sources of infection. Sporulation occurs when an infected carcass is exposed to the open air.

People who work on farms or in slaughterhouses, wool-sorting establishments, and tanneries are most apt to be exposed. Rarely, people are infected by consumption of uncooked or undercooked meat. The bacillus does not usually penetrate intact skin. Percutaneous infection occurs through open lesions or insect bites.

The pathogenesis depends on the route of exposure. There are four different syndromes:

1. *Cutaneous.* This is the most common form of infection in humans, representing approximately 95 percent of cases. Infection usually occurs on the arms, legs, or neck and head. Once the bacterium has entered through abraded skin, the symptoms begin after 1 to 12 days. A painless, nonpurulent lesion appears, and a zone of redness and edema forms around the lesion. Tissues in this zone begin to die, and then ulceration occurs. The lesions regress and healing occurs in most cases. About 10 percent of cases progress to involve the local lymph nodes and then dissemination with fatal septicemia.
2. *Pulmonary.* This form follows inhalation of tiny spore-containing particles of less than half a centimeter in diameter. These particles enter the lung alveoli, where they are engulfed by macrophages and transported to the lymph nodes. There, the spores replicate and disseminate with virtually 100 percent fatal septicemia.
3. *Gastrointestinal.* Ingestion of uncooked or undercooked meat can lead to the bacilli being passed into the digestive system, most commonly to the terminal ileum or cecum. There, lesions analogous to those in cutaneous anthrax result in fever, vomiting, abdominal pain, and bloody diarrhea; at least half of these cases are fatal.
4. *Oropharyngeal.* Bacilli sometimes enter through the oral or pha-

ryngeal mucosae, causing fever, mucosal lesions, and edema associated with cervical lymphadenopathy.

The pathogenesis of anthrax has been studied extensively in laboratory animals. In tests in mice and guinea pigs, subcutaneous inoculation of spores leads to rapid germination to form vegetative cells that replicate and elaborate toxin. Edema surrounds the primary lesion, after which the bacteria travel in lymphatics to the regional lymph nodes, then to the spleen. When the filtering capacity of the spleen is exhausted, bacteria are released into the bloodstream. The bacteria double their numbers in 50 minutes, and the animals die in 10 to 14 hours.

In tests in rhesus monkeys, inhalation of anthrax results in death of the animals. Hemorrhage in certain lymph nodes, the lungs, and the small intestines is prominent. Suppurative meningitis and lesions of the spleen occur in most of the animals.

There are three components of the anthrax toxin. Lethal factor is a zinc metalloprotease that is believed to stimulate activity of two proteins, interleukin-1 and tumor necrosis factor-alpha, that mediate the toxic death. Edema factor is a protein that is activated by calmodulin from the host and then produces a substance called cyclic adenosine monophosphate that stimulates edema. Protective antigen is a protein that is broken apart by cellular protease and then is capable of transporting lethal factor and edema factor to host cells.

The 1979 outbreak of anthrax in Sverdlovsk, a region in the former Soviet Union, was initially attributed by Soviet sources to the consumption of contaminated meat appearing on the black market. Careful examination of the autopsy specimens, however, revealed that the cases were inhalation anthrax, not gastrointestinal anthrax. Thus, the knowledge of the pathogenesis proved highly useful in solving this mystery.

Rift Valley Fever

Rift Valley fever (RVF) infects sheep, cattle, and humans and is caused by a particular type of RNA virus in the genus *Phlebovirus*. The virus is transmitted by a wide variety of mosquitoes, and it also can be spread by airborne particles. In sheep and cattle, RVF is characterized by acute hepatitis, abortion, and death, especially in young animals. The large-scale epidemic and epizootic in 1977 in Egypt was the first time that RVF occurred outside of sub-Saharan Africa. During that event, the disease afflicted an estimated 200,000 humans, causing about 600 deaths. Some patients also demonstrated late-onset RVF encephalitis and retinitis, with associated blindness. Among sheep and cattle, observers reported widespread abor-

tion, but no reliable estimates of the numbers of animals involved are available. The disease does not appear to cause abortion in humans.

There have been few studies in humans about the pathogenesis of RVF. Autopsies are not usually performed in sub-Saharan Africa, nor were they performed during the outbreak in Egypt. Most studies of RVF pathogenesis have involved animal experiments. Lambs, hamsters, and certain strains of rats develop high levels of the virus in their bodies and succumb in 2 to 3 days with acute hepatic necrosis. This appears to be a direct effect of the virus. Mice and other animals that are less susceptible either die later or survive acutely but develop encephalitis later, usually after 1 week. The encephalitis also appears to be a direct effect of the virus, which can be isolated from tissues of the central nervous system (CNS). It is not clear how the virus enters the CNS, but it appears that either viral entry is delayed or viral replication is delayed. Animals that were saved by treatment with drugs or other agents from acute hepatic death went on to develop encephalitis, thus confirming that the CNS was invaded.

Scientists have not yet determined the pathogenesis of the lesions that form in the eyes of infected animals. A model of the disease in rats has been developed. In infected rats, RVF antigen is found in the ganglion cells of the rat retina. Uveitis, necrotizing retinitis, and hemorrhages also occur.

In rhesus monkeys, RVF virus causes hepatic necrosis in a mid-zonal pattern and disseminated intravascular coagulopathy. Direct invasion of endothelial cells is believed to be involved in causing the vascular lesions.

Need for Additional Research

Anthrax and Rift Valley fever illustrate diseases for which there are good studies of the pathogenesis and virulence of the agents in humans or at least in animal models. Such studies may be long in coming for some of the newly emerged zoonoses, such as West Nile encephalitis and Nipah encephalitis. Part of the problem with Nipah encephalitis is the paucity of Biosafety Level 4 laboratories in which to carry out basic studies of the virus's pathogenesis. Regarding West Nile encephalitis, a major question centers on the apparent age difference in virulence. In the 1999 outbreak in New York City, it is probable that all age groups were infected, yet why were most of the cases and all of the deaths in persons over 60 years of age? Research is urgently needed to develop animal models simulating human disease for these and other zoonotic emerging diseases.

THE POTENTIAL "BIOWEAPONIZATION" OF ZOONOTIC DISEASES

David R. Franz, D.V.M., Ph.D.

Vice President, Chemical and Biological Defense Division
Southern Research Institute

Since World War I, a number of nations have conducted programs to develop biological agents as weapons of war. These nations have included the United States, the former Soviet Union, the United Kingdom, Canada, Japan, and others. The United States discontinued research on offensive biological weapons in 1970, and a multilateral agreement to halt offensive biological warfare programs, the Biological and Toxin Weapons Convention, was ratified in 1975. However, ratification of this agreement did not end the threat of biological weapons attacks. There is ample evidence that the former Soviet Union continued extensive research on and even production of some biological agents. In addition, U.S. forces entering Iraq during the Gulf War in 1990 found evidence of ongoing research and production of biological agents. After the demise of the Soviet offensive program, the concern about biological terrorism threats has increased, including terrorism carried out by individuals or groups, either acting alone or with sponsorship by a foreign government. Many observers now consider such terrorist attacks to be the major threat regarding biological attack against U.S. forces in peacetime deployment as well as against private citizens in major cities of the United States and the world.

A majority of the biological agents that have been considered as weapons are zoonotic. The zoonoses often considered in the context of biological warfare include anthrax, brucellosis, various strains of encephalitis-causing viruses, Ebola and Marburg viruses, histoplasmosis, plague, Q fever, rabies, and tularemia, among others. A number of factors make the zoonotics especially suitable for use as weapons. Perhaps most important, most zoonotic agents are not highly contagious, which would make them relatively easy to control when incorporated into a weapons system and deployed in a tactical situation. Many of these agents also are relatively well understood scientifically, and animal species are available in which to model human disease, to test and alter the virulence of the agent, or even to serve as living bioreactors in which to grow agents. Finally, their ubiquity and public health threat justify a state-sponsored research program, which may serve as a cover for a biological warfare program.

Terrorists have an even broader spectrum of zoonotic agents from which to choose than do military weaponeers. For example, the terrorist may need a less effective or lower-quality weapon, or a weapon that is

effective over smaller distances, than would be required for battlefield use. Such reduced requirements might make it possible to produce useful agents and delivery systems using less sophisticated equipment. In general, however, zoonotic agents that might prove useful in terrorist attacks must be produced as respirable aerosols, since nearly all of them are not highly contagious. Furthermore, unlike many chemical warfare agents, biological agents are neither volatile nor can they penetrate intact skin. There are a number of nonzoonotic human agents (e.g., smallpox virus) or animal agents (e.g., foot and mouth disease virus, Newcastle disease virus, hog cholera virus) that are highly contagious and thus might spread through a population without the necessity for weaponization and presentation as a respirable aerosol. Ironically, continued advances in biotechnology, while offering great promise for improving human health, also may make it easier for terrorists to make and deploy effective biological weapons.

While some features of zoonotic agents may make them less attractive for use by terrorists—they typically are harder to produce than, say, an explosive bomb, and their effects are less immediate—other characteristics may add to their attraction. One factor is the potential scale of their threat. It might be possible, for example, to expose thousands of people to an agent. Such exposure might lead eventually to hundreds of fatalities, certainly a tragic consequence, but it also would create tremendous social disruption and public fear, both highly desirable in the terrorist's mind. Indeed, public fear may even be created by hoaxes—claims by terrorists that they have released a biological agent into a given community. Such hoaxes have been numerous since 1997, and their numbers may well increase.

The United States has mounted a broad response to the threat of biological warfare, but until recently this response has not been well coordinated or integrated with sectors of the public health community. These responses have included improving capabilities for detecting biological agents; improving physical protection for soldiers; bolstering medical defense systems; continuing intelligence operations to monitor any research and production operations, both in other nations and in the United States; and participating in treaties and other international nonproliferation efforts.

A number of specific countermeasures are available or could be readily developed to protect individuals from biological agents. In addition to early detection and identification of agents and providing physical protection from exposure, these protective measures include immunization, passive forms of immunoprophylaxis, and decontamination, among others. It may be more difficult to protect citizens from unexpected terrorist attacks than to protect military troops. This dilemma heightens the importance of estab-

lishing and maintaining surveillance systems and diagnostic and reference laboratories to aid in rapidly identifying suspected biological agents.

Indeed, protecting U.S. citizens will require an integrated approach that combines education and teamwork. Federal agencies must collaborate, and military organizations must continue to work closely with the public health community. In learning to deal with "man-made" disease, there is much to be learned from current efforts targeted at understanding and controlling emerging infectious diseases.

In the future, as biological warfare proliferators introduce advanced technologies into their programs, it is unlikely that zoonotic agents will be broadly displaced; they may actually become a favored target for genetic manipulation. As we develop methods and programs to protect U.S. citizens, as well as livestock and crops, from naturally occurring diseases of animal and man, we must not forget the value of our efforts in protecting our nation from biological warfare agent attack as well.

XENOTRANSPLANTATION

Louisa E. Chapman, M.D., M.S.P.H.

Medical Epidemiologist, Division of AIDS, STD, and
TB Laboratory Research
Centers for Disease Control and Prevention

End-stage organ failure, an important health problem in the United States today, can be improved by transplantation of healthy donor organs. However, demand for donated human organs currently outstrips supply, and the gap between the number of people who could benefit from transplanted organs and the smaller number of organs donated annually is consistently increasing.

Xenotransplantation offers a means of helping to mitigate this shortage of available organs. Moreover, the concept of xenotransplantation has been expanded in recent years to encompass a broad range of approaches to using living nonhuman animal cells or tissues in humans for therapeutic purposes in ways that go beyond simple replacement parts for failing human organs. These purposes include, for example, implantation of fetal pig neuronal cells into the central nervous system of people suffering from Parkinson's disease, passing blood from people with liver failure through a device that contains pig liver cells, and infusing pig insulin-producing pancreatic islet cells into people with diabetes. For the purpose of Public Health Service policy discussions, xenotransplantation now refers to any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (1) live cells, tissues, or organs from a nonhuman

animal source, or (2) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

However, while xenotransplantation offers potential benefit for both individual recipients and society, it also is a public health concern. Xenotransplantation has the potential to infect human recipients with zoonotic and other infectious agents that are not endemic in human populations, thereby potentially introducing new infections to the human community (xenogeneic infections). This potential risk is presently unquantifiable.

Conceptually, xenogeneic infections should be recognized as part of a larger category of "bioproduct-acquired" infections, the most familiar of which are infections transmitted via blood transfusion. A growing number of therapeutic bioproducts provide opportunity for human exposure to infectious agents originating from nonhuman animals. Regardless of the fate of xenotransplantation technology per se, the lessons learned through attempts to develop rational public policy in this arena can serve as a model of approaches to science-based risk minimization for other bioproduct-associated biohazards.

The Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation describes a system of safeguards to minimize any health risk. This guideline (available at www.fda.gov/cber/gdlns/xenophs0101.htm) is built around two key concepts: pretransplant screening to minimize the risk of xenogeneic infections with recognized pathogens, and posttransplant surveillance for previously unrecognized xenogeneic infections.

Pretransplant screening is nested in animal husbandry techniques that limit and define the exposure history of the source animals. The risk that human recipients will be infected with exogenous viruses and other identifiable infectious agents can be reduced to negligible levels by limiting the geographic origin and lifelong contacts of potential source animals, combined with adequate pretransplant screening of the source animal, the colony from which it is chosen, and the xenotransplantation product itself. Posttransplantation surveillance will remain necessary to identify infectious agents that may have been transplanted with the xenograft. Such infection might occur because the agents were not known to exist (e.g., porcine hepatitis E prior to 1997), because diagnostic tools were inadequate to detect known agents (e.g., prions), or because the agents could not be removed from the xenograft (e.g., endogenous retroviruses).

Endogenous retroviruses exist as an inactive form of DNA integrated into the germline of all mammals adequately studied to date, including humans. Many of these endogenous retroviruses can express infectious virus but are no longer capable of causing active infection in the host species. However, endogenous retroviruses expressed by both pig and baboon cells can infect human cell lines in vitro. Thus, all xenotransplantation

products from any species may contain endogenous retroviruses that, on transfer into a human host, are capable of creating active persistent infection.

Recent scientific investigations have attempted to define the significance of endogenous retroviruses of pigs, the preferred source animal for xenotransplantation, in the xenotransplant setting. These tests demonstrate that porcine endogenous retrovirus (PERV) can be expressed from multiple porcine cell lines, as well as from multiple primary porcine tissues, including kidney, liver, heart, and spleen. Moreover, tests show that PERV released from both porcine cell lines and primary porcine cells can infect cell lines from humans and a variety of other mammals. Three variants of this virus have been characterized—PERV-A, PERV-B, and PERV-C—two of which can infect cells from humans. These observations support concerns that PERV expressed from porcine xenotransplantation products may be able to infect human recipients.

Since October 1997, when evidence that PERV could infect human cells in vitro emerged, the Food and Drug Administration has required all sponsors of porcine xenotransplantation product trials to demonstrate plans for posttransplantation surveillance for PERV infections in recipients using testing methods adequate to detect such infections. To date, limited studies of humans exposed to pig cells and tissues have produced no evidence of PERV infection. However, some studies have found evidence that certain types of porcine cells remain present in persons who had undergone transient hemoperfusion through pig spleens up to 8 years previously. These observations suggest that transient exposure to xenotransplantation products may provide enduring exposure to infectious agents carried within them.

Ironically, one of the approaches used to avoid the type of immune rejection that was the initial barrier to success with xenotransplantation has raised a potential problem regarding zoonotic infection. The endothelial cells of all lower mammals, including pigs, have a sugar-based compound called alpha-galactosyl (α-Gal) on their surface. This compound is absent from the cells of humans, who develop natural xenoreactive antibodies directed against α-Gal. To get around this hyperacute immune rejection, scientists genetically engineered a type of pig that lacks α-Gal. The problem stems from the fact that the characteristics of animal viruses are influenced by the characteristics of the cells in which they replicate. That is, if a virus replicates in a pig cell that contains α-Gal residues, then the outer envelope of the virus budded from the pig cell also will express α-Gal residues. If those pig cells were transplanted into a human, then the person's immune system would recognize the α-Gal as foreign and inactivate the virus. However, viruses budding out of cells from genetically modified pigs that do not express α-Gal on their cell surfaces may not be recognized and inactivated.

This finding raises suspicions that modifications intended to facilitate xenograft survival may also make it easier for PERV to survive in infectious form, thereby increasing the risk that PERV may infect human recipients.

Knowledgeable observers have argued that the risk to the public from xenotransplantation may be exaggerated when compared to that from other types of ongoing exposures, such as occupational risk of accidental exposure to simian retroviruses among animal workers and researchers. This may be true. But it is important to remember that xenotransplantation is an intentional exposure, and this raises the burden of preventive responsibility on scientists and research groups that conduct such trials. In addition, xenotransplantation occurs under controlled circumstances, which means that researchers have an added responsibility to implement known measures to minimize any associated biohazards.

Another issue that has been a source of public concern is whether the use of xenotransplantation products from nonhuman primates, rather than from lower mammals, poses a particular risk of introducing infections of devastating consequence to the human community. The present science is not adequate to provide a definitive answer to this question. Nor have we fully addressed the many ethical issues that would be involved in using nonhuman primates as "donors" for humans. However, from simply a practical standpoint, it is clear that we currently lack appropriate animal husbandry techniques, such as those in place for raising the pigs used in clinical trials, for maintaining a population of nonhuman primates. Taken together, these factors have led the Food and Drug Administration to ban xenotransplantation trials using nonhuman primates until adequate demonstration of safety and adequate public discussion of ethical issues have occurred.

ECONOMIC AND TRADE IMPLICATIONS OF ZOONOTIC DISEASES

Peter Cowen, D.V.M., Ph.D.

Associate Professor, Department of Farm Animal Health and Resource Management
North Carolina State University College of Veterinary Medicine

and

Roberta A. Morales, D.V.M., Ph.D.

Senior Research Scientist, Center for Regulatory Economics and Policy Research
Research Triangle Institute

Disease and trade have a long-standing, interwoven history. During the 14th century, Europeans began to value the exotic nature of goods and materials from Asia. In the summer of 1347, rats boarded Genoese ships at Caffa on the Black Sea, stowed away as the ships went through the Dardanelles, touched down at Messina, and later docked at Pisa, Genoa, and Marseilles. Less than a year later, plague had spread through rivers and roads deep into the interior and to ports on the Atlantic and Baltic coasts. Hungry fleas hidden in such trade goods as cloth, wool, and grain helped spread the disease between urban centers. In the five years of the Black Death, three out of every 10 Europeans, or some 24 million people, died. This pandemic, a substantial force in European history until the late 17th century, stands as a benchmark against which all other disease outbreaks have been measured. The interplay of trade, economics, and disease could be sketched out for many other zoonotic diseases, such as yellow fever in Panama (where the disease was linked to efforts to reduce shipping costs) and anthrax in North America (where the disease was distributed in alignment with settlement patterns).

Despite such health risks, global trade increased substantially in the 18th, 19th, and 20th centuries, so that we enter the new millennium perched on the brink of an integrated global economic system. This system is based on transnational flows of financial capital, global market penetration of products, multinational corporate structures, real-time information systems functioning as 24-hour monitors of the global business environment, and finally, but most importantly, a globalization of technology and knowledge-based assets creating the information economy. Globalization has reached a point where technical skills and intellectual capital know no borders—but neither do pathogens.

Food animal veterinarians over the past 30 or 40 years have adapted to revolutionary changes, driven by economics and technology, in the structure of animal agriculture. These changes include increasingly larger herd sizes, intensive production management systems, improvement of but simultaneous narrowing of the animal gene pool, vertical integration, and innovations of housing and physical facilities. All of these changes were predicated on the control of epidemic disease. The resulting production efficiencies have yielded an increase in global trade of animals and animal products.

In 1962, the Food and Agriculture Organization and the World Health Organization created the Codex Alimentarius Commission (Codex) to encourage fair international trade in food and to protect the health and economic interests of consumers. In 1995, the World Trade Organization (WTO) was established as a successor to the General Agreement on Tariffs and Trade, providing a common framework for the conduct of trade among member countries in matters related to the Uruguay Round Trade Agree-

ments. Prior to this time, national governments heavily subsidized many agricultural commodities. In addition, trade was inhibited by economic policies, including nontariff barriers erected by national governments to protect the country from the introduction of exotic animal diseases. However, the changes introduced by the Uruguay Round Trade Agreements included the Agreement on Trade-Related Aspects of Intellectual Property Rights, multilateral trade agreements, and the General Agreement on Trade in Services.

The common threads in these trade agreements have been harmonization, equivalence (not everybody has to ensure disease prevention in the same way, but there has to be similar risk between countries), and regionalization (whereby geographically distinct regions in a country may be designated disease-free and therefore able to export). Until recently, international standards have been the primary means of determining harmonization. The introduction of risk analysis into Codex and the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (called the "SPS Agreement") now provides other means for harmonization. Equivalence can be determined by specifying risk-based objectives. The provisions of the SPS Agreement include protective measures that must be based on scientific risk assessments. Each country has a right to set its own standards of protection, but a country cannot do so unjustifiably or arbitrarily.

A significant question for developing countries is whether there is a level playing field when it comes to trade in animals and animal products. For many developing countries, agriculture is the one segment of the economy where they have the resources and infrastructure for trade. It is therefore essential that developing countries are able to institute animal health monitoring programs that document risk, thereby opening the door to trade. The development benefits of agricultural trade in terms of infrastructure can be significant in agriculturally based economies. Countries that cannot turn their natural agricultural assets into capital needed for the development of adequate public health and animal health infrastructure may have to deal with the emergence of zoonotic diseases. Furthermore, trade in agricultural products results in better global nutrition, providing a wide variety of fruits and vegetables in developed countries and more plentiful and affordable meat in developing countries. Adequate nutrition affects host resistance on a population basis by providing an important preventive measure against the emergence of zoonotic diseases. Finally, trade promotes a sense of food security over time. A nation can be sure that it can obtain all the food that is required by its people, not by producing all of the food it needs itself but by having established avenues to trade for it.

Although the benefits of trade are substantial, there are legitimate concerns that efforts to keep exotic zoonotic diseases out of a country may fail.

The cost of such an introduction can be dramatic. At present, the increasing liberalization and realignment of economic forces will force us to examine the tradeoffs from trade. Food, live animals, and other commodities (such as vaccines and biological products) with zoonotic potential have inherent efficiencies of production in certain localities. These low-cost producers now have an open market, so long as they remain free of disease, unencumbered by health-based barriers to trade. Under these circumstances, since 1980 there has been a significant increase in the volume of trade. For example, the volume of hogs and cattle entering the United States has increased 10-fold, while total global exports and imports have increased by approximately 25 percent in the same period. However, importing ham from Belgium or live cattle from Mexico also may result in importing any pathogens associated with the products.

The direct and indirect costs of a zoonotic disease are hard to quantify comprehensively, since such costs involve many externalities for both the animal and human populations. Control in the animal population is crucial, as it represents primary prevention at the earliest opportunity. The most current example of costs involved with the emergence of a zoonotic disease is the outbreak in the United Kingdom of bovine spongiform encephalopathy (BSE), which eventually was identified as the causal agent of variant Creutzfeldt-Jakob disease. The outbreak was traced to the use of rendered meat and bone meal as cattle feed. One etiological hypothesis suggested use of such animal-derived feed had an economic basis—disposal of dead animals and an inexpensive source of high-quality protein. In the mid-1970s, both human safety considerations and new technology converged to suggest the elimination of a solvent extraction step in the carcass-rendering process. However, elimination of this step also meant that the product was heated one less time. While the new process promised monetary savings, the notion that it might give rise to an emerging zoonotic disease was not even on the horizon as a contingency—though it should have been. The costs for BSE eradication, which escalated dramatically after the European ban on importing British beef, have finally crested. These costs include extensive interventions to support farmers and markets because of the devastating economic conditions. Costs initially were manageable: about 237.6 million pounds sterling from 1989 to 1996. However, costs rose sharply after more extensive control measures, including the slaughter of infected and at-risk cattle, were fully instituted in 1996, totaling approximately 3 billion pounds sterling in the following 4 years.

Unfortunately, the specific relationships between trade, economics, and the emergence of disease have not been adequately characterized. One question, for example, is how the West Nile virus got to the Western Hemisphere. It may have been due to human travel, mosquitoes traveling in airplanes, altered patterns for migratory birds, traffic between zoological

parks, or some other mechanism. We need to get very specific in terms of what disease has been caused by what specific economic activity or demographic change. It is important that we begin to unravel the causal web in detail and put some specificity on trade as a cause of disease. Molecular epidemiology tools might be very valuable in such an endeavor. Whatever the etiology, the introduction of a major zoonotic disease has the potential for resulting in significant alterations in the structure of world trade. A particularly dramatic and threatening zoonotic disease linked to a trading incident could potentially shift globalization trends to a much more protectionist stance.

If trade is best viewed as a double-edged sword planted squarely between economic development and emerging diseases, how can we best mitigate its potential negative effects? One solution is to inject as much science as possible into decision making concerning the importation of animals and animal products. In order to make science-based decisions concerning trade, governments and international organizations are turning to risk analysis. For example, Codex has recently adopted principles and guidelines for the application of risk assessment as a means of enhancing food safety and reducing foodborne illness. Furthermore, risk assessment should be closely linked with steps to enhance import risk management. Import risk management can best be described as all the preventive steps and surveillance activities taken to reduce the possibility of foodborne disease related to importation of animals and animal products. Enhanced import risk management systems should include practical systems for surveillance, quarantine, regionalization of exporting countries, and testing.

As the volume of animal-based trade grows, the probability of emerging zoonotic diseases likewise increases. There are several significant impediments to be overcome as we implement a global system of science-based risk analysis to control the emergence of zoonotic disease. They include:

- the presence of significant resource imbalances in terms of the ability of different countries to implement surveillance and accurately measure the prevalence of disease in different populations;
- a lack of rapid, accurate diagnostic tests that provide real-time results with acceptable levels of false positive and false negative results;
- our ability to become comfortable with the ambivalence engendered by our need to trade and our legitimate fear of emerging zoonotic diseases.

It is correct to look at trade and other economic forces as important factors in the emergence of diseases, but we also must recognize that there is a strong logic behind trade. It is not a question of whether or not trade

promotes disease, but whether the benefits of trade are worth the risk of disease. We currently are in a period of global euphoria concerning the benefits of trade, but ascertaining the true risks of disease may prove to be sobering. It is for this reason that risk assessment for the occurrence of zoonotic and other animal diseases has moved front and center in the international system of trade regulation.

3

Factors of Emergence

VARIATION AND INTERSPECIES TRANSMISSION OF INFLUENZA A VIRUSES

Robert G. Webster, Ph.D.

Department of Virology and Molecular Biology
St. Jude Children's Research Hospital

The problem with influenza viruses is that, unlike other respiratory tract viruses, they undergo considerable antigenic variation. Antigens, which are located on the surface of the viruses, are the substances, typically glycoproteins, that stimulate an immune response. Influenza viruses carry two types of antigens: hemagglutinin (HA) and neuraminidase (NA). Both types undergo two forms of variation. The first type, called drift, involves minor changes in the antigens. New drift strains emerge constantly, giving rise to yearly epidemics and forcing the medical community to revise the viral strains used in vaccines. The second type of antigenic variation, called shift, involves major changes in the virus's genetic makeup. These new variants are of even greater concern: new strains to which most humans have no immunity appear suddenly, and the resulting pandemics vary from serious to catastrophic. While we currently know the complete genome sequences of many influenza viruses, we do not understand the molecular basis of pathogenesis and are unable to predict which combinations of viral genes have pandemic potential.

Studies on the ecology of influenza viruses have led to the hypothesis that all mammalian influenza viruses originate from a reservoir of viruses in aquatic birds, particularly ducks. In wild birds, the viruses are spread by fecal–oral transmission through the water supply. Initial transmission of avian influenza viruses to mammals, including pigs, horses, and humans, and to domestic birds, including chickens and turkeys, probably also occurs by fecal contamination of water. Another method of transfer is by feeding pigs untreated garbage or the carcasses of dead birds. After transmission to humans or other mammals, the method of spread of influenza is mainly respiratory.

Influenza represents one of the major success stories for the World Health Organization (WHO). To cope with the variability of influenza, WHO maintains a network of more than 100 laboratories that constantly survey influenza viruses, and this information is then analyzed in four reference centers. Based on these efforts, WHO makes annual recommendations for those virus strains to be included in the current vaccine in order to stay abreast of genetic drift.

The less well resolved problem of influenza is the pandemics, which occur at irregular intervals and are to date unpredictable. In the past century, three viral subtypes have caused pandemics in humans: the Spanish flu of 1918–19, which was caused by the H1N1 subtype; the Asian flu of 1957, which was caused by the H2N2 subtype; and the Hong Kong flu of 1968, which was caused by the H3N2 subtype. The H1N1 and H3N2 subtypes also have caused disease outbreaks in pigs, and the H3N8 and H7N7 subtypes have caused outbreaks in horses.

The Role of Swine in the Emergence of New Influenza Viruses

Generally, influenza viruses are host specific, and viruses from one host rarely establish stable lineages in another host species. Although whole viruses may rarely transmit, gene segments can cross the species barrier through the process of genetic reassortment. Pigs have been postulated to play an important role in the process of genetic reassortment by acting as the "mixing vessel" for such events. Pigs, unlike humans, seem to be readily infected by avian viruses, and most, if not all, avian HA subtypes are capable of replicating in swine. Researchers have proposed a molecular mechanism for the susceptibility of swine to avian virus infection. Viral receptors called sialyloligosaccharides, which are present on the pig tracheal cells, possess the ability to bind to both types of viruses, with human viruses preferentially binding in one location and manner and avian viruses preferentially binding in another location and manner. Thus, pig tracheal cells can be infected not only by human influenza viruses but also by avian viruses. However, the direct chicken-to-human transmission of H5N1 vi-

ruses, observed during the 1997 flu outbreak in Hong Kong, argues that factors in addition to receptor specificity must be involved in influenza interspecies transmission.

Influenza in swine is an acute respiratory disease, the severity of which depends on many factors, including pig age, virus strain, and secondary infections. Currently, three main subtypes of influenza virus are circulating in different swine populations throughout the world: H1N1, H3N2, and H1N2.

In North America, Asia, and much of Europe, viruses of the H1N1 subtype are the most commonly isolated. The circulating H1N1 viruses differ, however, in the origins of their genomic components. The H1N1 viruses in North America and Asia belong to the classical swine lineage, which is genetically related to human H1N1 viruses responsible for the 1918 Spanish influenza pandemic. In contrast, all eight genes of the H1N1 virus circulating in Europe are phylogenetically related to the avian lineage that entered pigs in about 1979. The avian-like H1N1 virus also is present in the United Kingdom, although the virus of current concern is a reassortant H1N2 virus with gene segments derived from both human and avian lineages.

Viruses of the H3N2 subtype circulate in Asia and Europe but have been infrequently isolated in North America. The most recent outbreak of this subtype in North America occurred in 1998, when a severe influenza-like illness was observed in pigs on a farm in North Carolina. Additional outbreaks among swine herds soon occurred in Minnesota, Iowa, and Texas. Genetic analysis of the viruses showed that at least two different genotypes were present. The initial North Carolina isolate contained gene segments similar to those of the human (HA, NA, PB1) and classical swine (NS, NP, M, PB2, PA) lineages, whereas the isolates from the other states contained genes from the human (HA, NA, PB1), swine (NS, NP, M), and avian (PB2, PA) lineages. Serological surveillance indicates that the latter triple reassortant virus has spread throughout the pig population of United States.

Examples of Recent Outbreaks in Birds

The avian H5N1 influenza virus that was transmitted to poultry and humans in 1997 in Hong Kong caused high mortality in both species, killing more than 70 percent of chickens and six of the 18 infected humans. (Hong Kong's location at the crossroads of many trade routes makes it particularly susceptible to the outbreak of new diseases.) Surveillance studies revealed that two antigenically and genetically distinguishable variants of H5N1 were circulating among avians and humans. There was no correlation between lethality in humans and one or other of the variants. The

slaughter of approximately 1.6 million chickens during a 2-day period stopped the further spread of the virus to humans. The failure of H5N1 to transmit from human to human, and the slaughter of poultry in a matter of days before another strain of influenza (H3N2) began circulating in humans in Hong Kong, probably prevented the generation of reassortants with pandemic potential.

Also in 1997, the avian H9N2 virus struck the live poultry market in Hong Kong. In 1998–99, observers reported that the virus had transmitted to humans and pigs. The initial report of five human cases in southern China was confirmed by the isolation of H9N2 viruses from two children in March 1999 in Hong Kong. The children had typical influenza and recovered. The isolates were genetically similar to H9N2 isolates found in quail. Further characterization of the viruses revealed that the human isolate from Hong Kong and the quail isolates shared similar genetic traits with the H5N1-like viruses from chickens and humans in Hong Kong in 1997. Thus, while avian influenza viruses can transmit directly to humans and cause disease, additional mutations and/or reassortant events are probably required to permit efficient human-to-human spread.

The fact that these viral strains can transmit to and cause respiratory disease in humans confirms that the surface glycoproteins can fulfill their primary functions in mammals. Indeed, several lines of genetic evidence suggest that some of these strains have a special propensity for interspecies transmission. The continued circulation of such viruses in poultry, especially in quail, alerts us to the continuing need for active surveillance for these viruses in humans and pigs in this region.

Recent Advances in Understanding Influenza Viruses

A major advance in the ability to manipulate the genome of influenza viruses occurred in 1990, when scientists established a "reverse genetic" system, which permits the generation of influenza viruses containing genes derived from cloned DNA, or cDNA. A further major advance occurred in 1999 when other researchers demonstrated the generation of influenza A viruses entirely from cloned cDNA with high efficiency. These advances permit complete manipulation of all genes of influenza viruses, which means that it is now possible to tailor-make future live attenuated vaccine strains and to define all of the functional domains in the viral genes and their interaction with the host. Thus, resolution of the molecular basis of pathogenesis will be possible in the near future, and the domains responsible for interspecies transmission and ability to spread in new hosts will eventually be known. With this information in hand, it may be possible to predict which influenza viruses have pandemic potential in humans.

Another potential advantage is that it will be possible to resolve the

question of the pathogenicity of the 1918 Spanish influenza. When the total genetic sequence of the 1918 virus is obtained, scientists will be able to re-create the virus. While of great scientific value, this possibility also raises considerable concern; such a study should be done only if the benefits warrant the risk and only if all work is performed in high-level biosafety laboratories. Once researchers have made the virus, tested its ability to interact with cultured cells, and determined which host genes are turned on or turned off, it will then be necessary to study the virus in an animal model, perhaps the mouse or the minipig. Before this happens, however, the research community and society must fully consider the ethics and safety of doing these experiments.

Preparing Our Defenses

Along with advancing our scientific knowledge, we also must improve our ability to detect and respond to new emerging strains of influenza virus, particularly those that appear suddenly and are capable of spreading over large areas. Many countries have prepared plans to cope with the next pandemic, which is considered imminent. Such documents must be updated as new information becomes available.

The cornerstone of pandemic preparedness is surveillance, both of humans and lower animals and birds, for if we develop the ability to predict which combinations of genes have pandemic potential, we must then maintain active surveillance to detect them. Viral surveillance will continue to be the key to providing time for the preparation of vaccines ahead of worldwide spread. In the interim between detection of a pandemic and vaccine availability, it will be essential to have adequate supplies of antiviral drugs, which means that urgent attention should be given to ensuring strategic stockpiles.

Overall, however, the reality is that we are not well prepared to cope with a pandemic, even a moderately severe one. We have identified where our weaknesses are, but we have not brought resources to bear on their solution.

ASSESSING THE THREAT AND THE OPPORTUNITIES ACROSS THE SPECTRUM OF ZOONOTIC DISEASES

Paul W. Ewald, Ph.D.

