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About This Guide

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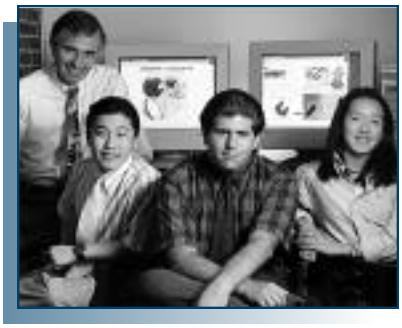


Each December the Howard Hughes Medical Institute (HHMI) presents the Holiday Lectures on Science, a lecture series that delivers the latest research by some of the world's leading biomedical researchers directly to classrooms worldwide. These lectures present complex scientific information in ways that appeal to high school students. This Teacher and Student Guide is designed to help students and instructors take full advantage of the 1999 series on infectious diseases – "2000 and Beyond: Confronting the Microbe Menace." The guide summarizes this year's lecture topics, provides information about the lecturers, lists publications and websites relevant to infectious diseases, identifies themes and concepts related to the Advanced Placement (AP) Biology Curriculum, and highlights the different components of the Holiday Lectures series.

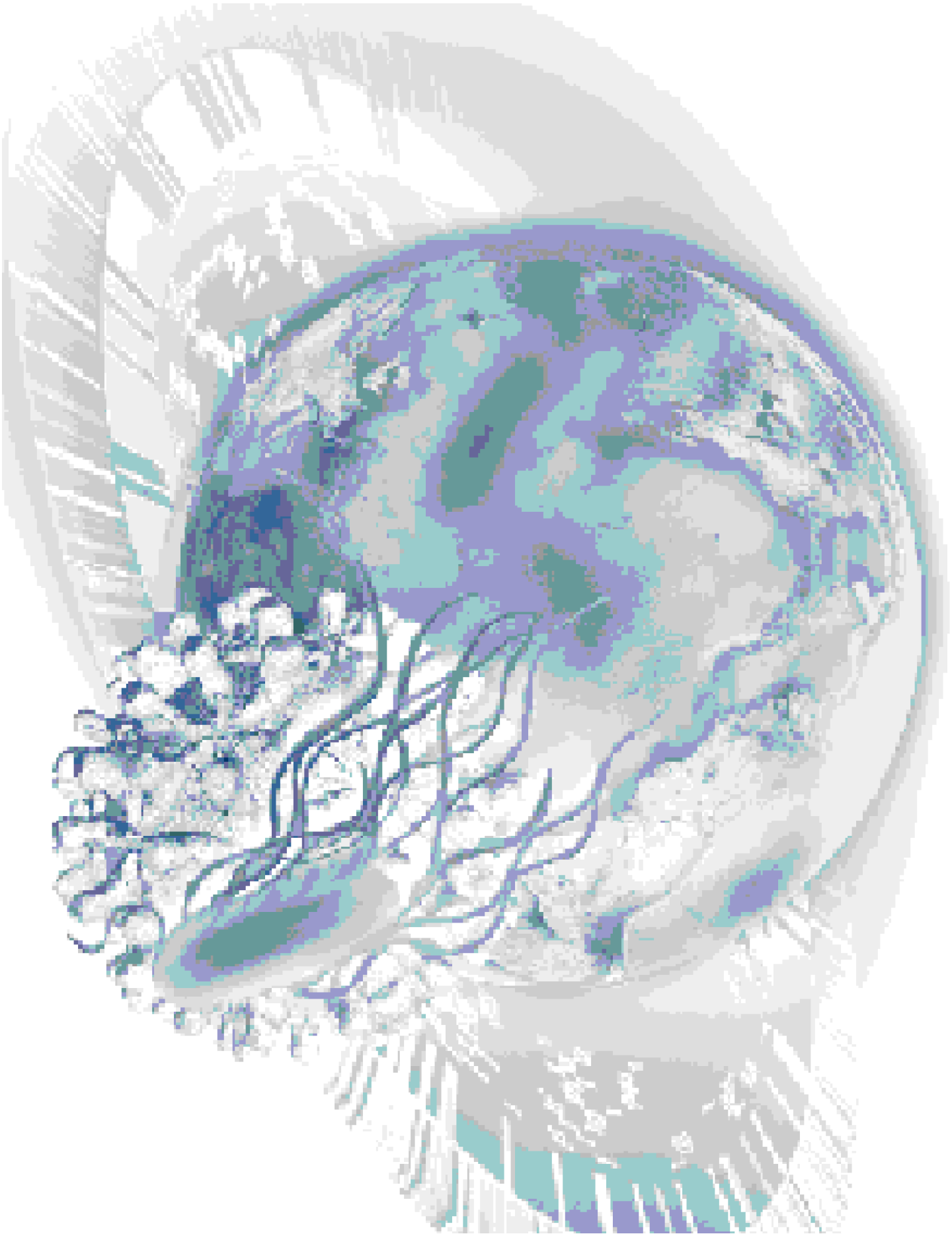
The **Classroom Connections** section provides a summary and list of key concepts for each of the four lectures. This year several **challenge questions,** developed by the Institute's advisory committee of high-school teachers, appear under each lecture topic. These questions are intended to stimulate classroom discussions before or after the lectures and to encourage students to explore the topics in greater depth. The lectures themselves may provide answers to some of these questions. Students can also use the Ask a Scientist feature on the Institute's website at www.hhmi.org/askascientist to pose questions on infectious diseases or other science topics. Finally, those who teach AP Biology may find the **AP correlations** useful for integrating the lectures into their curricula.

Lives in Science, the guide's biography section, contains **career highlights** for the two lecturers, Drs. Donald E. Ganem and B. Brett Finlay. These brief descriptions of their education, training, and accomplishments offer insights into the lecturers' professional lives. Their **biographies**, which follow career highlights, help reveal the person behind the science and illuminate the ways in which these scientists overcame the challenges they faced as they pursued their research. This information may help students appreciate the many satisfactions of a scientific career.

The **publications and websites** listed in this guide provide a wealth of information on infectious diseases that may help direct students to valuable resources and avenues for further exploration.

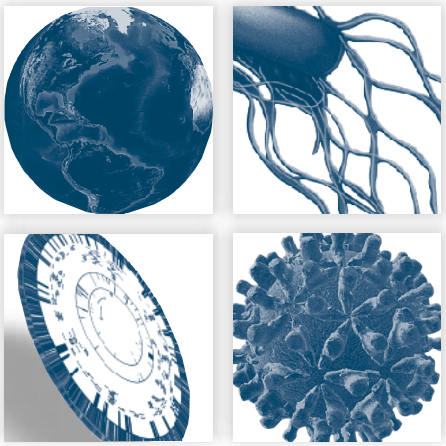
The guide also describes the many features of the **Holiday Lectures website** (www.holidaylectures.org). In addition to Ask a Scientist, which allows students to ask scientists questions via e-mail, the website also features a variety of multimedia activities and virtual laboratories. Many of these interactive features were developed with the assistance of high school interns who worked at the Institute during the summer. After the lectures are concluded, a detailed index to the lectures will be available on the Holiday Lectures website. The index will enable teachers to go directly to those portions of the lectures that support topics being studied in the classroom.

We hope this guide will help teachers and students make full use of these exciting lectures. Please continue to check the website at www.holidaylectures.org for program updates and topical resources.



2000 and Beyond
Confronting the Microbe Menace

This year the lectures will focus on a topic of renewed and increasing public concern: infectious diseases. For some years, it appeared that infectious diseases had been brought under control, at least in most of the developed world. Polio and smallpox, caused by viruses, had been wiped out by vaccines. Antibiotic drugs had stopped bacterial diseases from threatening lives. But recently, things have changed.



Seemingly new viral diseases such as AIDS and Ebola fever have emerged. Antibiotics are losing their power as bacteria become increasingly resistant. And we are learning that diseases such as stomach ulcers, some cancers, and even heart disease may be caused by infectious pathogens.

The four lectures are presented by Donald E. Ganem, M.D., HHMI investigator and professor of Medicine and of Immunology and Microbiology at the University of California – San Francisco, and B. Brett Finlay, Ph.D., HHMI international research scholar and professor of Biochemistry and Molecular Biology, Microbiology and Immunology, and of Biotechnology at the University of British Columbia.

Two presentations occur on the first day of the series. Dr. Ganem will begin by describing how new diseases are recognized as being caused by infection and how the guilty organisms are identified. Dr. Finlay will then discuss the serious health problem of bacterial diseases, how and why a broad range of pathogenic bacteria have become resistant to antibiotic drugs, and what we can do to prevent the same thing from happening with future medications.

On day two, Dr. Finlay will describe what scientists are learning about the molecules bacteria use to invade our bodies and cause disease, and how this knowledge is being used to develop new kinds of antibacterial drugs. Dr. Ganem concludes the 1999 series with a discussion on the causes of epidemics. He will explain how genetic changes in a virus or bacterium can suddenly make it more infectious or more deadly. In addition, he will explore how factors such as the destruction of forests, jet travel, and even the weather can cause an infectious disease to spread and create an epidemic.

To prepare for the lectures – The "Classroom Connections" and "Lives in Science" sections of this guide are designed to provide background information to this year's lecture topics.

Refer to the "About this Guide" section for more details.

To view the lectures – The 1999 lectures will be available live starting at 10:00 am EST on December 6th and 7th via satellite in the United States and Canada, and worldwide via webcast from www.holidaylectures.org/webcast. If you plan to view the live satellite broadcast, please refer to the back inside cover of this guide for information on satellite coordinates and telephone numbers to call in case of problems. If you plan to view the live webcast, make sure that RealPlayer™ has been successfully installed on your computer ahead of time. After December 7th, the webcast will be available on demand.

For more information about the webcast visit the Holiday Lectures website at www.holidaylectures.org/webcast *and the "Technical Tips" page at* www.hhmi.org/grants/help.htm

To ask questions – Students and teachers will have the opportunity to ask questions directly to Drs. Ganem and Finlay by participating in live Q&A sessions to be held each day from 1:30 pm – 2:30 pm EST on both the satellite broadcast and the webcast. Questions may be phoned in live to 1-800-223-9050 or e-mailed to asklive@hhmi.org.

For more information, visit www.holidaylectures.org/asklive99

To view the rebroadcast – If your school receives its satellite programming via the Channel One Network and if you have no other satellite capability, you will not be able to receive the Holiday Lectures at the times and coordinates listed on the back inside cover of this guide. Lectures 1 and 2 will be rebroadcast on January 12, 2000 and Lectures 3 and 4 on January 19, 2000 over Channel One Connection (formerly known as The Classroom Channel). Please ask your school's media specialist to tape the Channel One rebroadcast.

See your January Channel One Teachworld.com poster for more information.

To order educational materials – Videotapes of the lectures and a detailed index to the lectures will be available a few months after the live event. In addition, the interactive demonstrations and laboratory exercises are available on the Web and later on CD ROMs.

To order these materials from the 1999 or earlier Holiday Lectures, visit the HHMI website at www.holidaylectures.org/order *and fill out an order form.*

CLASSROOM CONNECTIONS

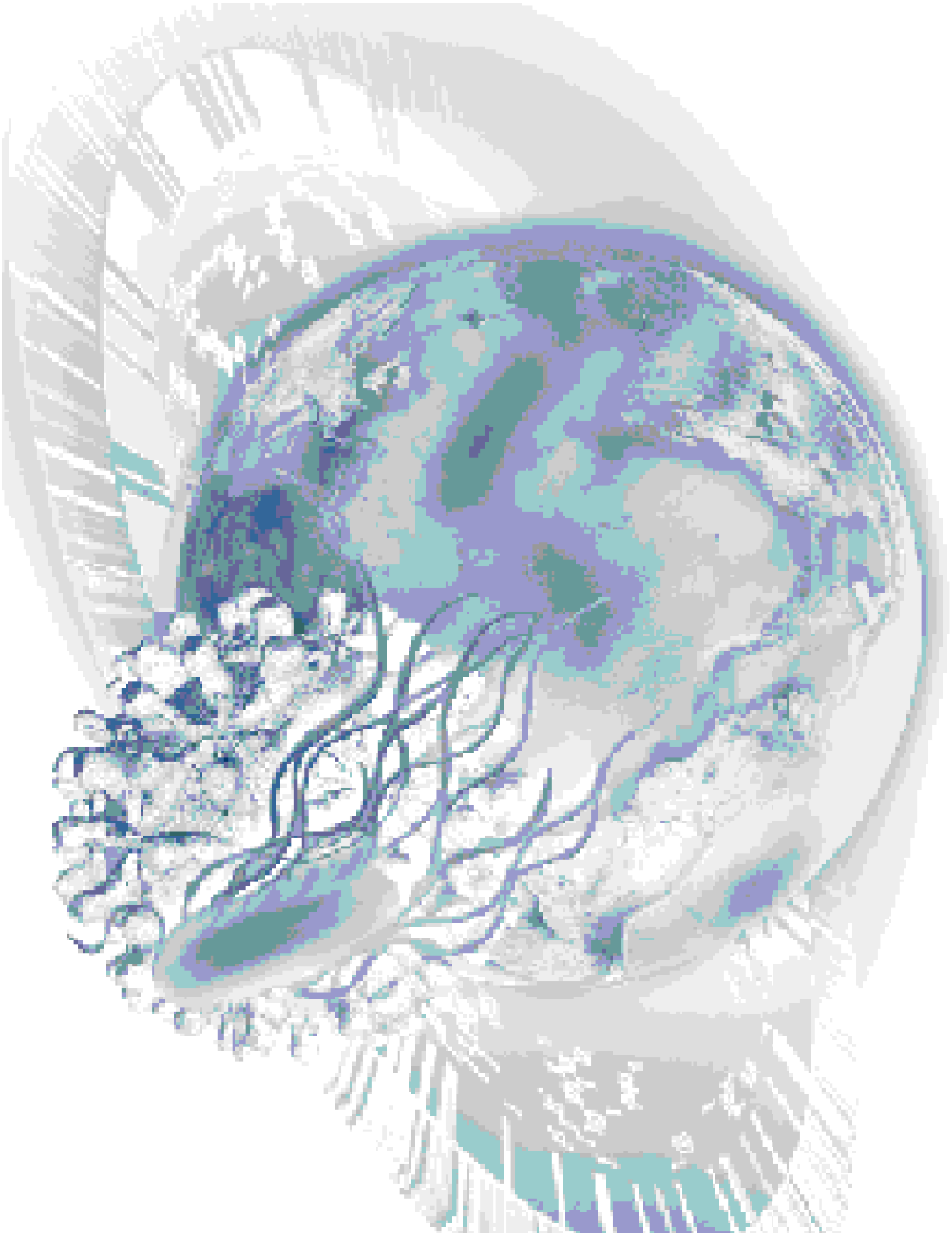
LECTURE SUMMARIES

KEY CONCEPTS

CHALLENGE QUESTIONS

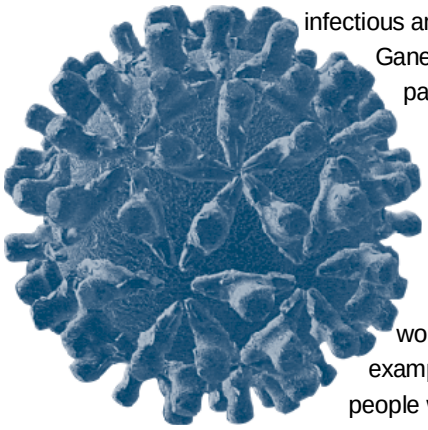
AP CORRELATIONS

WEB AND PRINT RESOURCES



Microbe Hunters: Tracking Infectious Agents

Infectious diseases have plagued us since before the dawn of history. Ancient diseases such as smallpox, plague, typhus, and malaria have profoundly shaped human history and evolution, and newer infectious diseases – AIDS is a prominent example – are constantly emerging. Even illnesses long thought to be noninfectious, such as ulcers and some cancers, can now be linked to a microbial agent. How are new diseases recognized as infectious and how are their causes identified? In his first lecture, Dr. Don Ganem will probe these questions, using examples from epidemics past and present.



Despite their central role in infectious disease research, micro biologists are rarely the first to suspect an infectious origin for a given disease. Rather, this task usually falls to practicing clinicians and to epidemiologists, specially trained investigators who plot the course of diseases in populations. Their detective work provides clues that a microorganism may be the culprit – for example, the discovery that liver cancer occurs more commonly in people with chronic hepatitis provided an early clue that infection with certain hepatitis viruses might lead to cancer.

Microbiologists then face the daunting task of identifying and characterizing the suspected organism. Until the past decade, they accomplished this largely by cultivating microorganisms in the laboratory or by transmitting the infection to laboratory animals. But these approaches have limitations – some organisms grow poorly or not at all in laboratory conditions, and establishing an infection in animal hosts is not always possible. In recent years scientists have turned to DNA-based technologies that directly identify the genetic sequence of potential pathogens.

Once a suspect organism is in hand, a scientific “courtroom drama” begins: What is the evidence that leads scientists to conclude that the suspected organism is guilty? Even healthy people harbor many normal microorganisms in and on their bodies, so finding a germ at the scene of the crime doesn’t necessarily distinguish the true criminal from an innocent bystander. To illustrate how scientists approach problems like this, Dr. Ganem will discuss the recent case of Kaposi’s sarcoma (KS), a once rare condition that is now the number one cancer in patients with AIDS. He’ll explain how the pattern of KS in the population led him and other scientists to suspect an infectious cause, how DNA-based research exposed the guilty virus, and how scientists are now working from these early clues to develop a deeper understanding of the disease.

Lecture One

KEY CONCEPTS

1. The first clues that a disease may be caused by an infectious agent come from the pattern of occurrence of the disease and its frequency in the population.
2. Techniques for identifying microbes include infecting animals, tissue staining, cultivation in vitro, and DNA-based technologies.
3. Proving that a microbe causes disease requires both laboratory work and patient-based investigations.
4. Kaposi's sarcoma (KS) is a type of tumor that occurs on the skin or mucous membrane and afflicts a subset of people with AIDS.
5. In 1994, the DNA of a new virus – human herpesvirus 8 – was found in samples of KS lesions.
6. Human herpesvirus 8 is necessary but not sufficient for the development of KS – additional cofactors, such as HIV infection, are also required.
7. For most of the chronic diseases now being studied, infection is likely to be one, but not the sole, causal factor.

CHALLENGE QUESTIONS

These questions, developed by the Holiday Lectures Teacher Resource Group, are intended to stimulate class discussion before and after the lectures. In some cases, the lecturers may provide the answers during their lectures or suggest paths students can follow to find the answers. Students watching the live broadcasts or webcasts can ask the lecturers questions during the live Q&A sessions following each day's lectures. In addition, students can pose e-mail questions to the "Ask a Scientist" website at www.hhmi.org/askascientist

1. How are new diseases recognized as infectious and how are their causes identified?
2. In the past, microbiologists often spent weeks or months identifying and characterizing suspected disease-causing organisms. Compare and contrast traditional methods of identifying microbial pathogens with recent DNA-based technologies, particularly with respect to speed and accuracy.
3. Name three or more new infectious diseases that have been recently diagnosed and identified.
4. Name three infectious diseases that are now considered "conquered."

THEMES AND CONCEPTS RELATED TO ADVANCED PLACEMENT BIOLOGY

The purpose of this section is to help correlate material covered in this lecture with relevant topics that compose the topic outline for the Advanced Placement Program in Biology as described in the College Board website at
www.sat.org/ap/biology/html/indx001.html

Lecture 1 – Microbe Hunters: Tracking Infectious Agents – focuses on how infectious agents are linked to specific diseases. DNA-based technologies now play a large role in pathogen identification.

1. Molecular Genetics
    a. DNA as information
        1. Why genes are mutable units
        2. How DNA acts as the genetic material
        3. How genes can be isolated
    b. Gene-to-protein conversion
        1. How messenger RNA is involved
        2. How proteins are synthesized
        3. Why a genetic code is involved
    c. Prokaryotic gene expression
        1. What the function of transcription is
        2. Why gene regulation is needed

WEB AND PRINT RESOURCES

These resources are listed roughly in order of relevance to the lectures.

Selected Websites

Donald E. Ganem, M.D., HHMI Research in Progress, Human Viral Pathogens. Overview of Dr. Ganem's research on the mechanisms by which viruses replicate and cause disease.
www.hhmi.org/science/cellbio/ganem.htm

Centers for Disease Control and Prevention. Information on pathogens in the news with a section for travelers and excellent links to detailed information on specific infectious diseases.
www.cdc.gov

Colorado HealthNet.: Cancer Center: Kaposi's Sarcoma. Definitions and facts about Kaposi's sarcoma (KS), KS library, and information on prevention and education.
www.coloradohealthnet.org/cancer/kaposi/ks_lib.html

The Body: An AIDS and HIV Information Resource. An extensive list of references on Kaposi's sarcoma.
www.thebody.com/treat/kaposi.html

Lecture One

American Museum of Natural History: Infection, Detection, Protection. Explains causes and prevention measures for infectious disease with examples of how scientists battle and prevent diseases caused by bacteria, viruses, and protozoa.
www.amnh.org/explore/infection

Non-CDC Reports: Epidemiology Methods. An extensive list of reports and publications explaining epidemiological research.
www.cdc.gov/genetics/reports/NCDCepi.htm

Epidemiology: The Ohio State University, Mansfield. Introductory course on epidemiology.
www.mansfield.ohio-state.edu/~sabedon/biol2045.htm

Selected Publications

Scientific

Ganem D. "KSHV and Kaposi's sarcoma: the end of the beginning?" *Cell* 91: 157-160, 1997.

Chang, Y., Cesarman, E., Pessin, M.S., "Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma." *Science* 266: 1865-1869, 1994.

Gallo, R.C. "The enigmas of Kaposi's sarcoma." *Science* 282: 1837-1839, 1998.

McNicholl, J.M., and Cuenco, K.T. "Host genes and infectious diseases. HIV, other pathogens and a public health perspective." *American Journal of Preventive Medicine* 16: 141-154, 1999.

Relman, D.A. "Detection and identification of previously unrecognized microbial pathogens." *Emerging Infectious Diseases* 4: 382-389, 1998.

Giesecke, J. "Choosing diseases for surveillance." *Lancet* 353: 344, 1999.

Cassell, G.H. "Infectious causes of chronic inflammatory diseases and cancer." *Emerging Infectious Diseases* 4: 475-487, 1998.

Perkins, B.A., Flood, J.M., Danila, R., et al. "Unexplained deaths due to possibly infectious causes in the United States: defining the problem and designing surveillance and laboratory approaches." *Emerging Infectious Diseases* 2(1): 47-53, 1996.

Popular

Laver, W.G., Bischofberger, N., Webster, R.G. "Disarming flu viruses." *Scientific American* 280: 78-87, 1999.

Larson, E. "The flu hunters." *Time,* February 23, 1998: vol. 151, no. 7, 54-64.

De Kruif, P. *Microbe Hunters.* New York: Blue Ribbon Books, 1926.

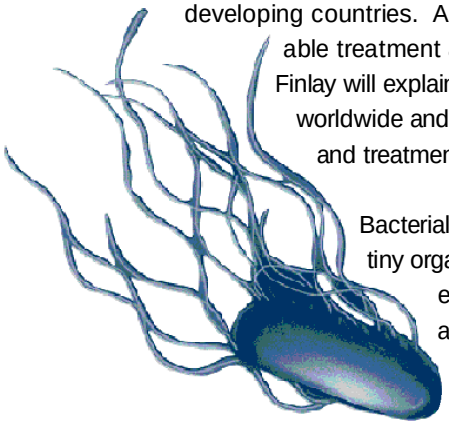
O'Brien, S.J., and Dean, M. "In search of AIDS-resistance genes." *Scientific American* 277: 44-51, 1997.

Klein, G. "Malign Evolution." *Discover* 18: 46-51, 1997.

Kolata, G. "Detective work and science reveal lethal bacteria." *The New York Times,* January 6, 1998: section A, National Desk, page 1.

The Microbes Strike Back

During the Middle Ages the Black Death – bubonic plague – killed 25 million people. Today, with the development of antibiotics and improvements in sanitation, the public has come to feel that bacterial diseases such as the plague had become a thing of the past. However, today bacterial infections cause the deaths of millions of children each year in developing countries. And bacterial infections that are resistant to any form of available treatment are now appearing everywhere in the world. In this lecture, Dr. Finlay will explain why bacterial diseases continue to be a major health problem worldwide and discuss the shortcomings of current methods of prevention and treatment.



Bacterial diseases are difficult to defeat because of the very nature of the tiny organisms that cause them. Bacteria are well adapted to colonize even the harshest environments on earth. Genes spead easily among members of a colony, which reproduce as quickly as every 20 minutes. One cell can become a million in a short time, so that strains adapted to surviving new challenges can quickly evolve. From a human standpoint, this means that some species of bacteria are able to evolve quickly enough to evade our defenses and thus cause disease.

Antibiotic drugs and vaccines have been our most powerful weapons to date against bacteria, but neither is completely effective. Since the introduction of antibiotics just six decades ago, people have assumed that these “wonder drugs” had won the war against bacterial infections. Because of their success, antibiotics have been overused in the clinic and in agriculture, a practice that has now selected for antibiotic resistance in many bacteria. Genes coding for antibiotic resistance are among those that can be passed easily among bacterial colonies – even among different species. As a result, bacterial infections that are resistant to one or more antibiotics are quickly becoming commonplace.

Vaccines are another powerful way to control both bacterial and viral infections. Vaccines work by stimulating the human immune system to eliminate incoming pathogens before they can establish infection. However, many bacteria are able to hide from the immune system by camouflage or by repeatedly changing the molecules on their surface. These organisms have been notoriously difficult foes in the battle to develop effective vaccines.

Lecture Two

KEY CONCEPTS

1. Bacteria are cells that typically develop in colonies.
2. Bacteria thrive under many conditions; they can reproduce rapidly and exchange useful genes readily.
3. Although most bacteria are not harmful to humans, some species have developed ways to evade the host defenses and cause disease.
4. Antibiotics have been powerful weapons against bacterial (but not viral) infections.
5. Many strains of bacteria carry resistance genes, which allow them to survive in the presence of antibiotics.
6. Resistance genes have spread to many types of pathogenic (disease-causing) bacteria and many have developed resistance to more than one type of antibiotic.
7. Vaccines prevent infections before they can begin by priming the immune system to attack particular organisms as soon as they enter the body.
8. Pathogens rarely become resistant to vaccines.
9. Many kinds of bacteria have evolved ways to hide their identity from the immune system, making vaccine development extremely difficult.

CHALLENGE QUESTIONS

These questions, developed by the Holiday Lectures Teacher Resource Group, are intended to stimulate class discussion before and after the lectures. In some cases, the lecturers may provide the answers during their lectures or suggest paths students can follow to find the answers. Students watching the live broadcasts or webcasts can ask the lecturers questions during the live Q&A sessions following each day's lectures. In addition, students can pose e-mail questions to the "Ask a Scientist" website at www.hhmi.org/askascientist

1. Can all types of bacteria make you sick?
2. Describe how bacteria have developed antibiotic resistance to become "superbugs."
3. Think about the vaccinations against disease that you received when you were young. Are all these diseases caused by bacteria?

THEMES AND CONCEPTS RELATED TO ADVANCED PLACEMENT BIOLOGY

The purpose of this section is to help correlate material covered in this lecture with relevant topics that compose the topic outline for the Advanced Placement Program in Biology as described in the College Board website at
www.sat.org/ap/biology/html/indx001.html

Lecture 2 – The Microbes Strike Back explores how bacteria deal with their natural environment and survive in a hostile environment created when therapy with antibiotics is started in an ill patient.

1. Prokaryotic cells
    a. Why prokaryotic pathogens are harmful
    b. What problems unicellular organisms face
    c. Why bacteria have complex envelopes and appendages
2. Subcellular organization
    a. How the cytoplasmic membrane functions
    b. How antibiotics target essential processes
    c. How flagella and pili help bacteria cope

WEB AND PRINT RESOURCES

These resources are listed roughly in order of relevance to the lectures.