Professor, Department of Biology, Amherst College

Attention to emerging diseases has focused largely on acute infectious diseases that have caused outbreaks after entering humans from other host

species. Most of these diseases have very limited potential for spreading in human populations, particularly in wealthy countries. Of far greater potential importance to public health is discovery of infectious causes of the widespread and damaging chronic diseases.

The logic leading to this conclusion emphasizes that the global emergence of highly virulent, acute infectious diseases requires special sets of conditions that are rarely met. Vectorborne diseases, for example, may persist evolutionarily in a highly virulent form, but only a very small proportion of vectorborne pathogens have the characteristics necessary to be transmitted persistently from person to vector to person. None of these pathogens have demonstrated this ability under conditions found in modern wealthy countries, characterized by screened houses, air conditioning, and primarily indoor life. Similarly, the newly emergent pathogens that cause deadly acute infections and are transmitted from person to person by air would need to have characteristics that enable them to be transmitted readily from sick hosts, particularly durability in the external environment, if they are to maintain transmission cycles. The smallpox virus and tuberculosis bacterium have these characteristics. The pathogens that have attracted the most public attention in recent years, such as Ebola and hanta viruses, do not.

Evolutionary principles, current evidence, and the recent track record of recognizing infectious causation indicate that many if not most of the damaging chronic diseases are caused by infection. Some of the candidate pathogens use humans as primary hosts. Others infect humans zoonotically. In contrast to the oft-mentioned examples of newly emerging acute infectious diseases, the most damaging chronic diseases are already globally distributed and prevalent. Some of these diseases are now causing damage in human populations that is comparable to the damage that is merely feared for emerging acute infectious diseases. Atherosclerosis is the most damaging chronic disease in this category, accounting for about half of the deaths in wealthy countries. Other such diseases include schizophrenia, bipolar disorder, Alzheimer's disease, diabetes, and breast cancer. Considering the damage, prevalence, and persistence of these diseases in human populations, investment of intellectual and economic resources in the investigation of infectious causation of these illnesses may be more beneficial than investments in efforts to monitor, study, and control the spread of the acute infectious diseases that make for sensational headlines but pose a relatively small global threat to human populations.

These investments may provide particularly great health benefits because the most damaging manifestations of infection tend to occur when the infection in humans is no longer transmissible. Consequently, strategic use of antibiotics may enable the causative agents to be controlled indefinitely without the evolution of antibiotic resistance. Recent evidence sug-

gests, for example, that schizophrenia may be caused by infection with *Toxoplasma gondii*, which is transmitted in its natural cycle between cats and rodents. *T. gondii* damages the mental health of rodents in ways that facilitate capture of the rodents by cats, and hence its transmission to cats. Because *T. gondii* is not transmissible from humans, evolution of resistance should be negligible if an antitoxoplasmal drug is used only for human infection.

This strategy for controlling antibiotic resistance, referred to as "dead-ending," requires that at least two and preferably more than two antibiotics be available, so that one antibiotic can be used for the human infection and another can be used for the infection in the reservoir host. This distinction is particularly apparent for *T. gondii*, because cats are domestic animals that receive extensive medical treatment. When the natural hosts are unlikely to be the target of antibiotic treatment, as with the Lyme disease spirochaete *Borrelia burgdorferi*, the principles of antibiotic dead-ending are less relevant.

The principles of dead-ending apply to vaccine use as well. Although evolutionary escape from vaccines has been documented only for a few pathogens, we can expect that the continued use of vaccines and generation of new vaccines will lead to more examples, particularly when pathogens are prone to genetic variation through high rates of mutation or genetic recombination. To reduce this danger, vaccines for humans should be antigenically different from vaccines generated for reservoir hosts. If, for example, *T. gondii* becomes widely recognized as a cause of schizophrenia and other damaging diseases, then the demand for a vaccine against *T. gondii* will increase for humans and for cats (to prevent infections in humans). If the same vaccine is used for both people and cats, then the use in cats would create a cumulative selective pressure favoring vaccine escape. The use in humans, however, would not generate a cumulative selective pressure because humans are dead-end hosts. To preserve the effectiveness of the best vaccine for humans, an antigenically different vaccine needs to be generated for cats.

Developing different antibiotics or vaccines for humans and reservoir hosts is not as formidable as it may seem, because the constraints are not as severe for nonhuman recipients as they are for humans. A higher frequency of adverse reactions would be more acceptable for nonhuman hosts than for humans, as would certain kinds of adverse reactions. Neuronal damage sufficient to reduce a person's IQ by 5 percent, for example, would not be acceptable for humans but probably would be acceptable for cats.

If the reservoir host is not a valued animal, then discovery of zoonotic causes of already common chronic diseases may provide other less technologically sophisticated options. For example, one of the major candidates for breast cancer is mouse mammary tumor virus (MMTV) or a closely

related virus. The normal host for MMTV is the house mouse, *Mus domesticus*, in which the virus causes mammary tumors. This virus has been found much more frequently in tissue from human breast cancer than in surrounding healthy tissue, and breast cancer is associated geographically with the distribution of *M. domesticus*. Details of transmission to humans are unknown. If each human infection is directly acquired from *M. domesticus*, then local extermination of *M. domesticus* may directly protect humans from breast cancer. If transmission occurs from person to person with occasional reseeding from *M. domesticus* (analogously to the transmission of yellow fever virus or *Yersinia pestis*), then extermination may indirectly and diffusely protect the human population.

Lyme disease is an example of a zoonotic agent that is already recognized as a cause of chronic disease, but the spectrum of chronic illnesses caused by *B. burgdorferi* appears to be broadening. Evidence indicates, for example, that *B. burgdorferi* is responsible for some cases of chronic diseases that have been diagnosed as multiple sclerosis, motor neuron disease, arthritis, paralysis, or myocarditis. Indeed, *B. burgdorferi* has been referred to as "The Great New Imitator" because of its potential involvement in chronic diseases that have been previously categorized as other diseases.

This use of the term "imitator," however, illustrates how an overarching trend that has been occurring in studies of chronic diseases may be inadvertently obscured. During the past half-century, a steadily increasing number of chronic diseases have been accepted as infectious. When a portion of a disease category is so recognized, that portion is typically given a new name to distinguish it from the rest of the category (e.g., reactive arthritis and neuroborelliosis), but this experience has not been used prospectively as a model for allocating research effort. Doing so would involve searching for the agents that will permit a subdivision of each of the umbrella categories, such as multiple sclerosis, schizophrenia, motor neuron disease, chronic fatigue syndrome, obsessive compulsive disorder, atherosclerosis, stroke, and Alzheimer's disease. Just as we now consider such diseases as hepatitis and pneumonia to be collections of different diseases with distinct infectious etiologies, we can expect a variety of infectious etiologies for each of these umbrella diseases. If we instead search for *the* infectious cause of an umbrella disease, then we risk being misled by studies that do not find an association with a particular agent because that agent is rare in the study area. The ongoing resolution of hepatitis and arthritis illustrates how diverse the infectious causation of a chronic disease can be. The potential applicability to other highly damaging chronic diseases is apparent from the current evidence on infectious causation of diseases for which causation is still controversial. Atherosclerosis, for example, is associated with infections by *Chlamydia pneumoniae*, *Porphyromonas gingivalis*, *Actinobacillus actinomycetocomitans*, *Bacillus forsythus*, and cytomegalovirus, with

each of these pathogens being found in the atherosclerotic plaques, and some being shown to cause atheromas in animal models. Sporadic Alzheimer's disease has been similarly linked to *C. pneumoniae* and human herpes simplex virus type 1.

Much of the controversy over infectious causation stems from discrepancies between research teams that are unable to replicate associations with their own versions of the assays. This problem may occur because research will tend to achieve consensus most readily for those infectious diseases that are detectable even when detection techniques vary greatly, leaving in their wake those infectious diseases that are detectable only with very specific versions of experimental protocols.

The candidate pathogens for atherosclerosis and Alzheimer's disease are regularly transmitted between humans. The ambiguities due to discrepancies between research teams may be even greater for diseases that are sometimes caused by zoonotic agents, because these agents are less likely to be detected in humans where the zoonotic reservoirs are absent. Thus, if breast cancers are caused in part by MMTVs that are transmitted directly to humans from *M. domesticus*, then studies might be confirmatory in New York, where *M. domesticus* is present, but not in Japan, where *M. domesticus* is absent. In Japan, another pathogen, such as Epstein Barr virus, might be playing a relatively more important role. Similarly, geographic variation in pathogens might help explain why studies have found the zoonotic borna disease virus to be associated with schizophrenia in Japan, but not in other areas, where *T. gondii*, human herpes simplex virus type 2, and an endogenous retrovirus have been associated with schizophrenia.

The proposed importance of infectious causation of chronic diseases emphasizes an irony in the attention devoted to emerging infectious diseases over the past two decades. This attention was triggered largely by the AIDS experience, in which a lethal disease arose from an exotic source and spread pandemically. This experience gave credence to concerns that other exotic diseases might similarly emerge. Concern focused on the most conspicuous examples—acute infectious diseases, such as Ebola, lassa fever, and hanta disease. But AIDS is a chronic disease syndrome. The irony, therefore, is that the alarm bell was rung in response to an emerging chronic disease syndrome, yet most of the subsequent attention has been devoted to emerging acute infectious diseases. The past two decades have not generated examples of new globally spreading acute infectious diseases that have been highly damaging to human populations; nor was there such an example for the entire 20th century. Resurgences of long-recognized global threats, such as influenza, have occurred, but concern over such resurgences was present before the recent interest in emerging infectious diseases.

This recent history therefore suggests that concern over the future threat

of emerging diseases needs redirection. In poor countries, the resurgence of long-recognized acute infectious diseases represents a grave danger. In both poor and rich countries, grave dangers are posed by the long-standing chronic diseases that are or may soon be recognized as caused by infection. Leaders of the effort to awaken concern over infectious diseases have emphasized the danger from resurgence of known acute infectious diseases, and to some extent the growing recognition of infectious causation of chronic diseases, but most of the media attention has focused on the exotic acute diseases. A broader emphasis on studies of infectious causation of chronic diseases and the distribution of current knowledge about these diseases may be needed to direct the attention of researchers, policy makers, and the public to support efforts to identify and reduce the greatest threats to human health.

PRACTICES AND POLICIES TO PROTECT HUMAN HEALTH FROM ANTIBIOTIC-RESISTANT PATHOGENS

Stephen F. Sundlof, D.V.M., Ph.D.

Director, Center for Veterinary Medicine
Food and Drug Administration
U.S. Department of Health and Human Services

Antimicrobial resistance is one of the highest-priority issues facing the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM). The evidence of harm to the public from certain uses of antimicrobials in food-producing animals continues to grow, so CVM is taking steps to address the problem. We hope to deal with this issue through regulatory changes in the way we manage and approve drugs; through improved monitoring systems; through better risk assessment, which we think is a critical area of need; and through education.

The issue of antimicrobial resistance has been around for some 30 years. The National Academy of Sciences, through the National Research Council (NRC) and the Institute of Medicine (IOM), has taken up this issue and provided input to FDA and the public. The NRC's first report, which basically was the first risk assessment, was released in 1980. The NRC was asked to address the issue of whether subtherapeutic use of antimicrobials in feed for food animals was a potential hazard to human health. The report concluded that existing data neither proved nor disproved the potential hazards.

That study was followed in 1998 by an IOM report titled *Human Health Risks with Subtherapeutic Use of Penicillin and Tetracycline in Animal Feeds*. The report concluded that the study committee was unable

to define a substantial body of direct evidence that established a definite human health hazard from the subtherapeutic use of these drugs in food animal feed. However, the committee did find considerable indirect evidence of that human health hazard. Another IOM report in 1998, on the benefits and risks of using drugs in food animals, reached a stronger conclusion: "There is a link between the use of antibiotics in food animals, the development of resistant microbes, and the zoonotic spread of pathogens to humans."

Because of the mounting evidence of risk to humans, FDA/CVM believes that there are issues we must address. From a regulatory standpoint, however, an issue as complex as antimicrobial resistance presents a tremendous challenge.

To begin the process, we published in November 1998 a document titled *Guidance for Industry #78*. This document affirmed FDA's position that it has the authority to regulate not just the toxic effects of drug residues, which has been FDA's traditional role, but also the microbial effects from the antibiotics and antimicrobials that FDA regulates. In the document, we asked that two types of questions be answered for approval of a drug. First, we asked for information regarding the quantity of resistance that would be created from the use of an antimicrobial in food animals. We want to know which organisms are affected, how much resistance is likely to be created, and at what rate would resistance be likely to develop. Second, we asked for information about the change in animal enteric bacteria that are human pathogens that would come from the use of the drug. From a scientific standpoint, the problem we face is that we have a very limited ability to predict the rate and extent of antimicrobial resistance that could result from the use of an animal drug.

A month later, in December 1998, CVM issued a second document, *Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*, also known simply as the "Framework Document." (The document is available on CVM's web site at www.fda.gov/cvm.) This document lays out a conceptual, risk-based approach for regulating antimicrobial drugs so that resistance is minimized. The primary public health goal is to ensure that significant human antimicrobial therapies are not lost due to antimicrobial use in food-producing animals. The framework document was not intended to be regulation. Instead, it was an attempt to lay out what we considered to be a rational approach to dealing with this issue and to do so in a way that would be informative for a variety of stakeholders, including the animal drug industry, animal producers, scientists, and the general public.

What we came up with was a fairly straightforward, risk-based approach to dealing with the regulatory issues of antimicrobial resistance. First, we thought in terms of assessing the risk. We want to know how

important a particular antimicrobial is for human medicine. The greater the importance, the less risk we would be willing to accept. In addition, we want to know what would be the likelihood that humans would be exposed to resistant pathogens as a result of the drug's use for food animals. This is a typical exposure-times-hazard type of risk analysis.

The framework document considers five main issues:

Drug categorization

Drug categorization is determining how important these drugs are in human medicine. As a basis for our risk analysis, we proposed to categorize antimicrobials according to their importance to human medical therapy. This determination had to come before we could determine what kind of regulatory approach we should take, so that the regulatory burden would be commensurate with the risk.

We proposed three categories. In Category 1 would be drugs of greatest importance to human medicine. These are drugs that would be essential for treating serious or life-threatening diseases in humans where there are no, or very few, satisfactory therapeutic alternatives. Simply put, these are the drugs of last resort with a life-threatening disease. We would put drugs in Category 1 particularly if they were important for the treatment of foodborne disease, because many zoonotic diseases are foodborne in nature. We also would put drugs in this category when resistance to alternative antimicrobial therapy may limit therapeutic success. Category 2 drugs would include those that are considered drugs of choice or that are important for the treatment of potentially serious disease, whether foodborne or otherwise, but satisfactory alternative therapy exists. Category 3 drugs would include those with very little or no use in human medicine.

Preapproval studies

We are trying to determine what kind of information drug sponsors should provide that will have some kind of predictive value regarding the drug's ultimate effects. We want the preapproval studies to indicate how rapidly resistance will emerge in pathogens of concern and to what degree. Preapproval studies will need to consider the proposed use of the drug in question. Is it going to be used in an entire herd or flock of animals or just for individual animals? How is the drug going to be used? How is it going to be administered? Once we have answers, we can design studies that will give us some predictive value. We also are considering asking for studies on pathogen load. After a drug is administered to an animal, is there a rebound effect in the number of pathogenic organisms that are found in the animal's

intestinal tract, and, if so, what can be done to minimize the food safety risk when those animals go to slaughter?

Thresholds

Before a new drug is used under field conditions, we cannot know in advance exactly which microbes are going to develop resistance, how fast the resistance will develop, and what the overall impact is going to be. But it is possible to describe the events that would make us concerned. CVM has outlined a possible approach for establishing thresholds to stimulate discussion. This approach would attempt to link an unacceptable level of human health impact to a level of resistance in animals. CVM acknowledges the complexity of establishing such thresholds and continues to seek further scientific input.

Monitoring

Perhaps the main reason the issue of resistance has been studied for so long without any resolution is that we have never had a good system for collecting data; that is, we lacked good surveillance and monitoring systems in the field. For years all such reports were based on anecdotal information. We felt that the only way to really get on top of this problem was to put a system in place to start tracking resistance. So, in 1996, we started the National Antimicrobial Resistance Monitoring System (NARMS). This system uses information that already was being collected through two other federal programs. The first is the Centers for Disease Control and Prevention (CDC)'s FoodNet system, which gives us a random sampling of foodborne diseases that occur in humans around the country. The second is the Department of Agriculture's (USDA) Food Safety Inspection Service (FSIS) program for collecting slaughterhouse samples, obtained under USDA's Hazard Analysis and Critical Control Point program, which gives us information about pathogens in food from animals.

With NARMS, we know both the incidence of resistant foodborne infections in humans and in animals. Thus, we can look to see if there is a correlation between those two sets of information to spot increases in resistance that may be related to the use of antimicrobials in food animals. We also can determine whether attempts to mitigate the rise in resistance have a positive or negative effect on the level of resistance.

Drug use information

We want information about how drugs are being used—in which species of animals they are being used, under what conditions they are being

used, and how much of the drugs are being used—in order to be able to relate drug use to the development of resistance. From a regulatory point of view, this is an important step, because we have to justify, on a scientific basis, why we might be taking an adverse regulatory action against a product. Having that chain of evidence in place is absolutely critical for us to be able to sustain our decision. Therefore, we now are developing guidance and regulations on new requirements for companies to report to FDA, on a yearly basis, information on drug sales and use. The information we will require includes the amounts of antimicrobial agents used in each food animal species, the routes of administration, and the claim made for their use.

After a year of review, FDA publicly presented the framework document in December 1999, and we asked for additional comments. Among the approximately 40 comments received, several common themes emerged. First, whatever approach FDA takes, it should be well founded in science. There was some concern that antimicrobial resistance is a politically hot issue, and that FDA therefore may feel pressure to do things that are not well based in science. We were cautioned against that. Second, any regulatory actions should follow an extensive quantitative risk assessment. There was concern that FDA had not done an adequate job of determining how much risk is involved with the use of these products. We were advised to undertake such risk assessments.

In FDA's first major attempt to conduct a quantitative risk assessment for microbial resistance, we focused on the use of fluoroquinolones in poultry and its effects on *Campylobacter*. Fluoroquinolones are administered to poultry in their drinking water; the drug is used to treat entire flocks, because it is impractical to treat individual birds. The model we developed is designed to directly assess the impact on human health that occurs from the use of this drug in chickens. The model determines the illness that results in humans from drug-resistant *Campylobacter* infections attributable specifically to fluoroquinolone use in chickens, and it relates the prevalence of resistant *Campylobacter* infections due to use of the drug in chickens to the prevalence of *Campylobacter* in chickens. In this way, we can predict what to expect in humans when we see a certain amount of resistance in *Campylobacter* in chickens.

We began with this model, in part, because we expected the relationship between fluoroquinolone use and development of resistance in *Campylobacter* to be fairly straightforward. In other words, we wanted to tackle an easier problem first, before moving on to those expected to be scientifically more complex. (Indeed, before this project, we tested several more complex assessment models but found that the uncertainty surrounding the assumptions was so great that the result was a finding of risk somewhere between zero and one—an outcome not at all helpful.) Based on

this experience, we believe that our risk assessment model should work fairly well for most enteric pathogens. We are now conducting another risk assessment of the new drug Synercid—a more daunting challenge, since it involves the indirect transfer of resistance from animal enterococcal organisms to human enterococcal organisms.

ECOLOGICAL SOURCES OF ZOONOTIC DISEASES

Robert B. Tesh, M.D.

Professor, Department of Pathology
University of Texas Medical Branch

Ecology is the branch of biology that deals with the interrelationships between organisms and their environment. Ecological factors play an extremely important role in the epidemiology of zoonotic diseases, since these infections are usually environmentally acquired, and most emerging zoonotic disease outbreaks result from ecological changes. Because of their complex ecology, zoonotic agents are difficult to study in their natural habitat; consequently, most zoonotic disease research now focuses on the pathogenesis of the microbes or on their biochemical and genetic characteristics. This focus on the microbe has led to a myopic view of zoonotic disease. Despite spectacular achievements in microbial genetics and genomics, we still do not really understand how most zoonotic agents are maintained in nature or how they respond to environmental (usually anthropogenic) changes, nor do we understand the precise ecological factors that lead to human infection and emergence. Consequently, textbook descriptions of the epidemiology of most zoonotic diseases are at best simplistic. If we want to prevent or control zoonotic diseases, we first must better understand the ecology of their respective etiologic agents.

The Institute of Medicine's 1992 report on emerging infectious diseases identified six factors that shape their emergence: human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, microbial adaptation and change, and breakdown of public health measures. Within this framework, consider the following three emerging zoonotic diseases, which illustrate the complex interaction of various ecologic factors on disease emergence and how little we really understand about the basic ecology of most zoonotic disease agents.

Venezuelan Hemorrhagic Fever

In 1989, physicians in central Venezuela began to report cases of a

severe hemorrhagic illness that was initially thought to be dengue hemorrhagic fever. Subsequent clinical and epidemiologic studies demonstrated that this was a new disease, which was given the name Venezuelan hemorrhagic fever (VHF), and that the etiologic agent, designated Guanarito virus, was a novel member of the Tacaribe complex of New World arenaviruses. VHF is sporadic and cyclic in occurrence and quite localized in distribution. To date, approximately 250 human cases have been reported; the mortality rate has been about 30 percent. VHF affects mainly male agricultural workers; it appears to be restricted to rural areas in two states in the central plains of Venezuela. The majority of cases have occurred during the dry season, when there is considerable agricultural activity in the endemic region. VHF has many clinical and epidemiological similarities with the other arenaviral hemorrhagic fevers (Lassa fever, Argentine hemorrhagic fever, and Bolivian hemorrhagic fever), so it is assumed that humans generally acquire the disease by inhalation of virus in aerosols of infected rodent excreta.

Epidemiologic studies in the VHF-endemic region have implicated the cane mouse, *Zygodontomys brevicauda*, as the principal reservoir host of Guanarito virus and the probable source of the virus to humans. Cane mice experimentally infected with Guanarito virus develop a persistent nonimmunizing infection and chronically shed infectious virus in their urine and saliva. *Z. brevicauda* is a grassland species and reaches high densities in fallow fields and abandoned pastures, as well as in tall grass along fence lines.

The broad geographic distribution of the various members of the *Arenaviridae*, their marked genetic diversity, and their intimate association with specific rodent species suggest that arenaviruses are ancient viruses that have coevolved or cospeciated with their rodent hosts. Thus, it is unlikely that Guanarito is a new virus or even that VHF is a new disease in humans. If so, then why was VHF not recognized until 1989?

The endemic region of Guanarito virus and VHF was once largely covered with forest, but during the past 50 years a significant part of the original forest has been cut down to create agricultural land. Much of the deforested land is now used for pasture or cultivation. The transformation from forest to agricultural land has created a highly favorable environment for grassland rodents, such as *Z. brevicauda*, and their population densities are probably much higher now than before. The economic prosperity brought by agriculture in turn has attracted many human migrants into the region. The resulting ecological changes have brought more people into contact with more infected cane mice, resulting in the emergence of VHF.

Observers noted a similar scenario in the 1950s with the emergence of Argentine hemorrhagic fever (AHF). It has been suggested that conversion of the Argentine prairie to cropland for corn and wheat production favored

vesper mice (*Calomys laucha* and *C. musculinus*), the natural reservoirs of Junin virus, the etiologic agent of AHF. These two rodent species are common in terrain disturbed by humans. Thus, in both VHF and AHF, changes in land use and human demographics appear to have created conditions favorable for the emergence of new zoonoses.

Yellow Fever

Yellow fever (YF) is a severe viral hemorrhagic fever that is transmitted by the bite of infected mosquitoes. The current geographic distribution of the disease includes tropical regions of sub-Saharan Africa and South America. YF exists in two forms: an endemic or sylvan cycle, thought to involve monkeys and certain forest mosquitoes that breed in tree holes, and an epidemic or urban cycle that involves humans and the domestic mosquito *Aedes aegypti*. During the 17th, 18th, and 19th centuries, YF caused major urban epidemics in Africa, European port cities, and the Americas. YF, and fear of it, played an important role in the settlement and commerce of the New World during that period. For example, in 1878 a massive YF epidemic devastated the lower Mississippi Valley; it is estimated that more than 100,000 people were infected and approximately 20,000 people died. The resulting panic and interruption of commerce caused major financial losses.

Because of the havoc and high mortality resulting from urban YF epidemics and the earlier success of American efforts at controlling the disease in Cuba and Panama by sanitation and vector control, Brazil embarked on a nationwide campaign to eradicate *Ae. aegypti* during the 1930s. The early success of that program, coupled with the introduction of the pesticide DDT, led the Pan American Sanitary Bureau to initiate a hemisphere-wide *Ae. aegypti* eradication campaign in 1947. By 1972, this mosquito had been eliminated from Central America and most of South America, and YF disappeared in urban areas.

The development of YF vaccine also played an important role in elimination of the urban disease from the Americas. The 17D YF vaccine was first used in Brazil in 1937, and during the next 30 years many millions of persons throughout the Americas received the vaccine. However, following the eradication of *Ae. aegypti* and the disappearance of urban YF, many countries in South America stopped mass vaccination campaigns. The current policy in most countries in the region is to wait for the appearance of sylvan cases and then to vaccinate people living in areas around the outbreaks in order to prevent spread of the disease to urban areas.

Ironically, during the past 20 years, as many South American countries discontinued or deemphasized YF vaccination campaigns, *Ae. aegypti*, the urban YF vector, was reinfesting the same countries. The mosquito now

occupies almost its entire preeradication geographic distribution, including most cities and towns in the Amazon Basin. The reemergence of dengue and dengue hemorrhagic fever in South America during the same period attests to the current widespread distribution and abundance of *Ae. aegypti* in the hemisphere. Recent dengue epidemics in the cities of Belem and Manaus in northern Brazil, in Iquitos and Pulcalpa in eastern Peru, and in Santa Cruz in eastern Bolivia demonstrate that *Ae. aegypti* has reinfested many urban communities in the Amazon Basin and now exists in close proximity to areas where sylvan YF occurs. Consequently, public health officials are deeply concerned that urban YF will reemerge in the Americas.

Sylvan YF is still endemic in tropical forested regions of South America. From 1969 to 1995, the Pan American Health Organization reported a total of 3,924 cases of sylvan YF in the hemisphere. This undoubtedly is an underestimate, since milder cases of the disease often are not recognized and the more severe forms can be confused with other endemic diseases, such as hepatitis B and D, leptospirosis, and dengue hemorrhagic fever.

Current knowledge about the ecology of sylvan YF in South America is still incomplete. The most widely accepted view is that YF virus moves in "epizootic waves" through the Amazon Basin in a sylvan cycle involving principally monkeys and arboreal mosquitoes of the genera *Haemogogus* and *Sabethes*. Human exposure to YF virus is strongly linked to occupational activities, such as forest clearing, lumbering, road construction, and jungle military maneuvers, that bring people into contact with the sylvan vectors. Consequently, most cases of sylvan YF occur in adult males.

Two recent outbreaks of YF, in Peru and Bolivia, illustrate some of the factors contributing to the emergence of sylvan YF and the increasing risk of urban outbreaks. During the late 1980s and early 1990s, terrorist activities of the Shining Path guerillas in eastern Peru drove many civilians out of the region. Following the defeat of the Shining Path, people moved back into the region to reclaim their land. As part of this migration, the government brought in tens of thousands of contract laborers from the impoverished highlands to help clear land and plant crops in rainforests in the eastern Andean foothills. Thus, a large number of people who lacked immunity to the disease moved into an area where YF virus was endemic. In 1995, about 500 cases of YF were reported from Peru, many of them among these contract workers. Since the region is quite remote and isolated, few of the patients were hospitalized. However, if the outbreak had occurred among a more mobile group, such as soldiers, mineral prospectors, or coca producers, some of the cases undoubtedly would have been evacuated by air and transported to urban areas for treatment. In that scenario, the risk of YF introduction into an urban area with *Ae. aegypti* would have been much greater.

A second and potentially more dangerous YF outbreak occurred in

1997–98 in Santa Cruz, a city in the tropical lowlands of southeastern Bolivia. In recent years, Santa Cruz, which has a population of about 1 million people, has become quite prosperous because of large deposits of natural gas, rich agricultural land, and its proximity to major urban centers in Brazil and Argentina. Dengue is endemic in Santa Cruz; it appeared after the reintroduction of *Ae. aegypti* in 1980. Sylvan yellow fever also is endemic in rural areas around the city.

During the past decade, the Bolivian government privatized its mines in the country's highlands; this led to many unprofitable mines being closed and to massive unemployment and economic hardship in a region where most of the country's population lives. Many unemployed miners and their families migrated into the area around Santa Cruz because of the economic prosperity and the availability of agricultural land and jobs. Most of the migrants, as well as a majority of the residents of Santa Cruz, lacked immunity to yellow fever virus. Many of the migrants established shanty towns around the city's periphery. Initially, such communities have poor sanitation and lack running water; thus, people by necessity store water in their houses and discard refuse in their yards, thereby creating multiple breeding sites for *Ae. aegypti*. Some of these urban migrants work as day laborers on farms and plantations near the city, where they have potential exposure to YF virus.

Between December 1997 and June 1998, six cases of yellow fever were confirmed in Santa Cruz; five of the cases were fatal. Five of the patients lived in the southern sector of the city in areas of substandard housing. Follow-up epidemiologic investigations indicated that several of the patients had had recent exposure in rural areas where YF is known to be endemic. But two of the patients reportedly had not left the city during the incubation period, suggesting urban transmission of YF. Emergency vaccination of persons living in close proximity to the YF cases and intensified vector control were instituted, and no further cases were reported.

In these two examples of recent YF outbreaks, human demographics and migration, economic change and land use, and the breakdown of public health measures all contributed to reemergence of the disease.

Zoonotic Visceral Leishmaniasis

From a worldwide public health perspective, zoonotic visceral leishmaniasis (ZVL) is one of the most important emerging parasitic diseases. ZVL is endemic in rural areas of tropical America, southern Europe, north Africa, sub-Saharan regions of east and west Africa, southwest Asia, and China. The disease typically affects young children and immunocompromised adults. In the New World, ZVL is caused by *Leishmania chagasi*, which is transmitted by the sand fly *Lutzomyia longipalpis*. In the Old

World, the disease is caused by *L. infantum*, which is transmitted by sand flies of the genus *Phlebotomus*, subgenus *Larroussius*. (Although the parasites causing ZVL in the New and Old Worlds still carry different names, many parasitologists now believe that they are in fact the same organism.) Dogs serve as the principal domestic reservoir of both parasites, while wild canids, including foxes, jackals, and wolves, serve as the major sylvan reservoirs.

In most locations where ZVL occurs, the essential maintenance cycle of the parasite in nature is presumed to involve a transmission cycle between wild canids (including feral and stray dogs) and sand flies living in caves and rock crevices. The parasite is introduced into the domestic cycle when infected wild animals visit houses to scavenge for food. During such visits, so-called "peridomestic" sand flies feed on the infected wild animals, pick up the parasite, and subsequently transmit it to dogs, which then act as domestic reservoirs. Once introduced into a community, the parasite can be maintained in a dog–insect–dog transmission cycle. Occasionally, some humans are infected directly by being bitten by sand flies, but humans are not thought to play a significant role in maintenance of the parasite. Introduction of the parasite into new regions (including occasionally the United States) occurs when infected dogs are transported from endemic areas to nonendemic areas.

Several factors are contributing to the rise of ZVL as a major public health problem. First, and probably the most important, are land use and demographic changes. This is most apparent in tropical Latin America, where massive destruction of primary forests, together with rapid human population growth and the concomitant development of new farmland and rural settlements, have led to conditions that now support large populations of the vector *Lu. longipalpis*, as well as large populations of the major reservoir hosts, dogs and foxes. As a consequence, ZVL now occurs in many regions of Latin America where it was not found previously.

In addition, ZVL recently has begun to appear in suburban areas of several major Brazilian cities, including Rio de Janeiro, where dogs alone now seem to be the major reservoir of the parasite. In most Latin American countries during the past 30 years, there has been a major migration of people from rural to urban areas. As noted in the case of Santa Cruz, new migrants typically settle in hastily constructed shanty towns on the periphery of large cities. These settlements are usually overcrowded, with inadequate housing and poor sanitation. The migrants often bring with them dogs, chickens, and pigs that they keep in or around their houses. These conditions create an excellent habitat for *Lu. longipalpis*, and the density of this insect in both houses and animal shelters may reach very high levels in such communities.

Another factor in the recent emergence of ZVL has been the elimina-

tion in many regions of public campaigns to control malaria by spraying houses with insecticides to kill mosquitoes. One of the side benefits of such spraying was a reduction in the number of sand flies present in a community. In most areas of the Mediterranean and Latin America, where active spray campaigns were in place, the incidence of ZVL decreased. However, as malaria control programs were discontinued, the number of ZVL cases increased, presumably due to increased numbers of sand flies and increased parasite transmission. A similar pattern also has been observed with other forms of leishmaniasis and with sand fly fever following the cessation of house-spraying programs.

Still other important factors involve human behavior and microbial adaptation. Until recently, ZVL was largely a disease of malnourished children. Tests in ZVL-endemic areas indicate that many people are infected with the parasite but that most well-nourished persons with normal cellular immune responses usually develop only mild, self-limited infections. However, the immunosuppression caused by HIV infection has changed this pattern. In the Mediterranean region, ZVL is now a common coinfection among HIV-positive adults. Some of these cases appear to be caused by reactivation of old inactive ZVL infections, while others represent new infections in immunosuppressed persons. In addition to natural transmission route by the bite of infected sand flies, there is accumulating evidence of direct person-to-person transmission of the parasite among intravenous drug users (many with HIV infection) sharing contaminated syringes.

The association between HIV and ZVL is especially ominous for another reason. Spanish investigators have reported infection of sand flies (*P. perniciosus*) by feeding the insects on blood from ZVL patients coinfected with HIV. The ease with which the insects were infected suggests that such patients could potentially serve as urban reservoirs of the parasite, establishing a focus of human–sand fly–human transmission and thereby eliminating the need for infected dogs to maintain a domestic cycle. Some scientists suggest that such a pattern has occurred with another disease: kala-azar. According to this argument, *L. donovani*, the etiologic agent of kala-azar, began as a true animal parasite and then evolved into a zoonosis. Finally, the animal reservoir host was completely eliminated, so that *L. donovani* is now maintained solely in a human–sand fly–human cycle. Since *L. chagasi*/*L. infantum* and its vectors already have adapted to the "peridomestic" environment, one wonders if, with the assistance of HIV, this parasite might evolve (emerge) in a manner similar to that of *L. donovani.*

These three examples are meant to illustrate the importance of ecologic factors in the maintenance and emergence of zoonotic diseases. The current paradigm of biomedical research, which focuses on mechanistic studies at the cellular, molecular, and genetic levels, frequently overlooks the importance of ecological factors in the development of human disease. Zoonotic

diseases provide some of the best examples that the factors responsible for human illness involve much more than cellular immune response and gene expression. Furthermore, the ultimate control of zoonotic diseases probably depends more on our understanding of their epidemiology than of their molecular biology.

VECTORBORNE ZOONOTIC DISEASES

John T. Roehrig, Ph.D.

Chief, Arbovirus Diseases Branch
Division of Vector-Borne Infectious Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention

A number of vectorborne zoonotic diseases, both bacterial and viral, have emerged in recent years or are now increasing in many regions. The agents that cause some of these diseases, such as plague and tularemia, also are of concern because of their potential use by bioterrorists. Thus, vectorborne zoonotic diseases, which are commonly transmitted from animals to humans by ticks or mosquitoes, are of immediate and growing concern in the United States and around the world.

From a public health viewpoint, viral diseases present particularly complex problems. There are more than 500 known arboviruses, or viruses transmitted by arthropods, and at least 110 of them have been associated with human disease, either in the form of natural occurrences or as laboratory-acquired infections. Thus, diagnosing new disease outbreaks can be a formidable task. In the United States, the good news is that we face only a few types of vectorborne viral diseases. The bad news is that these diseases are caused by members of a number of different virus families, including flaviviruses, which cause West Nile fever, and togaviruses, which cause several types of encephalitis. Many of the diseases caused by these viruses show very similar clinical symptoms.