Selected Websites

Dr. Brett Finlay's laboratory homepage. Overview of Dr. Finlay's research into pathogenic bacteria and the ways that bacteria interact with the host organism.
www.biotech.ubc.ca/faculty/finlay/homepage.htm

Information about Microbiology for the Public. Website offers a collection of information about microbiology.
www.bact.wisc.edu/GenInfo.html

The Bad Bug Book. Published by the U.S. Food Drug Administration, Center for Food Safety and Applied Nutrition. This handbook provides basic facts regarding foodborne pathogenic microorganisms and natural toxins.
www.vm.cfsan.fda.gov/~mow/intro.html

Survey of Infectious Diseases. List of Diseases for Online Research.
Austin Community College's online course on infectious diseases.
www2.austin.cc.tx.us/microbio/2993c/diseases.html

American Academy of Pediatrics: Your Child and Antibiotics. Website from the American Academy of Pediatrics that discusses treating children with antibiotics, and when antibiotics are useful.
www.aap.org/family/overuse.htm

WHO's pages on Vaccines and Immunization. Provides information about polio, vaccines, and the concept of disease eradication. Further information given on the safety of vaccines, vaccination requirements and health advice for international travel, and a link list to other sites for further information.
www.who.int/gov

The Vaccine Page: Vaccine News and Internet Resource. Contains news on vaccine development and related issues.
www.vaccines.com

Cold Spring Harbor Laboratory: Publications. List of publications discussing immunology, vaccines, and therapeutic proteins.
www.cshl.org/books/catalog/immuno_cat.htm

Exotic Birds: Bacterial Diseases. General overview of bacterial diseases and testing for bacteria.
www.keyinfo.com/bird/pages/articles/diseases.html

Selected Publications

Scientific

Finlay, B.B. "Bacterial disease in diverse hosts." *Cell* 96: 315-318, 1999.

Davies, J. "Inactivation of antibiotics and the dissemination of resistance genes." *Science* 264: 375-382, 1994.

Tenover, F. C., and Hughes, J. M. "The challenges of emerging infectious diseases: development and spread of multiply-resistant bacterial pathogens." *JAMA* 275: 300-305, 1996.

Young, D.B. and Robertson, B.D. "TB vaccines: global solutions for global problems." *Science* 284: 1479-1480, 1999.

Walsh, C. "Deconstructing vancomycin." *Science* 284: 442-443, 1999.

Popular

Weiner, D.B., and Kennedy, R.C. "Genetic Vaccines." *Scientific American* 281: 50-7, 1999.

Beardsley, T. "Innovative Immunity." *Scientific American* 280: 42, 44, 1999

Caldwell, M. "The dream vaccine." *Discover* 18: 84-88, 1997.

Radetsky, P. "Last days of the wonder drugs." *Discover* 19: 76-85, 1998.

Levy, S.B. "The challenge of antibiotic resistance." *Scientific American* 278: 46-53, 1998.

Outwitting Bacteria's Wily Ways

New weapons are urgently needed to fight bacterial invaders as the spread of resistance genes undermines current antibiotics. Using examples from his own work, Dr. Finlay will describe how scientists are trying to understand, on a molecular level, how pathogenic (disease-causing) bacteria interact with our cells and cause disease. This understanding will reveal new targets for antibacterial weapons.

First, we need to understand what makes bacteria pathogenic. Most bacteria are not harmful to people. The possession of "virulence factors" is what enables certain kinds of bacteria to evade host defense mechanisms and cause harm. These factors – as diverse as the host defense mechanisms they evade – can be transferred between different bacteria by genetic exchange, giving rise to new bacterial pathogens and diseases.

Researchers are working to identify virulence factors in different species of bacteria to develop strategies specifically aimed at inhibiting these molecules. Another promising strategy now being developed in the fight against pathogenic bacteria is to target the molecules bacteria use to adhere to host cells. For example, Dr. Finlay has discovered that *E. coli* injects its own receptor molecule into the host cell membrane. Based on this discovery, Dr. Finlay is currently developing a vaccine against this bacterial "docking molecule." Such a vaccine might be useful against different bacteria that use the same docking molecule.

Some species of bacteria, such as *Salmonella* and *Listeria*, live inside human cells. The ability of these pathogens to hide inside host cells shields them from the immune system, but also requires complex survival strategies on the part of the pathogen. As scientists learn more about the molecules that these and other bacteria use to survive, they will be able to design reagents to block specific steps in the disease process.

Another promising scientific development is that the entire genetic sequence of many pathogens will soon be known. Dr. Finlay will discuss how this information will be used by scientists to identify further targets for new therapies.

Lecture Three

KEY CONCEPTS

1. Scientists are beginning to unravel the molecular mechanisms of how bacteria cause infection and disease.
2. Some types of bacteria produce virulence factors that can neutralize the immune response or damage the host cells.
3. Virulence factors are essential for causing disease, but are not necessary for a pathogen to live in the environment.
4. Toxins are secreted virulence factors that cause a variety of disease symptoms ranging from diarrhea to severe tissue damage.
5. One of the strategies in the war against bacteria is to design drugs to inhibit or neutralize virulence factors in different species of bacteria.
6. Scientists have begun to identify bacterial molecules that pathogens use to adhere to host molecules to cause disease.
7. Some pathogens have different virulence factors that allow them to enter and live inside host cells.
8. Intracellular pathogens have developed ways to spread from cell to cell, a process critical to their ability to cause disease.
9. By understanding how pathogens function, scientists can better understand the disease and symptoms, as well as identify new targets to fight infection.
10. The entire genetic sequence of many pathogens will soon be known and should reveal further targets for new therapies.

CHALLENGE QUESTIONS

These questions, developed by the Holiday Lectures Teacher Resource Group, are intended to stimulate class discussion before and after the lectures. In some cases, the lecturers may provide the answers during their lectures or suggest paths students can follow to find the answers. Students watching the live broadcasts or webcasts can ask the lecturers questions during the live Q&A sessions following each day's lectures. In addition, students can pose e-mail questions to the "Ask a Scientist" website at www.hhmi.org/askascientist

1. What are some of the ways microbes evade the body's defense mechanisms?
2. Why is it difficult to rid the body of pathogens?
3. DNA sequencing of bacteria may distinguish those strains that are virulent from those that are harmless. How might such knowledge aid in the design of new antibiotic drugs?

THEMES AND CONCEPTS RELATED TO ADVANCED PLACEMENT BIOLOGY

The purpose of this section is to help correlate material covered in this lecture with relevant topics that compose the topic outline for the Advanced Placement Program in Biology as described in the College Board website at
www.sat.org/ap/biology/html/indx001.html

Lecture 3 – Outwitting Bacteria's Wily Ways – examines how pathogens colonize the body by evading the body's immune system. By developing new strategies that target sensitive sites and functions of pathogens, researchers are developing the means to battle bacterial survival.

1. Response to the environment
    a. How microorganisms enter the host
    b. How bacterial pathogens penetrate host defenses
    c. How bacterial pathogens damage host cells
2. Physiological adaptations
    a. How immunity is acquired
    b. How the immune system exhibits cellular versus humoral immune responses
    c. What antigens and antibodies are
    d. What antibody-mediated immunity does
    e. How T cells and cell-mediated immunity function

WEB AND PRINT RESOURCES

These resources are listed roughly in order of relevance to the lectures.

Selected Websites

Mechanisms of Bacterial Pathogenicity. Lecture notes from the University of Wisconsin Department of Bacteriology covering mechanisms of bacterial pathogenicity with links to other related websites.
www.bact.wisc.edu/bact303/bact303mainpage

Bugs in the News. A feature article with an archive that explores such subjects as antibiotics, antibodies, bacteria, *E. coli*, genes, and genetic engineering. Also general interest article archive and links to other sites of interest.
falcon.cc.ukans.edu/~jbrown/bugs.html

Links to Bacterial Pathogenesis Labs. A link from the University of Texas at Austin School of Biological Sciences that lists several laboratories that study bacterial pathogenesis. Institutions represented: Stanford University, Yale University, University of Maryland, Harvard University, Washington University, University of Kentucky, and the Pasteur Institute.
www.esb.utexas.edu/paynelab/bacteria.html

Lecture Three

Medical Microbiology. Provides an introduction to Medical Microbiology; information about immunology, bacteriology, and virology as well as practice exams, references, and links to other sites of interest.
www.cehs.siu.edu/fix.medmicro

Your Health. Playing it Smart in the War Against Disease-Causing Bacteria. An article from the National Wildlife Federation that discusses the onslaught of antibacterial products on the market and other "paradoxes of the antibiotic age."
www.nwf.org/nwf/natlwild/1999/healthf9.html

TIGR Microbial Database Provides link to microbial genome sequencing projects completed and underway.
www.tigr.org/tbd/mbd/mdb.html

Selected Publications

Scientific

Finlay, B.B., and Cossart, P. "Exploitation of mammalian host cell functions by bacterial pathogens." *Science* 276: 718-725, 1997.

Brumell, J.H., Steele-Mortimer, O., and Finlay, B.B. "Bacterial invasion: force feeding by *Salmonella*." *Current Biology* 9: 277-280, 1999.

Finlay, B.B., and Falkow, S. "Common themes in microbial pathogenicity revisited." *Microbiology and Molecular Biology Reviews* 61: 136-169, 1997.

Pettersson, J., Nordfelth, R., Dubinia, E., et al. "Modulation of virulence factor expression by pathogen target cell contact." *Science* 273: 1231-1233, 1996.

Cotter, P.A., Miller, J.F. "Triggering bacterial virulence." *Science* 273: 1183-1184, 1996.

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Pennisi, E. "Unraveling bacteria's dependable homing system." *Science* 284: 82, 1999.

Strauss, E. "Anti-immune trick unveiled in *Salmonella*." *Science* 285: 306-307, 1999.

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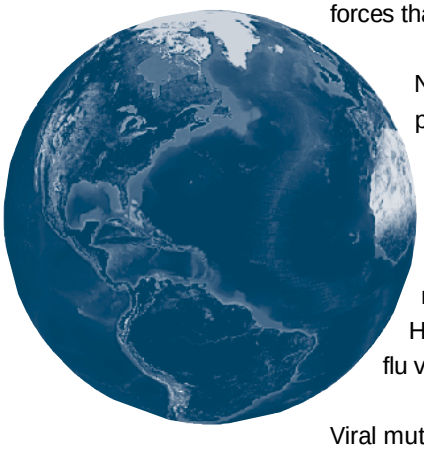
Losick, R., and Kaiser, D. "Why and how bacteria communicate." *Scientific American* 276: 68-73, 1997.

Oliwenstein, L. "Bacterium tells all, human tells a lot." *Discover* 7: 32-33, 1996.

Beardsley, T. "Evolution evolving. New findings suggest mutation is more complicated than anyone thought." *Scientific American* 277:15, 18, 1997.

Emerging Infections: How Epidemics Arise

We often think of infection as something that befalls us due to forces beyond our control. Epidemics seem to have a mysterious dynamic, arising unexpectedly and subsiding inexplicably. But science shows that this impression is inaccurate. While the determinants of epidemics are undoubtedly complex, they are understandable. In this lecture on interactions between viral pathogens and their hosts, Dr. Ganem will consider some of the forces that create and shape epidemic infection.



New infectious diseases usually result from an upset in a previously established balance between the virus and its natural host. Mutations or other genetic changes in the virus, for example, may confer upon it new properties, such as the ability to grow more efficiently in its natural host or to spread to a species that is not ordinarily susceptible. The most dramatic recent example of the hazards of genetic change in a virus is the Hong Kong influenza outbreak of 1997-98, in which a novel avian flu virus emerged in poultry flocks and spread to humans.

Viral mutation is only one way to perturb the balance. Changes in the environment, either natural or manmade, can also have disruptive effects. Such disturbances can, for example, bring a virus into contact with human hosts who had rarely encountered it in the past. This, in turn, leads to new forms of the disease that are often uncommonly severe – for example, smallpox epidemics were much more serious among the Inca and Maya peoples than among the Spanish conquistadors who introduced the disease to the Americas from Europe. Many new epidemics require both genetic change in the pathogen and a shift in exposure patterns between humans and viruses.

Once established, emerging viruses and their hosts continue to co-evolve over time, ultimately establishing a new balance. In this equilibrium, the virus drive to grow rapidly is tempered by the fact that anything that shortens the life of the host will curtail opportunities for the virus to spread. Thus, the virus affects host evolution, and vice versa. Viewed in this light, infectious diseases are an important force in human evolution and are likely to remain so indefinitely.

Lecture Four

KEY CONCEPTS

1. Epidemics typically arise from an upset in a previously established balance between a virus and its natural host.
2. Genetic change in the virus itself – caused by mutation, recombination, and selection – may generate a virus that can grow more efficiently in its natural host or one that can spread to new host species.
3. Changes in the environment can bring a virus into contact with a new host with little or no experience with the virus – thus lacking immunity – leading to more severe forms of a disease.
4. The spread of an infectious disease is critically influenced by social, economic, and behavioral factors in the human population.
5. In infected populations, viruses and their hosts co-evolve, with each influencing the other's destiny.
6. Often the most successful pathogens evolve to avoid killing their hosts.
7. Infectious diseases will unlikely be eradicated as a group but individual diseases can be controlled by public health measures, vaccination, and specific therapy.

CHALLENGE QUESTIONS

These questions, developed by the Holiday Lectures Teacher Resource Group, are intended to stimulate class discussion before and after the lectures. In some cases, the lecturers may provide the answers during their lectures or suggest paths students can follow to find the answers. Students watching the live broadcasts or webcasts can ask the lecturers questions during the live Q&A sessions following each day's lectures. In addition, students can pose e-mail questions to the "Ask a Scientist" website at www.hhmi.org/askascientist

1. What DNA evidence suggests a long-term relationship between viruses and humans?
2. In what ways do the environment and human behavior contribute to disease distribution?
3. Changes in the habitats of the host and/or mutations in a virus can upset an established balance between host and virus. A) Explain how these changes could result in a new epidemic; B) Explain the importance of the co-evolution of the emerging virus and its host over time.

THEMES AND CONCEPTS RELATED TO ADVANCED PLACEMENT BIOLOGY

The purpose of this section is to help correlate material covered in this lecture with relevant topics that compose the topic outline for the Advanced Placement Program in Biology as described in the College Board website at www.sat.org/ap/biology/html/indx001.html

Lecture 4 – Emerging Infections: How Epidemics Arise emphasizes the delicate balance between pathogens and their hosts that can result in sudden or periodic cycles of epidemics.

1. Population dynamics
    a. What constitutes the normal microbiota
    b. What the etiology of infectious disease is
    c. How infectious disease is classified
    d. What causes the spread of infection
    e. How patterns of disease are determined
2. Mechanisms of evolution
    a. How genetic material functions
    b. How mutation alters genetic material
    c. How genetic transfer and recombination work

WEB AND PRINT RESOURCES

These resources are listed roughly in order of relevance to the lectures.

Selected Websites

Epidemic: The World of Infectious Disease. Special exhibition at the American Museum of Natural History that documents the tremendous scientific advances in, and the cultural issues relevant to understanding infectious disease.
www.amnh.org/exhibitions/epidemic/index.html

Disease Links from the CDC. Contains links to a broad range of diseases.
www.cdc.gov/od.oc/media/diselink.htm

Communicable Disease Surveillance and Response (CSR). Provides information about international health regulations, disease outbreak news, the Weekly Epidemiological Record, as well as related fact sheets and press releases.
www.who.int/emc/

Anatomy of an Epidemic. Epidemic education website with information about epidemics, maps of disease distribution, and disease discussion.
http//library.advanced.org/11170/

All the Virology on the WWW. Collection of virology-related websites with an index to virus pictures called The Big Picture Book of Viruses, a bookstore from which you can order books on related topics, and a link to online courses in virology.
www.tulane.edu/~dmsander/garryfavweb.html

Lecture Four

ProMED: The Program for Monitoring Emerging Diseases. ProMED-Mail is an e-mail system used for the reporting of diseases.
www.healthnet.org/programs/promed.html

Addressing Infectious Disease Threats. Provides information about what an infectious disease is, emerging and reemerging diseases, and how bacteria, parasites, and fungi are transmitted. Links to an infectious disease facts index.
www.astdhpphe.org/infect/infectintro.html

Selected Publications

Scientific

Strausbaugh, L. J. "Emerging infectious diseases: A challenge to all." *American Family Physician* 55: 111-117, 1997.

Colwell, R.R. "Global climate and infectious disease: the cholera paradigm." *Science* 274: 2025-2031, 1996.

Drotman, D.P. "Emerging infectious diseases: A brief biographical heritage." *Emerging Infectious Diseases* 4: 372-3, 1998.

Binder, S., Levitt, A.M., Sacks, J.J., et al. "Emerging infectious diseases: Public health issues for the 21st century." *Science* 284: 1311-1313, 1999.

Lederberg, J. "Emerging infections: An evolutionary perspective." *Emerging Infectious Diseases* 4: 366-371, 1998.

Besser, R.E., Griffin, P.M. and Slutsker, L. "*Escherichia coli* O157:H7 gastroenteritis and the hemolytic uremic syndrome: An emerging infectious disease." *Annual Review of Medicine* 50: 355-367, 1999.

Raoult, D. "Infectious disease. Return of the plagues." *Lancet* 352 Suppl. 4:SIV18, 1998.

Alleyne, G.A. "Emerging diseases – what now?" *Emerging Infectious Diseases* 4: 498-500, 1998.

Levin, B.R., Lipsitch, M., and Bonhoeffer, S. "Population biology, evolution, and infectious disease: convergence and synthesis." *Science* 283: 806-809, 1999.

Popular

Watts, S.J., and Watts, Sheldon. *Epidemics and History: Disease, Power, And Imperialism.* New Haven: Yale University Press, 1998.

Kolata, G. "Scientists probe the genetic mysteries of a pair of deadly plagues." *The New York Times,* May 26, 1998: section F, Science Desk, page 1.

Foster, K.R., Jenkins, M.F., and Toogood, A.C. "The Philadelphia yellow fever epidemic of 1793." *Scientific American* 1279: 88-93, 1998.

Dold, C. "The cholera lesson." *Discover* 19: 71-75, 1999.

Kluger, J. "Anatomy of an outbreak." *Time,* August 3, 1998: vol. 152, no. 5, 56-62.

Ezzell, C. "It came from the deep." *Scientific American* 280: 22, 24, 1999.

SELECTED WEBSITES TO VISIT

Exploring Microbiology

Medical Microbiology: Neal Chamberlain's Look at Microbes! This medical microbiology web site contains infectious diseases and medical microbiology lecture notes, an interactive lab manual, and links to other infectious disease websites.
www.geocities.com/CapeCanaveral/3504

The Microbe Zoo. The Microbe Zoo is an educational resource about ecology and microbiology and includes information about microbes and the habitats they dwell in, as well as images of microbes.
http://commtechlab.msu.edu/sites/dlc-me/zoo

Microbes: Invisible Invaders...Amazing Allies. Material from an educational science exhibit sponsored by Pfizer in collaboration with the National Institutes of Health.
www.pfizer.com/rd/microbes

Microbial Underground's Guide to Microbiology on the Net. Links to microbiology and infectious diseases websites.
www.lsumc.edu/campus/micr/mirror/public_html/microbio.html

On the Microbe Trail: An Introduction to Bacteria and Aseptic Technique**.** This activity is a series of exercises that introduces students to bacteria and aseptic microbiology lab techniques.
www.accessexcellence.org/AE/AEC/AEF/1996/ziegenhirt_microbe.html

Washington State University, Department of Microbiology, Microbiology 310 Links. Links to microbiology departments, general references, pathogens, and emerging infectious disease sites.
www.sci.wsu.edu/bio/micro310links.html

Exploring Infectious Diseases

The American Experience: Influenza 1918. Part of PBS's American Experience film series with detailed information on the influenza epidemic.
www.pbs.org/wgbh/pages/amex/influenza/index.html

Discovery Online - Infectious Diseases: Plague Control. Reviews how infectious diseases are tracked and has links to related websites and "Ask the Researchers."
www.discovery.com/stories/science/infectious/infectious.html

Emerging Infectious Diseases. Tracks trends and analyzes new and reemerging infectious disease issues around the world.
www.cdc.gov/ncidod/eid/index.htm

Epidemic: On the Trail of Killer Diseases: Discovery Channel Online. Detailed discussion of tuberculosis, flu, polio, dengue fever, and hantavirus.
www.discovery.com/exp/epidemic/epidemic.html

Hopkins Infectious Diseases. Comprehensive database of infectious diseases including hepatitis, HIV, sexually transmitted diseases, and tuberculosis.
www.hopkins-id.edu

Infectious Disease Society of America. Organization of physicians, scientists and health care professionals working to promote disease prevention and education in the field of infectious diseases.
www.idsociety.org/

Additional Resources

National Center for Infectious Diseases. Division of the Centers for Disease Control and Prevention committed to combating and controlling traditional, new, and reemerging infectious diseases worldwide.
www.cdc.gov/ncidod/ncid.htm

National Institute of Allergy and Infectious Diseases (NIAID). Division of the National Institutes of Health devoted to diagnostic, treatment and prevention research on infectious diseases, and immune system disorders.
www.niaid.nih.gov

World Health Organization: Health topics and policy. Links to detailed information on a variety of communicable and infectious diseases.
www.who.int/home/map_ht.html

The World-Wide Web Virtual Library: Epidemiology. A large, well-organized collection of epidemiology resources.
www.chanane.ucsf.edu/epidem/epidem.html

Exploring Teaching Resources on Infectious Diseases

American Society for Microbiology: Education and Training. Listing of programs and resources for students and faculty in the microbiological sciences.
www.asmusa.org/edusrc/edu1.htm

American Society for Microbiology (ASM) Teaching Resources: information for teachers and schools. Includes links to possible mentors, outreach activities, biofilm images, and more.
www.asmusa.org/edusrc/edu9.htm

Selected WWW Links for Teacher/Scientist Partnership Programs. This site provides a large number of links to K-12 teaching sites on science topics, including links to sites specific to virology and microbiology.
www.urmc.rochester.edu/smd/mbi/linxdtsp.html

SELECTED PRINT PUBLICATIONS

Beck, G. and Habicht, G. S. "Immunity and the invertebrates." *Scientific American* 60-71, 1996.

Harrison, P. F., and Lederberg, J., Editors. *Antimicrobial Resistance: Issues and Options*. Washington: National Academy Press, 1998.

Koprowski, H., and Oldstone, M. B., Editors. *Microbe Hunters – Then and Now*, Bloomington, IL: Medi-Ed Press,1996.

Parsonnet, J., Editor. *Microbes and Malignancy: Infection as a Cause of Human Cancers*. New York: Oxford University Press, 1999.

Regis, E. *Virus Ground Zero : Stalking the Killer Viruses With the Centers for Disease Control*, New York: Pocket Books, 1996.

Rhodes, R. *Deadly Feasts: Tracking the Secrets of a Terrifying New Plague*. New York: Simon & Schuster: 1997.

Roth, J. A. *Virulence Mechanisms of Bacterial Pathogens*. Washington: American Society for Microbiology Press, 1995.

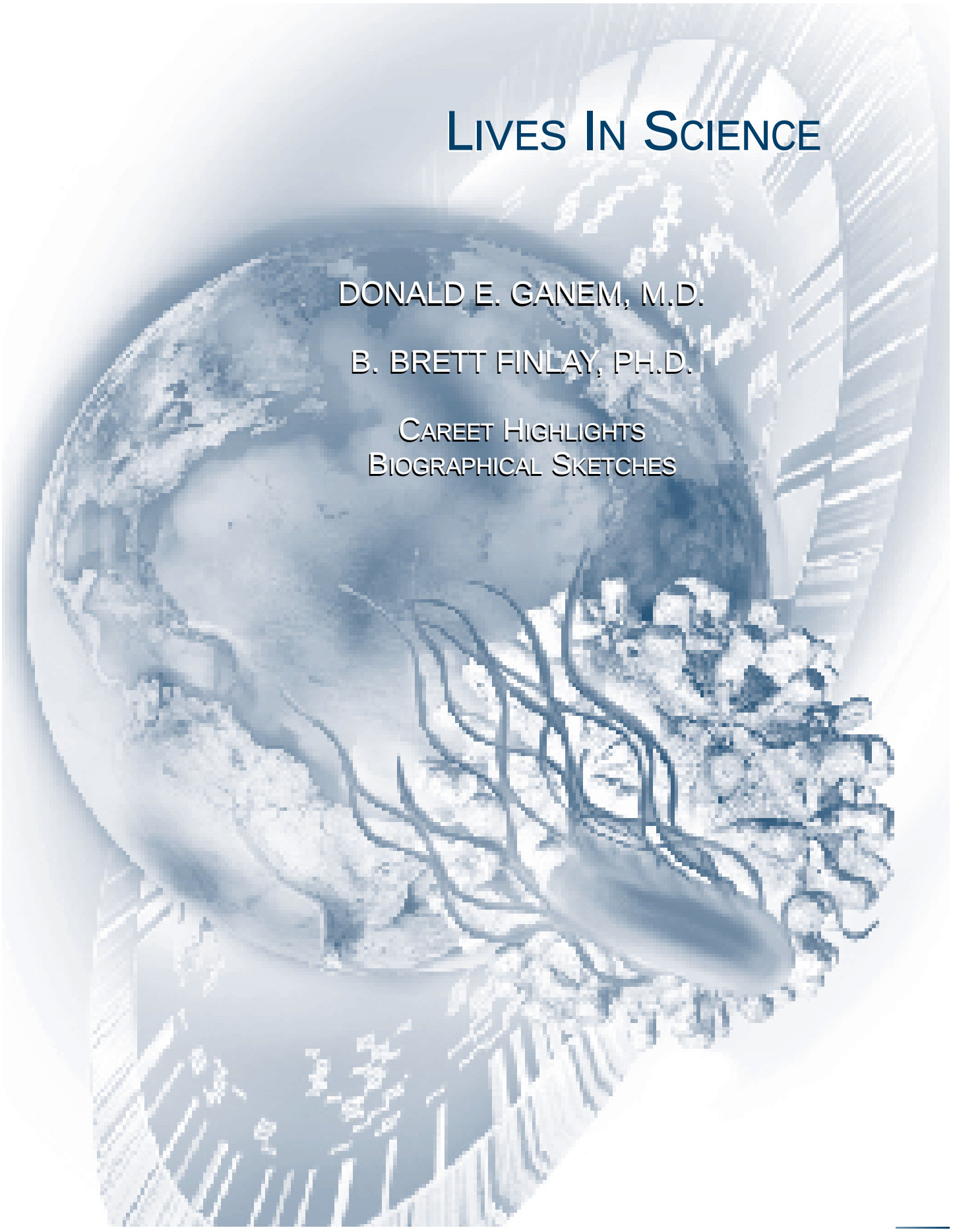
Salyers, A.A., and Whitt, D.D. *Bacterial pathogenesis: A molecular approach*. Washington: American Society for Microbiology Press, 1994.