A number of factors may be contributing to what appears to be an increase in arboviral diseases worldwide. Viruses may enter areas where they previously had not existed, as happened with the West Nile virus that emerged in the New York City vicinity in 1999. In addition, more people moving into areas where they have not normally lived, such as people moving into newly cleared forest areas in South America, may become exposed to the viruses. It also may be that members of the medical community in many regions have gained increased awareness of the possibility of encountering new viral diseases and are more likely to test for their presence. For example, in one study of LaCrosse encephalitis in the mid-Atlan-

tic region of the United States, we found that as awareness of the disease increased among health care personnel, more cases were detected. Taken together, these factors suggest that arboviral diseases are more common than has been suspected and that some new viruses are appearing or old viruses are appearing in new places.

The case of West Nile virus may illustrate how the federal government responds to an emerging infectious disease, as well as some of the policy issues and problems that can arise. The virus was discovered in Uganda in 1937, and major outbreaks of the disease periodically occurred worldwide. Before its introduction to the United States, the most recent human or veterinary outbreaks had occurred in Romania in 1996 and in Italy in 1998. There also was a large human outbreak in Russia concurrent with the outbreak in the United States. The CDC sent a team to investigate the outbreak in Romania, and the information gained proved valuable when veterinarians and physicians in New York began to detect encephalitis in horses, birds, and humans but could not immediately determine the causative virus. Collaborations between CDC and other international health agencies also helped diagnose this outbreak. In the months following the outbreak, scientists in CDC's Arbovirus Diseases Branch assisted local and state personnel in identifying the disease agent and in characterizing its geographic spread.

Among the questions that still remain is how the West Nile virus reached the United States. Several routes have been suggested. Someone infected with the virus may have traveled by airplane to New York, where they were bitten by a mosquito that picked up the virus. The mosquito, in turn, may have transmitted the virus to a bird, perhaps a crow or a sparrow, since these species have now been found to carry the virus. Once established in the bird population, the natural disease transmission cycle could begin. Humans may have played a part in other ways as well. Through either legal or illegal activities, someone may have brought in animals, perhaps birds, that carried the virus, which was then transmitted to mosquitoes. Alternatively, infected mosquitoes may have hitched a ride by ship, breeding in some remnant of water during the journey. (While bioterrorism remains a threat with some arboviruses, evidence suggests that this was not the case in this instance.) In addition, it is possible that the virus entered the country "naturally," carried by infected birds that had been blown across the ocean by storms, but this now appears to be a less likely route. CDC, in conjunction with other public and private agencies and organizations, continues to investigate the possible origins of the virus, though a number of technical problems may keep researchers from ever solving this mystery.

The initial investigations to identify the West Nile virus involved collaboration among many parties, both public and private, and at the federal, state, and local levels. By many accounts, this collaboration did not always

work as smoothly as might have been hoped. CDC has begun to establish a comprehensive national response plan to deal with the sort of problems that can arise during such a multijurisdictional investigation of a disease outbreak. Among the lessons that have emerged, for example, is that there should be centralized coordination of investigations that involve multistate disease outbreaks. Responsibility for coordinating data typically rests with CDC, and in doing so the agency must address such issues as maintaining the security of shared information; protecting states' rights to privacy; ensuring that surveillance methods are consistent from state to state; and maintaining a common, easy-to-use disease database.

Dealing with the West Nile outbreak also has reinforced the importance of having a strong relationship between the medical, public health, and veterinary communities, especially at the local level. In addition, it is important for all members of the human and animal health communities to maintain awareness of unusual disease possibilities. Finally, the experience has pointed out a dilemma in devising efforts to control emerging arboviral diseases: that is, while vaccines potentially can prevent arboviral diseases, pharmaceutical companies typically are not interested in developing such vaccines. Many of these diseases either threaten too few people or threaten people, often those in developing countries, who cannot afford to pay for vaccines, thus reducing the economic incentives of vaccine development.

In early 2000, CDC published preliminary guidelines for surveillance, prevention, and control of West Nile virus in the United States. The agency developed these guidelines with extensive input from a variety of stakeholders, including arbovirologists, epidemiologists, laboratory personnel, vector control specialists, wildlife biologists, and state and local health and agriculture officials. The goals include monitoring geographic and temporal spread of the virus; rebuilding vectorborne disease surveillance infrastructure at the state level; developing more effective strategies for surveillance, prevention, and control; defining regional distribution and incidence of other arbovirus diseases; and providing up-to-date national and regional information on West Nile and other vectorborne diseases.

Federal, state, and local public health officials are now using the guidelines in an effort to minimize the public and veterinary health impact of West Nile virus. To aid in this control effort, Congress has given CDC $2.7 million to enhance surveillance efforts in states along the Eastern seaboard, because of concern that migrating birds will carry the virus southward from New York. More recently, the Department of Health and Human Services (DHHS) has provided CDC with an additional $5 million to expand surveillance efforts into other states, although on a more limited basis. All of these surveillance programs will be conducted through cooperative agreements between CDC and state agencies, often the state health department.

Note: Since this IOM Forum, the CDC has held additional meetings, in

collaboration with other federal and state agencies, to review the effectiveness of the various activities related to West Nile virus, and it has issued updated guidelines to enhance surveillance, prevention, and control efforts. In 2001, Congress allocated another $21 million to CDC for West Nile surveillance, prevention, and control.

MATHEMATICAL MODELS AND PREDICTORS OF DISEASE OUTBREAKS

Dana A. Focks, Ph.D.

Senior Scientist, Center for Medical, Agricultural, and Veterinary Entomology
Agricultural Research Service, U.S. Department of Agriculture

Since World War II, the U.S. Department of Agriculture's Agricultural Research Service has worked with the Department of Defense (DoD) on developing mathematical models of human diseases. During the past decade, our laboratory in the Center for Medical, Agricultural, and Veterinary Entomology has developed risk assessment models for a number of diseases, including malaria, Lyme disease, and dengue hemorrhagic fever. The laboratory also has developed models for predicting the population dynamics of some of the mosquito species that serve as disease vectors, such as the mosquitoes that transmit Venezuelan equine encephalitis.

Among their strengths, models can help researchers and public health officials integrate large quantities of disparate information, thus permitting more sophisticated analysis of the factors involved in a particular disease or at a particular location. Models also can highlight critical unknown factors, and they can be used as a quick "first test" of various hypotheses before launching more costly and time-consuming evaluations in the field.

Perhaps the laboratory's most comprehensive modeling effort has focused on dengue fever. We have developed two types of models. One type is an entomological model, which can be used to predict with considerable accuracy how many *Aedes aegypti* mosquitoes (the vectors of dengue) there are in a given area. The second type is a transmission model, which combines input from the first model with detailed information about human population dynamics to predict how many people in the area are likely to become infected and develop dengue fever. Both models are built on a detailed knowledge base. Through earlier work with yellow fever, scientists have developed a thorough understanding of *Aedes* mosquitoes, including understanding of the mathematical relationships involved in how they propagate under particular conditions and how they spread disease. This level of understanding does not exist for any other arthropod vector. Vali-

dation studies comparing simulation results and predictions with actual field measurements conducted in a wide variety of locations indicate that the accuracy of the models is adequate.

These models are finding a variety of applications. For example, the models can help public health officials in a community threatened by dengue evaluate possible control measures. In most cases, it is impossible to completely eradicate all mosquitoes, since available insecticides and clean-up campaigns that target the containers in which mosquitoes breed are not completely effective. The models are meant to optimize control strategies using several methods in concert. An important use of the models in control projects is in teaching the dynamics of dengue as a function of a host of variables, such as weather, previous epidemics, and control measures.

To help make the insight of models more accessible for community officials, we have recently used the models to develop estimates of transmission thresholds. Put simply, this model can predict, for a specific set of environmental and population conditions, the relationship between the number of mosquito pupae present in an area (as a measure of the ultimate population of adult mosquitoes) and the number of cases of human disease that this vector population would be expected to cause. Thus, rather than conducting a full-scale test with the models, officials simply can conduct a survey to count the pupae present in their community and then compare the results to established standards. If the count reaches a certain level, then the officials know they need to undertake a control program of cleaning up or covering the most productive types of breeding containers. This type of information linking the extent of potential control measures to expected disease outcomes has been lacking in most control programs. The new method of targeted source reduction is being considered by the World Health Organization and the Pan American Health Organization and is in operation in countries in Southeast Asia and South America.

One encouraging recent finding from extensive work with this model is that it may not be too difficult for communities to mount effective mosquito control programs that will prevent or greatly reduce the spread of dengue fever. We have learned that rather than having to reduce overall mosquito populations in an area, it may be possible to focus control measures on a limited number of locations, such as specific types of containers in domestic areas, where most of the mosquitoes breed. Thus, local public health officials can conduct a rapid survey to identify the 1 percent or so of containers that, from our tests, may give rise to perhaps 99 percent of the mosquitoes in the community. Targeting these populations represents a far more manageable and less expensive undertaking. However, surveys in the Americas and in Southeast Asia indicate that this approach is not suitable for all situations.

In addition to these "mechanistic" types of models, which typically

involve relatively rote processing of huge quantities of disease-specific and location-specific information, another type of modeling is showing promise. This type involves remote sensing, in which models incorporate data on weather and geography, often compiled by satellites operated by the National Atmospheric and Space Administration and the National Oceanic and Atmospheric Administration. Our laboratory, for example, currently is working with these agencies, as well as with academic and industry researchers, to convert daily satellite imagery into constantly updated grids depicting weather on a 1.6-kilometer basis. Using this detailed information, we are working to derive models for such things as plant growth and pest management. With further advancement, it also may be possible to derive models of vectorborne diseases, including West Nile virus and St. Louis encephalitis. Such models not only may prove useful in predicting the spread of naturally occurring diseases but may help in predicting how a biological agent released by terrorists might spread geographically and from one animal community to another before finally reaching humans.

Of course, modeling has its limits—and, indeed, its potential has often been oversold. One major problem, for example, is that for many diseases we simply lack sufficient background for developing reliable models; we do not adequately understand the disease system and its interactions with the environment, nor do we have reliable series of disease incidence to validate the models. In many cases, such a knowledge base is likely to remain elusive for years to come. But capitalizing on the recognized strengths of models—in both practical application and research—has provided at least some help in the effort to predict, manage, and even prevent some emerging zoonotic diseases.

THE ROLE OF NATIVE BIRDS AND OTHER WILDLIFE ON THE EMERGENCE OF ZOONOTIC DISEASES

Milton Friend, Ph.D.

Executive Director, Salton Sea Science Subcommittee
U.S. Geological Survey

and

Robert G. McLean, Ph.D.

U.S. Geological Survey

Wildlife can be an important source of transmission of infectious disease to humans. One potential transmission route involves hunting and fishing, both common activities in the United States and worldwide. For

example, during 1996, approximately 77 million Americans, about 40 percent of the total population 16 years of age and older, took part in some recreational activity relating to wildlife and fish. Another potential route of infection focuses on urban and suburban environments. These locations are of special concern because of their increasing role as wildlife habitat, the greater interface between humans and wildlife that takes place within those environments, the paucity of knowledge about disease in those wildlife populations, and the general lack of orderly management for wildlife within those environments.

In the wild, several trends are contributing to the growing importance of zoonotic diseases. First, the spectrum of infectious diseases affecting wildlife today is greater than at any time during the previous century. Second, the occurrence of infectious diseases has changed, from sporadic, self-limiting outbreaks that generally resulted in minor losses to frequently occurring events that generally result in major losses of wildlife. Third, disease emergence has occurred on a worldwide scale in a broad spectrum of wildlife species and habitats.

Given the scope of the problem, current disease surveillance efforts are inadequate. Few state wildlife agencies allocate personnel and resources to address wildlife disease, despite their statutory responsibility for managing nonmigratory wildlife. Some state agencies provide minimal support for regional programs based at universities. At the federal level, the primary surveillance effort is conducted by the National Wildlife Health Center, operated by the U.S. Geological Survey. Outside of government, some veterinary schools, agriculture diagnostic laboratories, and other programs provide additional information on animal diseases, primarily by examining carcasses of dead wildlife submitted for analysis, and individual university-based researchers carry out a variety of studies.

Typically, information about the occurrence of disease in free-ranging wildlife is derived from surveys and mortality events in areas where wildlife observations by agencies and the public are frequent enough to detect their occurrence before carcasses are removed by scavengers and predatory animals. The result is that disease occurrence is grossly underreported, heavily biased toward mortality events, and biased toward species of special concern and interest, such as game and endangered species. Therefore, the available information should be viewed as the "proverbial tip of the iceberg" relative to disease activity within wildlife populations.

In general, mammals are the most important source of zoonoses transmitted by wildlife. However, birds are involved in the transmission of a number of serious zoonoses, especially vectorborne diseases. This is of special concern because of the greater geographic movement of many bird species. The 1999 outbreak in New York City of West Nile fever, which afflicted 62 people and killed 7 of them, serves as an example. After exten-

sive study, scientists determined that the virus apparently was carried by crows and transmitted to humans by mosquitoes. (However, it is not known how the virus was initially introduced to the region or, indeed, to the United States.) Waterfowl, such as Canada geese and mallard ducks, represent a particular threat for disease transmission to humans. These species are becoming increasingly common in urban and suburban areas, both because of habitat losses elsewhere and because of the current trend in landscape planning toward creating planned communities that feature "miniestates," natural areas, and golf courses—environments that are attractive to waterfowl. The urban/suburban environment also has become an increasingly important habitat for songbirds. *Salmonella typhimerium* has emerged as an important pathogen, causing large-scale epizootics, usually in association with bird feeding. The magnitude of the potential human–songbird interaction is reflected by the 1996 expenditure for bird food in the United States of approximately $2.7 billion, with nearly 39 million people participating in this activity during that year.

Environmental factors are the driving force for many emerging diseases of wildlife. In general, wildlife disease prevention and control will be most effective when environmental conditions are understood and the anthropogenic actions causing those conditions are addressed. The most important considerations can be classified under the headings of landscape changes, wildlife translocations, and human values.

Landscape changes include both changes to the physical environment and the introduction of exotic species. Changes in the wetlands of the Central Valley of California provide a case in point. These wetlands lie within the Pacific Flyway, one of four primary migration corridors for birds that typically breed in remote northern areas and winter in southern areas of the North American continent and beyond. Because of their location, the wetlands have always been an important stopover area for birds. In recent years, however, approximately 90 percent of the wetlands have been converted to agricultural lands and other uses. As a result, more than 60 percent of the entire Pacific Flyway waterfowl population is now channeled into about 10 percent of the former wetland habitat. Such mass concentrations of birds for prolonged periods facilitate exposure of large numbers of birds to disease agents that may be present. The frequency of outbreaks, variety of bird species involved, and numbers of birds exposed to various pathogens provide a continuum of opportunity for the development of novel host–parasite relations.

Human-created environments and exotic species are other important aspects of landscape change. For example, the Salton Sea, located in the desert of Southern California, was created in the early 1900s. Artificially sustained by agricultural drainwater, this highly saline body of water has the most productive fishery in the world and is one of the crown jewels of

avian biodiversity. However, since the 1990s, the ecosystem's species richness has been tarnished by an unprecedented array of disease outbreaks that have killed large numbers of birds. The Salton Sea is an often-repeated contemporary situation that involves the creation of new environments and the mixing within these environments of multiple species that do not have established ecological relations with those that do. The opportunity for disease emergence is a component of the resulting species interactions and environmental changes taking place.

Wildlife translocation, in which humans move free-ranging wildlife from one geographic area to another, is a common conservation tool that has clearly facilitated disease emergence, including zoonoses. An example was the government-directed translocation of raccoons trapped within a known enzootic area for raccoon rabies in the southeastern United States. These rabies-infected animals were the source of a raccoon rabies epizootic in West Virginia that spread to numerous other mid-Atlantic states, some coastal Atlantic states, and New England. The result is that enzootic foci for raccoon rabies are now established in geographic areas where rabies in raccoons previously had either been incidental cases due to epizootics in other species or small, self-limiting events in raccoons. Rabies also has been translocated with foxes and coyotes moved for sporting purposes. Other types of wildlife movements by humans that are contributing to disease emergence are captive rearing of wildlife for release into nature, wildlife rehabilitation and releases, and translocations for commercial purposes. Bovine tuberculosis has recently spilled over from the agriculture industry into white-tailed deer. Establishment of bovine tuberculosis within free-ranging white-tailed deer populations will pose a significant human health threat because of the pursuit of this species by millions within the hunting community.

Disease emergence is as much a social issue as it is a biological issue. Of particular note, the prevailing philosophical attitude among many people within the wildlife conservation community is that disease is a natural event that need not be addressed. (Exceptions are made for transient responses to high-impact mortality events and for limited diagnostic activities in response to public inquiry about cases of visible mortality.) Proponents of this view maintain that impacts on wildlife population rather than on the individual animal should primarily determine whether or not there is a need for actions to be taken. This is a fundamental difference relative to human health and companion animal considerations, where clinical disease in individuals is of prime concern.

A reasonable question is: Why is more not being done to address disease within wildlife populations? One contributing factor is that while most people believe it is possible to deal with disease threats involving humans and domestic animals, similar confidence is lacking regarding our ability to

control disease in free-ranging populations of animals. Response to disease in humans, livestock, and companion animals is governed by clear agency mandates supported by statutory authorities, legal mandates, laws, regulations, and other directives. The response process is facilitated by reporting systems, including designated reportable diseases; formal interagency infrastructures for disease diagnosis and control; infrastructures for epidemiological investigations; and systems for clinical treatment and fiscal considerations, among other factors. In general, all of those conditions are either absent or at best rudimentary for agencies with stewardship responsibilities for free-ranging wildlife. As a result, disease outbreaks in wildlife do not have a mandated responsibility to be investigated or dealt with. Because of the differences in agency responsibilities, agriculture agencies do not become involved unless the outbreak is known to be, or has a high probability of being, a disease of major concern for domestic animals. However, even in those instances, the wildlife are under the jurisdiction of wildlife agencies. Similar considerations are involved for zoonoses transmitted by wildlife. Complicating factors include animal rights advocates that give special attention to protecting wildlife, even when serious diseases are involved, and conservation legislation such as the Endangered Species Act and other laws that can constrain actions normally implemented when domestic animals are affected by a disease of major importance.

Free-ranging wildlife populations are under the legal stewardship of state and federal government agencies. Primary responsibilities are vested in different agencies depending on the types of species involved. Shared responsibilities between state and federal agencies generally exist despite one or the other having primary responsibility for a specific situation. This stewardship form of ownership leads to two results. First, there is no private ownership of free-ranging wildlife. Instead, wildlife are held in the public trust for human society. Second, the wildlife stewardship agencies are nonprofit organizations that have little economic incentive to address the costs of disease. Thus, there are no compelling reasons for government agencies to expend resources on disease prevention and little incentive for disease control.

To help in minimizing the emergence of diseases in wildlife, as well as the transmission of such diseases to humans, numerous observers have suggested a variety of actions. These actions include:

- *Interdisciplinary collaboration and cooperation.* Federal agencies should develop a tripartite cooperative program to address infectious diseases in humans, in domestic animals, and in wildlife. This program should serve as a focus for regular communications through working groups to address information transfer; to improve response to disease emergencies; to establish priorities for collaborative, focused investigations; and to pur-

sue other areas of mutual interest. The program also should serve as a model and catalyst to stimulate the development of similar cooperative programs between state agencies that would network with the federal program.

- *Database development*. Federal agencies should take the lead in developing a common database for disease surveillance and monitoring that can be used to track infectious diseases and the emergence of new diseases. As part of this effort, a work group should be established to develop a listing of "reportable" diseases that are to be entered into the system, with standards for data entry, reporting, and utilization by collaborating agencies and institutions. The CDC has proposed developing a national electronic disease surveillance network for state and federal public health information on emerging infectious diseases, and this network should be expanded to include wildlife surveillance information on emerging zoonotic diseases.
- *Focused collaborative investigations*. In ongoing research programs, joint development and planning can help ensure that high-quality specimens, reagents, information, and assays will be provided among collaborators at minimal costs. In other instances, joint budget initiatives will be required to provide the resources needed to carry out the monitoring programs and other focused investigations to address specific diseases. Agencies should develop agreements with one another to facilitate collaborative investigations on issues of mutual interest; such agreements should cover such issues as fund transfers, personnel assignments, and sharing of facilities and technical capabilities.
- *Biological repositories*. There is a need to develop and maintain systems for archiving materials from wildlife disease investigations for retrospective and comparative studies. Isolates of infectious disease agents, serum banks, histological specimens, and other biological reference materials need to be organized in a coherent manner that provides ready access to them by qualified investigators willing to work as true collaborators within the area of emerging infectious diseases.
- *Disease ecology*. Disease prevention and control activities will be enhanced by greater understanding of the epizootiology of wildlife diseases. This is a fruitful area for interagency and interdisciplinary collaboration. Efforts should extend beyond field and laboratory investigations to include the areas of mathematical modeling and geographic information system technology. These efforts should be supported by expanded databases of information from the physical, biological, and social sciences.
- *Urban wildlife disease studies*. Given the increasing importance of urban/suburban environments as habitats for some species of wildlife, this is an important area for collaborative investigation. Such studies have ur-

gency for protecting the well-being of migratory birds and other wildlife, as well as for protecting human health.

- *Public education.* A coordinated, ongoing process is needed to provide the general public with timely, accurate information about emerging diseases of wildlife and the importance of such diseases to public health, domestic animals, and the wild animals themselves. One possible route would be for federal agencies to work collaboratively with an independent organization dedicated to public outreach.
- *Emergency response.* Collaborative arrangements should be developed to integrate the emergency response capabilities within the public health, domestic animal, and wildlife conservation communities. Response to emerging infectious diseases of wildlife should be augmented as needed by the combined capabilities of the different programs to minimize the potential for establishment and spread of wildlife diseases capable of infecting other species, including humans.
- *Technical forum.* Communications need to be improved between officials with responsibility for managing wildlife on public lands and researchers who study diseases of wildlife or diseases transmitted from wildlife to humans and domestic animals. It is not sufficient to rely on the diverse scientific meetings that currently incorporate wildlife diseases as agenda topics. The North American Wildlife Conference can provide an appropriate forum for bringing wildlife disease issues before those individuals who manage public lands, and organizers of the conference should be encouraged to develop a regular forum devoted to emerging diseases. The human health community should develop a reciprocal opportunity for participation by members of the wildlife community.
- *Guidance on landscape change.* The expanding human population assures continued landscape changes. Thus, the government and other organizations should become proactive in terms of developing and disseminating information that can help guide land development in a manner that gives greater consideration to disease emergence. Initial actions that should be considered include distributing authoritative publications, sponsoring public forums, and providing consultations on particular problems.

To quote the comic strip character Pogo, "We have met the enemy and he is us." This observation continues to be demonstrated for emerging diseases. Human arrogance cannot overcome biological processes. However, by replacing arrogance with some humility and by addressing these issues from a truly collaborative perspective, we will be able to improve environmental conditions substantially and impede disease in a manner that will greatly benefit humankind and our planet's biological resources for decades to come.

ANIMAL HUSBANDRY PRACTICES AND RISK FACTORS, WITH PARTICULAR REFERENCE TO BOVINE SPONGIFORM ENCEPHALOPATHY

Fred Brown, Ph.D.

Visiting Scientist, Plum Island Animal Disease Center
U.S. Department of Agriculture

Bovine spongiform encephalopathy (BSE) is caused by a member of a group of agents that collectively are known as transmissible subacute spongiform encephalopathies. These agents cause fatal human and animal neurological diseases, which are characterized by a long symptom-free incubation period followed by a short acute phase. Many such diseases have been described over the years, but attention has been focused on them most recently by the massive outbreak of BSE in cows that started in the United Kingdom in 1986. This outbreak presented a new problem for the agricultural industry because it had no precedent. The disease occurred in many herds but was of low incidence in any individual herd, with one to three animals being affected. The animals became uncoordinated and irritable, fell frequently, and eventually died. The only diseases remotely connected to BSE seemed to be scrapie in sheep and goats and Creutzfeldt-Jakob disease (CJD) and kuru in humans. Histological examination of the brains of infected animals showed that all three diseases caused similar lesions.

Veterinary scientists quickly traced the source of BSE infection during the United Kingdom outbreak to the food concentrates—essentially, tissues of slaughtered cows—that were being fed to cattle to enhance their productivity. The clear question to be answered was why the disease had emerged then, when the feeding of concentrates had been part of animal husbandry for several decades. Why had the disease not emerged earlier? Another critical question was how an infectious agent could survive the severe heat treatment used in the preparation of these concentrates. The only clue to these questions seemed to be the change made in the rendering procedure by which the concentrates were produced—a change in the solvent step that was made to decrease the cost of the process. This change had been made in the 1980s, leading to the suggestion that the incubation period of the disease was about 5 years.

Despite the imposition in 1988 of a ban on the feeding of concentrates, the number of infected animals continued to rise dramatically. The peak in the outbreak occurred in 1992 and 1993, confirming the initial suggestion of a 5-year incubation period. Subsequent pathogenesis studies have shown that cattle fed large amounts of the BSE agent do not develop disease earlier than 36 months, nor do their tissues contain any infectious agent before

that time. This led to a ban on any use of meat or other animal tissues for human consumption from animals older than 30 months. (Of course, this raises a question: if an animal develops the disease when it has received the infected concentrate 36 months previously, how safe is the precursor of the infectious agent?)

Early on, many observers considered it unlikely that the agent causing BSE would lead to any problems in humans, since there was no evidence that the infectious agent that causes scrapie in animals causes disease in humans. Indeed, the Southwood Committee established by the British government reached this conclusion in 1989, as did the Spongiform Encephalopathy Advisory Committee (of which I was a member) in 1990. Still, the burning question in many quarters remained: Is beef safe? Such worries had a formidable impact on the British cattle industry.

Then, in March 1996, the U.K. Ministries of Agriculture and Health announced that human cases of a new form of Creutzfeldt-Jakob disease had been detected in a small number of young people. This was unexpected because CJD does not usually occur in young people, yet histological examination of the brains of these victims showed clear similarities to BSE. Subsequent evidence has confirmed that the new disease (now called new variant Creutzfeldt-Jakob disease) and BSE are caused by the same agent.

These new findings had perhaps an even greater impact, on both the cattle industry and the general public, than did the initial observations. Who was going to eat beef from a potentially infected animal? In a world demanding no risk, sales of beef plummeted, and some groups demanded that all 12 million cattle in the British herd be killed. The clear problem was to ensure public health but at the same time attempt to preserve an important and lucrative industry. Balancing these demands would require a delicate balancing act on the government's part.

The outcome, however, did not go well. Many individuals and groups argue that the BSE crisis was badly handled, both by the government and by its scientific advisers. But what were the options? There are several issues that need to be taken into account before judgment is rendered: (1) BSE was a new disease of cattle, (2) the disease was caused by an "old" agent, (3) the disease had a very long incubation period, (4) there was no in vitro diagnostic test, and (5) the assay system for detecting the agent relied on the use of mice and required months to complete.

One lesson seems clear, however: the problem in Britain was so large that the government should have appointed an "overlord" who would have devoted full-time attention to issues as they emerged. Advisory committees are no substitute for day-to-day involvement. (I suggested this approach to the British government in 1991, but it was rejected.) Would such an approach have made any difference? Because of the disease's long incubation period, it may not have done so. But having such a central authority would

have ensured that all the scientists who knew something about these agents and the diseases they cause would have been brought into the equation at the earliest possible stage. Neither worrying about "territory" or "turf," nor the seeking of glory, can solve such problems—and these issues should not cloud the work under way today on other emerging diseases.

NATURAL HISTORY OF SIMIAN IMMUNODEFICIENCY VIRUSES: CLUES TO THE EMERGENCE AND VIRULENCE OF AIDS VIRUSES

Lisa Chakrabarti, Ph.D.

Visiting Scientist, Aaron Diamond AIDS Research Center

Simian immunodeficiency viruses (SIVs) infect more than 20 species of Old World monkeys and apes, all of them of African origin. Those species naturally infected include chimpanzees, mangabeys, mandrills, baboons, colobus, African green monkeys, and guenons. African green monkeys (genus *Chlorocebus*) were the first nonhuman primates found to harbor SIV in the wild.

In most cases, SIVs are species specific, meaning that viruses obtained from animals of a given species will phylogenetically cluster together. The species-specific clustering of viral sequences suggests that virus and hosts evolved in parallel and that SIV infections are ancient. However, several exceptions to the species-specific clustering rule indicate that SIVs do occasionally cross species barriers. For instance, viruses from African green monkeys (SIVagm) appear to have been acquired by a talapoin, a patas, a white-crowned mangabey, and two baboons. The frequency of SIVagm cross-species transmission may reflect the fact that African green monkeys are particularly widespread and numerous and thus represent a major SIV reservoir.

SIV infection has not been shown to cause disease in its natural hosts. This issue is obviously difficult to address in the wild but has been addressed by the epidemiological studies of sooty mangabey and African green monkey populations bred in primate centers. SIV seroprevalence typically is low in young animals but rises sharply in juveniles and young adult mangabeys, suggesting that SIV is mainly transmitted through the sexual route.

However, SIVs have the potential to become pathogenic when transferred to new host species, including humans. There is compelling evidence that SIV from sooty mangabeys (SIVsm) is the recent ancestor of the human AIDS viruses HIV-2 and of SIVmac, the virus that causes simian AIDS in rhesus macaques. There also is evidence that SIV from chimpanzees (SIVcpz) is the ancestor of at least some types of HIV-1. The clustering of several

human and simian lentivirus pairs on phylogenetic trees indicates that cross-species transmission of SIVs to humans has been a repeated occurrence. Transmission events did not always result in the emergence of pathogenic and highly transmissible AIDS viruses, as indicated by the fact that only two of the six HIV-2 subtypes identified so far were associated with AIDS. HIV-1 types N and O are pathogenic but have a limited epidemic spread as compared to HIV-1 type M, suggesting differences in adaptation to the human host.

The factors responsible for the acquisition of virulence in the human host remain to be elucidated. This issue may be more easily addressed in simian models, by comparing SIV infection in species, such as the sooty mangabey and the rhesus macaque, that are resistant and susceptible to disease.

Sooty mangabeys range from Sierra Leone and Liberia to the western half of Ivory Coast. Converging evidence supports the idea that cross-species transmission of SIVsm to humans is at the origin of HIV-2. Among the evidence are the following observations: (1) SIVsm and HIV-2 are genetically close and share a common genome structure; (2) all known HIV-2 subtypes occur together only within the range of the sooty mangabey; and (3) ample opportunities exist for transmission, since people in the region hunt sooty mangabeys and keep them as pets, and the prevalence of SIVsm in sooty mangabeys is relatively high. The most convincing evidence is based on the phylogenetic clustering of SIVsm and HIV-2 isolated from the same geographic locale, either in Sierra Leone or Liberia.

Evidence for the origin of HIV-1 from chimpanzees can be found in the close genetic proximity between two SIVcpz from Cameroon and HIV-1 type N, which is found exclusively in the same country, indicating both phylogenetic and geographic coincidence between the two viruses. However, only seven SIVcpz have been characterized so far, and none of them cluster closely with the HIV-1 type M and HIV-1 type O. Thus, it may be premature to draw conclusions on the most recent ancestors for these two group of viruses. They are likely to belong to the SIVcpz group, but the detection of an ancestral HIV-1 type M or O in another species cannot be entirely ruled out at this stage. Chimpanzees are known to prey on other monkey species and may thus be exposed to transmission of heterologous SIVs.

One crucial question is whether cross-species transmission of SIVs to humans can readily generate an AIDS virus, or whether further adaptation to the new host is required for the emergence of a virulent HIV strain. Some insight can be obtained from studies of rhesus macaques. When infected with certain SIVsm isolates, such as B670, these monkeys readily develop AIDS, while inoculation with other SIVsm isolates does not appear to cause disease. It is also relevant to note that accidental SIVsm transmission to

laboratory and animal workers has been documented in at least two instances, with no cases of AIDS reported thus far. Taken together, these observations suggest that simian immunodeficiency viruses have the potential to cause disease upon transmission to a new host but that this may actually be a rare occurrence.

The most telling piece of evidence is epidemiological. Only two of the six HIV-2 subtypes described so far have spread epidemically. The four individuals infected with subtypes C to F were all healthy (or, in one case, afflicted with a disease that is not associated with AIDS). Thus, the divergent HIV-2 subtypes C to F may represent viruses poorly adapted to the human hosts. It appears likely, then, that either the epidemic HIV-2 subtypes originated from the transmission of specific variants that happened to be pathogenic for humans or that the emergence of pathogenic HIV requires further adaptation to the human host through unknown mechanisms.

What mechanisms might drive the acquisition of SIV virulence in the human host? Experiments in the macaque models have repeatedly shown that serial intravenous passages increase SIV and HIV virulence in this host. Thus, it is possible to draw a parallel and speculate that serial intravenous passages could have contributed to the propagation and the adaptation of SIVsm and SIVcpz in humans. Epidemiologists and historians have documented multiple instances of reuse of nonsterile needles or even of direct arm–arm vaccination in Africa since the beginning of the 20th century. The main reason why serial intravenous passages can promote SIV adaptation is that they provide the setting for successive viral jumps from primary infection to primary infection. A poorly adapted virus would induce a very low viral load and therefore would be very unlikely to be transmitted during the chronic phase of the infection. The only window of time during which transmission could occur would be the few weeks that precede the establishment of the antiviral immune response—that is, the primary infection.

4

Diagnosis and Control of Zoonotic Infections

PATHOLOGY AND EARLY RECOGNITION OF ZOONOTIC DISEASE OUTBREAKS

Tracey S. McNamara, D.V.M.

Head, Department of Pathology, Wildlife Conservation Society
Bronx Zoo

In Zambia, in 1987, thousands of animals—hippos, giraffes, wild dogs, lions—turned up dead. What was killing them? Was there a risk for villagers who harvest the meat and use the skins of local animals? In New York City, in 1999, crows and zoo birds were dying. People were dying. What was killing them? Would the risk spread? In both situations, as in many others, diagnosis of the disease outbreaks relied entirely on diagnostic pathology, that is, on analyzing dead animals.

This ability of diagnostic pathology to help in recognizing and understanding diseases—both old and emerging, in humans and in animals—often is overlooked. Basic anatomic pathology involves analyzing tissues from dead specimens, making observations, interpreting those findings, and following up with histopathology studies of samples under a microscope. In recent years, the advent of molecular pathology has heightened the power of diagnostic pathology. Using such tools as immunohistochemistry, in situ hybridization, and polymerase chain reaction (PCR) assays, pathologists now can identify the etiology, or cause of death, faster than ever before and,

in many cases, where it would otherwise have been impossible. However, current disease surveillance systems, for human diseases and zoonoses alike, fail to make adequate use of diagnostic pathology.

Veterinary pathologists are highly attuned to zoonotic diseases, because most of the diseases that threaten humans—brucellosis, Q-fever, leptospirosis, tularemia, rabies, and many more—are diseases that go hand in hand with being a veterinarian. Nor is this a one-way street: some diseases of humans can be passed to animals.

This animal–human link is particularly critical for veterinary pathologists who work in zoos. These individuals regularly work with a number of high-risk species, such as macaques, which can transmit herpes B virus that can be fatal to humans. In addition, zoos typically are located in urban areas, which have their own forms of indigenous wildlife that present a constant threat of introducing diseases to the zoo's collection. These introduced diseases hold potential to spread rapidly throughout an entire herd or flock, and from there to the veterinary staff, the keeper staff, and, in the worst-case scenario, to the public. Yet only six zoos nationwide have a full-time pathologist on staff. Thus, zoo pathologists lack the generations of information, as well as the arsenal of drugs and vaccines, that other veterinarians take for granted. As a result, zoo and wildlife pathology is still very much a frontier.