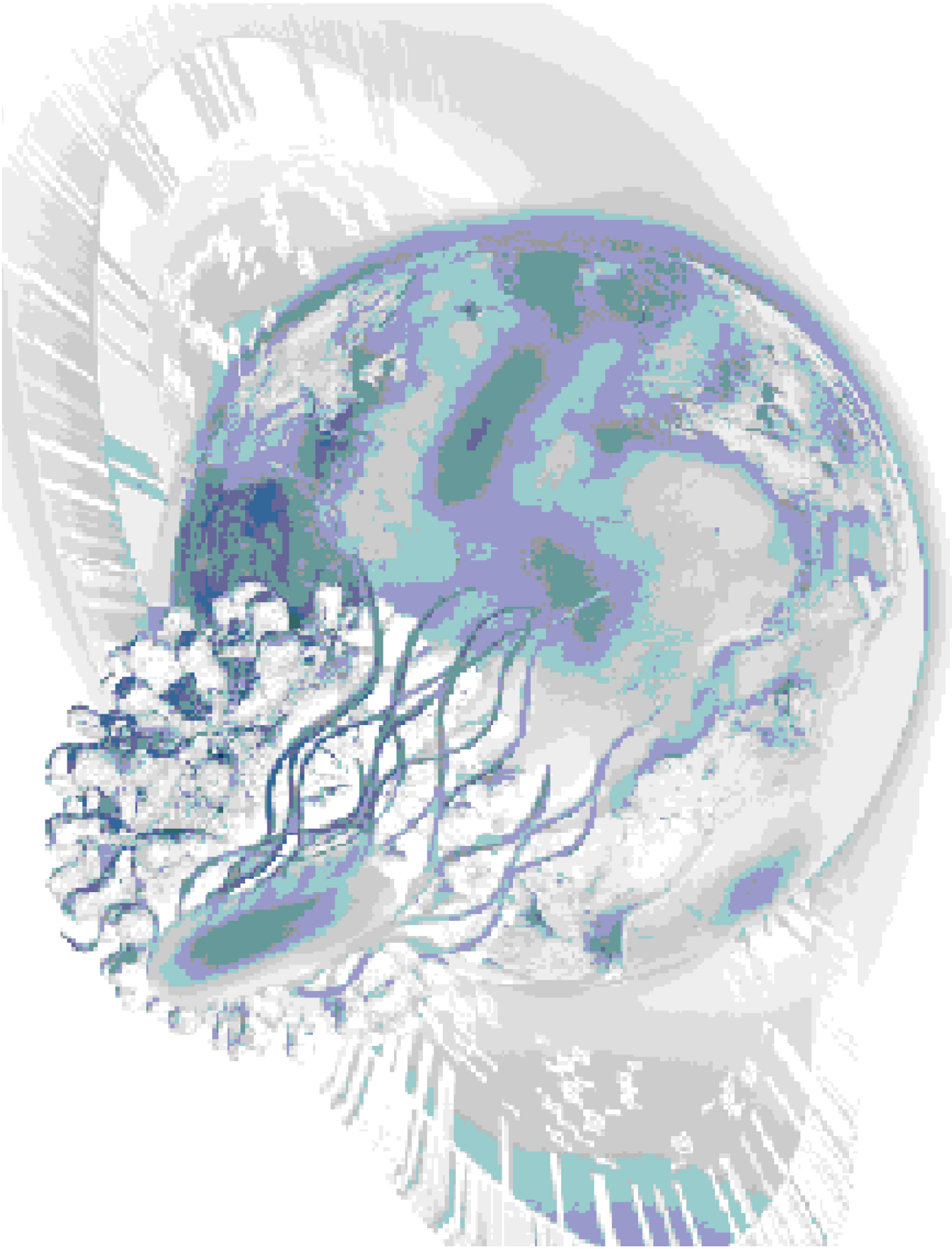
Lives In Science

DONALD E. GANEM, M.D.

B. BRETT FINLAY, PH.D.

Careet Highlights
Biographical Sketches





Career Highlights

Born September 23, 1950, in Boston, Massachusetts, U.S.A.

....majored in biochemistry

.....his favorite courses were Genetics, taught by Prof. Matt Meselson, and Microbial Genetics, taught by Prof. Jon Bechwith

.....Dr. Varmus is now director of the National Institutes of Health

.....What do students like about Dr. Ganem's teaching style?

"I include a lot of examples from the history of medicine, one of my big hobbies," says Ganem. "It turns out that medical students don't know much about medical history– but are eager to know more."

EDUCATION

High School Diploma Phillips Academy, Andover, MA, 1968
Undergraduate Degree (A.B., magna cum laude): Harvard College, Cambridge, MA, 1972
Medical Degree (M.D., magna cum laude): Harvard Medical School, Boston, MA, 1977

TRAINING

1974-1975: **Research associate** in molecular virology, Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts

1977-1979: **Medical intern and resident**, Peter Bent Brigham Hospital, Boston, Massachusetts

1979-1980: **Clinical fellow**, Department of Medicine, Infectious Diseases Division, University of California – San Francisco (UCSF)

1980-1982: **Postdoctoral fellow** in molecular virology in the UCSF laboratory of Nobel Laureate Harold Varmus

1982-1983: **Chief medical resident**, Brigham and Women's Hospital, Boston, Massachusetts

APPOINTMENTS

1982, 1998, 1990: Assistant Professor, Associate Professor, and **Professor** of Microbiology and Medicine, UCSF

1991, 1995: Associate Investigator and **Investigator**, HHMI

1995: Vice-Chair, Department of Microbiology and Immunology, UCSF

SELECTED AWARDS AND HONORS

Soma Weiss Award and Leon Resnick Prize at Harvard Medical School for **excellence in research**

Numerous awards for **excellence in teaching**, including 2nd Year Medical Students, Teaching Awards for small group teaching, lecturing, instruction in the medical humanities, and lab instruction

Elected to American Academy of Microbiology, 1993

Elected vice president, American Society for Clinical Investigation, 1997

SELECTED PROFESSIONAL ACTIVITIES

Editorial board member of five peer-reviewed journals

Ad hoc referee of over 12 professional journals

Visiting professor at Vanderbilt University, Mayo Clinic, and the University of California-San Diego

PUBLICATIONS

More than 120 original research articles and several review articles in peer-reviewed journals such as *Cell, Journal of Virology, Journal of Molecular Biology, Nature,* and *Science.*

Biographical Sketch

While other kids' parents were reading them tales of Peter Rabbit and Robinson Crusoe, Don Ganem's father read bedside stories to him from the *Encyclopedia Britannica*. "I discovered the joy of knowing things at a fairly early age," says Ganem. "Especially things other people didn't know. So I developed an addiction to facts. And if you're brought up with a fact addiction, science is a natural choice for a career."

Still, it wasn't always clear that Ganem was headed for a career in biomedical research. In eighth grade, for example, he got an F in algebra because "I was holding hands with a girl in class," he says. "I wasn't paying very much attention to y=mx+b." In high school biology, however, he learned that researchers were figuring out how specific molecules perform critical jobs inside cells, and slowly his interests began to veer in that direction. "To think you could understand life at that level was quite mesmerizing," he adds.

Diseases first captured Ganem's attention when he read *The Microbe Hunters*, Paul de Kruif's book about 18th and 19th century medical scientists who tracked epidemics to their microbial origins. Impressed by the acumen and ingenuity these men demonstrated as they met these immense challenges without the benefit of modern tools, Ganem quickly adopted them as his heroes. During his senior year of high school, his parents gave him an 800-page medical microbiology text for Christmas. Undaunted by its length, Ganem looked on this tome as a fantastic treat. "The idea that there was that much to know I found really cool," he says. "This seemed like a field you could really sink your teeth into."

A second book, *The Double Helix*, Nobel Laureate James Watson's account of how he and his colleagues worked out the structure of DNA, also made a big impression. "Watson described very vividly the lifestyle of research scientists: not only the hard work and the long hours, but also the glamorous parts – international travel, intense competition with photo finishes, and, especially, the thrill of discovery." Ganem says. "The people in the book displayed an extreme level of commitment, almost fanaticism. It was the same level of devotion that professional athletes have for their sport, but you could be a part of it even if you were a klutz – which I was."

Starting in his second year at Harvard College, Ganem pursued research in bacterial genetics in Watson's lab and found that "what I had read in his book was really true. The lab really was full of these phenomenally talented people who stayed up all night and discovered things no one knew before." His undergraduate lab experience inspired him, but it also unnerved him. "The Watson group's postdocs were so brilliant," he says. "I felt like I would never measure up to their level. It seemed like you had to be a transgalactic superstar to be a scientist."

Nevertheless, he persevered. But although Ganem's work at the bench taught him that he loved the intellectual rigor and challenges of studying basic biology, he felt something was missing – a more direct connection to human disease. So he decided to go to medical school, where he also did research, this time in virology. But there he discovered that he also enjoyed clinical medicine. “I liked taking care of people,” says Ganem. “Diagnosis was especially interesting. It was a deductive, scientific process with great immediacy. If you diagnosed people right, you could make them better. That was fantastic.” Infectious disease seemed particularly attractive in this regard, since it combined his early interest in microbes with his new interest in medicine.

By the time Ganem began his internship, he had made his life plan: He wanted to apply his training in molecular biology to the study of an infectious disease of humans. So he made a list of the viral diseases that he thought could be fruitfully studied. Scientists had just isolated the genetic material of the Hepatitis B virus (HBV). “It was a small piece of DNA with interesting biology, and very few people were studying it,” Ganem says. “This seemed like the perfect place for me to work.”

To train in infectious disease, Ganem knew that he would have to do an internship. Ultimately, he decided that if he were going to invest in an internship, he had “better find the hardest medical residency program I could find, so I could be sure when it was over that this was something I could do really well.” In addition to his “fact addiction,” Ganem explains, he had a quality addiction. “I got this from my mother,” he says. “She’s a big believer in the top of the line.” He stayed at Harvard for his internship and residency.

Not many researchers were studying HBV when Ganem was ready to resume research, but he figured that a stimulating environment mattered more than prior expertise with that particular microbe. Ganem asked Harold Varmus, then a professor of microbiology at UCSF (now director of the National Institutes of Health and winner of a Nobel Prize for cancer research) whether he was interested in HBV. “It turned out that Harold was interested, even though he wasn’t working on HBV at the time,” he recalls. With Varmus, Ganem studied how HBV reproduces itself inside its host cell, and how the virus particles orchestrate their assembly and release. After he finished his fellowship with Varmus, he stayed on as a faculty member at UCSF and continued to study HBV.

The HBV work satisfied his desire to uncover the molecular details of a known infectious disease. But Ganem's heroes still were the microbe hunters who worked at an even more remote frontier: the discovery of previously unknown infectious agents. So in the early 1990s, Ganem decided to broaden the scope of his work. He made another list, this time of “diseases likely to be infectious, but for which the causes weren't known.” At the top was Kaposi's sarcoma (KS), a type of tumor that occurs on the skin or mucous membrane.The pattern of this cancer in the population strongly suggested that an infectious agent was involved. First, KS was very rare before the HIV epidemic, but common afterward. Only a select group of people with AIDS – gay men – got KS, which suggested that it was associated with sexual contact. And although people with KS also harbored HIV in their bodies, HIV didn't appear in the KS tumor itself. Ganem thought that it was likely that some other infectious agent was transmitted with HIV. “The epidemiology was crystal clear to me,” he says. “There's a second infection here.”

After another group recovered fragments of the DNA of a suspect virus from KS tumors, Ganem's group developed a cell culture system that allowed researchers to grow the virus in the lab. Using this new technique, Ganem developed a blood test for the infection. With this tool, he provided a critical piece of proof that the suspect virus, called Human Herpes Virus 8, was the culprit: It was present in people at high risk for infection and absent in people at low risk for infection. His group then found that not only did people with KS carry Human Herpes Virus 8 in their blood, but also tumors contained the genetic material of the virus.

Satisfied that he and others have pinpointed the guilty virus, Ganem is now working out the molecular basis of disease. He is especially interested in how the KS virus interacts with HIV and which of the KS virus genes play critical roles in the development of the cancer.

Despite these accomplishments in the lab, Ganem says, his real talents lie in teaching. "It's one thing I know I'm really good at. And I love to teach." With regard to research, he says "I don't compare myself to the people with whom I trained. Those people (Watson and Varmus) are men of genuine genius on a global scale. My talents are much more modest." But Ganem does find comfort in contemplating one of his heroes, Louis Pasteur. "Pasteur was a thoroughly conventional stick-in-the-mud bourgeois Frenchman. And yet he made magnificent contributions to science and medicine. For someone thoroughly conventional like me, that's comforting – maybe even inspiring."

Career Highlights

Born March 4, 1959, in Edmonton, Alberta, Canada

....."My mentors were fathers to me, and guided and motivated me as I figured out how to be a scientist. They were wonderful teachers who let me learn by pointing me in the right direction and picking up the pieces when I went astray, instead of telling me how to do everything."

EDUCATION

High School Diploma Salisbury Composite High School, Alberta, Canada, 1977
Undergraduate Degree (Honors in Biochemistry): University of Alberta, Edmonton, Alberta, Canada, 1981
Graduate Degree (Ph.D.): Department of Biochemistry, University of Alberta, 1986

TRAINING

Summer 1980: **Undergraduate research student**, Department of Biochemistry, University of Alberta

1986-1989: **Postdoctoral fellow**, Stanford University, Stanford, CA

APPOINTMENTS

1989, 1994, and 1996: Assistant Professor, Associate Professor, and **Professor**, Biotechnology Laboratory, Departments of Biochemistry/Molecular Biology and Microbiology/Immunology, University of British Columbia, Vancouver, Canada

SELECTED AWARDS AND HONORS

HHMI international research scholar – two-time recipient of a $500,000 research award given to support prominent young medical researchers outside the U.S.

.....To what does Dr. Finlay attribute his success as a researcher? "Hard work, perseverance, organization, and the realization that everyone has something to offer – you just have to figure out how to get the best out of each member of your team."

E.W.R. Steacie Prize in the natural sciences – given to a Canadian scientist or engineer 40 years old or younger for outstanding contributions to research

University of British Columbia Killam Research Prize and Fisher Scientific Award from the Canadian Society of Microbiologists – both awards for excellence in research

SELECTED PROFESSIONAL ACTIVITIES

Editorial Board Member of 8 scientific journals

Presented invited lectures at more than 125 institutions and conferences worldwide

PUBLICATIONS

More than 100 original articles and reviews in peer-reviewed journals such as *Science, Cell, Proceedings of the National Academy of Sciences, Journal of Bacteriology, Journal of Infectious Diseases, EMBO Journal, and Journal of Virology*

Biographical Sketch

Brett Finlay knew that he wanted to become a scientist almost from the moment that he first toddled after his parents, both biologists, as they investigated the natural world in their community outside Edmonton, the capital of the Canadian province of Alberta. “I had no choice,” he laughingly recalls. “As kids, our life consisted of helping my dad track birds, or going down to the slough, scooping out green, slimy stuff, and putting it under the microscope with my mom. Back then I really liked dinosaurs, so my parents would drag me out to the Paleontology Department at the University [of Alberta] so I could help the scientists scrub dinosaur bones with a toothbrush.” His parents, whom he considers his first mentors, were constantly exposing him to a lot of science, and “I loved it,” he says.

Not content with simply observing living things, Finlay decided to study biochemistry and molecular biology as an undergraduate at the University of Alberta. “I really like to know how things work,” he explains. “I wanted to get down to the molecular level.” His research interests led him to continue on at the university, where he pursued a Ph.D, studying the mechanisms of bacterial conjugation – the ability of bacterial cells to transfer DNA between cells that are in physical contact.

After earning his Ph.D., Finlay moved south to Stanford University in California to train as a postdoctoral fellow in the laboratory of world-renowned microbiologist Stan Falkow. It was here that he realized that people had been taking the wrong approach to studying pathogenic bacteria. “Everyone was looking at these pathogens isolated in test tubes,” he explains. “I realized that no one was paying attention to what really happens when the bacteria hit the host cells. So I started to look at the process of infection. I wanted to figure out new ways we could explore it.”

In 1989, when he finished his postdoctoral research at Stanford, Finlay was much in demand. He was leaning toward a position at the Massachusetts Institute of Technology in Cambridge, Massachusetts, but his wife wanted to return to Canada. “I knew you could do good science in Canada,” he says, “so we agreed to settle in Vancouver, a city we’ve both loved.” His wife is a physician who also specializes in infectious diseases. “Our dinnertime conversations get pretty gross,” he laughs.

Once in charge of his own lab, Finlay focused on the process of infection by investigating how bacteria invade the body, survive inside host cells, and proliferate. He concentrated his efforts primarily on *Salmonella* and *E.coli* bacteria. Finlay chose to study these two organisms because they are important pathogens – Salmonella can cause diseases ranging from gastroenteritis to typhoid fever, and *E. coli* can cause severe diarrhea or even death, especially in infants and young children. From a researcher’s perspective, however, they

are relatively safe to work with and can be easily manipulated using molecular biology techniques. Over the years, Finlay pursued a number of different strategies to learn more about the early stages of bacterial infection – gaining a good deal of knowledge about the ways in which *Salmonella* and *E. coli* cleverly avoid the host cell's efforts to kill them off.

A few years ago, Finlay's research team at the University of British Columbia discovered what Finlay has called a "completely new paradigm" for bacterial infection. While every previously identified pathogen adhered to an existing protein on host cells, the *E. coli* bacterium, Finlay learned, actually encodes its own receptor and injects that receptor molecule into the host cell's membrane. Building on that knowledge, his latest research focuses on testing a number of bacterial molecules discovered in his laboratory for use as vaccines to prevent infections and as targets for new drugs to treat people once they've been infected. Some of these molecules are unique to a single species of bacteria like *E. coli* or *Salmonella*. But at least one family of proteins, called "syringe," is made by several kinds of infectious bacteria. "What gets shot into the host cells may be totally different for different bacteria," explains Finlay, "but the actual syringe mechanism is the same. So it makes a good target."

Not all the research paths he has pursued have led to expected answers, as wily bacteria continue to throw researchers unexpected curves. "There are always twists and turns in this field," he says. "Probably two or three times a year we get a result that's completely unexpected, where we just realize these bugs are so smart! They don't read the cell biology books – they find their own way of doing things. That's what makes this field so exciting. You've got to learn to expect the unexpected, and to look for it."

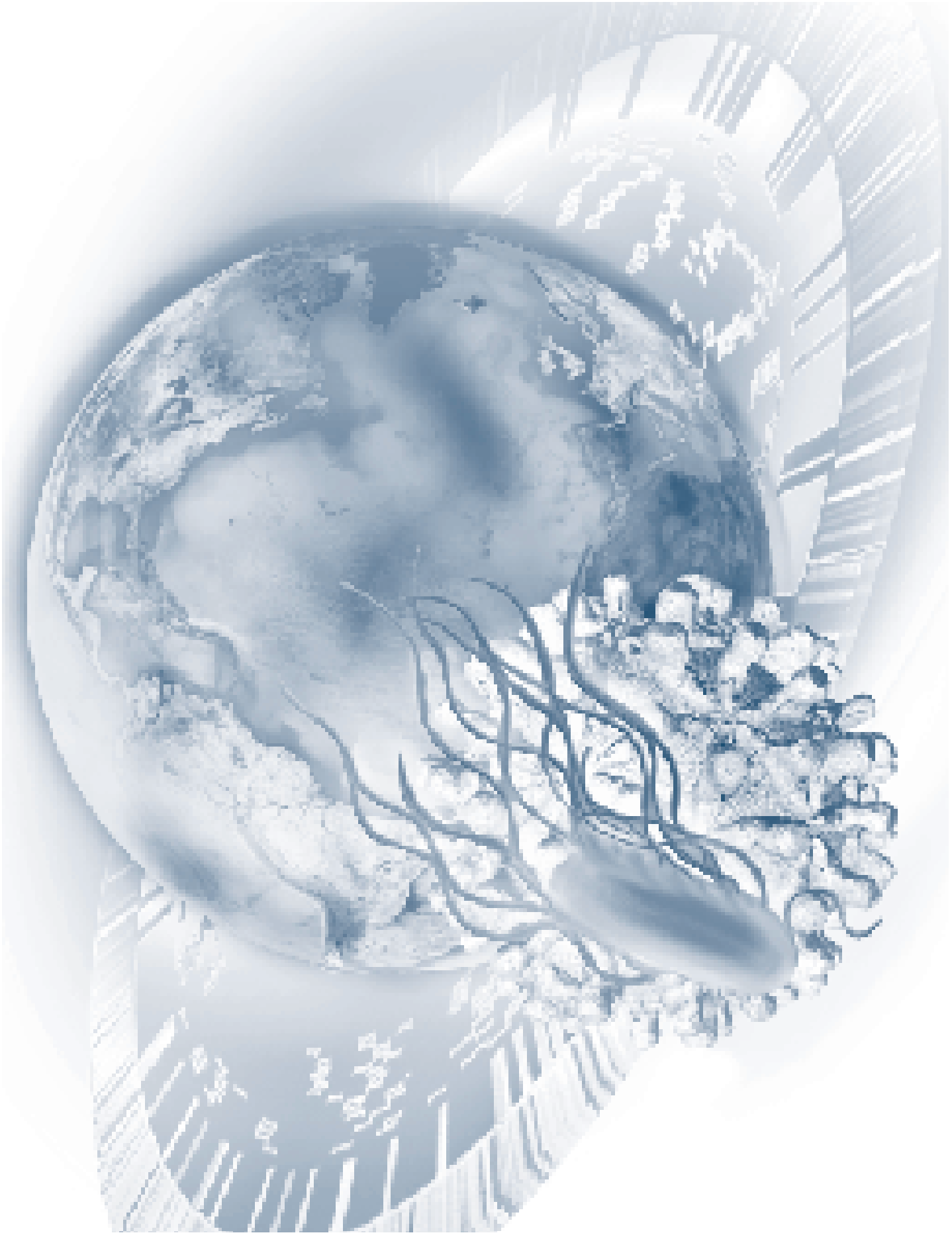
Although unexpected results have sometimes meant throwing months of work out the window, Finlay, like all successful scientists, has learned to be philosophical and to keep an open mind about "failure." When experiments don't work, Finlay believes that a researcher needs to take a step back and ask: "Did the experiment really not work, or are the results trying to tell you something that you didn't think of before?" That's an important lesson to learn about science: a failed experiment is often actually trying to tell you something.

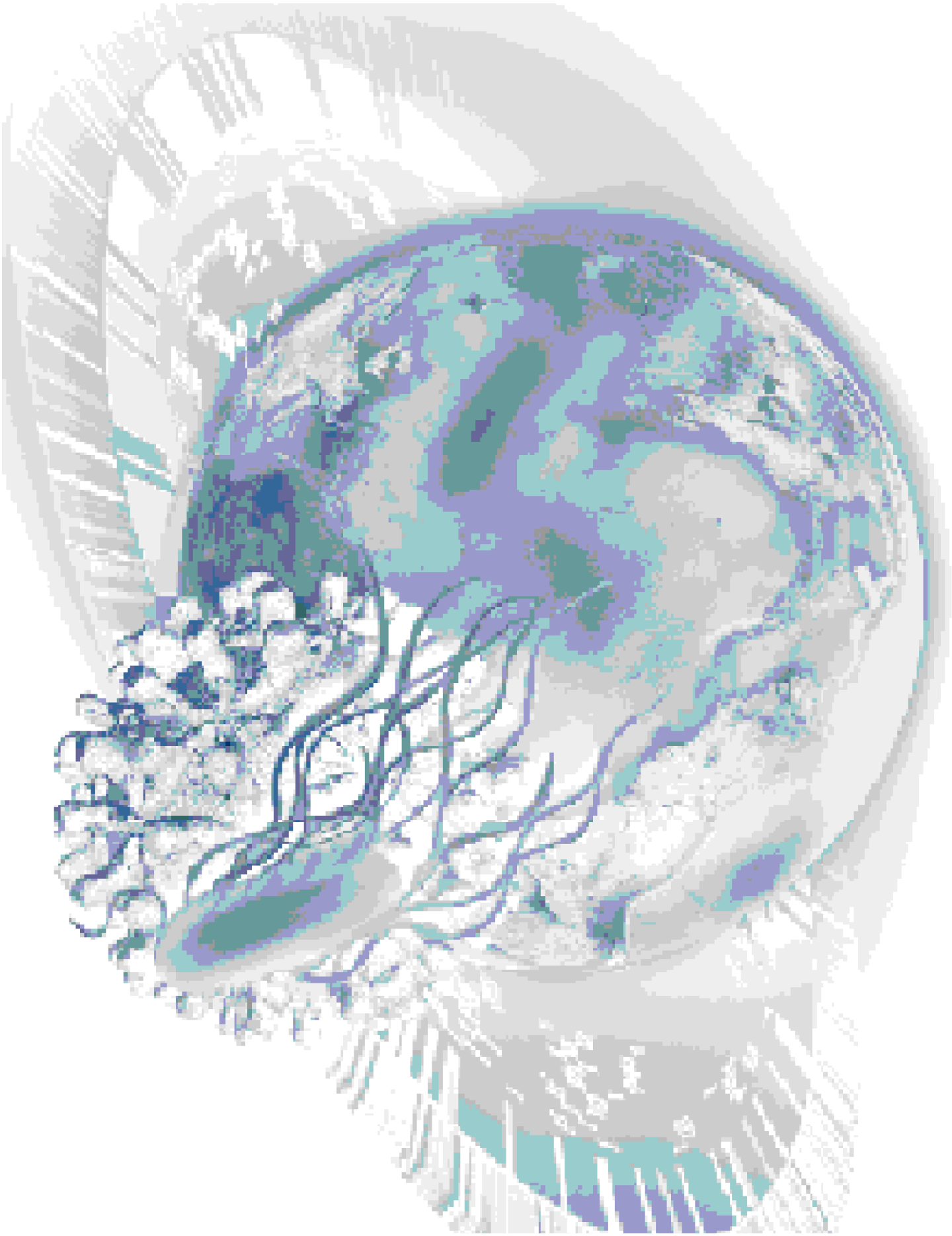
His laboratory work has given him a healthy respect for the sophisticated ways in which bacteria behave, but visiting the hospital wards with his wife – and seeing children with life-threatening infections – has given Finlay a sense of the societal, as well as the intellectual importance of his work. His reputation as a scientist and the numerous prizes he has won often bring him into contact with both local and national media. He has made a special effort during these interviews to "get the word out" that we must stop overusing antibiotics, which contribute to the problem of drug-resistant infections. He also wants people to understand that millions of children in developing countries are dying needlessly from infections that could be prevented with clean water and better sanitation.

Traveling to numerous conferences around the world, Finlay has encountered many of the world's finest scientists. While the scientists he's met have a wide range of personalities, they share one trait: impatience. "I think scientists are some of the most impatient people around," he says. "The main thing is, you just have to have a burning thirst for knowledge, an internal curiosity – wanting to know, how does that work?"

But a scientist also has to be able to handle frustration. “When you’re in school, you read all these scientific articles, and it looks so easy on paper. And you think, ‘oh, you just do this, and publish it.’ What you don’t see is the anguish that goes into each article – all the endless days and nights in the lab, trying to get the thing to work. Everyone goes through this.”

Those occasional frustrations have not diminished his love of science nor his enjoyment in the scientist’s life. “It’s a great life. It’s an awesome life!” he says. “You get to play all the time. You get to find things that no one else has ever seen before. You don’t know what’s going to happen each day. I mean, what a concept, to live in a world where you don’t know what you’re going to find that day. You continually get to learn. After you’ve been out in the real world for a while, you realize that’s really hard to come by, and it’s such a joy. And teaching is really rewarding, when you get to turn someone on to what interests you, or when one of your students gives you an idea out of the blue. And, you’re basically working for yourself. You’re not going to get rich, but you have the freedom to follow your own ideas – and you get paid for doing it!”





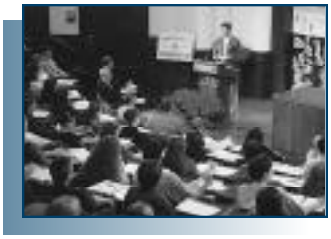
Overview of the Event

In 1993 the Howard Hughes Medical Institute established the Holiday Lectures on Science, an annual series of presentations by leading scientists especially for high school students. The program aims to add depth to public science education and to generate enthusiasm for the pursuit of science. The Holiday Lectures on Science give students and their teachers the opportunity to experience presentations by some of the world's leading biomedical scientists.