This means veterinary pathologists always must expect the unexpected. In today's changing world, with unknown disease threats, this is perhaps a good model for other fields to follow. At the Bronx Zoo, this philosophy of expecting the unexpected leads us to perform a necropsy on every animal that dies and to use a variety of techniques to study tissue samples. Before making a final diagnosis, we consider all known possibilities, including diseases in both domestic animals and wildlife, as well as the chance that an unknown agent may be responsible. When our analyses are complete—with, it is hoped, a definitive diagnosis—we "bank" microscope slides of representative sections of every organ. The zoo has accumulated a massive library of samples, some dating to the 1930s, and we now are incorporating the slides on CD-ROM. We also are computerizing a variety of other data from as far back as 1895. In this way, members of the larger veterinarian community will be able to readily share these valuable, often unique, resources.

By taking all of the above steps, every time and in an ordered fashion, we greatly improve our ability to reach a definitive diagnosis of etiology. This approach also adds to the scientific community's knowledge base; enables zoo staff members—and, with the new database, other researchers as well—to carry out powerful retrospective studies; increases the zoological community's ability to detect disease trends; and enables researchers to

more fully detect and define diseases that threaten captive and free-ranging wildlife.

Indeed, the value of this systematic approach to diagnostic pathology was demonstrated during the 1999 emergence of West Nile virus in birds, and ultimately in humans, in New York. The Bronx Zoo played a major role in identifying the virus, which had never before been detected in the United States. In this effort, members of the zoo's pathology department worked with several other researchers, including another veterinary pathologist and a virologist, as well as with a variety of local, state, and federal organizations, including the Centers for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).

Several observations emerged from this experience. First, although the West Nile outbreak highlighted the need for expanded disease surveillance, there is doubt about who will be responsible for such effort. In the medical community today, many unexplained deaths are not being subjected to rigorous pathology studies. In more than 31 states, local officials, many of them not skilled in the latest techniques in diagnostic pathology, perform postmortems. Second, zoos can be important in disease surveillance. This will require more zoos to add a veterinary pathologist to their staff, as well as to train their staff members in how to carry out such studies and how to take necessary safety precautions. Third, the nation has no Biosafety Level-4 laboratories devoted to veterinary research, a situation that can impede the process of identifying unknown pathogens.

Perhaps the most fundamental need is for improved collaboration and cooperation among government agencies at all levels—local, state, and federal. When our zoo's staff first began investigating the disease outbreak that ultimately would be linked to West Nile virus, scientific exchanges were relatively free. But as more organizations and people became involved—and, ironically, as the magnitude of the problem escalated—the situation degenerated: some states seemed unwilling to work with other states or with federal agencies; some organizations did not seem willing to work with other organizations. In remedying this situation, the CDC's new program to provide states with funding to develop strategies and capabilities to cope with bioterrorism may provide a model. In particular, Montana, North Dakota, and South Dakota have developed what appears to be an effective regional surveillance system that integrates both veterinary and human public health. Lessons from their experience may help as the nation seeks to improve its ability to detect, prevent, and control zoonotic diseases.

MOLECULAR AND OTHER TECHNOLOGIES FOR RAPID DIAGNOSIS OF ZOONOTIC AGENTS

Alfred D. Steinberg, M.D.

Consulting Physician-Scientist, MITRETEK

In recent years a number of previously uncharacterized or unknown diseases have affected humans in various regions of the world. In addition, diseases previously confined to certain parts of the globe have appeared in new areas. Thus, we have a need to be able to recognize new diseases and to identify their causative agents.

Some successes in this process have included the human immunodeficiency virus (HIV) as a cause of AIDS, *Legionella pneumophila* as the cause of Legionnaires' disease, Nipah virus as the cause of the 1998–99 outbreak of disease in Malaysia, and West Nile virus as the agent of disease emerging in the New York City area in 1999.

The most promising method of assessing new disease involves parallel and multidisciplinary approaches:

Clinical recognition. Some astute individual or group of people recognizes a disorder that is not typical of any known disorder. It may be an atypical presentation for a previously described disease, or it may be a new disease. In order to foster such recognition, it is helpful to educate emergency room physicians, hospital infectious disease experts, and other individuals in the line of battle to the possibility of a new disease or one not previously encountered in the region.

Standard laboratory assessments. An important finding may occur as a result of clinical recognition when special attention is given to laboratory analyses of material from subjects identified as having an unusual presentation or when astute laboratory personnel notice something unexpected in material from a patient(s) not yet considered to have an unusual disorder.

Epidemiology studies. These studies may disclose the geographic region encompassed by the new disorder; the age, gender, and races of susceptible individuals; the immune status of resistant and susceptible individuals; potential vectors or animal hosts; and the incubation period and modes of transmission.

Laboratory tests. When there is evidence of a new and important disease, all possible laboratory tests should be done early in the process. These tests include:

- Microscopy.
- Electron microscopy.

- Culture. Culture everything—all mucosal surfaces, all secretions and excretions, including:
  - Bacteria—both routine and special cultures.
  - Viral cultures.
  - Rickettsial cultures.
- Measurement of antibody titers in host sera.
- Antigen capture assays. Use antibodies to putative agents to identify potential pathogens.
- Nucleic acid amplification (RNA, DNA) by probe hydrolysis PCR or reverse transcriptase PCR and use of chip arrays.
- Mass spectrometry.
- Genetic analyses—prions, etc.
- Inoculation of test animals.

A few additional issues of importance:

1. *Host range of pathogen.* A pathogen that once infected only dogs or swine or cats but now causes life-threatening disease in humans.
2. *Change in tissue tropism.* A virus that previously caused only mild enteritis now causes severe encephalitis or severe myocarditis.
3. *Immune avoidance.* Large DNA viruses, such as orthopox viruses, have many genes that serve to avoid or subvert the host's immune system. Mutations in these genes have the potential to change the host range of the virus. Even smaller viruses, including RNA viruses, may jump species as a result of mutations. And some RNA viruses, such as Rift Valley fever virus, are segmented and can recombine so as to produce new variants that evade the immune systems of both humans and animal reservoirs.
4. *Human actions on the environment.* Such actions include building roads through the jungle and the movement of animals or vectors.
5. *Zoonoses not requiring a vector.* For example, in the case of hantavirus Sin Nombre, the virus persists in deer mice for months despite antibodies and is transmitted to humans when they inhale virus-containing excretions from the deer mice.

A few comments on laboratory tests:

1. For viruses especially, typing sera may determine that a pathogen is in a particular virus group or family even if the specific virus is previously unknown. A polyclonal antibody reagent is far more likely to cross-react and identify an unknown than is a monoclonal typing reagent. Such relatedness helped in the diagnosis of Nipah virus in Malaysia (the new virus reacted strongly with antisera to Hendra virus but not to antisera against

other paramyxoviruses) and of West Nile virus in New York City (the virus reacted with antisera to other flaviviruses).

2. Electron microscopy may point to a specific type of virus (e.g., size, shape, enveloped versus nonenveloped).

3. Mass spectrometry is a relatively new and emerging technology for identifying bacteria and viruses. Each molecule of the organism is measured in terms of mass. As libraries of patterns for various organisms become available, mass spectrometry will become a more and more powerful analytical tool for pathogen identification.

4. PCR reactions can use primers that will amplify even distantly related members of a virus family. PCR can be coupled with sequencing of the amplicons to provide additional information on relatedness to known viruses.

In summary, a systematic approach to analysis of specimens from individuals suspected of having a novel zoonosis will facilitate pathogen identification. The higher the index of suspicion early on in the outbreak, the greater the likelihood of identifying the pathogen in time for suitable public health measures.

METHODS AND MODELS FOR PATHOGEN DISCOVERY

W. Ian Lipkin, M.D.

Louise Turner Arnold Professor of Neuroscience,
Director, Emerging Diseases Laboratory
University of California-Irvine
Director, Laboratory for Immunopathogenesis
and Infectious Diseases, and
Director, Center for Developmental Neuroscience
Mailman School of Public Health, Columbia University

Establishing a causal relationship between infection with an infectious agent and a specific chronic disease may be complex. In most acute diseases, the responsible agent is readily implicated because it replicates at high levels in the affected tissue at the time the disease is manifest, morphological changes consistent with infection are evident, and the agent is readily cultured with standard microbiological techniques. Implication of infectious agents in chronic diseases may be confounded because persistence requires restricted gene expression, classical hallmarks of infection are absent, and/or mechanisms of pathogenesis are indirect or subtle. Methods for cloning nucleic acids of microbial pathogens directly from clinical specimens offer new opportunities to investigate microbial associations in chronic

diseases. The power of these methods is that they can succeed where methods for pathogen identification through serology or cultivation may fail due to absence of specific reagents or fastidious requirements for agent replication.

Various methods are employed or proposed for cultivation-independent characterization of infectious agents. These can be broadly segregated into methods based on direct analysis of microbial nucleic acid sequences (e.g., DNA microarrays; consensus polymerase chain reaction, or PCR; representational difference analysis; differential display), direct analysis of microbial protein sequences (e.g., mass spectrophotometry), immunological systems for microbe detection (e.g., expression libraries, phage display), and host response profiling. Over the past decade, the application of molecular pathogen discovery methods resulted in identification of novel agents associated with both acute and chronic diseases, including Borna disease virus, hepatitis C virus, Sin Nombre virus, HHV-6, HHV-8, *Bartonella henselae*, and *Tropherema whippeli*. Despite these achievements and the fact that novel pathogens and new relationships between known pathogens and diseases are dependent on this type of research, few academic scientists pursue work in the field of pathogen discovery. Funding is limited and pathogen discovery projects are high risk. In contrast to hypothesis-driven projects where virtually all outcomes are reportable, pathogen discovery projects may fail to yield meaningful data within the timeframe of a traditional 3- to 5-year fellowship or grant allocation.

Pathogen discovery in central nervous system diseases is particularly challenging. Syndromes may blend, particularly in psychiatry. Thus, associations between infectious agents and diseases may be obscured unless discrete analyses of specific syndromic subsets are performed. Another difficulty is access to clinical material. One cannot readily biopsy brain or spinal cord. It is also difficult to obtain short postmortem interval tissue. Therefore, human materials are frequently not optimal for microbiological or molecular biological studies. Additional potential confounders include the fact that an agent may cause damage through an indirect mechanism without replicating in the tissue showing signs of disease, or it may disappear by the time tissue becomes available for analysis ("hit-and-run" mechanisms for pathogenesis).

Nucleic acid-based methods for pathogen detection can be broadly defined as binary or not. Subtractive cloning methods like representational difference analysis are ideal for examining a homogeneous population such as a tumor or a cell line, or animal models exposed to an environmental factor such as an infectious agent or toxin, where pre- and postadministration comparisons are feasible. They may fail, however, to elucidate polyfactorial disorders in which some individuals may be infected but not show disease or where more than one agent can result in a similar disorder. To

address such nonbinary problems, the investigator needs methods that enable recognition of patterns that may not be uniform in disease and control samples. The approach we have used for such population analyses is based on consensus PCR and the differential display method of Liang and Pardee. Radiolabeled cDNA libraries are prepared by PCR from different nucleic acid populations using specific but arbitrary primers. The libraries are then size fractionated in acrylamide gels or by using capillary electrophoresis. Patterns of amplification products from several individuals with or without disease are displayed in side-by-side comparisons. Those that appear to be specific for the disease are sequenced and used to probe databases to yield a variety of outcomes: identification as known host gene, known pathogen, or something novel. This method has been modified to emphasize virus detection using primers representing viral families.

The first practical test of this method, termed domain-specific differential display, was in the context of the CDC's Unexplained Encephalitis Project, a collaborative network comprised of investigators in New York, California, and Tennessee, as well as investigators at CDC's laboratories in Atlanta. This group has determined that despite use of state-of-the-art microbiological methods, 50 percent to 70 percent of encephalitis is unexplained. In 1999 the New York State Department of Health asked that we examine brain samples from victims of what was then described as a St. Louis encephalitis outbreak, because efforts to isolate virus or viral nucleic acids had been unsuccessful. Within 3 days of receipt, flaviviral sequences were amplified from four of five patients. At approximately the same time, work was pursued with a cultured bird isolate by investigators at CDC's laboratories in Fort Collins, Colorado. The two independent lines of evidence converged on September 24, when the information from our group, based on sequence from human brain, and from the Fort Collins group, based on analysis of a cultured bird isolate, indicated that the New York City outbreak was a zoonosis due to West Nile virus. Neither group initially called the agent West Nile virus. It was called West Nile-like virus by the Fort Collins group. We called it a Kunjin/West Nile-like virus. The Kunjin/West Nile distinction is now moot because Kunjin virus was subsequently classified as a West Nile virus. After the entire viral genome was sequenced, it became apparent that the New York virus was virtually identical to a lineage I West Nile virus isolated from a goose in Israel in 1998.

In contrast to West Nile virus, Borna disease virus, an agent associated with persistent infection, required considerably more effort to isolate, characterize, and implicate in human disease. Our experience in these two systems illustrates the differences in strategy required to investigate the pathogenesis of acute and chronic diseases. Borna disease was originally described as an encephalitis of ungulates in the early 1800s. Nonetheless, interest was modest until immunoreactivity to the virus in subjects with

bipolar disorder was reported in 1985. In response to this finding, after classical methods for isolation had failed, we cloned Bornaviral nucleic acids by subtractive hybridization. We reasoned that introduction of tools based on molecular reagents would rapidly resolve the prevalence of Bornavirus infection and its role in human disease; however, this was not to be the case. Since the first reports of human infection based on nucleic acid studies appeared in 1995, Bornaviruses have been implicated in an improbably long list of disorders, including major depressive disorder, bipolar disorder, panic disorder, multiple sclerosis, amyotrophic lateral sclerosis, schizophrenia, and chronic fatigue syndrome. Most of these reports are based on nested PCR, a sensitive method, yet prone to artifact. Because Bornavirus sequences are highly conserved, it is difficult to recognize contamination of assays with laboratory strains. To address these challenges, the National Institutes of Health is supporting a multicenter project comprised of investigators in North America, Europe, and Asia, wherein samples are collected from subjects and yoked case controls following standardized interviews, encoded, and shipped to a central site for blinded analysis using automated molecular and serological methods. The structure of this study provides a model for research into the pathogenesis and epidemiology of chronic infectious diseases.

The future of microbial epidemiology in public health and clinical medicine depends on development of new tools for rapid, sensitive, molecular detection of infectious agents. Toward this end, we are establishing software programs to facilitate automated retrieval, filtration, and curation of microbial sequences from databases. In turn, these bioinformatics data will be used to design hybridization reagents and optimize methods for signal amplification. Beyond the differential display and real-time PCR methods described above, we are now emphasizing higher throughput strategies, including DNA microarrays and multiplexed, bead-based, flow cytometric assays. The application of these types of technologies to acute diseases will be straightforward. More challenging will be investigation of chronic illnesses, such as neoplastic, rheumatologic, and neuropsychiatric disorders, where host genetic context, toxins, nutritional status, and timing of exposure to an agent (e.g., multiple sclerosis or schizophrenia) may influence expression of disease. A key resource in the success of such research will be large banks of well-characterized clinical materials collected prospectively over the lifespan. Equally important will be an openness within the biomedical community to invest in new concepts in microbial pathogenesis.

VACCINES FOR EMERGING ZOONOSES: MARBURG VIRUS PARADIGM

Alan L. Schmaljohn, Ph.D.*

Chief, Department of Viral Pathogenesis and Immunology
Virology Division
U.S. Army Medical Research Institute of Infectious Diseases

A well-educated immune system is the body's last and best defense against viral disease, and vaccines were almost singularly responsible for reducing the impact of many human viruses in the United States during the 20th century. However, the complete cycle of vaccine development and licensure is time-consuming and relatively expensive: one published estimate cites 10 to 18 years and $30 million to $100 million per vaccine, when success proves achievable at all; other estimates are higher. The time and cost are expected to be reduced if unambiguous precedents for scientific rationale, safety, manufacture, potency testing, and assessment of efficacy have been established with one or more closely related agents. For the total array of emerging viral zoonoses, the stockpiling of licensed vaccines is scientifically daunting, a controversial use of resources, and likely unrealistic politically.

Marburg virus (MBGV) provides an archetype that is useful in considering many of the issues involved in the development of vaccines for emerging viruses, including viral zoonoses.

The first issue regarding development of any vaccine is determining actual need. For MBGV the answer emerges from a series of questions. First, is the virus currently a major global health problem? No. While there is an ongoing outbreak with high mortality rates in the Democratic Republic of Congo, other outbreaks have been localized, sporadic, and of low global impact. Second, does MBGV have significant potential for mutation to pandemic spread? Unknown. Human-to-human spread occurs but has proven self-limiting to date. Third, does MBGV have potential for import and establishment in new ecological niches, including disruption of agriculture? Unknown. The virus's host species has not been identified, and domestic species have not been tested. Fourth, does MBGV pose a risk to laboratory and health care workers? Yes, but the number of people at risk is relatively small, and risk can be minimized by safe laboratory procedures

*Opinions and statements made herein are solely those of the author and are not to be construed as official USAMRIID or Department of Defense positions or policy unless supported as such by separate documentation.

and appropriate barrier medical care. Fifth, is MBGV a potential strategic, tactical, or terrorist weapon? Yes. The virus is highly infectious and stable in aerosol form, causes a terrifying disease with high morbidity and mortality rates, can be readily grown using low-tech methods, and exhibits significant if ultimately limited human-to-human spread. Sixth, are there any known therapies or alternatives to vaccine? No, none that have proven effective in nonhuman primates against either MBGV or Ebola viruses; state-of-the-art palliative care may reduce mortality rates. And seventh, what is the cost of ignoring the risk altogether, deprioritizing even the discovery phase of vaccine development that could establish a rationale and seed source for manufacture of an efficacious vaccine? Incalculable. The fifth question and the seventh question, along with published reports that MBGV has already been weaponized, are sufficient for the Department of Defense to seek countermeasures. Responsibility for developing such countermeasures, including a vaccine, naturally falls to USAMRIID.

In 1995, USAMRIID began to determine the requirements for a safe and efficacious MBGV vaccine. We anticipated a number of problems. First, because of its high human mortality rate and known aerosol infectivity, MBGV is restricted to Biosafety Level 4 laboratories; this automatically restricts the sites in which live virus research can be conducted and increases the overall time and expense. Second, there was a paucity of baseline scientific information to guide vaccine development: protective antigens had not been identified, the nature of protective immunity was almost completely unknown, a nonhuman primate model of viral disease was incompletely understood and a guinea pig model incompletely developed, and prior reports of classical (formalin-inactivated) vaccine formulations had failed to protect more than half of animals. Third, an MBGV vaccine should protect against all routes of infection, including aerosol infection, since this is a potential route of infection in both laboratories and hospitals, as well as an obvious risk with intentionally released virus. Fourth, MBGV is a single virus only in a taxonomic sense: it actually is a constellation of antigenically distinct viruses, all highly pathogenic, and a vaccine should be efficacious against all. Fifth, related to the sparse understanding of immunity, there were no established predictors or correlates of immune status. Sixth, due to the unpredictability of outbreaks and the severity of disease, it will be either impossible or unethical to test any vaccine's efficacy in humans in a placebo-controlled fashion; this means that licensure must ultimately proceed under new guidelines issued by the Food and Drug Administration for such circumstances.

While the problems are formidable, a number of factors also favor successful vaccine development. First, this is a transitional period in vaccine technology, with several new strategies and platforms available to the vaccinologist. Second, it has been relatively easy to establish two animal

models, guinea pigs and nonhuman primates, in which viral disease not only approaches 100 percent lethality within 14 days but also resembles human disease. Third, there is a relatively solid mandate and funding in an institute that has the research expertise and vaccine pragmatism to discover and develop a vaccine. Fourth, as a not-for-profit venture, there are relatively few inherent biases that necessarily exclude any promising vaccine approaches.

Given the paucity of previous information on the subject, these new efforts provided a rationale and a logical need to look simultaneously at several possible vaccine approaches, ranging from the classical to the most newly available. This provided a limited opportunity for direct comparison of several approaches against a single agent. To discern further the relative merits of different vaccine approaches, we examined the capacity of each prototypical vaccine to protect guinea pigs not only against subcutaneous infection but also against aerosol infection.

Classical Viral Vaccines

Classical viral vaccines have exploited either killed viruses as immunogens or live but relatively benign "attenuated" versions of the virus. For MBGV, the efficacy of using killed viruses was in doubt: tests had shown that inactivated MBGV protected only about 40 percent of guinea pigs and 50 percent of nonhuman primates, an observation consistent with the dubious efficacy of killed Ebola virus vaccines. Taking a somewhat different approach to using killed viruses, we recently showed that purified, irradiated MBGV administered in adjuvant (an additive intended to potentiate immune responses) could evoke solid immunity in small numbers of guinea pigs. However, the immune response to killed viruses may well be qualitatively different and possibly inferior to that elicited by live virus infection. Thus, while it seems highly unlikely that a live-attenuated MBGV vaccine could be proven acceptable for human use, it is useful for experimental purposes to test whether such a vaccine might elicit a qualitatively superior form of immunity. To this end, we have obtained a derivative of MBGV that causes viremia but no overt disease or deaths over a wide range of doses in one particular strain of guinea pigs, providing a useful virus with which to immunize animals and confer a "natural" form of immunity.

Baculovirus Recombinant, Soluble Envelope Antigen

Only a single MBGV antigen, the glycoprotein (GP), is known to reside on the exterior of virions and the surfaces of MBGV-infected cells. We used a variety of recombinant DNA methods to produce GP and other antigens of MBGV to test as vaccines. In tests with guinea pigs, soluble GP antigen,

made by a recombinant insect virus in insect cells, could immunize most of the animals against lethal subcutaneous infection, though some 20 percent of the animals remained unprotected. This observation became the basis for testing GP as a protective antigen that could be delivered via either of two new alternative vaccine approaches: DNA immunization or packaged RNA replicon.

DNA Vaccines

DNA immunization involves the delivery into animals of DNA that contains genes for foreign antigens, uptake of the genetic material into cells and their nuclei, and expression of the vaccine antigen in much the same manner that other cell proteins are made (that is, DNA makes RNA makes protein). In our work with the MBGV glycoprotein, we chose as our leading approach and benchmark the "gene gun"—that is, delivery of genes into skin cells ballistically, on gold microspheres. Our experience, as well as a variety of other published results, has confirmed this approach to represent fairly the potency of this antigen delivery method. This is a relatively new technology that is in a state of continual improvement.

RNA Vaccines

Using the same GP antigen gene as for the DNA immunization, this approach bypasses the DNA requirement by reshaping a virus that consists of RNA and copies itself and its proteins in a wholly RNA mode (thus, RNA makes RNA makes protein). We have focused on a molecule of RNA, called an RNA replicon, derived from the virus that causes Venezuelan equine encephalitis (VEE). In brief, this RNA replicon directs synthesis of its own polymerase within the cytoplasm of cells, replicates itself in a single cell, and produces abundant quantities of a second RNA that, in turn, produces the MBGV glycoprotein. For delivery as a vaccine, the replicon is provided the coat proteins of VEE so that the RNA can easily enter cells; however, since the genes for the VEE coat are not packaged, the replicon particles can infect only one set of cells, produce MBGV antigen, and spread no farther.

Our studies suggest that genetic approaches—DNA vaccines and replicon-based vaccines among them—are particularly attractive, for several reasons. Such vaccines avoid the production biohazard and safety issues of both the classical killed and lived attenuated vaccines. Safety, production, and quality assurance issues, once optimized for a single vaccine, are expected to be highly similar for each succeeding vaccine that uses the same technology. The vaccines focus the immune system's attention on one or more important antigens, thus avoiding incorporation of superfluous or

even harmful antigens. They express antigen via host cellular pathways and thus effectively elicit several types of immune system response, including both the production of T cells and antibodies. They are theoretically amenable to simultaneous delivery of vaccines to multiple unrelated pathogens. If insufficiently potent on their own, the vaccines may provide immunological priming that improves the performance of a "boosting" antigen.

Despite major conceptual breakthroughs and proofs of vaccine feasibility that we have published recently on the above approaches, much remains to be done in bringing a safe and effective MBGV vaccine to fruition. There are questions, for example, about the basic formulation of the ultimate vaccine (precisely which antigens should be used?), about immunology (what markers predict efficacy?), and about the optimum delivery system (the RNA replicon is the leading candidate because of its impressive protection of nonhuman primates, but it is not the certain winner). There also remain important unresolved issues regarding development of the manufacturing process (how can production best be scaled up?), and numerous regulatory requirements will have to be satisfied before a new vaccine can enter general use.

Based on this work in developing a Marburg virus vaccine, combined with lessons emerging from work on other vaccines, a number of needs stand out if the nation is to move ahead in preparing to deal with zoonotic diseases:

- Public support is needed, and this should be rooted in science education. Education focused on emerging viruses and viral zoonoses is critical and should be expanded. An alarmed but poorly informed Congress, responding to an alarmed but poorly informed public, will rarely if ever craft anything but an inefficient emergency response.
- Broad support of vaccine discovery efforts is crucial. The threat of emerging zoonoses will be reduced if there is preexisting knowledge of the antigens required in a vaccine and of the immune responses to be elicited. A cadre of experts in these diseases cannot be maintained, nor steady progress made in vaccine development, without consistent support. In an emergency, the experiments to obtain such answers cannot be done more quickly than a succession of vaccine regimens and viral incubation periods, results could be unexpected, and the delay could be catastrophic.
- Emphasize vaccinology, and reward basic research efforts that team to make actual vaccine progress. The National Institute of Allergy and Infectious Diseases took a significant step in this direction in 1999 by requesting applications for "Vaccine Immunology Basic Research Centers." However, this is a relatively modest initiative, and its emphasis is on vaccine immunology and high-impact human diseases, not on emerging or zoonotic diseases.

- Set priorities for vaccine manufacture. The lengthy process of advanced vaccine development and licensure should be reserved for agents for which vaccines are thought to be needed within the next several years. For other agents, secure the scientific underpinnings. The antigen requirements of a modern vaccine will remain relatively unchanged once discovered and well defined, as will the phenotype of a protective immune response. However, the optimal vaccine platforms by which such antigens will be constructed and delivered may change almost as rapidly as computer hardware.

5

Surveillance and Management of Zoonotic Disease Outbreaks

PUBLIC HEALTH LABORATORY SURVEILLANCE

Mary J. R. Gilchrist, Ph.D.

Director, University Hygienic Laboratory, University of Iowa

Public health laboratories traditionally have conducted surveillance for critical infectious diseases, such as influenza, rabies in animals, and arboviruses. As new infectious diseases emerge and older ones alter their patterns of distribution, these laboratories may have to employ new strategies and tactics for disease surveillance.

One lesson is clear: surveillance strategies must be sufficiently flexible to adapt to the circumstances that we recognize as a disease emerges. With zoonoses, the emergence may be complete before detectable disease occurs in humans. This provides an opportunity to anticipate disease in a population and prevent its appearance by implementing appropriate control measures. The ecosystems are complex, however, and we must adapt our surveillance strategies as we learn more about the pathogens, their vectors, and the reservoirs. Temporal and spatial relationships should cause us to change our strategies as the disease advances. Different strategies should apply in areas where emergence is complete than in areas where disease is emerging or yet unknown.

It also will be imperative to devise adequate financial means to support surveillance programs. Unfortunately, waning public interest in a disease

during a quiescent period often leads to reduction in political, and hence financial, support for surveillance activities. Ironically, it is during these quiescent periods that surveillance would best be conducted, to detect the appearance of an infectious agent in environmental reservoirs and eradicate the agent before it infects humans. When surveillance is abandoned, an outbreak of human disease may be well under way before it is detected.

Of course, surveillance is of little use if not shared with other groups or individuals who can act on the information to prevent or diagnose disease. In Iowa, for example, the University Hygienic Laboratory has posted influenza surveillance data on its web site (www.uhl.uiowa.edu/HealthIssues/index.html) for the past several flu seasons. Data are updated automatically each night. Anyone wanting to know which viruses are circulating in their area can easily view a table that shows numbers of Influenza A and B detected during the current week, the past week, or all year. This information may influence a decision to administer prophylactic or therapeutic drugs or to control exposures. The web site also provides the latest data on a variety of other diseases, including some zoonoses. Sharing data with those who participate in its reporting and accumulation will encourage timely reporting and dialogue between the private and public health care communities.

In our efforts to improve surveillance for zoonotic agents, we can learn much by analyzing current programs, such as the Centers for Disease Control and Prevention (CDC)'s Emerging Infections Program and its Epidemiology and Laboratory Capacity Program. In addition, examining some of the diseases that public health laboratories now face may help to illustrate some possible new approaches to designing surveillance strategies, as well as possible means to sustain them.

Arbovirus Encephalitis

Surveillance for arboviruses in the United States has focused primarily on three types of encephalitis viruses: St. Louis, Western equine, and Eastern equine viruses. One method of surveillance involves trapping mosquitoes, pooling and enumerating individual species, and checking extracts of the pools for the presence of these viruses. This activity is labor intensive and limited in sensitivity by the selection of the location and number of sites for mosquito collection. Another method of surveillance is to use birds, often chickens, as sentinels for the appearance of virus in a region, since the mosquitoes that transmit these viruses preferentially feed on birds. Surveillance can be accomplished by sampling wild birds or by housing chickens outdoors and bleeding them periodically during the summer to monitor for the appearance of antibodies to an encephalitis virus. Seroconversion requires time, however, and may not occur sufficiently early to signal the

introduction of virus in advance of human infections. In some circumstances, tandem sequential surveillance is employed: chicken sentinels, when positive, elicit the institution of mosquito surveillance. In other settings, both arms of surveillance are carried out simultaneously throughout the season.

The Association of Public Health Laboratories conducted a survey to determine which states had been engaged in arbovirus surveillance prior to the summer of 2000, when funding for West Nile virus surveillance reinvigorated many state programs. Surveillance was by no means universal. Roughly 32 percent of states had ongoing programs of both mosquito and chicken surveillance, while an additional 24 percent performed either mosquito or chicken surveillance but not both. (Information was not collected regarding the extent of the programs, so it is not known whether all of these states had sustained fully competent surveillance programs.) Although New York had sustained a modest surveillance program, New York City, where the West Nile virus was first detected in the United States, had no surveillance program. Approximately 40 percent of states had completely abandoned surveillance for arboviruses, presumably because of the reduction in funding during a period of inactivity of arboviruses.

The challenge to public health remains the identification of a means to sustain surveillance programs for arboviruses in periods of relative quiescence. Our experience in Iowa suggests a possible alternative to the on-again, off-again cycle of surveillance, which almost inevitably leads to periodic outbreaks of human disease. Since the major outbreak of arbovirus encephalitis in the Midwest in the 1970s, Iowa has retained a very modest surveillance program. Participants are committed to its operation. An entomologist at Iowa State University trains students in medical entomology to collect and pool mosquitoes by species. Local health departments identify outdoor sites to house flocks of chickens and periodically bleed the chickens. The University Hygienic Laboratory performs the laboratory tests, seeking evidence of arboviruses in mosquitoes and of arboviral antibodies in the chickens. The program costs approximately $50,000 per year, but even at this modest cost it has come under consideration for abandonment. When stakeholders were assembled to address the issue, local health department officials asserted that the program should be retained. They also maintained that they were able to decrease pesticide spraying in areas where negative surveillance results suggested the absence of encephalitis viruses. This reduced spraying may help offset the cost of the surveillance program. Presumably, if the medical consequences of pesticide exposure in humans were also considered as costs of abandoning surveillance, then an intensified surveillance program would be economically justifiable. A medical economist's assessment of these speculations is recommended. Ideally, such an assessment also would model the economic value in saving human lives

and in preventing incapacitating sequelae that often follow nonfatal cases of arbovirus encephalitis and may require the individual to receive institutional care for life.

In some locations, however, outbreaks of human arbovirus disease have precipitated the introduction of massive surveillance programs that could not be sustained in the subsequent quiescent period and were thus abandoned completely. Such a cycle might best be blunted by programmed contraction from a control mode to a sentinel mode when the outbreak has subsided. Modeling of ideal programs might specify such blunted cycles and suggest means to tailor them to conditions in different parts of the country. Our knowledge of the complex arbovirus ecosystem has grown greatly in recent decades, but our approach to surveillance has not been concomitantly adjusted. The West Nile virus outbreak has reunited the public health community with partners in the wildlife, veterinary, and entomology communities. It is time to devise a surveillance strategy involving a cycle of expansion and contraction instead of our historical cycles of engorgement and extinction.

Tickborne Diseases

Several tickborne diseases have emerged over the past several decades, including two *Ehrlichia* diseases known as human monocytic ehrlichiosis (HME) and human granulocytic ehrlichiosis (HGE). HME occurs most often in Missouri, Arkansas, and Oklahoma, but cases have been reported in at least 30 states. HGE is common in Wisconsin and Minnesota, and it occurs sporadically in other regions of the country. Iowa is located next to the two states where HGE is common, yet few cases of the disease are reported in the state. Some observers have suggested that since Iowa is intensely agricultural, with few public lands that might provide habitat for the mammals that serve as reservoirs of disease and as hosts for the ticks, *Ehrlichia* might not have penetrated into the state. However, Iowans converge each summer on public lands in Minnesota, Wisconsin, and Missouri. Thus, the infrequent, or absent, reports of human disease in Iowa cannot account for all the disease that must occur in its citizens who regularly travel to these states for recreation.

One explanation for this suspected underreporting is that clinicians and citizens may not be alert to the possibility of encountering human ehrlichiosis, even among travelers to recognized endemic areas. To help determine whether HGE may be more prevalent than reported, the University Hygienic Laboratory and the Iowa Department of Public Health performed surveillance of human serum samples that were collected and submitted during tick season to be analyzed for some other disease. These tests found numerous instances in which serum was positive for HGE, with

other samples proving positive for HME or Lyme disease. When the results were reported to the patients' clinicians, a common response was, "What is ehrlichiosis?" It is apparent that these diseases are underrecognized in Iowa.

How should surveillance for tickborne diseases be conducted? For Iowa, some insight can be gained by looking at the results of how disease-carrying ticks are moving through the state. The University Hygienic Laboratory has examined blood taken from some 2,000 deer killed by hunters, testing the samples for antibodies to HME. Counties where positive samples occurred proved to be contiguous with the Missouri and Mississippi rivers, as well as with many of their tributaries. It appears that the hosts and reservoirs for the disease have moved northward into Iowa from Missouri along the riverbanks, where there is more cover than in farm fields.

In general, tickborne diseases most often spread at a leading edge (in contrast with arboviruses, which often are spread to remote areas by birds). By using ground warfare and air warfare, respectively, as analogous phenomena, it is easy to understand why different surveillance strategies are necessary for these different modes of spread. Birds that fly into an area unexpectedly bring arboviruses in a manner not unlike bombers in air warfare. With ticks, the surveillance strategy must be tailored to the mode of contiguous spread in a manner that is not unlike the front lines in ground warfare. In areas where there is widespread recognition of emergence of a tickborne disease, activities might focus more on control of the vector and education of the citizens. In adjacent areas where disease is not yet recognized, surveillance might be focused on detecting initial appearance and tracking ultimate distribution of vectors and agents. In areas remote from the emerging margins of infection, human surveillance would be the focus, to identify disease in those individuals who had traveled to endemic areas or who were victims of unexpected introductions, as, for example, from ticks on hunting dogs brought into the area. As with arboviruses, the proposed surveillance strategy for tickborne diseases should be tailored to the cycle of emergence and the region of the country, and the strategy should be altered if there is a change in circumstances. Maintaining a system that does not change with changing conditions likely will be futile.

Rabies in Animals

Rabies virus in animals has long been the subject of surveillance. In cases where humans have been exposed to a suspect animal, detection of the virus also is used to guide decisions about prophylaxis with immune globulin and vaccine. Surveillance of rabies enables officials to track and attempt to prevent the dispersal of infected animals, as is happening with the current spread of rabies among raccoons. Surveillance focused on silver-haired bats also has intensified in recent years, since it became known that

these bats might be responsible for transmitting rabies in cases where there was no other known bite exposure. Laboratories doing such surveillance should be encouraged to record the species of bat as well as its rabies virus status; laboratory personnel can receive training in speciation of bats from a local wildlife expert.