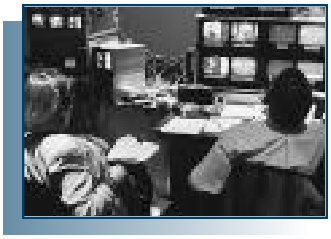
While the content of the lectures is contemporary, their format builds on traditions established in 1827 by the British scientist Michael Faraday and on science lecture series offered annually by colleges and universities around the world.

The scientists who deliver the annual lectures have made significant contributions to biomedical research. Their work has been published in major medical and scientific journals and frequently described in the popular media. Traditionally the lecturers have been chosen from among the outstanding scientists who are HHMI investigators. For the first time in 1999, an international research scholar will be one of the two lecturers. In addition to their scientific credentials, the lecturers are chosen for their ability to present complex concepts in ways that effectively reach a high school audience.

The lecture series has several complementary components:

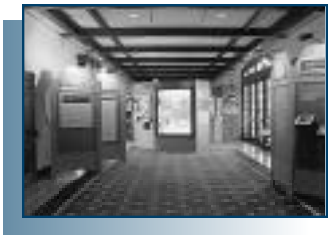


A LIVE EVENT – About 200 students from 80 high schools in the metropolitan Washington, D.C., area attend the lectures, which are held for two days in December at Institute headquarters in Chevy Chase, Maryland. Department chairs and principals at each school nominate participants.

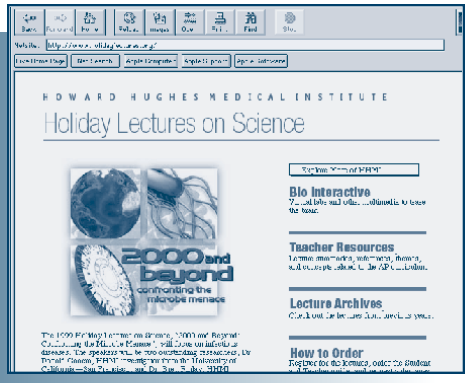


A BROADCAST EVENT – Lectures are broadcast live via satellite and over the Web, reaching thousands of students worldwide. Students have the opportunity to direct questions to the scientists through a real-time, live Q&A session following each day's lectures. Instructions on how to participate can be found on the website at www.holidaylectures.org. The lectures are rebroadcast over Channel One Connection and are available on demand on the website. Videotaped versions of the lectures are available to teachers free of charge.

AN EXHIBIT – A museum-quality exhibit is created each year to complement the lectures topic. It includes historical and modern artifacts and a biography kiosk featuring videotaped interviews with the lecturers. The exhibit later appears on the Institute's website in an interactive format.



The Holiday Lectures On Science Series

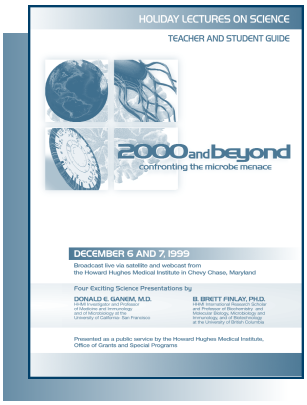


RESOURCES ON THE WEB –

Lectures are available on the Web at
www.holidaylectures.org
any time after the lectures. Previous Holiday Lectures may also be viewed on the website. In addition the website contains a virtual laboratory, complete with interactive laboratory tools and a notebook, as well as a host of demonstrations that enable students to gain hands-on experience with scientific concepts.

TEACHER AND STUDENT GUIDE –

The guide contains summaries and key concepts for each lecture, biographies of the lecturers, an extensive list of relevant publications and websites for teachers and students, and challenge questions. The guide is sent to teachers prior to the lectures and is meant to help them prepare to use the lectures in the classroom as a supplement to AP Biology or other science curricula.



RESOURCE GROUPS –

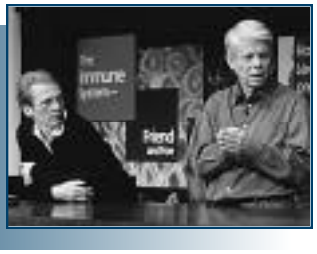
Many components described above are developed with the advice and assistance of the HHMI Holiday Lectures Teacher Resource Group, which is composed of high school educators from the Washington, D.C., area and the HHMI Holiday Lectures Museum Resource Group, which is composed of curators from Washington, D.C., area museums. Student interns from Washington, D.C., area high schools help create demonstrations and laboratories that appear on the website.

Previous Lectures

During its six-year history, the Holiday Lectures on Science have covered a wide range of subjects.

The 1998 lectures, "Of Hearts and Hypertension: Blazing Genetic Trails," featured Christine E. Seidman, M.D., HHMI investigator at Harvard Medical School, and Richard P. Lifton, M.D., Ph.D., HHMI investigator at Yale University School of Medicine. Their lectures discussed the genetic basis of heart disease and hypertension.

The 1997 lectures, "Senses and Sensitivity: Neuronal Alliances for Sight and Sound," featured A. James Husdspeth, Ph.D., M.D., HHMI investigator at Rockefeller University, and Jeremy H. Nathans, M.D., Ph.D., HHMI investigator at Johns Hopkins University. They discussed how two highly specialized organs, the eye and the ear, enable humans and other animals to see and hear.



The 1996 lectures, "The Immune System: Friend and Foe," featured John W. Kappler, Ph.D., and Philippa Marrack, Ph.D., both HHMI investigators at the National Jewish Center for Immunology and Respiratory Medicine in Boulder, Colorado. They described how the immune system functions and, on rare occasions, malfunctions.

The 1995 lectures, "The Double Life of RNA," featured Nobel Laureate Thomas R. Cech, HHMI investigator at the University of Colorado at Boulder, who will become HHMI president in January 2000. Dr. Cech described the discovery of a catalytic function for RNA that may help fight viruses, cancer, and genetic disease.

The 1994 lecures, "Genes, Gender, and Genetic Disorders," featured Shirley M. Tilghman, Ph.D., HHMI investigator at Princeton University, and Robert L. Nussbaum, M.D., of the National Human Genome Research Institute at the National Institutes of Health. They presented the latest findings on sex determination in mammals and other animals.

The 1993 lectures, "DaVinci and Darwin in the Molecules of Life," featured Stephen Burley, M.D., D.Phil., and John Kuriyan, Ph.D., both HHMI investigators at Rockefeller University. These lectures, the first in the series, discussed the three-dimensional structure of biologically important molecules and their role in health and disease.

Web Resources

The Holiday Lectures website is an integral part of the Institute's efforts to make the lectures and related curricular materials available to the largest audience possible. The website is continually being updated, so please visit often at

www.holidaylectures.org

WEBCAST

The 1999 Holiday Lectures on Science will be broadcast live over the Web **starting at 10:00 am EST on December 6 and 7, 1999**. Using a Web browser, students, teachers, and other visitors around the world can view the lectures with full-motion video and audio. **To watch the webcast, you will need to download *RealPlayer*™**. (We recommend that you do this a few days prior to the lectures to make sure that the software works.) The Holiday Lectures website at www.holidaylectures.org/webcast and the "Technical Tips" page at www.hhmi.org/grants/help.htm offers instructions for downloading software. You may also email technical questions to websupport@hhmi.org

ASKLIVE99

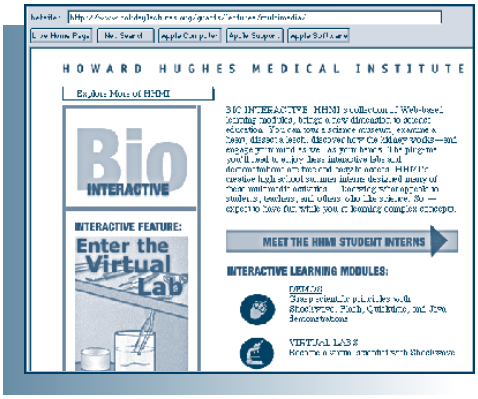
Students and teachers will be able to send questions to Drs. Ganem and Finlay online at www.holidaylectures.org/asklive99

The lectures will respond to the questions submitted during real-time, online Q&A sessions that will take place from **1:30 pm to 2:30 pm, EST, on December 6 and 7, 1999**. Please continue to visit the website for instructions.

1998 Live Q&ASession

VIRTUAL EXHIBIT

The onsite exhibit, described on page 41 of this guide, will be available in virtual format on the web. QuickTime Virtual Reality technology allows Web visitors to view the exhibit hall and browse artifacts and explanatory text.



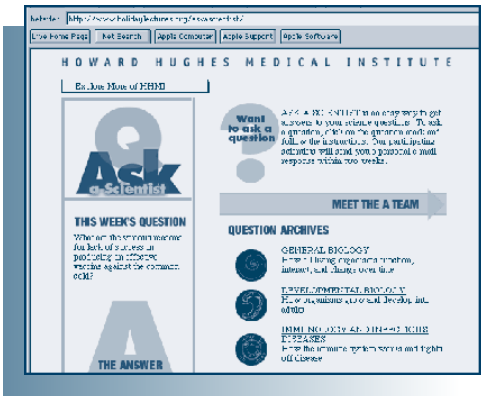
INTERACTIVE WEB LABORATORIES AND DEMONSTRATIONS

Virtual Bacterial Identification Lab: Through this interactive laboratory students will learn the principles of polymerase chain reaction (PCR) and DNA sequencing and how these techniques are used to identify bacterial pathogens in patient samples.

Animated Demonstrations: Visitors to the Holiday Lectures website will be able to view animated demonstrations on various topics related to infectious disease. These include influenza virus infection; how antibiotics work and how resistance to them develops; how heartworms reproduce and how infection is diagnosed and treated.

PREVIOUS LECTURES

Videos of previous lectures can be viewed on demand on the Holiday Lectures website. These lectures are indexed by topic so Web visitors can go directly to the portions of the lectures that most interest them. Past laboratories, demonstrations, and exhibits are also available.



RELATED WEB RESOURCES

Teacher and students can access a list of websites that are related to each year's lecture topics.

ASK A SCIENTIST

This feature enables Web visitors to e-mail questions on the current lecture topic and on a range of other biological topics to teams of scientists associated with HHMI-funded programs. The majority of questions receive at least one personal e-mail response within two to three weeks. An interesting question and answer is posted on the website at www.hhmi.org/askascientist each week. Visitors to the site can also read profiles of some of the scientists who volunteer their time to "Ask a Scientist."

Exhibit

This year's Holiday Lectures on Science features a museum-quality exhibit that complements the lecture series and provides an interactive experience for students. A documentary of the exhibit will be broadcast via satellite and the Web during the breaks between the lectures. After the lectures are concluded, the onsite exhibit will continue to exist in an interactive format on the Web at www.holidaylectures.org, providing visitors with an experience that is rich and compelling and includes some resources not found in the onsite exhibit.

The exhibit will explore the nature of human pathogens and the various strategies for preventing and treating infection. Historical and modern artifacts and images will trace advances in understanding and treating microorganisms and the epidemics they cause – from the "Black Death" of the 14th century, when bacteria and viruses were unknown, to the present and future, as molecular medicine offers new insights and suggests new possibilities for treatment and prevention.

Students will see protective suits that have evolved over the past 700 years to shield physicians and researchers from contagion. Examples will illustrate how understanding the life cycle of pathogens has led to improved methods to prevent and treat infection. Advances in eradicating infectious disease will be traced through artifacts from the National Museum of Health and Medicine, the DeWitt Stetten, Jr. Museum of the National Institutes of Health, the Smithsonian Institution, Fort Detrick, and other individual and corporate contributors.

Visitors to the exhibit will see and interact with online computer software used to match unknown genetic sequences with known ones stored in a national database. Students will be able to operate instruments that have made possible the analysis of entire genomes of pathogens and people; to witness how antibiotics and the immune system fight infection; and, learn how vaccines have reduced the incidence of disease.

This is the fourth year that the Holiday Lectures on Science has included an exhibit, developed with the efforts and guidance of the HHMI Holiday Lectures Museum Resource Group, which is composed of curators from Washington, D.C., area museums.

Cross Connections

To make its Holiday Lectures on Science more widely known and accessible to teachers and students, HHMI is working with a variety of organizations that help bring science to the public. Many of these organizations have previously assisted the Institute in disseminating its past lectures.

CHANNEL ONE CONNECTION

This major cable network, which can reach 8.2 million teenagers at 12,000 secondary schools, will rebroadcast the 1999 holiday lectures in January 2000. In addition, the lectures will be promoted in Channel One's new educator's guide to programming, which is now in poster form, and on its new website, www.TeachWorld.com

DISCOVER

Discover magazine and its website (www.discover.com) reach a broad audience of parents, students, teachers, and other members of the public interested in science. As it did last year, the Institute will promote the lectures through the magazine, which reaches nearly 7 million readers each month, and through its website, with an estimated 1 million visits per month. Teachers who are *Discover* magazine subscribers will also be able to learn about the lectures through the magazine's new online educator's guide. *Discover's* website will feature video highlights of the lectures, as well as curricular materials and biographies of the lecturers. It will also contain a tour of the top sites that directly relate to the lectures.

TURNER LEARNING

HHMI has opened exploratory discussions with Turner Learning, a division of CNN and Time, Inc., to determine the ways in which the Institute and Turner can work together to deliver biomedical research and education through Turner's far-reaching media outlets. Through its CNN Newsroom, Turner Learning offers free daily instructional programs for teachers and students. Each Thursday's "Science Desk" features the latest developments from the world of science. Through the CNN Student Bureau, high school and college students gather and report the news from their perspective.