Of concern to the medical community is the accurate determination of the rabies status of each animal for which a human exposure has been documented. Unfortunately, the federal Clinical Laboratory Improvement Act (CLIA) provides rules for testing human clinical specimens but not rules for animal specimens, even when such test results may affect human therapy and outcome. The government should expand CLIA coverage to include testing of animal specimens when it impacts on treatment of humans. The government also should require laboratories performing rabies tests on animals involved in human exposures to enroll in proficiency testing and quality assurance programs equivalent to those used to license laboratories that test human clinical specimens. The adverse consequences of poor testing are grave: false negative tests may produce fatal human disease because prophylaxis would not be administered, while false positive tests may lead to excessive use of expensive interventions and to a general loss of confidence in the tests.

Hantavirus Pulmonary Syndrome

First detected in the U.S. Southwest in the early 1990s, hanta-virus pulmonary syndrome, which is transmitted to humans by rodents, has since been found throughout the Americas. In the United States, most states in the West, Midwest, and mid-Atlantic regions have recognized one or several cases, while most states in the Southeast and New England remain untouched. Until the past 3 years, most midwestern states had few or no reported cases. In Iowa, following the first reported case, extensive surveillance of rodents in the implicated exposure area did not yield evidence of a reservoir of disease. It remains to be proven whether surveillance can anticipate and prevent disease, and under what circumstances surveillance might be efficacious. Meaningful surveillance protocols should be developed in a research mode and evaluated for their ability to anticipate and prevent human disease. Unless proven to be efficacious, surveillance of animals should not be instituted on a routine prospective basis. Instead, good surveillance of human populations, augmented with excellent prevention education programs, would be the primary undertaking.

Traditional Zoonoses

Traditional zoonoses include such diseases as anthrax, plague, tularemia, and brucellosis. The agents that cause these diseases are currently considered prime candidates for deployment in bioterrorism and biowarfare. Recent attention to the potential for such activities in the United States has led the government to institute the Laboratory Response Network, sponsored by the CDC and managed by the Association of Public Health Laboratories, to enhance the detection of these agents in humans. As part of this nationwide program, personnel in laboratories that test clinical specimens from humans will receive training in the means to rule out these agents, as well as in how to forward the isolates to public health laboratories for specific identification and subsequent molecular fingerprinting. By providing a link between public and private laboratories, this network will increase the nation's capacity to detect and prevent the spread of zoonoses, whether they are transmitted naturally or intentionally.

New Zoonotic Challenges

A variety of agents of zoonoses have emerged or reemerged during the past several years, including *Campylobacter*, *E. coli* O157:H7, *Cryptosporidium*, and antibiotic-resistant bacteria from animal origin. The current practices used to detect and control these agents are suboptimal, for a variety of reasons. Some laboratories have been slow to adopt routine methods for detecting these agents. Moreover, in some managed care settings, tests are done that may detect evidence of a toxin but not yield an isolate of the organism that produces the toxin. Unfortunately, the origin of the organism cannot be tracked without the isolate. As a result, the foodstuff that is the source of the infections cannot be identified, which means that other individuals may continue to ingest the foodborne organisms and succumb to the disease. One way to help rectify these circumstances would be for the government to specify expectations of clinicians and laboratories in the private health care setting. For example, it would be useful to clarify what circumstances dictate the performance of a culture and submission of the isolate to a public health laboratory. To help increase participation by private managed care organizations, the government, perhaps through the Health Care Financing Administration (HCFA), may at first need to offer some type of incentive. Adjustments in both reimbursement policies and quality indicator requirements are candidate incentives that HCFA might entertain.

CHALLENGES OF VECTORBORNE DISEASE SURVEILLANCE FROM THE LOCAL PERSPECTIVE: WEST NILE VIRUS EXPERIENCE

Marcelle C. Layton, M.D.

Assistant Commissioner, Bureau of Communicable Diseases
New York City Department of Health

New York City's Communicable Disease Program investigates 52 different human infectious diseases and conditions that are mandated to be reported by physicians, hospitals, and laboratories. We handle between 70,000 and 90,000 case reports annually. However, since our General Communicable Disease Unit has only four field staff members, we are not able to investigate each of these cases fully with a medical record review and/or patient interview. This means we have to prioritize our investigations to focus on the diseases of current public health concern.

For all diseases, our standard practice is to examine routine demographic data, geographic location, and the time of infection, in order to determine whether there is an increase or clustering of disease that requires further investigation. We process our data weekly to ensure rapid recognition of outbreaks. For certain diseases, we assign all case reports for further investigation; this will include reviewing a patient's medical charts and conducting in-person interviews to look at risk factors for infection and the clinical spectrum of illness. Prior to the recognition of the West Nile outbreak in New York City in 1999, viral encephalitis cases were not prioritized for more detailed case investigations, so there was no active follow-up to ensure that full viral laboratory testing was completed, and thus the specific viral etiology for most cases remained unknown.

In recent years the city has faced several outbreaks of zoonotic and vectorborne diseases. In addition to the outbreak of West Nile encephalitis, these outbreaks have included a cluster of locally acquired malaria cases in Queens in 1993, the reintroduction of raccoon rabies in 1992, a foci of Rocky Mountain spotted fever in the South Bronx, and the spread of Lyme disease into areas at the city's borders from adjacent jurisdictions where Lyme disease has been endemic for years (e.g., Westchester County).

Prior to the West Nile outbreak, the bureau's surveillance system for vectorborne and zoonotic diseases was primarily passive (with the exception of our active laboratory-based surveillance program for malaria that was instituted in response to the 1993 outbreak). Thus, cases come to our attention only when reported by a laboratory or clinician, generally by telephone, telefax, or regular mail. Like most other cities, New York City did not have a formal infrastructure for monitoring diseases in the animal

kingdom. The only animal disease that veterinarians are required to report is rabies. At one time, we did have a mosquito surveillance and control program, but its funding was discontinued in 1988. We do conduct limited tick surveillance, focused primarily on areas of the city that are at high risk for Rocky Mountain spotted fever and Lyme disease. The bureau's laboratory capacity to investigate arboviral and other vectorborne diseases also was quite limited, and in most cases we sent specimens that needed analysis to another reference laboratory, either at the state level or to the federal CDC.

Because the bureau must rely on passive surveillance, the role of physicians is especially important, especially for diseases, such as encephalitis, where the diagnosis is usually based on a constellation of clinical findings, as opposed to a positive laboratory test. An astute clinician who reports something unusual may be our first indication of a citywide trend. Indeed, this is what happened on August 23, 1999, when a physician called to report two cases of an unusual neurologic disease. Her initial concern was that at least one of the patients might have botulism, as suggested by the presence of severe muscle weakness. Based on the clinical and laboratory evidence, however, we determined that botulism was unlikely. Rather, some of the symptoms (e.g., fever, altered mental status, and an inflamed spinal fluid) suggested that a viral encephalitis infection might be the cause of illness. Thus, we recommended that the physician send appropriate clinical specimens to the state laboratory for additional tests. We also stayed in touch with the physician, and we sent staff out to further investigate these cases. Four days later, on a Friday, the physician called to report that another patient with similar symptoms had been admitted to her hospital, and that by now all three cases had developed muscle paralysis—and in the middle of this call, a neurologist colleague entered her office and reported to us that he was treating a similar case at another hospital nearby.

So, by the end of this telephone call we were aware of four cases of viral encephalitis—all associated with severe muscle weakness, all clustered in one small area of the city, and all occurring during a 1-week period. In a typical year, we usually receive reports on only nine encephalitis cases citywide. Faced with what appeared to be an unusual outbreak, our staff spent the weekend at the two hospitals, investigating these cases. We also began some active case-finding efforts at other nearby hospitals. By Sunday morning, we had identified a total of eight suspected cases. Of particular concern, the cases were nearly identical—all in healthy older adults who lived at home; all with similar symptoms, including fever, confusion, and severe diffuse muscle weakness; and all living in close proximity to each other.

Our investigation focused on the possibility of two types of viral encephalitis that can occur in clusters in the summertime: one caused by an

enterovirus (which is transmitted from person to person and is known to be common in New York City during the late summer months, although primarily among children), and the other by an arbovirus (which is transmitted to humans by arthropods, although there had been no reports of arboviral disease in the city in more than 100 years and there had been no recognized arboviral activity in the Northeast that summer). Based on extensive interviews with the patients' families, we determined that the only thing that linked the patients in time and place was that they all spent time outdoors in their backyards or neighborhoods, especially in the evening hours.

That same weekend we consulted with enteroviral and arboviral experts at CDC, and everyone agreed that the general facts of these cases—the predominant finding of severe muscle weakness, the older age range, and the absence of prior or nearby arboviral activity in the New York City area—were not typical for either family of viruses. So, we continued to prioritize getting clinical specimens to the state laboratory to help determine the specific diagnosis. On Monday morning, we began extensive case-finding citywide. We broadcast a fax alert to several departments in all 70 city hospitals, asking the staff to report any similar cases, and we began calling physicians citywide who specialized in infectious diseases and neurology to determine if they were aware of additional cases. As the week unfolded, we learned of nearly 40 suspected cases throughout the city.

Because arboviruses were a possibility, we sent a communicable disease team that included an entomologist to do an assessment of where these patients lived. (Since the bureau did not have an entomologist on staff, we borrowed one from the American Museum of Natural History.) Based on the findings of significant larval and adult mosquito activity in the neighborhood of these patients, the team became more convinced that the suspect virus was being transmitted to humans by mosquitoes.

Soon, the state laboratory issued the results of its analysis, preliminarily identifying the disease as St. Louis encephalitis (SLE). CDC then reported that its results using a nonspecific immunoassay test were also most consistent with SLE, based on the clinical and epidemiologic findings. This was on the Friday afternoon before Labor Day weekend. The city's health department immediately launched a mosquito control program, at first in the neighborhoods in northern Queens where the initial cases were concentrated. This was no small task, since the city lacked an existing infrastructure for such programs. We also continued active surveillance, and as we identified more cases in other parts of the city, we expanded mosquito control citywide. We sprayed pesticide by air and on the ground; we applied larvicide extensively in locations that had standing water where mosquitoes could breed; and we implemented an extensive multimedia educational campaign to inform the public about the outbreak and the need for

mosquito control precautions, as well as to address concerns about exposure to the pesticides being used. This effort required extensive communication and coordination among a number of agencies at the local level, as well as with state and federal agencies. Indeed, as the outbreak unfolded and was recognized to involve jurisdictions throughout the greater New York City metropolitan area, the number of agencies involved grew considerably.

As it turned out, the cause of this outbreak was West Nile virus, a flavivirus closely related to SLE, but one that had never before been identified in the Western Hemisphere. By the time West Nile virus was recognized, more than a month after the initial outbreak, all necessary mosquito control measures had been implemented and the outbreak was essentially over. It is important to note that the identification of West Nile virus was due, in part, to observations during this period by veterinarians that a large bird die-off was occurring, especially among crows. Two independent investigations, by the veterinary pathologist at the Bronx Zoo and by the wildlife biologist at the New York State Department of Environmental Conservation, found pathologic evidence of widespread viral inflammation, including encephalitis, among dead birds found in the greater New York City area. Avian tissues were submitted for viral testing, and a flavivirus was isolated that was subsequently determined by CDC to be West Nile virus.

In all, there were 62 persons diagnosed with West Nile virus in the greater New York City metropolitan area, including 59 patients who required hospitalization and seven who died. West Nile viral activity in birds involved a much larger geographic area, with infected dead birds found in areas where no human cases were detected, including eastern Long Island; the lower Hudson Valley; eastern New Jersey; southern Connecticut; and Baltimore, Maryland. Although thousands of birds were estimated to have died from West Nile virus in 1999, with over 23 species affected, the highest percentage of avian fatalities (88 percent) occurred among crows.

Concerned that the West Nile virus might return the following year, we conducted surveillance during the winter, looking for evidence of West Nile viral infection among overwintering mosquitoes hibernating underground. We did find evidence of infected overwintering mosquitoes in northern Queens, the epicenter of the 1999 outbreak. In addition, in February a dead bird (thought to be nonmigratory) discovered in Westchester County tested positive for the virus. Based on such evidence, local, state, and federal agencies mounted an aggressive surveillance and control plan throughout the northeastern United States for the 2000 summer mosquito season.

In New York City we implemented a program to eliminate mosquito breeding sites on city property; this effort included putting larvicide in every one of the city's 150,000 storm sewer drains and all sewage treatment sites. We also encouraged private citizens to eliminate breeding sites near their

homes. In addition, we developed several types of surveillance programs—including monitoring "sentinel" chickens, reports of dead and infected birds, larval and adult mosquito activity, and human cases of meningoencephalitis cases—to determine whether West Nile virus would re-emerge in 2000 and to track its spread in the city.

Among the lessons learned from this outbreak, perhaps the most important is the need to expand and maintain strong relationships among a variety of professional and public communities, including the medical and public health communities, the veterinary and wildlife communities, the entomology community, and the emergency management community. For example, the local public health community was unaware that the scientists at the state wildlife agency and the Bronx Zoo had found that birds in the city were dying of viral encephalitis until a month after the human outbreak was first recognized. We later learned, by reviewing newspaper reports, that crows had been dying at least 6 weeks before the first human cases were reported. Therefore, had the avian outbreak been recognized and investigated earlier, it is possible that the presence of West Nile virus may have been identified prior to the onset of illness among humans, and had mosquito control measures been implemented earlier, it is possible that this outbreak may have been averted.

The experience also reaffirms the power of physician reporting. Again as we later learned, by the time the New York City Department of Health received the first call from the infectious disease physician at the hospital in northern Queens, there were 15 similar cases in city hospitals that had not yet been reported. Had that alert physician not contacted our office, the human outbreak may have been missed completely or its recognition significantly delayed.

The introduction of West Nile virus into New York City in 1999 and the rapid spread of the epizootic throughout much of the northeast by 2000 illustrate how vulnerable we remain to imported disease threats. This outbreak demonstrates the ease with which pathogens can move between continents and infect susceptible humans and animals.

VETERINARY SURVEILLANCE FOR ZOONOTIC DISEASES IN THE UNITED STATES

Randall L. Crom, D.V.M.

Staff Veterinarian, Veterinary Services
Animal and Plant Health Inspection Service
U.S. Department of Agriculture

The U.S. Department of Agriculture's (USDA) Animal and Plant Health

Inspection Service (APHIS)—specifically, Veterinary Services (VS) within APHIS—has responsibility for the aspects of livestock health that have national or international scope or impact. These aspects include preventing the intrusion of foreign livestock pests or diseases through activities at U.S. ports and in foreign countries, detecting and monitoring animal diseases in the United States, carrying out emergency control and eradication operations if foreign pests or diseases enter the United States, and combating certain domestic animal diseases. Because several zoonotic diseases that have large potential public health impact fall within this scope of responsibility, APHIS-VS plays an important role in veterinary public health at the national and international levels.

The nation has both generalized passive surveillance and more targeted active surveillance in place to detect zoonotic diseases among livestock in the United States. Traditionally, the largest component of U.S. veterinary surveillance for zoonotic diseases has been that of the APHIS-VS programs to detect and eradicate bovine brucellosis (*Brucella abortus*) and bovine tuberculosis (*Mycobacterium bovis*). In addition, a number of newer programs have been implemented. These programs are described below. Although the USDA's Food Safety and Inspection Service (FSIS), as well as other agencies, also conducts veterinary surveillance for foodborne zoonotic pathogens, such programs will not be covered.

Zoonoses Surveillance Systems

West Nile Virus

In September 1999, due primarily to the efforts of one veterinary pathologist at a local zoo, it was determined that an outbreak of encephalitis among humans in New York City was related to the deaths of wild birds in the area and of exotic birds at the zoo. Researchers identified the causative organism as West Nile virus (WNV), an arthropodborne flavivirus never before detected in the United States. During that same month, a private veterinarian on Long Island, New York, began seeing multiple cases of equine encephalitis. After exhausting other plausible explanations for the cluster of disease, the practitioner contacted the state veterinarian and requested assistance in reaching a definitive diagnosis. This official, in turn, contacted APHIS-VS to discuss the possibility of the presence of an exotic zoonotic disease.

The state veterinarian accepted an offer from APHIS-VS to help investigate the situation, and a veterinarian trained in recognition of exotic diseases, known as a foreign animal disease diagnostician (FADD), was sent to investigate the most current equine case. Based on the findings of the FADD and further discussions, an Early Response Team (ERT) was dis-

patched to the area. By October 18, the outbreak was confirmed as WNV and the ERT had completed investigations of all known affected premises in the area. Eventually, 25 cases of equine infection with WNV were found, all on Long Island and all with clinical onset between August 26 and October 18. It was also found that at least 38 other horses on Long Island had been infected with WNV but did not develop clinical signs of illness.

This example demonstrates the primary veterinary surveillance system in place to detect exotic, unusual, or previously unknown livestock health problems, including zoonotic diseases. More than 40,000 federally accredited private veterinary practitioners assist APHIS-VS and state animal health authorities in disease detection and control. These private practitioners report cases of unusual livestock disease or patterns of disease that may suggest the presence of a foreign animal disease to the APHIS-VS area veterinarian in charge (AVIC) or to the state veterinarian.

The specially trained FADDs then investigate these cases. More than 300 FADDs are located nationwide. APHIS-VS headquarters tracks the investigations carried out by FADDs, and APHIS National Veterinary Services Laboratories (NVSL) give the highest diagnostic priority to the specimens they submit. The FADDs undergo training that includes, but is not limited to, recognition of "List A" diseases of the Office International des Epizooties (OIE). The most potentially significant zoonoses among List A diseases are Rift Valley fever and highly pathogenic avian influenza.

In the West Nile investigation, APHIS-VS and the state of New York decided to dispatch an ERT in addition to the FADD. These teams are composed of one or more FADDs, along with an epidemiologist, a pathologist, and, as needed, experts in such areas as carcass disposal and the cleaning and disinfection of premises.

A related but less formal system for detecting livestock disease involves private practitioners submitting diagnostic specimens to state or university veterinary diagnostic laboratories (VDLs). These specimens often originate from cases that are difficult to diagnose or are unusual in their presentation but are not initially suspected of being possible exotic animal diseases. Although not a structured surveillance system, this nonetheless is an important way in which zoonotic and other significant disease conditions may be detected. At least 48 states maintain a list of notifiable diseases (most based on OIE's List A) that private practitioners and VDLs are obligated to report. This system is very likely to be the mechanism by which a previously unknown disease would come to the attention of state and national authorities.

Bovine Spongiform Encephalopathy

Bovine spongiform encephalopathy (BSE) was diagnosed in cattle in the

United Kingdom in 1986, but not until 1996 did scientists determine that potentially severe implications for public health were likely to be associated with BSE. Within the next several years, more than 176,000 cases of BSE in cattle had been diagnosed in the United Kingdom. (This number has now grown to more than 178,000 cases.) In the United States, because of the need to assure foreign trading partners and the public that U.S. herds were—and still are—free of BSE, APHIS-VS in 1990 implemented a surveillance system specifically to detect BSE and other transmissible spongiform encephalopathies (TSEs) in cattle. This surveillance program incorporates both active and passive components.

Several agencies, including the FSIS, participate in the active surveillance. APHIS-VS leads this interagency effort, which is targeted at adult animals most likely to be infected. Included among the animals tested are farm cattle with signs of neurologic disease, cattle condemned at slaughter for neurologic reasons, cattle submitted to VDLs and teaching hospitals because of neurologic abnormalities, rabies-negative cattle submitted to public health laboratories, and cattle that are nonambulatory at slaughter ("downer cattle").

More than 60 VDLs and USDA's NVSL examine hundreds of cattle brains collected nationwide each year. Examiners use both histologic examination and immunohistochemistry (IHC). Laboratories began using IHC in 1993 and have since been increasing the percentage of samples tested with that method. The ultimate goal is to evaluate all submissions with IHC. As of April 30, 2000, a total of 10,499 brains had been tested for BSE or other TSEs. (As of March 31, 2001, 12,341 brains had been tested.) Examiners found no evidence of disease, nor did they observe that there had been an increase in the number of neurologic diagnoses or referrals.

Passive surveillance takes advantage of existing sources of information and reporting:

- USDA's FSIS performs antemortem slaughter inspection at all federally inspected slaughter establishments, and inspectors are alert for central nervous system disorders. Any suspect animals are condemned and tested.
- Public health laboratories submit to APHIS-VS samples of animals that had been suspected of having rabies but tested negative.
- The Veterinary Medical Data Base maintained by Purdue University compiles diagnoses, including many neurologic cases, submitted by 27 U.S. veterinary schools.
- Veterinary pathologists at zoos nationwide routinely conduct postmortem examinations on the brains of animals exhibiting neurologic signs.

Avian Influenza

The occurrence of highly pathogenic avian influenza (H5N2) in Mexico in 1995 and of human and avian cases of influenza (H5N1) in Hong Kong in 1997 reemphasized the need for vigilance in looking for potentially pathogenic strains of avian influenza (AI) virus. This need is met through a comprehensive set of surveillance systems, including targeted active surveillance, that monitor various levels of production and marketing of poultry.

The National Poultry Improvement Plan (NPIP), a cooperative industry–state–federal program, is a key part of surveillance. Currently, 48 states use this monitoring and surveillance. Poultry breeders who participate in NPIP make their flocks available for testing. For a flock to be declared free of AI, at least 30 birds of more than 4 months of age must test negative every 90 to 180 days, depending on the type of flock.

In addition, APHIS, state, and industry representatives coordinate state surveillance efforts for low-pathogenicity AI virus in live bird retail markets, flea markets, supply flocks, and dealer facilities. When particular strains of AI viruses are isolated, APHIS provides this information to the state, which then attempts to trace the infection back to source flocks.

There also is a national slaughter blood surveillance program that evaluates the AI status of U.S. broiler and turkey flocks on a state-by-state basis. Blood sampling occurs at slaughter for 75 flocks per quarter per cooperating state. In addition, sick birds with respiratory problems are routinely sampled and submitted to state laboratories for virus isolation and antibody testing. Virus isolation procedures are carried out on dead birds if warranted from history and clinical signs. Spent laying hens are monitored at slaughter.

Detecting Risk Factors and Prevalence Trends

To detect zoonotic agents that may cause little or no disease in livestock or poultry, as well as to identify risk factors or prevalence trends for a variety of agents, various agencies have developed additional surveillance and epidemiologic tools. These tools include:

National Animal Health Monitoring System

APHIS-VS's National Animal Health Monitoring System (NAHMS) collects, analyzes, and disseminates data on animal health, management, and productivity in several livestock populations, including swine, dairy and beef cattle, equine, poultry, and sheep. Baseline animal health and management data from NAHMS national studies can be used to identify

risk factors or trends associated with zoonotic pathogens, such as identifying associations between cattle management practices and the shedding of *Salmonella* and *E. coli* O157:H7. National prevalence estimates for cattle shedding *Salmonella* and *E. coli* O157:H7, and for calves shedding *Cryptosporidium* and *Giardia*, also have been generated through NAHMS.

National Antimicrobial Resistance Monitoring System

Much recent national and international attention has been given to the potential human health impact of using antimicrobials in food-producing animals. The emergence of resistance to antimicrobials among zoonotic bacteria is a global problem. Multiple resistance has emerged among several bacterial strains, including *Salmonella*. One particular strain, *Salmonella typhimurium* DT104, is causing disease in both animals and humans. Poultry also have been implicated in increasing levels of resistant *Campylobacter jejuni* infections in humans.

To address such problems, in 1996 the Food and Drug Administration's Center for Veterinary Medicine, the CDC, and USDA (including APHIS, the FSIS, and the Agricultural Research Service) established the National Antimicrobial Resistance Monitoring System (NARMS). This cooperative veterinary and medical surveillance system is intended to prospectively monitor the emergence and spread of resistance in enteric bacteria and to help ensure the continued safety and effectiveness of veterinary antimicrobials. Evaluators test specimens from human and animal clinical cases, from healthy farm animals, and from carcasses of food-producing animals at slaughter. Most of the nonhuman specimens come from cattle, swine, and poultry. More than 2,000 isolates of nonhuman origin are tested annually.

Among its efforts, NARMS is monitoring susceptibilities of *Salmonella* and *E. coli* isolates to 17 antimicrobials and *Campylobacter* isolates to eight antimicrobials. The antimicrobials are representative of common antimicrobials (or classes of antimicrobials) used in animal and human medicine. Seventeen state and local health departments submit human clinical isolates of nontyphoid *Salmonella* and *E. coli*, and eight health departments submit *Campylobacter* isolates.

Issues of Concern

Important issues of concern related to veterinary surveillance for zoonotic diseases include:

- Trade impact of finding an agent or disease.
- Use, data sharing, and diagnostic capabilities of VDLs.

- Better use of disease intelligence.
- Communication with medical and wildlife communities.

Trade Impact

One barrier to implementation of veterinary surveillance systems is the impact that the findings of such systems may have on trade. That is, if observers look for something, they might find it and then be obligated to make the information known. This could lead to trade restrictions, sometimes instituted by governments outside the country conducting the surveillance, that result in huge economic impacts. It has been difficult, for example, for the U.S. government to sustain efforts to share VDL data because of concerns some industry and state officials have about the impact of public disclosure of certain information. This issue lacks an obvious solution; it also is an issue of which other public health professionals should be cognizant. One potential approach is to establish voluntary certification programs to encourage more open reporting of disease or, if the programs are successful, freedom from disease.

Veterinary Diagnostic Laboratories

These laboratories, and the submissions they receive from field practitioners, are crucial for the early identification of an emerging disease or of small outbreaks of a well-known disease. There are several issues that concern the ability of such laboratories to do so.

VDLs may be less likely to receive diagnostic specimens from field practitioners than in the past. This may be attributable, in part, to increased use of laboratory user fees. More funding for state and university laboratories to allow more free testing of diagnostic specimens may be critical in getting more submissions for testing. There also is an apparent decline in the amount of contact between livestock practitioners and producers. Larger producers are more often doing their own individual sick animal care, while veterinarians are more often focusing on improvement of overall herd or flock health. This may decrease or delay the submission of diagnostic specimens and thus delay the recognition of potential zoonotic diseases.

Data sharing by and among laboratories is a problem. At least two issues are involved: ability to share and willingness to share. First, laboratory information systems must be compatible and developed with data sharing as an objective. Standardization of variables and output formats is often lacking. Many systems are developed primarily or solely to facilitate billing-related functions. Second, cooperation among laboratories in sharing information is often absent as data are more and more often viewed as proprietary.

Many VDLs are primary service laboratories that can do a very good job of detecting common, known disease agents. In order to do a better job of detecting unknown or less commonly seen agents, potentially including many zoonotic agents, upgrading of facilities and staffing levels is required. This means additional funding is needed.

Disease Intelligence

The sensitivity of a passive surveillance system is always a concern. In general, any system will find large outbreaks. Finding smaller outbreaks or scattered cases of disease, or finding large outbreaks earlier in their development, are the real challenges. In the case of detecting West Nile virus in horses, we may have been near the sensitivity limits of the passive reporting system by which it became known. Had 21 of the 25 total cases detected not occurred within the observation of a single veterinarian, we might not have identified the equine component of the outbreak. Therefore, other factors may need to be considered in order to better anticipate when and where disease may be likely to occur so that more targeted surveillance may be considered. In other words, we need to utilize better disease intelligence.

The production of "actionable" intelligence may derive from analyses of changes in climatic conditions, wildlife demographics, trade patterns, or vector distribution. This can enhance the ability of surveillance systems to anticipate risks and deal with them. Perhaps New York City and Long Island should have been a focus for earlier veterinary and human surveillance, based on the available knowledge that a mosquito species previously unseen in North America, *Aedes japonicus*, had been discovered in the area about 12 months before the 1999 West Nile outbreak.

APHIS-VS is working to develop new information collection and analysis methodologies, as well as new relationships with intelligence groups, such as the Armed Forces Medical Intelligence Center (AFMIC), where potentially useful information already is being collected. International surveillance will be critical in the identification of foreign diseases that would place the United States at risk. In addition, APHIS has more than 100 foreign service officers in 28 countries, and USDA's Foreign Agricultural Service has representatives in about 100 countries. Furthermore, APHIS offers assistance to other countries in detecting and responding to diseases on their soil, rather than potentially having to deal with them here. In addition, we are striving to make better use of domestic sources of information, including a pilot project to collect information from a sentinel practitioner reporting system.

Communication

Communication and collaboration among the veterinary, human, and wildlife health communities is crucial. Through better communication, the effectiveness of all surveillance for zoonotic diseases will be enhanced. One of the few positive aspects of the West Nile virus outbreak may be that it is illuminating this issue and will hopefully carry over to the detection of and response to future zoonotic disease outbreaks. NARMS is a good example of cross-community collaboration in surveillance.

Finally, both the veterinary community and the medical community, for example, may each currently feel that they provide to the other an adequate level of access to information. Yet both communities probably feel that early and specific information is not forthcoming from the other. This issue needs to be addressed in a direct fashion, and concrete steps need to be taken to solve whatever real problems or misperceptions exist.

PETBORNE ZOONOSES: DETECTION AND SURVEILLANCE CHALLENGES

Lisa Conti, D.V.M., M.P.H.

Public Health Veterinarian, Florida Department of Public Health

Florida has statutory requirements for physicians, veterinarians, and laboratories to report selected human diseases to the Department of Health. Surveillance is based on case definitions provided by the Council of State and Territorial Epidemiologists, with input on zoonoses by the National Association of State and Public Health Veterinarians. Disease surveillance is passive for the most part. The health department provides ongoing regional training for health care providers to increase epidemiologic capacity.

Veterinarians are a part of the public health team, especially in recognizing zoonoses and treating diseased animals to reduce a source of infection for people. However, surveillance challenges include the confusion about what veterinarians must report and to whom diseases should be reported: to the state public health veterinarian at the health department or to the state veterinarian at the agriculture department. Florida's health statutes require veterinarians to report only animal rabies, psittacosis, and zoonosis outbreaks, while its agricultural statutes require reporting of diseases mainly of agricultural importance. In practice, small-animal veterinarians rarely report diseases or talk to public health or agriculture staff.

The Department of Health is attempting to engage more fully small-animal practitioners in the surveillance realm. Recent success may be attributed to federal funding for bioterrorism training and increasing capacity for

zoonosis disease control networking by adding veterinary positions to the health department staff. The latter includes the state public health veterinarian and a regional epidemiologist (who is also a veterinarian) at the department's main diagnostic laboratory. The department provides laboratory support for work related to zoonoses; this support includes providing the only testing facilities in the state for animal rabies.

The health department also conducts special surveillance studies regarding zoonoses. One study, for example, was triggered by inquiries from people with AIDS who had been told by their health care providers to eliminate all pet contact but who instead thought about limiting health care so they could maintain their human–animal bonds. As a basis for this study, we used the Supplement to HIV/AIDS Surveillance Project, funded by the CDC, and added a short module about pet ownership among persons with AIDS. In the study, we interviewed 408 people in Jacksonville, Fort Lauderdale, and Miami who were 18 years or older in age and had been diagnosed with AIDS within 2 months prior to interview. We also had access to the participants' medical records and diagnoses of AIDS-defining opportunistic infections (many of which are zoonoses). The participants did not differ sociodemo-graphically from the AIDS population in their respective counties. We wanted to know what proportion of the participants owned pets, what kinds of pets they owned, and the degree of human–pet attachment. We also wanted to assess the participants' level of understanding about zoonoses and safer practices for pet ownership.

We found that about half of the participants were living with pets (whether they owned them or were in a household with pets), and one-quarter had two or more pets. Of the pet owners, 81 percent said they felt very attached to their pets. We did not find a significant difference between pet owners and nonowners in most of the study's variables, which included mode of HIV transmission, whether or not the participants had completed high school, and the status of their living situation (some participants were living on the streets). Neither did we find significant differences among pet owners and nonowners in terms of their reported opportunistic infections.

Only about 10 percent of participants said they had received any information about zoonotic diseases from medical or other official sources. Further probing revealed that one-quarter of the information they had "learned" was incorrect. (While they may have been given appropriate information, the patient's perspective was reported.) This misinformation included such notions as "fleas can give you rabies" and "cats can give you AIDS." Two percent felt that they had been infected with diseases from their pets; such putative infections included such things as "parasites," "something from the litter box," and "cat scratch fever." The participants' medical records did not reveal any indication of additional zoonotic diseases.

In a follow-up to this study, we determined that 79 percent of the participants had died. We were not able to show any significant difference between pet owners and nonowners with regard to reported zoonotic diseases as contributing or underlying causes of death.

Certainly, there are both risks and benefits of pet ownership. The health department feels that discussions regarding "safer pet ownership" and zoonosis risk reduction remain warranted, both for the human and veterinary medical communities and for the general public. As many of the common zoonoses are not reportable diseases, the task of assessing the magnitude of the problem remains a challenge. Nevertheless, a number of commonsense activities can play a large part in promoting healthier human–pet relationships. These activities include strategic deworming of cats and dogs (kittens and puppies should be dewormed at 2 weeks of age and then every 2 weeks until they are 3 months old), engaging dogs in obedience training to reduce the threat of bite injuries, and encouraging reptile owners to wash their hands after handling their pets in order to reduce the risk of salmonella infection. Safer pet ownership measures also include not allowing pets to feed on garbage or to hunt prey for their food. In addition, people would be well advised to avoid keeping exotic or wild animals as pets.

To help improve zoonotic disease surveillance in Florida, the Department of Health has developed a draft program to encourage veterinarians, especially small-animal practitioners, to report selected diseases to their county health departments. Diseases to be reported include those requiring an emergency response (for example, a possible bioterrorism situation), those required by statute, and those that are of research interest. At present, however, veterinary reporting in general seems to have low priority.

At the national level, improvements to the current system for monitoring and responding to zoonoses should include:

- Designating a state public health veterinarian in each state as the key person in a zoonosis disease control program. Such trained personnel should be provided with adequate support and infrastructure to enable them to respond to emerging public health needs.
- Increasing education—among the general public, the commercial pet community, and the human and veterinary medical communities—about zoonosis risk reduction and the human–animal bond issue. Health care providers should recognize the important rewards of pet ownership, and they should be comfortable discussing the realistic risks of such interactions.
- Developing laboratory standards and evaluation/monitoring programs for zoonotic disease testing in people to increase the positive predictive value of such tests from commercial laboratories. Zoonosis detection

remains challenging, and diagnostic testing should provide the clinician with appropriate information.

- Developing a nationally agreed upon list of notifiable animal zoonoses and their case definitions, to assist in standardizing surveillance. Animals can be sentinels for human disease and, in the extreme, may be useful for early warning of bioterrorist activities.

Improving the nation's ability to mount an effective and comprehensive zoonosis program will require national leadership. It will be important to ensure that veterinarians are included in developing such leadership, as these professionals have too often been left out of considerations of this increasingly important issue.

IDENTIFICATION AND CONTAINMENT OF UNKNOWN AND RARE PATHOGENS

C. J. Peters, M.D.

Chief, Special Pathogens Branch
National Center for Infectious Diseases
Centers for Disease Control and Prevention

One major objective of the Special Pathogens Branch at the CDC is to identify previously unknown pathogens and keep them as rare as possible. Strategies to combat these pathogens, including zoonotic agents, depend on "lessons learned" and on extrapolations from past emergences. Devising effective strategies will include considering both general ideas about what determines emergences and particular ideas about how to deal with emerging diseases in specific places and times.

The Institute of Medicine's 1992 report on emerging infectious diseases identified a number of factors that play a role in the emergence of pathogens. These factors can be divided into three broad categories: ecological shift, genetics, and changing patterns of human travel and transport. Ecology, if interpreted in the broadest sense, is the driving force behind most emergences, particularly those involving viruses. Ecology, in this sense, does not refer simply to the natural world about us, but rather is focused from the pathogen's point of view. After all, *oikos*, the Greek root of "ecology," means "house," and humans serve this function for some viruses. For example, the human immunodeficiency virus (HIV) would not see deforestation as a direct ecological change, but the virus would see the social changes that accompany deforestation, typically including changes in the sexual behavior of humans moving into those areas, as beneficial changes in its own ecology. Viral genetics, in general, has what might be considered a permissive role in disease emergence, by helping keep the virus

fit for its new circumstances. (Of course, some emergences, such as with influenza or canine parvovirus, have been driven by mutation, but most viral mutations occur randomly and are then selected by the immune pressures of the host or other external factors.) Travel of humans and transport of vectors and reservoir host animals then stirs the mixing pot, moving a particular pathogen into an ecological milieu where it can test itself, perhaps with its appropriate helper vector or host reservoir.

Social and environmental changes are occurring at an increasing rate, in both the developed and developing worlds. The developed world has the greatest travel and transport, providing particular risks. However, ecological change is greatest in the developing world and biodiversity is greatest in the tropics, which makes these regions the best "hunting ground" for new pathogens. In the final analysis, we really do not know which zoonotic pathogen will emerge next or cause the biggest problem. Given the obvious link between human health and viruses that circulate in domestic animals and wildlife, we cannot ignore pathogen flow in any of these areas.

One issue that is particularly important but also contentious is the ability of some pathogens to establish themselves as disease agents in humans without need for their previous host reservoirs. Measles and other viruses appear to have made this transition in the past, and it is now established that influenza A makes the leap with some regularity (although flu prognosticators cannot determine how regular such leaps may be). This cross-species traffic could form the basis for "new" human diseases that might be particularly difficult to control because they have cut the zoonotic link; in such cases, we will have to deal with a human-adapted virus. HIV is such an example, but HIV has the same survival strategy in humans as it did in chimpanzees or sooty mangabeys. Can other viruses switch their basic transmission cycles? One concrete example would be filoviruses, which have a proven capability to pass through several generations of interhuman transmissions. Thus, we should remain alert to end the chains of spread to prevent any opportunities to adapt to continuous interhuman spread. In any case, there is a candidate for the breeding ground of these possible human pathogens: the megacity, with its crowded conditions, poor sanitation, and weak surveillance. This situation, of course, has counterparts in agriculture and crop production today.

What sort of response is needed to these threats? The usual answer, "increased surveillance," is correct but insufficient. We also need "trip wires" that will launch active investigations. These investigations need to be multidisciplinary, involving physicians, veterinarians, entomologists, mammalogists, ecologists, molecular biologists, vaccinologists, epidemiologists, and a large number of other specialties (including pathogenesis and immunology). Formal designation of the specialties is unimportant, but having the right expertise present on the team is crucial. It also will be

important that the leader of the team have the ability to communicate effectively with the representatives from all the disciplines, as well as with other people who will play key roles in control efforts. In addition, with the increasing numbers of alarms being raised as communications and awareness increase, there has to be a reasonable way to sort through the possibilities to arrive at priorities for investigation. Such prioritization might best derive from collaboration between multidisciplinary teams of researchers and a central specialty group, such as the CDC's Special Pathogens Branch or the National Institute of Virology in South Africa, both of which have particular expertise in certain areas, as well as access to special expertise in infectious disease pathology, and therefore are well prepared for conducting pathogen-specific analyses.

In determining what pathogens to study, we can identify a rogues' gallery of agents to receive special attention. We know that some viruses already have proved themselves to be bad actors with major human disease potential, and we also know that at some point they are likely to return to center stage. This list includes Venezuelan equine encephalitis virus, West Nile virus, yellow fever virus, Rift Valley fever virus, and Nipah virus, among many others. Is it too much to ask to understand more about the transmission of these agents and to have useful antiviral drugs and prototype vaccines available for such established threats? Of course, we also are certain to face the emergence of previously unknown pathogens. Thus, we would be well advised to do basic groundwork now, and not when we are faced with a "mystery disease" or a new, challenging pathogen. One approach would involve studying certain classes of viruses, such as filoviruses and parvoviruses, so we will not be caught without at least the basic tools to respond to new threats.

Of course, most plans will not work unless they are developed with an eye to their functioning in addition to their goals. Experience points to a number of potential problems and needs:

- There needs to be a specific organization that can take the first call in cases of new disease emergences. Maintaining such a group, from providing adequate funding to ensuring employee morale, has often proved difficult. This will be especially challenging in the international arena.
- Most laboratories, including those at CDC, do not have adequate reagents for all viruses to share with all researchers who want to study them. This function should be covered with generic reagent production, either explicitly funded through CDC or through a program similar to the one once used by the National Institutes of Health for producing arbovirus reagents.
- Better mechanisms are needed for distributing supplementary funding for handling emergencies. This problem was particularly evident with

funding for studies of the West Nile virus and hantavirus. Such funding now must be disbursed according to federal acquisitions regulations, and this process too often leads to delays in the distribution of funds and to inflexibility in selecting funding recipients.

- Cooperation among U.S. agencies and among U.S. and international agencies often proves difficult. The National Science and Technology Council's Committee on International Science, Engineering, and Technology—whose main mission is to develop, on an interagency basis, policies for furthering international science and technology cooperation in the national interest—has markedly improved the interactions of federal agencies. Nevertheless, during some recent disease outbreaks, the interactions of federal agencies within such varied departments as Health and Human Services, Defense, and Agriculture were not coordinated and efficient in important aspects of containing the diseases. In the international arena, there is no strong and efficient leadership in responses to emerging disease epidemics, and the organization of such responses often is complicated by the need to coordinate the actions of multiple international and national agencies as well as the increasingly assertive initiatives by some nongovernmental organizations.
- There needs to be up-front recognition of some of the things that now can be done scientifically but, for a variety of practical considerations, cannot or will not be done in everyday practice. In diagnostics and vaccine development, for example, scientists can make prototypes, but the complexities of manufacture, distribution, and quality control are beyond the scope of universities or government laboratories, and usually below the interests of industry. This inability to produce new human vaccines and diagnostics on a practical level may become a serious deficiency in our ability to respond to emerging infectious diseases. There also are problems in supporting expensive longitudinal studies and innovative high-risk research.
- Public education programs are needed both to increase awareness of the problems and to minimize undue fears. A joint approach should involve developing a better curriculum for use in schools and devising information programs to reach influential organizations and the media.
- In an era of deregulation, the biomedical community is being choked with regulations that often do not address real risks or abuses but rather reflect political perceptions. Such regulations affect animal experimentation, shipping of various disease-related agents, research on certain agents, and the use of certain vaccines for occupational safety, among many other areas. Not only do unwarranted restrictions fail to improve public or occupational safety appreciably, they also limit research that may indeed reduce the risk from threat diseases.

Many people in the United States, within government and among the public, have only minimal understanding of conditions in other countries. This is especially true regarding the developing world, where new zoonotic diseases are most likely to originate. It is critical to improve our general understanding of the various cultural, infrastructure, and other issues that will affect how the United States can best work with the world community to improve the surveillance, control, and management of disease.

FOODBORNE ZOONOTIC AGENTS: *SALMONELLA ENTERITIDIS* IN EGGS

Kaye Wachsmuth, Ph.D.

Deputy Administrator, Office of Public Health and Science
Food Safety and Inspection Service, U.S. Department of Agriculture

In the United States the most common foodborne bacterial pathogen is *Campylobacter*, which causes almost 2 million cases of infection per year, according to a 1999 report from the CDC. Second is *Salmonella*, with more than 1.3 million cases. However, *Escherichia coli* O157:H7 and *Listeria monocytogenes* appear to cause the most severe illnesses, as judged by their rates of reported hospitalizations and deaths. All of these pathogens, with the possible exception of *Listeria*, are zoonotic; they are silent infections in the animal host, causing no overt symptoms or problems at that point in the food supply.

Salmonella, which hospitalizes and kills the most people each year, serves as an example of this class of pathogens. In recent years, *Salmonella enteritidis* (SE) has become a leading cause of *Salmonella* infection, increasing from about 5 percent of all such infections in 1976 to about 26 percent by the mid-1990s.

SE infections primarily are associated with the consumption of eggs. Of particular note, this problem exemplifies a new scenario of foodborne infection that moves beyond the traditional church supper or potato salad outbreaks. As described by CDC's Robert V. Tauxe, this new scenario involves low-level contamination of a widely distributed commercial food product. Such outbreaks typically are detected only because of a fortuitous concentration of cases in one location. A diffuse increase in sporadic cases can occur well before a local or large outbreak focuses attention on the emergence of a pathogen. With SE, for example, the egg connection was not really appreciated until 1986, when a large multistate outbreak of infections was traced to stuffed pasta made with raw eggs rather than fully cooked eggs. Since then, SE has been found on farms of egg-laying chickens, and the pathogen has been demonstrated to be the cause of outbreaks and

sporadic cases of infections. Part of the difficulty of preventing SE from reaching humans is that infected hens exhibit no outward signs of carrying the pathogen. The hens' reproductive tracts become colonized with SE, and there now is convincing evidence that SE can be passed to the inside of eggs during egg formation.

With the emergence of health problems posed by SE and egg consumption, the USDA and several other government agencies collaborated to bring everything known about the pathogen into the organized framework of risk assessment. The goal was to determine exactly where information gaps occurred and how to best address this issue. The risk assessment was conducted by a multidisciplinary team that included veterinarians, physicians, epidemiologists, microbiologists, and risk analysts, and the team consulted extensively with industry officials to determine current industry practices.

The risk assessment model built from this framework is based on the flow of eggs from production through, in some cases, processing, preparation, and consumption. The model consists of four basic modules concerning eggs consumed as "shell eggs." Each of these modules has unique inputs and outputs. Ultimately, the model predicts the probability of human illness of varying severity (that is, risk) associated with consumption of egg-containing servings.

The first module focuses on egg production at the farm. Its first input is the approximate number of infected flocks in the country. However, these data are not readily available and in many cases are difficult to interpret. For example, evidence collected from different regions of the country often cannot be extrapolated to every state, for a number of reasons. Consequently, the model incorporates uncertainty regarding the estimated fraction of all flocks that are infected. The module also seeks to determine how many eggs produced are likely to carry the pathogen, as well as the final destinations of SE-contaminated eggs. Under current conditions, the module predicts that the most likely frequency of contaminated eggs in the United States is one in every 20,000 eggs produced. Since the industry produces about 65 billion eggs a year, this means that several million contaminated eggs reach the marketplace, with many of them being consumed as shell eggs by individuals.

Information from the production module then flows into the various other modules. One module, for example, mathematically models the potential for SE growth and death within an individual egg as it moves from the farm to the consumer. A major rate-limiting determinant of SE growth involves changes in the permeability of the yolk membrane, with increased permeability associated with elevated temperatures and/or times of storage. When the yolk membrane is totally compromised, it releases nutrients into the albumen (or white) of the egg, creating an egg in which the pathogen

may multiply to large numbers—and thus the egg poses a very high risk of causing human illness.

Another module deals with how eggs are prepared. More often than not, they are going to be cooked, which should eliminate SE and thus any risk of infection. Nevertheless, the number of different cooked food dishes that have been implicated in SE outbreaks suggests that many individuals, as well as many companies that make or sell food items, may not be fully cooking the eggs they use. The list includes eggnog, Caesar's salad, omelets, French toast, lasagna, and meringue pies. One SE outbreak several years ago, which caused approximately 250,000 cases, was traced to ice cream that had been contaminated postprocessing by exposure to raw eggs during transport.

The final module, which incorporates information from all of the others, deals with the public health consequence of exposure to contaminated egg meals. Outputs include projected numbers of illness, postillness sequelae, recovery without a physician visit, recovery with and without hospitalization, and death.

Among the efforts to validate both the individual modules and their combined performance, we compared their projections with various field observations. For example, we compared outputs from the public health module with the number of illnesses estimated from national disease surveillance systems. Although the results were not a perfect match, they did suggest that the model's output was approximately consistent with independently derived data. Moreover, any discrepancies noted occurred in favor of public health, with the model projecting more illnesses than were reported. Whether this is the model's fault, or whether surveillance systems are failing to detect all cases of illness, remains to be determined.

Thus, experience suggests that the model can provide a scientific basis for policy decisions related to consumption of eggs. Among its uses, the model can examine which types of changes, especially in production and distribution, would be most effective in terms of human health outcome, and this insight will help in selecting the most efficient and cost-effective intervention or management strategies. For example, the model predicts that immediately transferring a freshly laid egg, which has a temperature of over 99 degrees Fahrenheit, into an environment with an ambient temperature of 45 degrees can reduce human illness by 8 percent. In current practice, however, freshly laid eggs are first washed in warm water and then packaged in cartons. These cartons are put on a large pallet with many other cartons, stacked up to 10 feet high, and wrapped in plastic. Even in a refrigerated environment, eggs toward the middle of the stack will stay at about 80 degrees for up to a couple of weeks. Obviously, changing that industry practice can reduce the level of SE in the eggs and thus reduce the risk of disease among people who consume those eggs.

In developing the model, several lessons emerged that may help in developing risk assessment tools targeted at other foodborne health threats. Stakeholder input is imperative; without early and continued participation by all parties involved, including the general public and industry, development efforts may be slowed and acceptance of the results endangered. A multidisciplinary approach is essential. Given the scope of the food chain, a modular approach that breaks problems into integrated parts can facilitate modeling. Finally, the modeling process must be iterative, with newly gathered data being used to revise the model and its outputs. With the SE model, for example, we now are examining new FoodNet data, and we will be revising some of the modules based on recent industry changes in egg production and distribution, as well as on new data on the occurrence and distribution of SE in the egg industry.

In 1999 the President's Food Safety Council convened a multiagency group to examine egg safety. After gathering input from a variety of stakeholders, the group proposed an action plan that calls for eliminating SE illness associated with egg consumption, with an interim goal of reducing the risk by 50 percent by the year 2005. The plan, which draws heavily on USDA's modeling efforts, has eight objectives, built on a modular construct from farm to table. (Details of the plan are available on the World Wide Web at www.foodsafety.gov/~fsg/ceggs.html.) The plan lays out a time line for reaching each objective, and in many cases it specifies which agencies should be responsible.

Such guidelines will prove valuable, given the complexity of the "egg continuum." The Food and Drug Administration has jurisdiction at the farm level, but the agency does not really have a presence on farms. FDA sets standards for producers, and the states are responsible for inspecting eggs and for enforcing regulations on producers. USDA's FSIS is responsible for establishing and enforcing standards for egg packers and processors. CDC is responsible for surveillance programs to monitor human health and will ultimately document whether the new egg-safety program is meeting its goals.

The government is beginning to use this risk assessment approach for other foodborne pathogens. FDA is leading a study of *Listeria monocytogenes* in ready-to-eat foods. One of the objectives of this study is to rank various foods on the basis of their risk to human health, so that regulatory agencies can better focus their scarce resources. The FSIS has used its modular approach to study *Escherichia coli* O157:H7 in ground beef, and these results will become the basis for new USDA policy and regulatory considerations. Of course, this pathogen is found in many other foodstuffs as well, such as lettuce, apple juice, and even water. The FSIS model may help in the modeling of these routes of infection, because it

incorporates on-farm inputs that can be used as a starting point in these other risk assessments.

Campylobacter is another major concern for FSIS. This pathogen, which is the most frequent cause of sporadic bacterial foodborne disease, is readily found on poultry farms, in chickens, and in chicken carcasses at slaughter. Canada has mounted a relatively large risk assessment study of this problem, and U.S. efforts will build on that work. In addition, FSIS is supporting a project, in collaboration with the APHIS, on BSE, or mad cow disease. We have contracted with the Harvard Risk Analysis Center to evaluate current U.S. risk management actions to prevent BSE from occurring in this country.

Many other countries that the United States trades with face similar, and often worse, safety problems related to foodborne pathogens. As the global marketplace increasingly becomes reality, U.S. consumers are becoming more concerned about the origins of their food and the public health situation in the countries of origin. Concerns may be particularly acute regarding developing countries, some of which lack any surveillance systems for monitoring foodborne diseases. The federal government is trying to address these issues through the Codex Alimentarius Commission (Codex), which sets international food safety standards. Risk assessment will play a role in mitigating this enormous potential problem. Within Codex, the Committee on Food Hygiene has developed a priority list for risk assessment activities. The pathogens singled out for immediate attention include those described above. The hope is that this approach will provide officials in different countries with a sound scientific basis for discussing food safety, particularly in cases where countries now disagree.

LEGISLATIVE AND POLICY CONCERNS IN PROTECTING THE NATION'S HEALTH

David C. Bowen, Ph.D.

Congressional Fellow
Office of U.S. Senator Edward M. Kennedy (D-MA)

Senators Edward M. Kennedy and Bill Frist (R-TN) have grown increasingly concerned that the United States is inadequately prepared for dangerous outbreaks of infectious disease. Through hearings and conferences with experts in the field, the senators set out to discover where the nation's needs for increased preparedness were greatest. As chairman and ranking member of the Senate Subcommittee on Public Health, the two senators maintain close ties with the medical and scientific communities. Through this contact with medical experts, the senators realized that infec-

tious disease outbreaks were a growing threat to the nation's health. When the senators began this investigation, the dangers of infectious disease outbreaks were not widely discussed in the media or other public forums. Now, because of widespread awareness of disease outbreaks, such as the emergence of West Nile virus in New York and the "mad cow" epidemic in Britain, the American public has become increasingly attuned to the need to improve our nation's defenses against disease outbreaks.

Extensive consultation with the medical community revealed that the nation's local, state, and national public health agencies are poorly equipped to detect, monitor, and respond to outbreaks of infectious disease. This deficiency impairs the nation's ability to respond to infectious disease outbreaks of all types but is particularly troubling in light of two disease threats that pose particular danger to the public health: the rise of microbes resistant to antibiotics, and the threat that a terrorist may deliberately release a dangerous infectious agent.

To address both the general threat of infectious disease outbreaks and the specific threats of resistant bacteria and bioterrorism, Senators Frist and Kennedy introduced the Public Health Threats and Emergencies Act of 2000. The bill lays out a blueprint for strengthening the nation's capacity to detect and respond to the threat that disease emergencies pose to the public's health. The legislation authorizes major initiatives to improve public health capacity, to address the threat of antimicrobial resistance, and to improve preparedness for acts of bioterrorism. (Since this IOM Forum, many of the provisions contained in the Frist–Kennedy bill have been enacted into law as part of the Public Health Improvement Act of 2000 [Public Law 106-505]).

To improve the nation's ability to respond effectively to infectious disease threats, the bill will strengthen the capacity of public health agencies to detect, diagnose, and contain infectious disease outbreaks. Many public health agencies lack the basic computer equipment to communicate data on disease outbreaks electronically or cannot perform simple laboratory tests to diagnose infections. Most agencies do not even have an up-to-date assessment of their current capacities and needs. To address these weaknesses, the Frist–Kennedy bill establishes grant programs to enable state and local public health agencies to:

- Assess their current capacities and identify their areas of greatest need.
- Upgrade the ability of public health laboratories to identify disease-causing microbes.
- Improve and expand electronic communication networks.
- Develop plans to respond to public health emergencies.
- Train public health personnel.

The widespread use of antibiotics beginning in the 1940s provided, for the first time in history, effective treatments for infectious diseases. Antibiotics that once had the power to cure dangerous infections are now often useless, however, because microbes have become resistant to all but the newest and most expensive drugs. Disturbingly, some patients have contracted infections resistant even to these drugs of last resort. The World Health Organization (WHO) estimates that 14,000 Americans die every year from drug-resistant infections and that the United States spends $10 billion a year treating antibiotic-resistant infections—and this burden will grow heavier as more and more microbes become resistant. To meet the grave and growing problem of antimicrobial resistance, the Frist–Kennedy bill:

- Directs the Department of Health and Human Services (HHS) to conduct a nationwide campaign to educate patients and doctors about the appropriate use of antibiotics.
- Authorizes HHS initiatives to monitor and contain the spread of resistant microbes.
- Authorizes grants for public health agencies to combat antimicrobial resistance.
- Establishes demonstration grants for hospitals and clinics to promote more responsible use of antibiotics and to control the spread of resistant infections.

The HHS Office of Emergency Preparedness estimates that 40 million Americans could die if a terrorist released smallpox into the population. Anthrax could kill 10 million. Although experts may dispute the probability of a bioterrorist attack, few would disagree that the consequences of such an attack could be devastating. To enhance the ability of the nation's public health agencies to respond to acts of bioterrorism against the civilian population, the Frist–Kennedy bill:

- Establishes grants to train health care professionals in recognizing and treating illnesses caused by such attacks.
- Improves coordination among federal agencies to develop public health countermeasures against bioterrorism, such as stockpiles of necessary drugs.
- Authorizes expenditures to revitalize and improve the security of laboratory facilities at the CDC.
- Reauthorizes an existing provision of law that allows the Secretary of HHS to protect the public health in the event of a bioterrorist attack or other disease emergency.

Through these measures the Public Health Threats and Emergencies Act can lay the foundation for a strong public health response to the danger of infectious disease outbreaks. With the passage of this legislation, the sustained involvement of the medical and scientific communities will now be essential in ensuring that the programs authorized by the act are properly funded and implemented.

6

Summary and Assessment

Joshua Lederberg, Ph.D.

Nobel Laureate and Sackler Foundation Scholar
The Rockefeller University

Throughout history humans have been afflicted by zoonoses—that is, diseases transmitted to people from animals. These diseases can be acquired directly, as when a person is bitten by an infected animal. They also can be acquired indirectly, in a number of ways. For example, a person might be bitten by an arthropod vector, such as a mosquito or tick, that has picked up a pathogen from a host animal; come in contact with pathogen-bearing fluids produced by an infected animal; or consume foodstuffs contaminated with an animal-derived pathogen. Some zoonotic agents maintain an ongoing reservoir life cycle in animals or arthropods, without the permanent establishment of a new life cycle in humans. Other agents are "species jumpers" that derive from an ancient reservoir life cycle in animals but have subsequently established a new life cycle in humans that no longer involves an animal reservoir.

In recent years a number of new zoonoses have emerged, in both developing and developed countries, and a number of known zoonoses have reemerged in areas where they had been absent for decades or have spread to animal species in which the pathogens had not previously been detected. For example, beginning in the mid-1980s, cattle herds in the United Kingdom have been hit by an outbreak of bovine spongiform encephalopathy, or "mad cow disease." After extensive study, this animal disease has now been linked to the occurrence of a progressive and often deadly neurological disorder, called new variant Creutzfeldt-Jakob disease, in humans who have presumably been exposed to diseased cattle or products therefrom. In another zoonotic outbreak, the first human cases in the Western Hemi-

sphere of West Nile encephalitis, a potentially fatal disease caused by a virus that commonly infects birds and can be transmitted by mosquitoes, were documented in the New York City metropolitan area in late summer of 1999. The West Nile virus has now been detected in a number of states along the major migratory flyways of the eastern seaboard.

Many different determinants contribute to the emergence of new zoonotic agents, and it is rare that these factors act singly. Among the forces that shape their emergence are human demographics and behavior; technology, industry, and agriculture; economic development and land use; international travel, commerce, and military expeditions; microbial adaptation and change; and breakdown of public health measures. Indeed, social and environmental changes are accelerating, in both the developed and developing worlds. The developed world has the greatest travel and transport, providing particular risks for rapid spread. Ecological change is greatest in the developing world and biodiversity is greatest in the tropics, which makes these regions potentially productive breeding grounds for new pathogens. In the final analysis, it cannot be predicted which zoonotic pathogens are likely to emerge next or cause the biggest problem. Given the obvious link between human health and pathogens that circulate in domestic animals and wildlife, we must be alert to pathogen flow in any of these areas.

Among other issues, there is concern regarding the potential "bioweaponization" of zoonotic diseases, particularly by individuals or groups either acting alone or with sponsorship by a foreign government. Many observers now consider such terrorist attacks to be the major threat, embracing biological attack against U.S. forces in peacetime deployment, as well as against private citizens in major cities. Zoonotic agents have a number of attributes, including their potentially large impact when released into a human or animal community, that make them especially suitable for use as weapons. Ironically, continued advances in biotechnology, while offering great promise for improving human health, may concomitantly make it easier for terrorists to manufacture and deploy effective biological weapons.

In addition, a number of human activities undertaken with the best of intentions may have harmful potential. For example, the food and farming industries increasingly use antimicrobial agents and other types of drugs to boost the efficiency of food-producing animals and to prevent certain troublesome organisms from reaching consumers. Use of these chemicals probably enhances the proliferation of antibiotic-resistant microbes. Some observers also suggest that xenotransplantation, broadly defined as the use of nonhuman animal cells or tissues in humans for therapeutic purposes, may inadvertently introduce new zoonotic infections to recipients of such material. This risk raises the burden of preventive responsibility on scientists and research groups conducting such trials.

The challenge taken up by participants in this workshop is to identify strategies that will help the nation, and the world, in preventing and controlling zoonotic diseases. The following sections offer some highlights of the presentations and discussions.

ADDITIONAL RESEARCH

Many gaps remain in our understanding of zoonotic agents and the diseases they cause. More research is needed on the pathogenesis of zoonotics in relation to host biology. The transmission of an infectious agent from an animal to a human initiates a series of events that constitute the pathogenesis of the infection. The final outcome is either termination of infection (either through cure or demise of the host), chronic persistence and latency of infection, transmission to another host, or some combination of these. The zoonoses, involving two or more hosts, and often other vectors, illustrate some of the more interesting and complex patterns of virulence and pathogenesis that have evolved in nature.

Despite spectacular achievements in microbial genetics and genomics, we know relatively little about how most zoonotic agents are maintained in nature or how they respond to environmental (often anthropogenic) changes. The precise ecological factors that lead to human infection and emergence are murky, and textbook descriptions of the epidemiology of most zoonotic diseases are at best simplistic. In order to more effectively prevent or control zoonotic diseases, it will be necessary to better understand the ecology of their respective etiologic agents.

Basic research is needed to underpin vaccine discovery. The threat of emerging zoonoses will be reduced if there is preexisting knowledge of the antigens required in a vaccine and of the immune responses to be elicited. A cadre of experts in these diseases cannot be maintained, nor can steady progress be made in vaccine development, without consistent support for research. At the same time, priorities need to be set for vaccine manufacture. The cost- and time-intensive process of advanced vaccine development and licensure should be reserved for agents for which vaccines are thought to be needed soonest. Except for rapidly evolving influenza, the epitope specifications of a modern vaccine will remain relatively unchanged once discovered and well defined, as will the phenotype of a protective immune response. However, the optimal vaccine platforms by which such antigens will be constructed and delivered may change almost as rapidly as computer hardware.

In determining which zoonotic agents to study, it is possible to identify a rogues' gallery of pathogens to receive special attention. For example, some viruses, including the West Nile virus and the yellow fever virus have been known to have major human disease potential. We should be prepared

with vector control, antiviral drugs, and prototype vaccines for when they reemerge. Of course, we also are certain to face the emergence of previously unknown pathogens. Thus, we are obliged to do basic groundwork now and not wait until we are faced with a "mystery disease" or a new, challenging pathogen. One approach would involve generic studies of certain classes of pathogens, such as filoviruses and parvoviruses, so we will not be caught without at least the basic tools to respond to new threats. Work on retroviruses that preceded the emergence of HIV greatly accelerated our response to AIDS.

ENHANCED LABORATORY CAPABILITIES

To support an expanded research base, a variety of additional laboratory facilities are needed. This will mean, for example, improving in number and capacity the national Biosafety Level 3 and Level 4 laboratories, which offer the kinds of equipment and protection measures required for conducting research on exceptionally hazardous materials. Of particular note, the nation has no Biosafety Level 4 laboratories devoted to veterinary research, a situation that can impede the process of identifying unknown pathogens. These laboratories should operate multifaceted research programs, and they must be ready to deal with large episodes of disease. There also is a need to construct several small high-containment laboratories in academic institutions, yet specific federal commitment or funding for such facilities remains lacking. Also needed are facilities, located in various parts of the country, to meet such emergencies as bio-terrorism threats.

The nation's system of veterinary diagnostic laboratories needs to be strengthened, including upgrading facilities and staffing levels. Typically located in state agencies and universities, these laboratories, which analyze specimens submitted by field practitioners, are crucial for the early identification of an emerging disease or of small outbreaks of a well-known disease. However, the laboratories are now less likely to receive specimens for diagnosis than they were in the past. This may be due, in part, to the increased burden of laboratory user fees. More funding for the laboratories to enable them to provide more free testing of diagnostic specimens may be critical in acquiring more submissions. Data sharing by and among laboratories also is a problem. At least two issues are involved: ability to share and willingness to share. First, laboratory information systems must be compatible and developed with data sharing as an objective. Standardization of variables and output formats are often lacking. Many systems are developed primarily or solely to facilitate billing-related functions. Second, cooperation among laboratories in sharing information is often absent as data are more and more often viewed as proprietary or economically threatening to trade.

Within the medical community, physicians want help in obtaining accurate determinations of the rabies status of each animal for which a human exposure has been documented. The federal Clinical Laboratory Improvement Act now requires testing human clinical specimens but not animal specimens, even when such test results may affect human therapy and outcome. The government should expand the rules to include testing of animal specimens when it impacts the treatment of humans. The government also should require laboratories performing these rabies tests to enroll in proficiency testing and quality assurance programs equivalent to those used to license laboratories that test human clinical specimens.

Many laboratories, including those maintained by the federal Centers for Disease Control and Prevention (CDC), are in short suppply of reagents for some viruses to share with all needful qualified researchers. Generic reagent production should be explicitly funded through CDC or a program similar to the one once used by the National Institutes of Health for producing arbovirus reagents.

EXPANDED SURVEILLANCE SYSTEMS

Surveillance can provide an early-warning system for emerging zoonoses, and such monitoring must be the first link in the chain of public health action. The U.S. current surveillance systems include active systems to detect particular known pathogens and passive systems for more generalized monitoring. For example, the Animal and Plant Health Inspection Service (APHIS) of the Department of Agriculture (USDA) maintains a National Animal Health Monitoring System that collects, analyzes, and disseminates data on animal health, management, and productivity in several livestock populations, including dairy and beef cattle, swine, and poultry. Data from such national studies can be used to identify risk factors or trends associated with zoonotic pathogens. Following the emergence of the West Nile virus in New York City, the CDC launched a comprehensive program to monitor the geographic and temporal spread of the virus in states along the eastern seaboard; to develop more effective strategies for surveillance, prevention, and control; and to provide up-to-date national and regional information on West Nile encephalitis and other vectorborne diseases. More recently, CDC has expanded surveillance efforts into other states, although on a more limited basis.

Many other nations, as well as a number of international groups, also conduct surveillance programs. For example, to cope with the genetic variability of influenza, the World Health Organization (WHO) maintains a network of more than 100 laboratories that constantly survey influenza viruses, and this information is then analyzed in four reference centers. Based on these efforts, WHO makes annual recommendations for those

virus strains to be included in the current vaccine in order to stay abreast of genetic drift or, more tellingly, major shifts.

Still, improvements are needed in our ability to detect and respond to emerging zoonotic agents, particularly those that appear suddenly and are capable of spreading over large areas. The sensitivity of passive surveillance systems is one area of concern. Almost any system should find large outbreaks. Finding and assessing smaller outbreaks or scattered cases of disease, or finding large outbreaks at incipient stages, is the real challenge. Other factors may help anticipate when and where disease may be likely to occur for more targeted surveillance. In other words, we need better disease intelligence. The production of "actionable" intelligence may derive from analyses of changes in such factors as climatic conditions, vegetation, wildlife demographics, trade patterns, or vector distribution. Toward this end, APHIS is working to develop new information collection and analysis methodologies as well as relationships with intelligence groups, such as the Armed Forces Medical Intelligence Center, already collecting useful information. International surveillance will be critical in the identification of exotic diseases that would place the United States at risk. In addition, APHIS has more than 100 foreign service officers in 28 countries, and USDA's Foreign Agricultural Service has representatives in about 100 countries. Further, APHIS offers assistance to other countries in detecting and responding to diseases on their soil, which is better than having to deal with the diseases here.

Enhancing surveillance systems may be particularly important for protecting U.S. citizens from terrorist attacks. This potential has led the government to institute the Laboratory Response Network, sponsored by CDC and managed by the Association of Public Health Laboratories, to enhance the detection of these agents in humans. Personnel in laboratories that test clinical specimens from humans will receive training in the means to rule out these agents as well as in forwarding the isolates to public health laboratories for specific identification and subsequent molecular fingerprinting. By providing a link between public and private laboratories, this network will increase the nation's capacity to detect and prevent the spread of zoonoses, whether they are transmitted naturally or intentionally.

Of course, surveillance is of little use if not shared with other groups or individuals who can act on the information to prevent or diagnose disease. In Iowa, for example, the University Hygienic Laboratory has posted influenza surveillance data on its web site for the past several flu seasons. Data are updated automatically each night. Anyone wanting to know which viruses are circulating in their area can easily view a table that shows the numbers of Influenza A and B detected during the current week, the past week, or all year. This information may influence a decision to administer prophylactic or therapeutic drugs or to control exposures. The web site also

provides region-specific data on a variety of other diseases, including some zoonoses. Sharing data with those who participate in its reporting and accumulation will encourage timely reporting and dialogue between the private and public health care communities.

Improvements in the nation's surveillance systems and ensuring their continued operation depend on adequate financial support. Unfortunately, waning public interest in a disease during a quiescent period often leads to reduction in political, and hence financial, support for surveillance activities. Ironically, it is during these quiescent periods that surveillance would best be conducted, to detect the appearance of an infectious agent in environmental reservoirs and eradicate the agent before it infects many humans. When surveillance is abandoned, an outbreak of human disease may be well under way before it is detected.

IMPROVED COLLABORATION AND COOPERATION

Perhaps the most fundamental need is for improved collaboration and cooperation among government agencies at all levels—local, state, and federal—as well as among members of the veterinary, human health, and wildlife health communities. One positive aspect of the West Nile virus outbreak may be that it is illuminating this issue and may carry over to the detection of and response to future zoonotic disease outbreaks. When staff members at the Bronx Zoo first began investigating the disease outbreak that ultimately would be linked to West Nile virus, scientific exchanges were relatively free. But the zoo staff found that as more organizations and people became involved—and, ironically, as the magnitude of the problem escalated—the situation degenerated: some states seemed unwilling to work with other states or with federal agencies; some organizations did not seem willing to work with other organizations. To help remedy this situation, CDC's new program to provide states with funding to develop strategies and capabilities to cope with bioterrorism may provide a model. In particular, Montana, North Dakota, and South Dakota have developed what appears to be an effective regional surveillance system that integrates both veterinary and human public health.

To improve interdisciplinary collaboration, one step might be for federal agencies to develop a tripartite cooperative program to address infectious diseases in humans, in domestic animals, and in wildlife. This program can serve as a focus for regular communications through working groups to address information transfer; to improve response to disease emergencies; to establish priorities for collaborative, focused investigations; and to pursue other areas of mutual interest. The program also can serve as a model and catalyst to stimulate the development of similar cooperative programs between state agencies that would network with the federal pro-

gram. Collaborative arrangements also can be developed to integrate the emergency response capabilities within the public health, domestic animal, and wildlife conservation communities. Response to emerging infectious diseases of wildlife should be augmented as needed by the combined capabilities of the different programs to minimize the potential for establishment and spread of wildlife diseases capable of infecting other species, including humans.

Collaboration can be improved at the international level as well. Although many international activities have succeeded, often via the WHO, difficult circumstances have required the involvement of institutions outside the usual public health agency loop, such as agricultural agencies. This was true when the West Nile virus emerged in the United States in 1999, when the H5N1 influenza virus emerged in Hong Kong in 1997, and when the Hendra virus emerged in Australia in 1994. In each case, turf issues arose, and in some instances efforts to protect agricultural markets seemed to be deemed more important than efforts to protect the public health. The Hong Kong public health authorities were exemplary in their decisive actions and early involvement of international collaborators. We may have been lucky that these zoonotics did not spread to cause further harm, but who is to say what the next agent will be like? The next step in solving such turf issues will involve recognizing the primacy of prevention and control of human disease.