PBS AND CABLE STATIONS

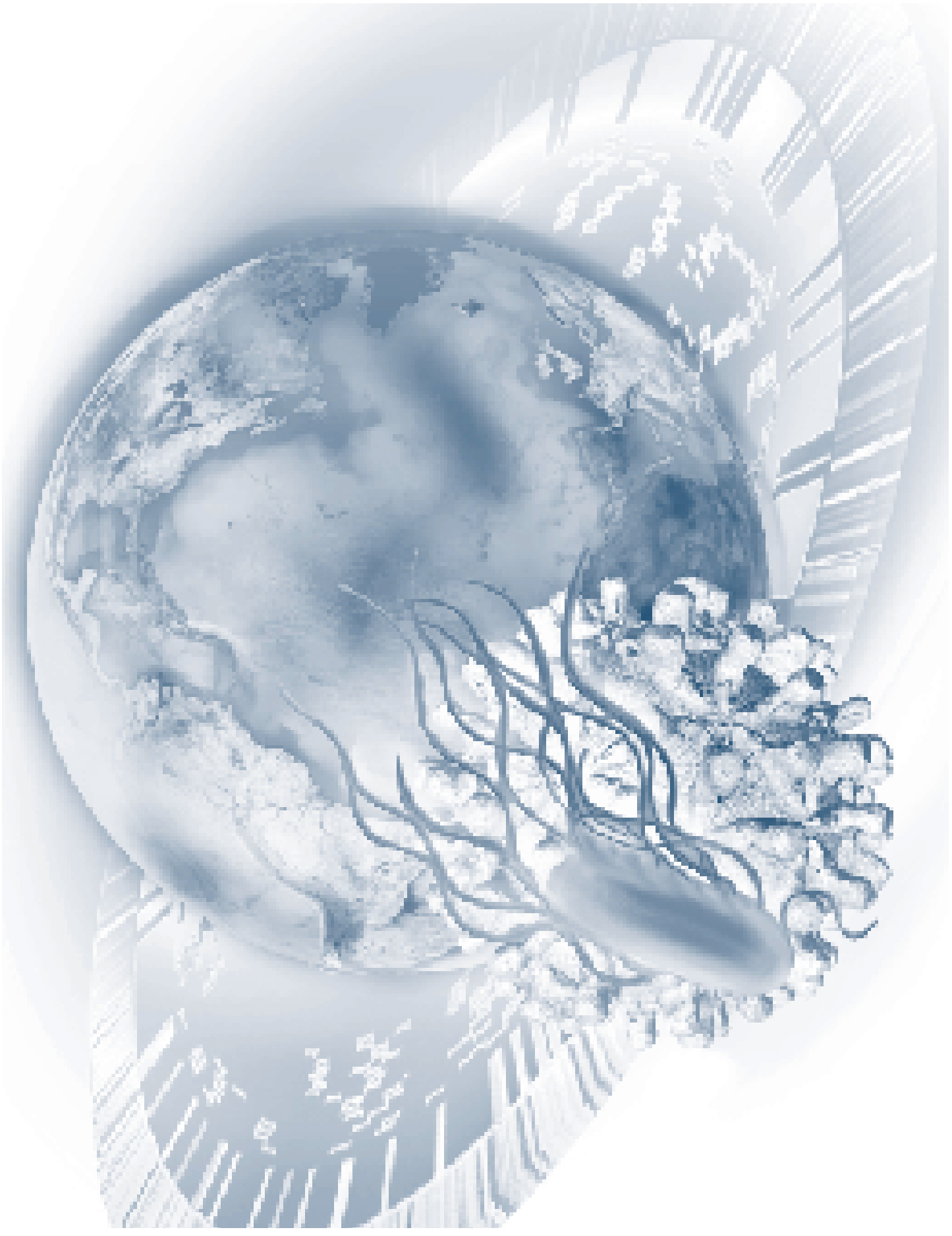
The Institute has contacted the National Educational Telecommunications Association, which serves as a source of educational programming for PBS stations across the country. Many individual PBS stations have expressed interest in showing the 1999 holiday lectures and have aired previous lectures. For example, Channel 21 (WLIW), a PBS station that serves Long Island, Nassau County, Suffolk County, and Northern New Jersey, regularly airs holiday lectures. To increase its Canadian audience, HHMI has contacted Canadian Cable in the Classroom, a government initiative that alerts Canadian cable stations to programming opportunities.

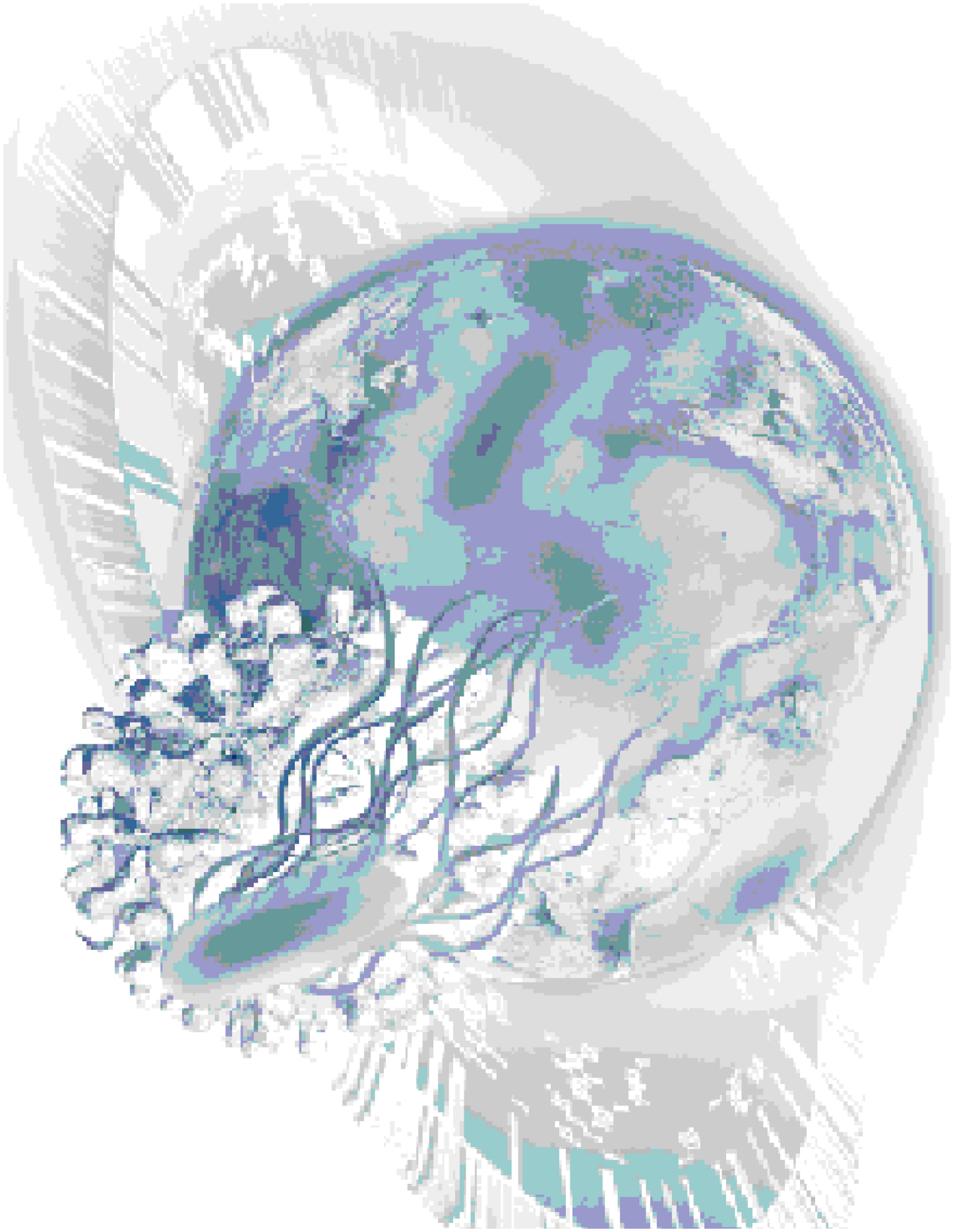
PRESS

National newspapers have expressed interest in publishing articles relating to the content of the lecture series. Journalists who attended a week-long summer program, "Covering Public Health," at the Knight Center for Specialized Journalism at the University of Maryland, received information about holiday lectures and were invited to cover the lectures.

GRANTEES

HHMI is working closely with directors of its precollege and undergraduate grants programs to arrange live broadcasts of the holiday lectures or to promote them more widely. Numerous grantees are planning to make the lectures a community-wide event that draws students from a variety of local high schools and institutions of higher learning





Overview of Programs

The Howard Hughes Medical Institute was founded in 1953 by aviator-industrialist Howard R. Hughes. Its charter, in part, reads: *The primary purpose and objective of the Howard Hughes Medical Institute shall be the promotion of human knowledge within the field of the basic sciences, principally the field of medical research and medical education, and the effective application thereof for the benefit of mankind.*

BIOMEDICAL RESEARCH PROGRAM

The Howard Hughes Medical Institute (HHMI) is a nonprofit medical research organization dedicated to basic biomedical research and education. Its principal objectives are the advancement of fundamental knowledge in biomedical science and the application of new scientific knowledge to the alleviation of disease and the promotion of health.

Through its program of direct conduct of medical research, it employs more than 300 independent investigators based at over 70 locations throughout the country. HHMI conducts research in five broad areas: cell biology, genetics, immunology, neuroscience, and structural biology.

To aid these research efforts, HHMI is involved in the training of graduate and postgraduate students in its investigators' laboratories, has given substantial support to the international genome mapping program, provides research training to medical students through the Research Scholars Program (conducted jointly with the National Institutes of Health), and organizes scientific conferences, workshops, and program reviews.

GRANTS AND SPECIAL PROGRAMS

To complement its research activities, HHMI has a grants program committed to strengthening education in the biological and related sciences at all levels – from kindergarten through postgraduate training. Other important objectives of HHMI's grants program are to advance public understanding and appreciation of science and to broaden access to science for all persons, including women and members of underrepresented minority groups.

HHMI grants are administered by the Office of Grants and Special Programs and focus on two major areas: (1) undergraduate and precollege science education and (2) graduate science education and research . HHMI's grants programs are supported by an array of interrelated Web-based data-collection and reporting initiatives that facilitate grants management, communication and outreach, and HHMI grants program assessment. HHMI's home page, with direct links to grantee home pages, is at www.hhmi.org

Grants for Undergraduate and Precollege Science Education

These grants support HHMI's mission to strengthen teaching in biology and other scientific disciplines, prepare the next generation of scientists, and increase scientific literacy for all students. To this end, these HHMI grants seek to stimulate young people's interest in

science and the pursuit of scientific research and education careers. HHMI initiatives in this area comprise the undergraduate, precollege, and local (i.e., Washington, D.C., metropolitan area) programs. The grants reach a wide range of institutions involved in formal and informal science education, including colleges and universities, schools, museums, medical schools, and research institutes.

To date, the Undergraduate Biological Sciences Education Program has awarded $426 million to strengthen science education at 224 of the public and private colleges and universities invited to submit proposals. A year 2000 competition is expected to award $48 million in four-year grants from among the master's, baccalaureate, and science and technology institutions invited to compete. HHMI's Precollege Science Education Program has awarded $42 million to 74 science museums, aquaria, botanical gardens, and zoos and to 54 biomedical research institutions to support innovative science education programs and to interest youngsters in science. Through this program, HHMI also has awarded $6.5 million for science education activities in the Washington, D.C., metropolitan area, and $4 million for the Woodrow Wilson National Fellowship Foundation's summer institutes for high school biology teachers. Another precollege program initiative, HHMI's annual **Holiday Lectures on Science**, reaches high school students and teachers throughout the country via satellite broadcast and the World Wide Web.

Grants for Graduate Science Education and Research

These grants are intended to attract and train graduate and postgraduate students for careers in biomedical research, enhance the research capabilities of biomedical research organizations, and support foreign scientists. The grants are awarded under the Graduate Science Education, Research Resources, and International Programs.

HHMI's Graduate Science Education Program supports graduate students, medical students, and physician-scientists who show strong promise of becoming tomorrow's leading biomedical investigators as they move along the continuum from graduate education to junior faculty positions. Support is awarded through three fellowship programs: predoctoral fellowships in biological sciences, research training fellowships for medical students, and postdoctoral research fellowships for physicians. Since 1988 HHMI has awarded $200 million in graduate fellowship support to more than 2,000 students and physician-scientists in the early stages of their careers.

Through its Research Resources Program, HHMI provides support to medical schools and to research organizations that serve the biomedical community as unique resource laboratories and teaching facilities. In 1995 HHMI awarded $80 million to 30 U.S. medical schools to help them sustain their commitment to biomedical research. The four-year grants are used to strengthen the research infrastructure and promote the career development of junior faculty in the basic and clinical sciences. Expanding its support for this program, HHMI will award $90 million in four-year grants to selected U.S. medical schools in January 2000.

Complementing these initiatives is HHMI's International Program, which supports outstanding foreign scientists who are conducting fundamental biomedical research outside the United States. Since 1991 HHMI has awarded more than $53 million in five-year grants to 177 international research scholars. In 1999, the Institute announced two new competitions under the international research scholars program.

Web-Based Initiatives

The World Wide Web has emerged as a key tool for grants management, communication and outreach, and program assessment. Data for grant applications, grantee annual program reports, and financial reports have been collected through various Web-based systems and have then been archived in central HHMI electronic databases. Grantees submit their annual program and financial reports electronically to HHMI.

The Web has also become a powerful mechanism for communicating with grantees and the public, particularly those seeking funding for biomedical research and education projects. For example, HHMI's graduate program website not only provides eligibility and other information for the three graduate fellowship competitions, but also allows users to download the program announcements and application forms. The Graduate Fellows Tracking System is used not only for current fellows' annual reports but also for career updates by former fellows. Selected information on research interests is available in a searchable database of all fellows, to facilitate networking among fellows and program assessment by HHMI.

HHMI also supports a Web-based initiative that disseminates information about grant opportunities beyond HHMI. GrantsNet (www.grantsnet.org), a collaboration with the American Association for the Advancement of Science, is a database of funding opportunities in the biomedical sciences for graduate students, medical students, postdoctoral associates, and junior faculty. GrantsNet is searchable by field and education level and provides direct links to funders' home pages. It is an adjunct to *Science's* Next Wave site (www.nextwave.org), which is oriented to scientists in the early stages of their careers.

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