GOVERNMENT ACTIONS

Some observers maintain that a number of government practices and policies have hindered the nation's efforts to address emerging infectious diseases, including zoonoses. For example, they cite the need for better mechanisms for distributing supplementary funding for handling emergencies. This problem was particularly evident with funding for studies of the West Nile virus and of hantavirus which emerged in the U.S. Southwest in the early 1990s. Such funding today must be disbursed according to federal acquisitions regulations, and this process can lead to delays in the distribution of funds and to inflexibility in selecting funding recipients. The network of regulations surrounding the biomedical community also has been singled out for criticism, with charges that the rules often do not address real risks or abuses, but rather reflect political perceptions. Such regulations affect animal experimentation, shipping of various disease-related agents, research on certain agents, and the use of certain vaccines for occupational safety, among many other areas. Critics maintain that not only do unwarranted restrictions fail to appreciably improve public or occupational safety, but they also limit research that may indeed reduce the risk from threat diseases.

There also is a role for expanded government action. For example, some private laboratories and managed care organizations have been slow to adopt the latest technology for identifying a number of the nontraditional zoonotic agents that appeared in foodstuffs in recent years. As a result, the foodstuff that is the source of the infections cannot be identified, which means that other individuals may continue to ingest the foodborne organisms and succumb to the disease. One way to help rectify these circumstances would be for the government to specify expectations of clinicians and laboratories in the private health care setting. For example, it would be useful to clarify what circumstances dictate the performance of a culture and submission of the isolate to a public health laboratory. To help increase participation by private managed care organizations, the government, perhaps through the Health Care Financing Administration (HCFA), may at first need to offer some type of incentive. Adjustments in both reimbursement policies and quality indicator requirements are candidate incentives that HCFA might entertain, as these investments are made more to benefit the public health than improve the outcome for the individual patient.

Federal agencies can take the lead in developing a common database for disease surveillance and monitoring that can be used to track infectious diseases and the emergence of new diseases. As part of this effort, a work group should be established along with existing advisers to develop a listing of "reportable" diseases that are to be entered into the system, with standards for data entry, reporting, and utilization by collaborating agencies and institutions. CDC has proposed developing a national electronic disease surveillance network for state and federal public health information on emerging infectious diseases, and this network should be expanded to include wildlife surveillance information on emerging zoonotic diseases and should be linked to agricultural intelligence.

In addition, the government can take additional steps to increase the capacity of public health agencies to detect, diagnose, and contain infectious disease outbreaks. Many of these agencies lack the basic computer equipment to communicate data on disease outbreaks electronically, and they cannot perform simple laboratory tests to diagnose infections. Most agencies have no up-to-date assessment of their current capacities and needs. (Indeed, since this workshop, Congress has passed the Public Health Improvement Act of 2000, which establishes grant programs to enable state and local public health agencies to assess their current capacities and identify their areas of greatest need, upgrade the ability of public health laboratories to identify disease-causing microbes, improve and expand electronic communication networks, develop plans to respond to public health emergencies, and train public health personnel.)

EDUCATION AND LEADERSHIP

Public education programs focused on emerging infectious diseases, including zoonoses, are critical and should be expanded. Such programs are needed both to increase awareness of the problems and to minimize undue fears. A joint approach might involve developing a better curriculum for use in schools and devising information programs to reach influential organizations and the media. One possible route would be for federal agencies to work collaboratively with an independent organization dedicated to public outreach.

There also are specific topics that might benefit from expanded public education efforts. For example, the expanding human population assures continued landscape changes, many of which can affect the emergence of zoonoses. Thus, the government and other organizations should become proactive in terms of developing and disseminating information that can help guide land development in a manner that gives greater consideration to disease prevention. Initial actions that can be considered include distributing authoritative publications, sponsoring public forums, and providing consultations on particular problems.

Many people in the United States, within government and among the public, have only minimal understanding of conditions in other countries. This is especially true regarding the developing world, where new zoonotic diseases are most likely to originate. It is critical to improve our general understanding of the various cultural, infrastructure, and other issues that will affect how the United States can best work with the world community to improve the surveillance, control, and management of disease.

Of course, improving the nation's ability to mount an effective and comprehensive program to manage zoonoses will require national leadership. To bring all elements of such a program together, the zoonosis community, working in concert, must devise a comprehensive plan that addresses all aspects of this problem, including research needs and the needs of an effective system for disease prevention and control.

As a model, the community might look to CDC's emerging disease plan. Strategic planning must not be biased by the most recent zoonotic disease episode, the West Nile virus. Although this virus might seem an ideal model, we would be better served by using a more complex model, one that would test all facets of candidate plans. The ultimate test of candidate plans is bovine spongiform encephalopathy and the resultant new variant Creutzfeldt-Jakob disease. Today, with the wisdom of hindsight, many observers are saying that the ministries of agriculture and health in the United Kingdom failed to react in a timely fashion and with proper scope and scale of actions to deal with what was clearly a great risk

to public health. Every aspect of the ministries' disease prevention and control responsibilities has been called into question. This zoonosis also may be instructive in a larger historic sense, especially in its unbridled extension into the worlds of macroeconomics, international trade, national politics, and even regional governance.

Appendix A

Glossary and Acronyms

GLOSSARY

This glossary is intended to define terms commonly encountered throughout this report as well as some terms that are commonly used in the public health arena. This glossary is not all inclusive. New terms and new usages of existing terms will emerge with time and with advances in technology. The definitions for the terms presented here were compiled from a multitude of sources.

Anthropogenic: Of, relating to, or resulting from the influence of human beings on nature.

Antibiotic: Class of substances or chemicals that can kill or inhibit the growth of bacteria. Originally antibiotics were derived from natural sources (e.g., penicillin was derived from molds), but many currently used antibiotics are semisynthetic and are modified by the addition of artificial chemical components.

Antibiotic resistance: Property of bacteria that confers the capacity to inactivate or exclude antibiotics or a mechanism that blocks the inhibitory or killing effects of antibiotics.

Antimicrobial agents: Class of substances that can destroy or inhibit the growth of pathogenic groups of microorganisms, including bacteria, viruses, parasites, and fungi.

Attenuate: To reduce the severity of (a disease) or virulence or vitality of (a pathogenic agent).

Bacteremia: The presence of bacteria in the bloodstream.

Bacteria: Microscopic, single-celled organisms that have some biochemical and structural features different from those of animal and plant cells.

Bacteriophage: A virus that infects bacteria—also called phage.

Basic research: Fundamental, theoretical, or experimental investigation to advance scientific knowledge, with immediate practical application not being a direct objective.

Benchmark: For a particular indicator or performance goal, the industry measure of best performance. The benchmarking process identifies the best performance in the industry (health care or nonhealth care) for a particular process or outcome, determines how that performance is achieved, and applies the lessons learned to improve performance.

Broad-spectrum antibiotic: An antibiotic effective against a large number of bacterial species. It generally describes antibiotics effective against both gram-positive and gram-negative classes of bacteria.

BSL (Biosafety Level): Specific combinations of work practices, safety equipment, and facilities, designed to minimize the exposure of workers and the environment to infectious agents. Biosafety Level 1 applies to agents that do not ordinarily cause human disease. Biosafety Level 2 is appropriate for agents that can cause human disease but whose potential for transmission is limited. Biosafety Level 3 applies to agents that may be transmitted by the respiratory route, which can cause serious infection. Biosafety Level 4 is used for the diagnosis of exotic agents that pose a high risk of life-threatening disease, which may be transmitted by the aerosol route and for which there is no vaccine or therapy.

Campylobacter: The leading cause of bacterial food poisoning, caused by a Campylobacter jejuni, most often spread by contact with raw or undercooked poultry. A single drop of juice from a contaminated chicken is enough to make someone sick with campylobacteriosis (disease due to Campylobacter bacteria).

CDC (Centers for Disease Control and Prevention): A public health agency of the U.S. Department of Health and Human Services whose mission is to promote health and quality of life by preventing and controlling disease, injury, and disability.

Clinical practice guidelines: Systematically developed statements that assist practitioners and patients with decision making about appropriate health care for specific clinical circumstances.

Clinical research: Investigations aimed at translating basic, fundamental science into medical practice.

Clinical trials: As used in this report, research with human volunteers

to establish the safety and efficacy of a drug, such as an antibiotic or a vaccine.

Clinician: One qualified or engaged in the clinical practice of medicine, psychiatry, or psychology, as distinguished from one specializing in laboratory or research techniques in the same fields.

Cutaneous: Related to the skin.

DHHS (U.S. Department of Health and Human Services): The U.S. government's principal agency for protecting the health of all Americans and providing essential human services, especially for those who are least able to help themselves (www.os.dhhs.gov).

DoD (U.S. Department of Defense): DoD trains and equips the armed forces through three military departments—the Army, Navy, and Air Force—whose primary job is to train and equip their personnel to perform war fighting, peace keeping, and humanitarian/disaster assistance tasks.

Emerging infections: Any infectious disease that has come to medical attention within the last two decades or for which there is a threat that its prevalence will increase in the near future. Many times, such diseases exist in nature as zoonoses and emerge as human pathogens only when humans come into contact with a formerly isolated animal population, such as monkeys in a rain forest that are no longer isolated because of deforestation. Drug-resistant organisms could also be included as the cause of emerging infections since they exist because of human influence. Some recent examples of agents responsible for emerging infections include human immunodeficiency virus, Ebola virus, and multidrug-resistant Mycobacterium tuberculosis.

Encephalitis: An acute inflammatory disease of the brain due to direct viral invasion or to hypersensitivity initiated by a virus or other foreign protein.

Endemic: Disease that is present in a community or common among a group of people; said of a disease continually prevailing in a region.

Enzootic: A disease of low morbidity that is constantly present in an animal community.

Epizootic: A disease of high morbidity that is only occasionally present in an animal community.

***Escherichia coli O157:H7*:** A dangerous form of *Escherichia coli,* the colon bacillus, a bacterium that normally lives in the human colon. *E. coli O157:H7* is a major health problem, causing hemorrhagic colitis, the hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura.

Etiology: Science and study of the causes of diseases and their mode of operation.

FDA (Food and Drug Administration): A public health agency of the U.S. Department of Health and Human Services charged with protecting American consumers by enforcing the Federal Food, Drug, and Cosmetic Act and several related health laws.

Flavivirus: Any of a group of arboviruses that contain a single strand of RNA, are transmitted by ticks and mosquitoes, and include the causative agents of dengue, Japanese B encephalitis, and yellow fever.

FoodNet: A set of activities designed to determine and monitor the burden of foodborne diseases and improve understanding of the proportion of foodborne diseases attributable to various pathogens. It is an example of population-based surveillance in the emerging infections programs.

Formulary: List of drugs approved for the treatment of various medical indications. Originally created as a cost control measure, it has been used more recently to guide the use of antibiotics on the basis of information about resistance patterns.

GP (glycoprotein): A molecule that consists of a carbohydrate plus a protein.

Gram-negative: Gram-negative bacteria lose the crystal violet stain (and take the color of the red counterstain) in Gram's method of staining.

Gram-positive: Gram-positive bacteria, such as anthrax, retain the color of the crystal violet stain in the Gram stain. This is characteristic of bacteria that have a cell wall composed of a thick layer of a particular substance (called peptidologlycan).

Immunogenicity: The property that endows a substance with the capacity to provoke an immune response or the degree to which a substance possesses this property.

Incidence: The frequency of new occurrences of disease within a defined time interval. Incidence rate is the number of new cases of a specified disease divided by the number of people in a population over a specified period of time, usually 1 year.

Infection: The invasion of the body or a part of the body by a pathogenic agent, such as a microoganism or virus. Under favorable conditions the agent develops or multiplies, the results of which may produce injurious effects. Infection should not be confused with disease.

Listeria monocytogenes: A bacteria that can cause encephalitis, meningitis, bloodborne infection and death. It is especially hazardous for pregnant women (posing a threat of miscarriage or stillbirth), newborn babies, the elderly, and immune-deficient patients. It causes about 28% of deaths due to food poisoning.

Macrophages: A type of white blood cell that ingests foreign material. Macrophages are key players in the immune response to foreign invaders such as infectious microorganisms.

NCID (National Center for Infectious Diseases): Its mission is to prevent illness, disability, and death caused by infectious diseases in the United States and around the world. NCID conducts surveillance, epidemic investigations, epidemiological and laboratory research, training, and public education programs to develop, evaluate, and promote prevention and control strategies for infectious diseases.

NIAID (National Institute of Allergy and Infectious Diseases): A division of NIH that provides the major support for scientists conducting research aimed at developing better ways to diagnose, treat, and prevent the many infectious, immunological, and allergenic diseases that afflict people worldwide.

NIH (National Institutes of Health): A public health agency of the U.S. Department of Health and Human Services whose goal is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability, from the rarest genetic disorder to the common cold.

Pandemic: Occurring over a wide geographic area and affecting an exceptionally high proportion of the population.

Parvoviruses: A group of extremely small, morphologically similar, ether-resistant DNA viruses; the group includes the osteolytic hamster viruses and adeno-associated viruses.

Plasmids: A self-replicating (autonomous) circle of DNA distinct from the chromosomal genome of bacteria. A plasmid contains genes normally not essential for cell growth or survival. Some plasmids can integrate into the host genome, be artificially constructed in the laboratory, and serve as vectors (carriers) in cloning.

Prions: A newly discovered type of disease-causing agent, neither bacterial nor fungal nor viral, and containing no genetic material. A prion is a protein that occurs normally in a harmless form. By folding into an aberrant shape, the normal prion turns into a rogue agent. It then coopts other normal prions to become rogue prions.They have been held responsible for a number of degenerative brain diseases, including mad cow disease, Creutzfeldt-Jacob disease, and possibly some cases of Alzheimer's disease.

Prophylactic antibiotics: Antibiotics that are administered before evidence of infection with the intention of warding off disease.

PulseNet: A national network of public health laboratories that perform DNA "fingerprinting" on bacteria that may be foodborne. The network permits rapid comparison of these "fingerprint" patterns through an electronic database at CDC.

Purulent: Containing, consisting of, or being pus.

Salmonella: A group of bacteria that cause typhoid fever, food poisoning, and enteric fever from contaminated food products.

Serotype: The kind of microorganism as characterized by serologic typing (testing for recognizable antigens on the surface of the microorganism).

Sporulate: To form spores.

Surveillance systems: Used in this report to refer to data collection and record keeping to track the emergence and spread of disease-causing organisms such as antibiotic-resistant bacteria.

Toxoplasma: A genus of sporozoa that are intracellular parasites of many organs and tissues of birds and mammals, including man.

USAMRIID (U.S. Army Medical Research Institute of Infectious Diseases): It is the lead medical research laboratory for the U.S. Biological Defense Research Program, which conducts research to develop strategies, products, information, procedures, and training programs for medical defense against biological warfare threats and naturally occurring infectious diseases that require special containment. It is an organization of the U.S. Army Medical Research and Materiel Command (USAMRMC).

USDA (U.S. Department of Agriculture): Founded in 1862, its mission is to enhance the quality of life for the American people by supporting production of agriculture and ensuring a safe, affordable, nutritious, and accessible food supply.

VA (Department of Veterans Affairs): A cabinet-level department that has the care of veterans as its primary mission and is composed of three administrations: Veterans Health Administration, Veterans Benefit Administration, and National Cemetery Administration.

Vaccine: A preparation of living, attenuated, or killed bacteria or viruses, fractions thereof, or synthesized or recombinant antigens identical or similar to those found in a disease-causing organism that is administered to raise immunity to a particular microorganism.

VHF (viral hemorrhagic fevers): A group of illnesses caused by viruses of four distinct families: arenaviruses, filoviruses, bunyaviruses, and flaviviruses.

Virulence: The ability of any infectious agent to produce disease. The virulence of a microoganism (such as a bacterium or virus) is a measure of the severity of the disease it is capable of causing.

Xenogeneic: Derived from, originating in, or being a member of another species.

Zoonotic disease or infection: An infection or infectious disease that may be transmitted from vertebrate animals (e.g., a rodent) to humans.

ACRONYMS

AFMIC	Armed Forces Medical Intelligence Center
APHIS	Animal and Plant Health Inspection Service
BSE	bovine spongiform encephalopathy
FSIS	Food Safety and Inspection Service
HCFA	Health Care Financing Administration
LRN	Laboratory Response Network
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NLS	National Laboratory System
NPIP	National Poultry Improvement Plan
NVSL	National Veterinary Services Laboratory
PCR	polymerase chain reaction
PHLS	Public Health Laboratory Service
TSE	transmissible spongiform Encephalopathy
VDL	veterinary diagnostic laboratory
VEE	Venezuelan equine encephalitis
VHA	Veterans Health Administration
VS	Veterinary Services

APPENDIX
B

Workshop Agenda
The Emergence of Zoonotic Diseases

June 7–8, 2000
Lecture Room
National Academy of Sciences
2101 Constitution Avenue, N.W., Washington, DC

AGENDA

Wednesday, June 7, 2000

8:00 Continental Breakfast
8:30 **Welcome and Opening Remarks**
Joshua Lederberg, Ph.D., Chair, Forum on Emerging Infections
8:45 **Keynote Address**
Frederick A. Murphy, D.V.M, Ph.D.
Professor, Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California at Davis

Session I: The Importance of Zoonotic Diseases

This session will address the question of why policy makers, public health officials, and the public should be concerned about zoonotic diseases. The session will explore this question from the perspectives of disease severity in humans and the economic and trade implications.

9:30 **Pathogenesis and virulence of zoonotic infections in humans**
Robert E. Shope, M.D., Professor of Pathology,
Department of Pathology, University of Texas Medical Branch

10:00 **The potential "bioweaponization" of zoonotic diseases**
David R. Franz, D.V.M, Ph.D., Vice President,
Chemical and Biological Defense Division,
Southern Research Institute

10:30 **Break**

10:45 **Xenotransplantation**
Louisa Chapman, M.D., Medical Epidemiologist,
Division of AIDS, STD, and TB Laboratory Research, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

11:15 **The economic and trade impacts of zoonotic diseases**
Peter Cowen, D.V.M, Ph.D., M.P.V.M., Associate Professor,
Department of Food Animal Health and Resource Management,
North Carolina State College of Veterinary Medicine

11:45 **Lunch**

Session II: Factors of Emergence

In this session, we will examine the factors that are involved in the emergence of zoonotic diseases. We will examine the current state of the science in several areas and identify gaps in our knowledge.

12:30 **Interspecies transfer of infectious agents**
Robert G. Webster, Ph.D., Chairman,
Department of Virology and Molecular Biology, St. Jude Children's Research Hospital

1:00 **Variation and evolution in zoonotic pathogens**
Paul W. Ewald, Ph.D., Professor,
Department of Biology, Amherst College

1:30 **Practices and policies to protect human health from antibiotic-resistant pathogens**
Stephen F. Sundlof, D.V.M., Ph.D., Director,
Center for Veterinary Medicine, Food and Drug Administration,
U.S. Department of Health and Human Services

2:00 **Ecological sources of zoonotic diseases**
Robert Tesh, M.D., Professor of Research,
Department of Pathology, University of Texas Medical Branch

2:30 **Vectorborne zoonotic diseases**
John Roehrig, Ph.D., Chief, Arbovirus Diseases Branch,
Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

3:00 **Break**

3:15 **Mathematical models and predictors of disease outbreaks**
Dana A. Focks, Ph.D., Senior Scientist,
Center for Medical, Agricultural and Veterinary Entomology,
Agricultural Research Service, U.S. Department of Agriculture

3:45 **The role of native birds and other wildlife on the emergence of zoonotic diseases**
Milton Friend, Ph.D., Executive Director,
Salton Sea Science Subcommittee, U.S. Department of the Interior

4:15 **Animal husbandry practices and risk factors**
Fred Brown, Ph.D., Visiting Scientist,
Plum Island Animal Disease Center, U.S. Department of Agriculture

4:45 **Natural history of HIV: A zoonotic disease**
Lisa Chakrabarti, Ph.D., Senior Scientist, Pasteur Institute, and Staff Investigator, Aaron Diamond AIDS Research Center

5:15 **Adjournment of the first day**

Thursday, June 8, 2000

7:30 Continental Breakfast

8:00 **Opening Remarks**
Joshua Lederberg, Ph.D., Chair, Forum on Emerging Infections

Session III: Diagnosis and Control of Zoonotic Infections

Detection of zoonotic diseases requires a variety of disciplines and techniques, from the field to the lab and from the molecular to the organismal levels. The ability to recognize and treat outbreaks of zoonotic disease is linked to accurate and timely diagnostic methods. This section will explore current methodologies and future needs to detect and treat zoonotic infections.

8:15 **Pathology and early recognition of zoonotic disease outbreaks**
Tracey S. McNamara, D.V.M., Head, Department of Pathology,
Wildlife Conservation Society, Bronx Zoo

8:45 **Molecular and other technologies for rapid diagnosis of zoonotic agents**
Alfred D. Steinberg, M.D., Senior Fellow, Mitretek

9:15 **Methods and models for pathogen discovery**
W. Ian Lipkin, M.D., Professor, Departments of Neurology,
Anatomy and Neurobiology, and Microbiology and Molecular Genetics, University of California, Irvine

9:45 **Vaccines for emerging zoonoses: Marburg virus paradigm**
Alan Schmaljohn, Ph.D., Chief, Department of Viral Pathogenesis & Immunology, Virology Division, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD

10:15 **Break**

Session IV: Surveillance and Management of Zoonotic Disease Outbreaks

The complexity of zoonotic disease detection, prevention, and control requires a multidisciplinary approach. We need to learn how to better communicate across disciplines and to have in place rapid and effective surveillance and response efforts based on scientifically sound measures.

10:30 **Public health laboratory surveillance**
Mary J. R. Gilchrist, Ph.D., Director,
University of Iowa Hygienic Laboratory

11:00 **Challenges of vectorborne disease surveillance from the local perspective: West Nile virus experience**
Marci C. Layton, M.D., Assistant Commissioner,
Bureau of Communicable Diseases, New York City Department of Health

11:30 **Veterinary public health surveillance**
Randall L. Crom, D.V.M., Staff Veterinarian,
Veterinary Services Emergency Programs, Animal and Plant Health Inspection Service, U.S. Department of Agriculture

12:00 **Lunch**

1:00 **Petborne zoonoses: Detection and surveillance challenges**
Lisa Conti, D.V.M., M.P.H, Dipl. ACVPM, State Public Health Veterinarian, Florida Department of Health

1:30 **Identification and containment of unknown and rare pathogens**
C. J. Peters, Ph.D., Chief, Special Pathogen Branch,
Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

2:00 **Technological and personnel investments for a robust public and animal health system**
Tentative Confirmation: Roger Breeze, Ph.D., Associate Administrator, Agricultural Research Service, U.S. Department of Agriculture

2:30 **The threat and impact of animals as carriers of human diseases**
Kaye Wachsmuth, Ph.D., Deputy Director,
Food Safety Inspection Service, U.S. Department of Agriculture

3:00 **Legislative and policy concerns in protecting the nation's health**
David Bowen, Ph.D., Office of U.S. Senator Edward M. Kennedy (D-MA)
3:30 **Break**

Session V: Identifying the Threats and Mitigating the Impact

The challenges and opportunities to address the threat of emerging and reemerging zoonotic diseases and to effect public policy in this area will be identified through summary and assessment discussions with all participants.

3:45 **Summary and Open Discussion with Forum Members, Speakers, and Workshop Attendees**
4:45 **The compelling evidence to investigate and prevent zoonotic diseases: Where do we go from here?**
Joshua Lederberg, Ph.D., Chair, Forum on Emerging Infections
5:15 **Adjournment**

APPENDIX C

Forum Member and Speaker Biographies

FORUM MEMBERS

JOSHUA LEDERBERG, Ph.D. *(Chair)*, is professor emeritus of molecular genetics and informatics and Sackler Foundation Scholar at the Rockefeller University, New York, New York. His lifelong research, for which he received the Nobel Prize in 1958, has been in genetic structure and function in microorganisms. He has a keen interest in international health and was co-chair of a previous Institute of Medicine Committee on Emerging Microbial Threats to Health (1990–1992) and currently is co-chair of the Committee on Emerging Microbial Threats to Health in the 21st Century. He has been a member of the National Academy of Sciences since 1957 and is a charter member of the Institute of Medicine.

VINCENT AHONKHAI, M.D., is vice president and director at SmithKline Beecham Pharmaceuticals and is responsible for Clinical R&D and Medical Affairs in Anti-Infectives and Biologicals, North America. He has held this position since 1995, overseeing a product portfolio that includes antibiotics, antivirals, and vaccines. After completing medical school and internships in Nigeria, Dr. Ahonkhai obtained additional training in pediatric residency, followed by a fellowship in infectious diseases in adults and pediatrics at the State University of New York–Downstate Medical Center, Brooklyn, N.Y., from 1975 to 1980. He then joined the faculty as assistant professor, Department of Pediatrics. In 1982, Dr. Ahonkhai started his pharmaceutical industry career as associate director of infectious diseases at Merck, where he rose to director level. Subsequently, he moved to

the Robert Wood Johnson Pharmaceutical Research Institute, where he served first as head of infectious diseases and later as executive director of dermatology and wound healing. Dr. Ahonkhai is board certified in pediatrics and is a long-standing member and fellow of several professional organizations, including the American Medical Association, National Medical Association, American Society for Microbiology, Infectious Diseases Society of America (fellow), Pediatric Infectious Diseases Society, and American Academy of Pharmaceutical Physicians (vice president, Membership Development Committee, and board member).

STEVEN J. BRICKNER, Ph.D., is research advisor for antibacterials chemistry at Pfizer Global Research and Development. He received his Ph.D. in organic chemistry from Cornell University and was an NIH postdoctoral research fellow at the University of Wisconsin-Madison. Dr. Brickner is a medicinal chemist with nearly 20 years of research experience in the pharmaceutical industry, all focused on the discovery and development of novel antibacterial agents. He is an inventor/co-inventor on 21 U.S. patents and has published numerous scientific papers, primarily in the area of the oxazolidinones. Prior to joining Pfizer in 1996, he led a team at Pharmacia and Upjohn that discovered and developed linezolid, the first member of a new class of antibiotics to be approved in the last 35 years.

GAIL H. CASSELL, Ph.D., is vice president of infectious diseases research, drug discovery research, and clinical investigation at Eli Lilly & Company. Previously, she was the Charles H. McCauley professor and (since 1987) chair of the Department of Microbiology, University of Alabama, Schools of Medicine and Dentistry, Birmingham, a department which, under her leadership, has ranked first in research funding from the National Institutes of Health since 1989. She is a member of the Director's Advisory Committee of the Centers for Disease Control and Prevention. Dr. Cassell is past president of the American Society for Microbiology (ASM) and is serving her third three-year term as chairman of the Public and Scientific Affairs Board of ASM. She is a former member of the National Institutes of Health Director's Advisory Committee and a former member of the Advisory Council of the National Institute of Allergy and Infectious Diseases. She has also served as an advisor on infectious diseases and indirect costs of research to the White House Office on Science and Technology and was previously chair of the Board of Scientific Counselors of the National Center for Infectious Diseases, Centers for Disease Control and Prevention. Dr. Cassell served eight years on the Bacteriology-Mycology-II Study Section and served as its chair for three years. She serves on the editorial boards of several prestigious scientific journals and has authored over 275 articles and book chapters. She has been intimately involved in the establishment of science policy and legislation related to biomedical research and public health. Dr. Cassell has received several national and

international awards and an honorary degree for her research on infectious diseases.

GARY CHRISTOPHERSON is senior advisor for force health protection at the U.S. Department of Defense, Reserve Affairs. Previously, as principal deputy assistant secretary of defense for health affairs, he managed policy, the Defense Health Program budget, and performance for the Military Health System, including the $16 billion TRICARE health care system and force health protection. In that role he also launched the Department of State's infectious disease surveillance and response system and served as co-chair on the White House's infectious disease surveillance and response subcommittee. He has also been a key figure in the department's force health protection initiative against anthrax. In early 1998 he also served as the acting assistant secretary of defense for health affairs. Joining the Department of Defense in 1994, he has served as health affairs acting principal deputy assistant secretary and senior advisor where he provided advice on a wide range of health issues and managed the relationships with the White House and other federal agencies. Previously, he served 2 years (1992–1994) with the Office of Presidential Personnel at the White House and the Presidential Transition Office. As associate director, he managed the President's appointments to the Departments of Health and Human Services and Defense as well as 10 other departments. Prior to that, he served in a number of senior health positions with the Congress and with public and private health agencies.

GORDON DEFRIESE, Ph.D., is professor of social medicine and professor of medicine (in the Division of General Medicine and Clinical Epidemiology) at the University of North Carolina, Chapel Hill School of Medicine. In addition, he holds appointments as professor of epidemiology and health policy and administration in the UNC-CH School of Public Health and as professor of dental ecology in the UNC-CH School of Dentistry. From 1986–2000, he served as co-director of the Robert Wood Johnson Clinical Scholars Program, co-sponsored by the UNC-CH School of Medicine and the Cecil G. Sheps Center for Health Services Research. He received his Ph.D. from the University of Kentucky College of Medicine. Some of his research interests are in the areas of health promotion and disease prevention, medical sociology, primary health care, rural health care, cost–benefit analyses, and cost effectiveness. He is a past president of the Association for Health Services Research and a fellow of the New York Academy of Medicine. He is founder of the Partnership for Prevention, a coalition of private-sector business and industry organizations, voluntary health organizations, and state and federal public health agencies based in Washington, D.C. that have joined together to work toward the elevation of disease prevention among the nation's health policy priorities. He is an at-large member of the National Board of Medical Examiners. Since 1994

he has served as President and CEO of the North Carolina Institute of Medicine. He is Editor-in-Chief and Publisher of the North Carolina Medical Journal.

CEDRIC E. DUMONT, M.D., is medical director for the Office of Medical Services (MED) at the U.S. Department of State. Dr. Dumont graduated from Columbia University with a B.A. in 1975 and obtained his medical degree from Tufts University School of Medicine in 1980. Dr. Dumont is a board-certified internist with subspecialty training in infectious diseases. He completed his internal medicine residency in 1983 and infectious diseases fellowship in 1988 at Georgetown University Hospital in Washington, D.C. Dr. Dumont has been a medical practitioner for over 19 years, 2 of which included service in the Peace Corps. Since joining the Department of State in 1990, he has had substantial experience overseas in Dakar, Bamako, Kinshasa, and Brazzaville. For the past 3 years, as the medical director for the Department of State, Dr. Dumont has promoted the health of all U.S. government employees serving overseas by encouraging their participation in a comprehensive health maintenance program and by facilitating their access to high-quality medical care. Dr. Dumont is a very strong supporter of the professional development and advancement of MED's highly qualified professional staff. In addition, he has supported and encouraged the use of an electronic medical record, which will be able to monitor the health of all its beneficiaries, not only during a specific assignment but also throughout their careers in the Foreign Service.

JESSE L. GOODMAN, M.D., M.P.H., was professor of medicine and chief of infectious diseases at the University of Minnesota and is now serving as deputy director for the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research, where he is active in a broad range of scientific, public health, and policy issues. After joining the FDA commissioner's office, he has worked closely with several centers and helped coordinate FDA's response to the antimicrobial resistance problem. He was co-chair of a recently formed federal interagency task force which developed the national Public Health Action Plan on antimicrobial resistance. He graduated from Harvard College and attended the Albert Einstein College of Medicine followed by training in internal medicine, hematology, oncology, and infectious diseases at the University of Pennsylvania and University of California, Los Angeles, where he was also chief medical resident. He received his master's of public health from the University of Minnesota. He has been active in community public health activities, including creating an environmental health partnership in St. Paul, Minnesota. In recent years, his laboratory's research has focused on the molecular pathogenesis of tickborne diseases. His laboratory isolated the etiological intracellular agent of the emerging tickborne infection, human granulocytic ehrlichiosis, and identified its leukocyte receptor. He has also been an active

clinician and teacher and has directed or participated in major multicenter clinical studies. He is a Fellow of the Infectious Diseases Society of America and, among several honors, has been elected to the American Society for Clinical Investigation.

RENU GUPTA, M.D., is vice president and head of U.S. clinical research and development at Novartis Pharmaceuticals. Previously, she was vice president of medical, safety, and therapeutics at Covance. Dr. Gupta is a board certified pediatrician, with subspeciality training in infectious diseases from Children's Hospital of Philadelphia and the University of Pennsylvania. She was also a postdoctoral research fellow in microbiology at the University of Pennsylvania and the Wistar Institute of Anatomy and Biology, where she conducted research on the pathogenesis of infectious diseases. Dr. Gupta received her M.B.,Ch.B with distinction from the University of Zambia, where she examined the problem of poor compliance in the treatment of tuberculosis in rural and urban Africa. She is currently active in a number of professional societies, including the Infectious Diseases Society of America and the American Society of Microbiology. She is a frequent presenter at the Interscience Conference on Antimicrobial Agents and Chemotherapy and other major congresses and has been published in leading infectious diseases periodicals. From 1989 to mid-1998, Dr. Gupta was with Bristol-Myers Squibb Company, where she directed clinical research as well as strategic planning for the Infectious Diseases and Immunology Divisions. For the past several years, her work has focused on a better understanding of the problem of emerging infections. This has led to her pioneering efforts in establishing the Global Antimicrobial Surveillance Program, SENTRY, a private-academic-public sector partnership. Dr. Gupta chaired the steering committee for the SENTRY Antimicrobial Surveillance Program. She remains active in women and children's health issues, and is currently furthering education and outreach initiatives. More recently Dr. Gupta has been instrumental in the formation of the Harvard-Pharma Management Board, of which she is a member, to further the educational goals of the Scholars in Clinical Science Program at the Harvard Medical School.

MARGARET A. HAMBURG, M.D., is vice president for biological programs, Nuclear Threat Initiative, Washington, D.C. The NTI is a new organization whose mission is to strengthen global security by reducing the risk of use of nuclear and other weapons of mass destruction and preventing their spread. Dr. Hamburg is in charge of the biological program area. Before taking on her current position, she was assistant secretary for planning and evaluation at the U.S. Department of Health and Human Services, serving as a principal policy adviser to the Secretary of Health and Human Services with responsibilities including policy formulation and analysis, the development and review of regulations and/or legislation, budget analysis,

strategic planning, and the conduct and coordination of policy research and program evaluation. Prior to this, she served for almost 6 years as the commissioner of health for New York City. As chief health officer in the nation's largest city, Dr. Hamburg's many accomplishments included the design and implementation of an internationally recognized tuberculosis control program that produced dramatic declines in tuberculosis cases, the development of initiatives that raised childhood immunization rates to record levels, and the creation of the first public health bioterrorism preparedness program in the nation. She completed her internship and residency in internal medicine at the New York Hospital/Cornell University Medical Center and is certified by the American Board of Internal Medicine. Dr. Hamburg is a graduate of Harvard College and Harvard Medical School. She currently serves on the Harvard University Board of Overseers. She has been elected to membership in the Institute of Medicine, the New York Academy of Medicine, and the Council on Foreign Relations and is a fellow of the American Association for the Advancement of Science.

CAROLE A. HEILMAN, Ph.D., is director of the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Heilman received her bachelor's degree in biology from Boston University in 1972 and earned her master's degree and doctorate in microbiology from Rutgers University in 1976 and 1979. Dr. Heilman began her career at the National Institutes of Health as a postdoctoral research associate with the National Cancer Institute, where she carried out research on the regulation of gene expression during cancer development. In 1986 she came to NIAID as the influenza and viral respiratory diseases program officer in DMID, and in 1988 she was appointed chief of the respiratory diseases branch, where she coordinated the development of acellular pertussis vaccines. She joined the Division of AIDS as deputy director in 1997 and was responsible for developing the Innovation Grant Program for approaches in HIV vaccine research. She is the recipient of several notable awards for outstanding achievement. Throughout her extramural career Dr. Heilman has contributed articles on vaccine design and development to many scientific journals and has served as a consultant to the World Bank and the World Health Organization. She is also a member of several professional societies, including the Infectious Diseases Society of America, the American Society for Microbiology, and the American Society of Virology.

JAMES M. HUGHES, M.D., received his B.A. in 1966 and M.D. in 1971 from Stanford University. He completed a residency in internal medicine at the University of Washington and a fellowship in infectious diseases at the University of Virginia. He is board-certified in internal medicine, infectious diseases, and preventive medicine. He first joined the Centers for Disease Control and Prevention as an Epidemic Intelligence Service officer

in 1973. During his CDC career, he has worked primarily in the areas of foodborne disease and infection control in health care settings. He became director of the National Center for Infectious Diseases in 1992. The center is currently working to address domestic and global challenges posed by emerging infectious diseases and the threat of bioterrorism. He is a fellow of the American College of Physicians, the Infectious Diseases Society of America, and the American Association for the Advancement of Science. He is an assistant surgeon general in the U.S. Public Health Service.

SAMUEL L. KATZ, M.D., is Wilburt C. Davison professor and chairman emeritus of pediatrics at Duke University Medical Center. He has concentrated his research on infectious diseases, focusing primarily on vaccine research, development and policy. Dr. Katz has served on a number of scientific advisory committees and is the recipient of many prestigious awards and honorary fellowships in international organizations. He earned his M.D. at Harvard Medical School and completed his residency training at Boston hospitals. He became a staff member at Children's Hospital, working with Nobel Laureate John Enders, during which time they developed the attenuated measles virus vaccine now used throughout the world. He has chaired the Committee on Infectious Diseases of the American Academy of Pediatrics (the Redbook Committee), the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention, the Vaccine Priorities Study of the Institute of Medicine (IOM), and several World Health Organization (WHO) and Children's Vaccine Initiative panels on vaccines. He is a member of many scientific advisory committees including those of the National Institutes of Health, IOM, and WHO. Dr. Katz's published studies include abundant original scientific articles, chapters in textbooks, and many abstracts, editorials, and reviews. He is the co-editor of a textbook on pediatric infectious diseases and has given many named lectures in the United States and abroad. Currently he co-chairs the Indo-US Vaccine Action Program as well as the National Network for Immunization Information (NNii).

MARCELLE LAYTON, M.D., is the assistant commissioner for the Bureau of Communicable Diseases at the New York City Department of Health. The bureau is responsible for the surveillance and control of 51 infectious diseases and conditions reportable under the New York City Health Code. Current areas of concern include antibiotic resistance; foodborne, waterborne, and tickborne diseases; hepatitis C; and biological disaster planning for the potential threats of bioterrorism and pandemic influenza. Dr. Layton received her medical degree from Duke University. She completed an internal medicine residency at the University Health Science Center in Syracuse, New York, and an infectious disease fellowship at Yale University. In addition, Dr. Layton spent two years with the Centers for Disease Control and Prevention as a fellow in the Epidemic Intelligence

Service, where she was assigned to the New York City Department of Health. In the past, she has volunteered or worked with the Indian Health Service, the Alaskan Native Health Service, and clinics in northwestern Thailand and central Nepal.

CARLOS LOPEZ, Ph.D., is a research fellow with Research Acquisitions, Eli Lilly Research Laboratories. He received his Ph.D. from the University of Minnesota in 1970. Dr. Lopez was awarded the NTRDA postdoctoral fellowship. After his fellowship he was appointed assistant professor of pathology at the University of Minnesota, where he did his research on cytomegalovirus infections in renal transplant recipients and the consequences of those infections. He was next appointed assistant member and head of the Laboratory of Herpesvirus Infections at the Sloan Kettering Institute for Cancer Research, where his research focused on herpes virus infections and the resistance mechanisms involved. Dr. Lopez's laboratory contributed to the immunological analysis of the earliest AIDS patients at the beginning of the AIDS epidemic in New York. He is coauthor of one of the seminal publications on this disease as well as many scientific papers and is co-editor of six books. Dr. Lopez has been a consultant to numerous agencies and organizations, including the National Institutes of Health, the Department of Veterans Affairs, and the American Cancer Society.

STEPHEN S. MORSE, Ph.D., is director of the Center for Public Health Preparedness at the Mailman School of Public Health of Columbia University and a faculty member in the Epidemiology Department. Dr. Morse recently returned to Columbia from 4 years in government service as program manager at the Defense Advanced Research Projects Agency (DARPA), where he co-directed the Pathogen Countermeasures program and subsequently directed the Advanced Diagnostics program. Before coming to Columbia, he was assistant professor of virology at the Rockefeller University in New York, where he remains an adjunct faculty member. Dr. Morse is the editor of two books, *Emerging Viruses* (Oxford University Press, 1993; paperback, 1996) (selected by "American Scientist" for its list of "100 Top Science Books of the 20th Century"), and *The Evolutionary Biology of Viruses* (Raven Press, 1994). He currently serves as a Section Editor of the CDC journal "Emerging Infectious Diseases" and was formerly an Editor-in-Chief of the Pasteur Institute's journal "Research in Virology". Dr. Morse was chair and principal organizer of the 1989 NIAID/NIH Conference on Emerging Viruses (for which he originated the term and concept of emerging viruses/infections); served as a member of the Institute of Medicine-National Academy of Sciences' Committee on Emerging Microbial Threats to Health (and chaired its Task Force on Viruses), and was a contributor to its report, *Emerging Infections* (1992); was a member of the IOM's Committee on Xenograft Transplantation; currently

serves on the Steering Committee of the IOM's Forum on Emerging Infections, and has served as an adviser to WHO (World Health Organization), PAHO (Pan American Health Organization), FDA, the Defense Threat Reduction Agency (DTRA), and other agencies. He is a fellow of the New York Academy of Sciences and a past chair of its Microbiology Section. He was the founding chair of ProMED (the nonprofit international Program to Monitor Emerging Diseases) and was one of the originators of ProMED-mail, an international network inaugurated by ProMED in 1994 for outbreak reporting and disease monitoring using the Internet. Dr. Morse received his Ph.D. from the University of Wisconsin-Madison.

MICHAEL T. OSTERHOLM, Ph.D., M.P.H., is director of the Center for Infectious Disease Research and Policy at the University of Minnesota where he is also professor at the School of Public Health. Previously, Dr. Osterholm was the state epidemiologist and chief of the Acute Disease Epidemiology Section for the Minnesota Department of Health. He has received numerous research awards from the National Institute of Allergy and Infectious Diseases and the Centers for Disease Control and Prevention (CDC). He served as principal investigator for the CDC-sponsored Emerging Infections Program in Minnesota. He has published more than 240 articles and abstracts on various emerging infectious disease problems and is the author of the best selling book, Living Terrors: What America Needs to Know to Survive the Coming Bioterrorist Catastrophe. He is past president of the Council of State and Territorial Epidemiologists. He currently serves on the National Academy of Sciences, Institute of Medicine (IOM) Forum on Emerging Infections. He has also served on the IOM Committee, Food Safety, Production to Consumption, the IOM Committee on the Department of Defense Persian Gulf Syndrome Comprehensive Clinical Evaluation Program and as a reviewer for the IOM report on chemical and biological terrorism.

MARC RUBIN, M.D., joined Glaxo, Inc. in 1990 as director of anti-infectives. From 1991 to 1995 he was director of infectious diseases and clinical research, and from 1995 to 1997 was international director and vice president of infectious diseases and rheumatology. In 1997 he became vice president of U.S. clinical research and in 1998 vice president of infectious diseases and hepatitis. He received his B.A. in biology from Cornell University and his medical degree from Cornell University Medical School. Dr. Rubin completed his internship and residency at the Johns Hopkins Hospital, Department of Internal Medicine, and his fellowship and postdoctoral work at the National Cancer Institute. He is board certified in internal medicine, oncology, and infectious diseases.

DAVID M. SHLAES, M.D., Ph.D., is vice president and therapeutic area co-leader for infectious diseases at Wyeth. Before joining Wyeth, Dr. Shlaes was professor of medicine at the Case Western Reserve University

School of Medicine and chief of the Infectious Diseases Section and the Clinical Microbiology Unit at the Veterans Affairs Medical Center in Cleveland, Ohio. His major research interest has been the mechanisms and epidemiology of antimicrobial resistance in bacteria where he has published widely. He has recently become more involved in the area of public policy as it relates to the discovery and development of antibiotics. He has served on the Institute of Medicine's Forum on Emerging Infections since 1996.

JANET SHOEMAKER is director of the American Society for Microbiology's (ASM) Public Affairs Office, a position she has held since 1989. She is responsible for managing the legislative and regulatory affairs of this 42,000-member organization, the largest single biological science society in the world. She has served as principal investigator for a project funded by the National Science Foundation (NSF) to collect and disseminate data on the job market for recent doctorates in microbiology and has played a key role in ASM projects, including production of the ASM *Employment Outlook in the Microbiological Sciences* and *The Impact of Managed Care and Health System Change on Clinical Microbiology*. Previously, she held positions as assistant director of public affairs for ASM; as ASM coordinator of the U.S./U.S.S.R. Exchange Program in Microbiology, a program sponsored and coordinated by the National Science Foundation and the U.S. Department of State; and as a freelance editor and writer. She received her baccalaureate, cum laude, from the University of Massachusetts and is a graduate of George Washington University's programs in public policy and editing and publications. She has served as commissioner to the Commission on Professionals in Science and Technology and as the ASM representative to the ad hoc Group for Medical Research Funding and is a member of Women in Government Relations, the American Society of Association Executives, and the American Association for the Advancement of Science. She has co-authored published articles on research funding, biotechnology, biological weapons control, and public policy issues related to microbiology.

P. FREDERICK SPARLING, M.D., is J. Herbert Bate professor emeritus of medicine, microbiology and immunology at the University of North Carolina (UNC) at Chapel Hill and is director of the North Carolina Sexually Transmitted Infections Research Center. Previously, he served as chair of the Department of Medicine and chair of the Department of Microbiology and Immunology at UNC. He was president of the Infectious Disease Society of America in 1996–1997. He was also a member of the Institute of Medicine's Committee on Microbial Threats to Health (1991–1992). Dr. Sparling's laboratory research is in the molecular biology of bacterial outer-membrane proteins involved in pathogenesis, with a major emphasis on gonococci and meningococci. His current studies focus on the biochemistry and genetics of iron-scavenging mechanisms used by gonococci and menin-

gococci and the structure and function of the gonococcal porin proteins. He is pursuing the goal of a vaccine for gonorrhea.

KAYE WACHSMUTH, Ph.D., serves as deputy administrator of the Office of Public Health and Science in the USDA's Food Safety and Inspection Service. Before joining the USDA, she was the deputy director for programs at the Food and Drug Administration's Center for Food Safety and Applied Nutrition. Dr. Wachsmuth was with the Centers for Disease Control and Prevention in Atlanta from 1972 to 1994, where she was deputy director of the Division of Bacterial and Mycotic Diseases from 1991 to 1994 and chief of the Enteric Diseases Laboratory Section from 1985 to 1991. While at CDC she developed programs and conducted studies in the areas of molecular epidemiology and bacterial pathogenesis. She also worked extensively in Southeast Asia and South America to establish laboratory-based diarrheal disease surveillance programs. In addition to her positions at the FDA and CDC, Dr. Wachsmuth chairs the National Advisory Committee on Microbiological Criteria for Foods and the Codex Committee for Food Hygiene and is a member of the World Health Organization's (WHO) Expert Advisory Panel on Food Safety. She has been director of WHO's International Collaborating Center for Shigella. Through adjunct faculty appointments at the University of North Carolina School of Public Health, Emory University, and Georgia State University, Dr. Wachsmuth was doctoral research adviser to students in the microbial sciences. She also mentored postdoctoral students through the National Research Council, WHO and Fogarty and Fulbright fellowship programs. At CDC in the early 1990s, she directed the summer research program for students enrolled in the University of Tuskegee Veterinary School and Morehouse University Medical School. Dr. Wachsmuth received her B.S. from Stetson University, Deland, Florida, and her Ph.D. in microbiology from the University of Tennessee. She is a fellow of the Infectious Diseases Society of America and the American Academy of Microbiology. She has received awards for benchmark epidemiological investigations of Legionnaire's disease, cholera in Latin America, drug-resistant tuberculosis, hantavirus in the western United States, and diphtheria in the former Soviet Union. The author of more than 160 scientific papers, she is on the editorial board of scientific journals and is editor of a book on cholera.

C. DOUGLAS WEBB, Jr., Ph.D., received his bachelor's degree in biology from Emory University and his master's and doctoral degrees in microbiology from the University of Georgia. He served in the Public Health Service at the Centers for Disease Control and Prevention (CDC) as both a research microbiologist and supervisory microbiologist. After the CDC, Dr. Webb went to Pfizer Pharmaceuticals and was involved in the development of ampicillin-sulbactam, carbenicillin, cefoperazone, fluconazole, azithromycin, and trovafloxacin. Dr. Webb is senior medical director of

Infectious Diseases in U.S. Medicines at Bristol-Myers Squibb, working on the strategy and development for the antiinfective portfolio.

CATHERINE E. WOTEKI, Ph.D., is undersecretary for food safety for the U.S. Department of Agriculture. Before receiving Senate confirmation to her present position on July 31, 1997, she served as acting undersecretary for research, education, and economics. From 1994 to 1995, she was deputy to the associate director of science of the Office of Science and Technology Policy. From 1990 to 1994, she was director of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. A biology and chemistry major at Mary Washington College, she pursued graduate studies in human nutrition at Virginia Polytechnic Institute and State University and received a Ph.D. in human nutrition. She is a registered dietitian. For 2 years she performed clinical research in the Department of Medicine, University of Texas Medical School at San Antonio. She was appointed assistant professor in the Department of Nutrition and Food Science at Drexel University in Philadelphia in 1975. In July 1977 she joined the congressional Office of Technology Assessment as nutrition project director. From 1980 to 1983 she worked for the U.S. Department of Agriculture in two capacities: as leader of the Food and Diet Appraisal Research Group in the Consumer Nutrition Center and as acting associate administrator of the Human Nutrition Information Service. Dr. Woteki was deputy director of the Division of Health Examination Statistics, National Center for Health Statistics, U.S. Department of Health and Human Services, from 1983 to 1990. Dr. Woteki has published 48 articles and numerous technical reports and books on food and nutrition policy and nutrition monitoring. She is the co-editor of *Eat for Life: The Food and Nutrition Board's Guide to Reducing Your Risk of Chronic Disease*. Dr. Woteki is a member of the Institute of Medicine.

SPEAKERS

DAVID C. BOWEN, Ph.D., is currently a congressional fellow sponsored by the American Association for the Advancement of Science. He is serving his fellowship in the office of Senator Edward Kennedy on the minority staff of the Senate Committee on Health, Education, Labor and Pensions. In this position Dr. Bowen has focused on some of the emerging threats to health in the new century, such as bioterrorism, antibiotic-resistant pathogens, and infectious disease. His portfolio also includes issues relating to biotechnology and biomedical research, including stem cells, genetic discrimination, and medical records privacy. Prior to joining the Kennedy staff, Dr. Bowen received his undergraduate education at Brown University and then earned a Ph.D. in neurobiology at the University of California, San Francisco. He subsequently had a postdoctoral appoint-

ment at Regeneron Pharmaceuticals before joining NeuralStem, a start-up biotechnology company, as a senior staff scientist. At the conclusion of his fellowship, Dr. Bowen plans to continue working in the science and health policy field in Washington.

FRED BROWN, Ph.D., is a visiting scientist at the U.S. Department of Agriculture's Plum Island Animal Disease Center, Greenport, New York. He was a member of the Spongiform Encephalopathy Advisory Committee, which gave advice to the British government on the outbreak of mad cow disease.

LISA CHAKRABARTI, Ph.D., is an investigator at the Pasteur Institute in Paris. She received her Ph.D. in microbiology from the Paris 7 University in 1991 and completed her postdoctoral training in the laboratory of Luc Montagnier. She joined the Pasteur Institute in 1993 and has served as chargé de recherches since 1996. She recently spent 4 years as a visiting scientist at the Aaron Diamond AIDS Research Center of New York (1997–2001). Dr. Chakrabarti's research focuses on identifying pathogenic determinants of simian immunodeficiency viruses. During her stay at ADARC, she had the opportunity to work with the group of Pr. Preston Marx on nonpathogenic SIV infections in the sooty mangabey. Pr. Chakrabarti also worked with Pr. Cecilia Cheng-Mayer and benefited from the experience of her group in the study of pathogenic SHIV infections.

LOUISA E. CHAPMAN, M.D., M.S.P.H., attended Macalester College, St. Paul, Minnesota, on a National Merit Scholarship and earned a B.A. in biology and philosophy. She subsequently earned an M.S.P.H. in parasitology and laboratory practice from the School of Public Health and an M.D. from the School of Medicine of the University of North Carolina at Chapel Hill. Dr. Chapman completed residency training in internal medicine at the University of Minnesota and fellowship training in infectious diseases at Boston University and is board certified in both specialties. She was commissioned as an officer in the U.S. Public Health Service when she came to the Centers for Disease Control and Prevention as an epidemic intelligence officer in 1988 and currently holds the rank of commander. Since 1988 Dr. Chapman has worked in public health research and practice, specializing in the epidemiology of viral diseases with a focus on zoonoses. She is an author on more than 70 publications. While Dr. Chapman has worked with a variety of viruses, her most extensive experience has been with non-HIV retroviruses, influenza, Cercopithecine herpesvirus 1, and viral hemorrhagic fever agents. Since 1994 she has led CDC efforts addressing infectious disease issues associated with xenotransplantation and is the CDC ex officio representative to the Secretary's Advisory Committee on Xenotransplantation. Dr. Chapman has served as a reviewer or consultant for the National Research Council's Institute of Laboratory Animal Research, the Department of Defense's Biomedical Technology Area

Review and Assessment Panel, the World Health Organization, the Organization for Economic Cooperation and Development, the Institute of Medicine, the Hastings Center, the Defense Advanced Research Projects Agency, and others.

LISA CONTI, D.V.M., M.P.H., Diplomate A.C.V.P., received her undergraduate degree in chemistry at the University of Miami, her doctor of veterinary medicine at the University of Florida in 1988, and her master's of public health from the University of South Florida in 1993. She earned specialty board certification from the American College of Veterinary Preventive Medicine in 1994. Dr. Conti currently serves as the Florida State public health veterinarian. She has been with the Florida State Health Office since 1988, during which time she also taught anatomy and physiology at Tallahassee Community College and epidemiology at Florida State University. She was recently the program administrator for the HIV/AIDS Surveillance Section in the Bureau of HIV/AIDS. She has authored or coauthored numerous journal articles on HIV/AIDS surveillance, public health, and zoonoses. Dr. Conti has been an active member of her local, state, and national veterinary medical and public health associations for many years. She has been a representative of the Florida Veterinary Medical Association Executive Board since 1994 and established and has chaired the Public Health Committee since 1995. She was a founding member of the Florida Rabies Control and Prevention Advisory Committee. In 1997, Dr. Conti was elected to the American Veterinary Medical Association Council on Public Relations representing public health.

PETER COWEN, D.V.M., Ph.D., obtained a B.A. in sociology from Beloit College in 1971. He spent 5 years in Ibadan, Nigeria, earning his doctor of veterinary medicine degree in 1979. A master of preventive veterinary medicine (M.P.V.M.) degree from the University of California-Davis followed in 1980. He then worked under the supervision of Calvin W. Schwabe meriting a Ph.D. degree from UC-Davis in 1985. He accepted a position at North Carolina State University in 1985 and is currently associate professor of epidemiology and public health with the Department of Farm Animal Health and Resource Management, College of Veterinary Medicine. Dr. Cowen spent a year on leave during 1998–1999 at the U.S. Department of Agriculture in the Epidemiology and Risk Assessment Division, Office of Public Health and Science, Food Safety Inspection Service, working with Kaye Wachsmuth. Since 1996, Dr. Cowen has been a moderator for ProMED-mail, the largest independent global electronic reporting system and forum on emerging diseases. His other disciplinary interests and publications include the design of surveillance systems, medical geography, food safety, risk assessment and international aspects of the delivery of veterinary services.

RANDALL L. CROM, D.V.M., is currently a staff veterinarian as-

signed to the Emergency Programs staff in Veterinary Services (VS) of the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS). Since February 2000 he has worked as coordinator of West Nile virus issues for APHIS-VS. From 1997 to 1999, Dr. Crom was seconded by APHIS to the Communicable Diseases Cluster of the World Health Organization in Geneva, Switzerland. While there he worked on emerging zoonotic disease issues ranging from antimicrobial resistance related to use in food-producing animals to an outbreak of avian influenza in birds and humans in Hong Kong. Since joining APHIS-VS in 1984, he has worked in field programs in Puerto Rico to eradicate brucellosis, tuberculosis, and cattle ticks and as an epidemiologist with the Center for Emerging Issues of the Centers for Epidemiology and Animal Health in Fort Collins, Colorado. Dr. Crom received training and experience in epidemiology as an Epidemic Intelligence Service officer for the Centers for Disease Control and Prevention from 1986 to 1988. He received his doctor of veterinary medicine degree in 1980 from the College of Veterinary Medicine at Iowa State University.

PAUL W. EWALD, Ph.D., is professor of biology at Amherst College. Dr. Ewald earned his B.Sc. from the University of California, Irvine, in biological sciences and his Ph.D. in zoology from the University of Washington, specializing in ecology and evolution. A major focus of his research takes a comparative approach to the evolution of virulence, with a focus on human diseases and the evolutionary effects of various public health interventions.

DANA A. FOCKS, Ph.D., is senior scientist at the Center for Medical, Agricultural, and Veterinary Entomology at the Agricultural Research Service, U.S. Department of Agriculture.

DAVID R. FRANZ, D.V.M., Ph.D., is vice president of the Chemical and Biological Defense Division, Southern Research Institute. He served in the U.S. Army Medical Research and Materiel Command for 23 of his 27 years on active duty. Dr. Franz has served as both deputy commander and then commander of the U.S. Army Medical Research Institute of Infectious Diseases and as deputy commander of the U.S. Army Medical Research and Materiel Command. Dr. Franz served as chief inspector on three United Nations Special Commission biological warfare inspection missions to Iraq and as technical adviser on long-term monitoring. He also served as a member of the first two U.S.–U.K. teams that visited Russia in support of the Trilateral Joint Statement on Biological Weapons and as a member of the Trilateral Experts' Committee for biological weapons negotiations. He was technical editor for the *Textbook of Military Medicine on Chemical and Biological Defense* released in 1997. Dr. Franz holds a D.V.M. from Kansas State University and a Ph.D. in physiology from Baylor College of Medicine.

MILTON FRIEND, Ph.D., was nominated by Secretary of the Interior Bruce Babbitt to be the executive director of the Salton Sea Science Subcommittee. Dr. Friend retains an affiliation with the U.S. Geological Survey where he is the originator and the first and immediate past director of its National Wildlife Health Center. Prior to that position, he was the section chief for pesticide-wildlife ecology at the Denver Wildlife Research Center of the U.S. Fish and Wildlife Service. In addition to his government service, Dr. Friend is an adjunct professor in the Department of Animal and Biomedical Sciences, University of Wisconsin-Madison. Dr. Friend is the recipient of numerous awards for outstanding research, meritorious service, and professional accomplishment. He is the author of over 100 publications. He earned his B.S. in wildlife conservation with a minor in forestry from the University of Maine; an M.S. in wildlife management, minor in epidemiology from the University of Massachusetts; and a Ph.D. in veterinary science and wildlife ecology, with an epidemiology minor, from the University of Wisconsin-Madison.

MARY J. R. GILCHRIST, Ph.D., was named the director of the University Hygienic Laboratory on July 1, 1995. She holds a bachelor's degree in microbiology from the University of Iowa and M.S. and Ph.D. degrees in microbiology from the University of Illinois at Urbana–Champaign. She is a diplomat of the American Board of Medical Microbiology. After a fellowship in clinical and public health microbiology at the Mayo Clinic, Dr. Gilchrist served in the state public health laboratories of Minnesota and Iowa and at two hospitals in Ohio. She was director of clinical microbiology at the Children's Hospital Medical Center and at the Veterans Affairs Medical Center in Cincinnati and associate professor at the University of Cincinnati. In 1991, after the Persian Gulf War, she was nominated as Federal Employee of the Year for her contributions to the bioterrorism response and planning for the Department of Veterans Affairs. In 1994, Dr. Gilchrist was named the Eagleson Institute Lecturer of the American Biological Safety Association. Dr. Gilchrist served for 9 years on the Public and Scientific Affairs Board of the American Society for Microbiology. She is on the Board of Directors of the Association of Public Health Laboratories and chairs its Committee on Emerging Infectious Diseases. She served on the Hospital Infection Control Practices Advisory Committee at CDC until this year when she was appointed to the NCID Board of Scientific Counselors. Dr. Gilchrist is very active in the public health response to bioterrorism at the local, state, and national levels and has several committee appointments related to bioterrorism.

W. IAN LIPKIN, M.D., is director of the Emerging Diseases Laboratory and professor in the Departments of Neurology, Anatomy and Neurobiology, and Microbiology and Molecular Genetics at the University of California, Irvine. Dr. Lipkin was the first to identify an infectious agent by

subtractive cloning (Borna disease virus in 1990). He also led the team that used unique molecular methods to identify the West Nile virus as the cause of the encephalitis outbreak in New York state in the fall of 1999. His laboratory investigates the role of infectious agents and immune responses in the pathogenesis of acute and chronic central nervous system diseases through molecular epidemiology and animal modeling. Dr. Lipkin received a B.A. from Sarah Lawrence College in 1974 and an M.D. from Rush Medical College in 1978. His postgraduate training included a residency in internal medicine at the University of Washington (1979–1981), a residency in neurology at the University of California, San Francisco (1981–1984); and a fellowship in neurovirology and molecular neurobiology at the Scripps Research Institute (1984–1990). He was a 1991 Pew Scholar.

TRACEY S. McNAMARA, D.V.M., Diplomate A.C.V.P., is head of the Department of Pathology at the Wildlife Conservation Society (WSC). After graduating from the New York State College of Veterinary Medicine at Cornell University, she completed a joint residency program in comparative veterinary anatomic pathology at the Animal Medical Center and WSC. She remained at the zoo, where she now holds the Schiff Family Distinguished Scientist in Wild Animal Pathology endowed chair. She is a member of the American College of Veterinary Pathology and vice president of the Charles Louis Davis, D.V.M., Foundation for the Advancement of Veterinary and Comparative Pathology in addition to being the head of its zoo and wildlife pathology program. Dr. McNamara also holds the title of visiting assistant professor of pathology at Albert Einstein College of Medicine of Yeshiva University.

ROBERTA A. MORALES, D.V.M., Ph.D., is a senior research scientist with the Research Triangle Institute's (RTI) Center for Regulatory Economics and Policy Research in North Carolina. Dr. Morales received a doctor of veterinary medicine degree from the University of the Philippines in 1980, a master's degree in preventive veterinary medicine from the University of California, Davis in 1982, and a Ph.D. in economics from North Carolina State University in 1995. Her areas of expertise are in epidemiology, risk assessment, and economics of food safety and animal health. She is a member of the National Advisory Committee on Microbiological Criteria for Foods and has served on the U.S. Delegation for the Codex Alimentarius Commission Committee for Food Hygiene. Dr. Morales is an adjunct assistant professor at North Carolina State University's College of Veterinary Medicine. Prior to joining RTI, she was assistant professor of food safety at the Virginia–Maryland Regional College of Veterinary Medicine where she co-directed the Epidemiology Residency Program. She has also worked with the USDA's Food Safety and Inspection Service on an Interagency Personnel Agreement with North Carolina State University, as an agricultural economist with the USDA Economic Research Service, and

as a consultant for industry and academia. Dr. Morales has authored seven book chapters on food safety and has published in peer-reviewed journals, including the *Journal of Food Protection, Risk Analysis, International Journal of Food Microbiology, Journal of the American Veterinary Medical Association,* and *Preventive Veterinary Medicine*.

FREDERICK A. MURPHY, D.V.M., Ph.D., is professor of virology at the School of Veterinary Medicine, University of California, Davis. He received a B.S. and a D.V.M. from Cornell University and a Ph.D. from the University of California, Davis. Previously, he served as director of the Division of Viral and Rickettsial Diseases and later as director of the National Center for Infectious Diseases, Centers for Disease Control, in Atlanta. From 1991 to 1996 he served as dean of the School of Veterinary Medicine at UC Davis. His honors include membership in the Institute of Medicine, the Presidential Rank Award, membership in the Deutsche Akademie der Naturforscher Leopoldina (German Academy of Natural Sciences) and the USSR Academy of Medical Sciences, the K.F. Meyer Gold Headed Cane, an honorary doctor of medicine and surgery from the University of Turku in Finland, and an honorary doctor of science from the University of Guleph, Ontario, Canada.

C. J. PETERS, M.D., is a professor in the Department of Microbiology and Immunology and Pathology at the University of Texas Medical Branch in Galveston. Dr. Peters was recently named director of the Center for Biodefense at UTMB, which will serve as a catalyst for research and development efforts on effective medical countermeasures against bioterrorism and biological warfare. He had been chief of special pathogens at the Centers for Disease Control and Prevention in Atlanta. Formerly chief of the Disease Assessment Division at USAMRIID, he has worked in the field of infectious diseases for three decades with the CDC, the U.S. Army, and the U.S. Public Health Service. He was head of the unit that contained the outbreak of Ebola in Reston, Virginia. He was also called in to contain an outbreak of deadly hemorrhagic fever in Bolivia. He received his M.D. from Johns Hopkins University and has more than 275 publications virology and viral immunology. Dr. Peters is currently a member of the National Research Council's Committee on Occupational Health and Safety in the Care of Nonhuman Primates and the Institute of Medicine's Committee on Emerging Microbial Threats to Health in the 21st Century.

JOHN T. ROEHRIG, Ph.D., is currently chief of the Arbovirus Diseases Branch at the National Center for Infectious Diseases, Centers for Disease Control and Prevention. Dr. Roehrig is a director of the WHO Collaborating Center for Arboviruses for the Western Hemisphere and a member of the WHO Steering Committee on Dengue and Japanese Encephalitis Vaccines. He is a faculty affiliate in the Department of Microbiology at Colorado State University. His prior positions include chief of the

Immunochemistry Section, Molecular Biology Branch, and chief and supervisory microbiologist, Immunochemistry Branch, all at CDC. Dr. Roehrig received his bachelor's degree in microbiology from the University of Illinois-Urbana and then earned a doctoral degree in microbiology from the University of Missouri-Columbia. He was a postdoctoral fellow (Milton J. Schlesinger) in the Department of Microbiology and Immunology at the Washington University School of Medicine in St. Louis, Missouri. He is a member of several infectious disease societies and his editorial activities include reviewing for more than 12 infectious disease journals. He is the author or co-author of 83 scientific publications. Dr. Roehrig's scientific interests include the immunology of vectorborne viral diseases, protein biochemistry, vectorborne viral encephalitides, yellow fever, dengue fever, and rubella.

ALAN L. SCHMALJOHN, Ph.D., is chief, Department of Viral Pathogenesis and Immunology, in the Virology Division of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Frederick, MD. His current efforts center on discovery and nonclinical testing of viral vaccines for exotic and hazardous viruses. His interests and published works span several virus genera (filoviruses, orthopoxviruses, alphaviruses, hantaviruses, bunyaviruses, arenaviruses); immunologic niches (cytotoxic T lymphocytes, humoral immunity, including monoclonal antibodies, peptides, antiidiotypes); virologic topics (isolation and characterization of new viruses, receptors, antibody escape mutants, epitope mapping, reassortants, envelope structure/function); and vaccine strategies (alphavirus replicons, DNA vaccines, baculovirus recombinants, vaccinia virus recombinants, classical live or killed vaccines). Seminal scientific contributions have included a candidate vaccine for Marburg virus, isolation of an American hantavirus later to be called Sin Nombre virus, and establishment of the importance of nonneutralizing antibodies in resistance to viral infections. Dr. Schmaljohn received his Ph.D. in microbiology from Colorado State University, Fort Collins, followed by postdoctoral training at the Johns Hopkins University and the University of Maryland Medical Center. After 3 years as faculty in the Microbiology Department at UMAB, Dr. Schmaljohn took a civilian position at USAMRIID in late 1986.

ROBERT E. SHOPE, M.D., is professor of pathology in the WHO Center for Tropical Diseases at the University of Texas Medical Branch, Galveston. The center serves as the repository for a major collection of arboviruses and rodent-associated viruses. Dr. Shope is a virologist/epidemiologist and former director of the Yale Arbovirus Research Unit. He was a member of the teams that investigated outbreaks of Rift Valley fever, Lassa fever, Venezuelan hemorrhagic fever, and other often fatal hemorrhagic diseases caused by zoonotic viruses. He also has expertise in the diagnosis and rapid identification of human-pathogenic viruses carried by

arthropods and rodents, and in 1992 he co-chaired the Institute of Medicine's study on emerging infections.

ALFRED D. STEINBERG, M.D., graduated Phi Beta Kappa from Princeton University and cum laude from Harvard Medical School. He took an intership and residency in internal medicine in New York and a fellowship in immunology-rheumatology at the National Institutes of Health. He remained at NIH as a senior investigator and then chief of the Cellular Immunology Section, NIAMS. An author of more than 450 papers, he has published extensively in immunology and molecular genetics. He has also studied endogenous retroviruses. Dr. Steinberg currently works at Mitretek, a nonprofit think tank, and serves as a consultant to several government agencies in the areas of immunology, molecular genetics, and medical microbiology.

STEPHEN F. SUNDLOF, D.V.M., Ph.D., is Director of the Center for Veterinary Medicine, Food and Drug Administration. He received both his doctorate in veterinary medicine and Ph.D. in toxicology from the University of Illinois and is a diplomat of the American Board of Veterinary Toxicology. He served on the faculty of the University of Florida, College of Veterinary Medicine, from 1980 through 1994 where he held the rank of professor. Dr. Sundlof has published numerous articles in scientific journals on drug residues and food safety. He has presented more than 100 invited lectures at national and international meetings. He presently serves as chairman of the WHO/FAAAO Codex Alimentarius Committee on Residues of Veterinary Drugs in Foods and is past president of the American Academy of Veterinary Pharmacology and Therapeutics.

ROBERT B. TESH, M.D., is a physician with training in pediatrics and epidemiology. He spent 12 years on the staff of the National Institute of Allergy and Infectious Diseases and 15 years on the faculty of Yale University School of Medicine. Since 1995, he has been professor of pathology and professor of microbiology and immunology at the University of Texas Medical Branch. He has lived and worked in a number of countries in tropical America and is the author of more than 200 publications, primarily on the epidemiology of vector- and rodentborne zoonotic diseases.

ROBERT G. WEBSTER, Ph.D., received his B.Sc. and M.Sc. in microbiology from the Otago University in New Zealand. In 1962 he earned his Ph.D. from the Australian National University and spent the next two years as a Fulbright Scholar in the Department of Epidemiology, School of Public Health, at the University of Michigan, Ann Arbor. Since 1968, Dr. Webster has been in the Department of Virology and Molecular Biology at St. Jude Children's Research Hospital, Memphis, Tennessee. In 1988 he was appointed to the Rose Marie Thomas Chair in the above department. In 1989 Dr. Webster was admitted to the highly prestigious Royal Society of London in recognition for his contribution to influenza virus research. In 1998 he

was appointed to the National Academy of Sciences. In addition to his position at St. Jude, Dr. Webster is director of the U.S. Collaborating Center of the World Health Organization dealing with the ecology of animal influenza viruses. Dr. Webster's interests include the structure and function of influenza virus proteins and the development of new vaccines and antivirals and the importance of influenza viruses in wild birds as a major reservoir of influenza viruses and their role in the evolution of new pandemic strains for humans and lower animals. His curriculum vitae contains over 385 original articles and reviews on influenza viruses and related topics.