

EMERGING AND RE-EMERGING INFECTIOUS DISEASES

By the mid-20th century, some scientists thought that medicine had conquered infectious diseases. With the advent of antibiotics and modern vaccines, as well as improved sanitation and hygiene, many diseases that formerly posed an urgent threat to public health were brought under control or largely eliminated. However, the emergence of new infectious diseases and the re-emergence of infectious diseases that previously affected human population have continued, as they have throughout history. Factors such as rapidly changing human demographics; extensive and rapid global travel; changes in land use patterns; mutations in and evolution of the pathogens; resistance to previously effective antibiotics (see page 52); and ecological, environmental, and technological changes are contributing to the emergence of new diseases. These factors, which act as selective pressures, are shaping the evolution of microbes and bringing people into closer and more frequent contact with microbes. Unsanitary conditions in animal agriculture and increasing commerce in exotic animals (for food and as pets) have also increased opportunities for animal microbes to jump from animals to humans. From time to time, with the right combination of selective pressures, a formerly innocuous human or animal microbe can evolve into a pathogen that can cause a major outbreak of human disease.

At times, changes in behavioral and environmental factors can also lead to the re-emergence of diseases that were previously under control. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistant pathogens, allowing many diseases that were formerly treatable with drugs to make a comeback (e.g., tuberculosis, malaria, hospital-acquired and food-borne infections). Recently, decreased compliance with vaccination policy also has led to the re-

emergence of diseases such as measles and pertussis, which were previously under control. Moreover, many important infectious diseases have never been adequately controlled on either the national or international level, leaving open the possibility that those diseases could spread to new locations or re-emerge where they had previously been controlled. There is also potential for the emergence or re-emergence of infectious disease should a deadly pathogen such as smallpox or anthrax be used as an agent of bioterrorism.

To an unprecedented extent, issues related to global health and infectious diseases are on the agendas of world leaders, public health agencies, and nonprofit organizations. This attention has been focused on scientific challenges, such as vaccine development, and on the deleterious effects that infectious diseases can have on economic development and political stability.

NIAID Programs and Resources for Emerging Infectious Disease Research

NIAID has several programs and resources available to the scientific community to enhance research on a broad array of emerging infectious diseases. These include the following:

- NIAID's national network of 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs) support research focused on countering threats from bioterror agents and emerging infectious diseases. Each RCE is comprised of a consortium of universities and complementary research institutions serving a specific geographical region. The RCEs, located throughout the United States, will build and maintain a strong scientific infrastructure supporting multifaceted research and development activities that promote scientific discovery and translational research capacity required to create the next

generation of therapeutics, vaccines, and diagnostics for biodefense and emerging infectious diseases.

- NIAID's national network of 2 National Biocontainment Laboratories (NBLs) and 13 Regional Biocontainment Laboratories (RBLs). The NBLs will serve as national and regional resources for research on biodefense and emerging infectious disease agents that require biosafety level (BSL)-4/3/2 biocontainment, and the RBLs will serve as a regional resource for research that requires BSL-3/2 biocontainment. These laboratory facilities are being designed and built using the strictest Federal standards, incorporating multiple layers of safety and security to protect laboratory workers and the surrounding environment while conducting research on emerging infectious diseases and Category A, B, and C priority pathogens.
- NIAID's Biodefense and Emerging Infections Research Resources Program supports the acquisition, authentication, storage, and distribution to the scientific community of state-of-the-art research and reference reagents related to biodefense and emerging infectious diseases. Included are the capabilities to validate, expand, and produce biological agents, including cell lines, clones, proteins, monoclonal and polyclonal antibodies, and diagnostic tools.
- Contracts funded under the *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program provide a range of resources for preclinical testing of new therapies, as well as vaccines for biodefense and emerging infectious diseases. Included in this activity are safety, toxicology, and pharmaceutical testing in small and large animals, including the capability for conducting challenge studies.

- NIAID's Food and Waterborne Diseases Integrated Research Network expands the Institute's capacity to conduct clinical research studies of food- and waterborne enteric pathogens.
- NIAID's International Collaborations in Infectious Disease Research (ICIDR) program is a multidisciplinary project to study diseases of major importance to people living in tropical countries. Areas of research supported by the ICIDR program include epidemiology, vector biology, pathology, immunology, diagnosis, and treatment of tropical diseases caused by parasitic, viral, and bacterial infections, including emerging infectious diseases.

Emerging and Re-emerging Infectious Diseases

Severe Acute Respiratory Syndrome—SARS

In the spring of 2003, the world became aware of an outbreak of a newly recognized pneumonia that was named "severe acute respiratory syndrome," or SARS. The outbreak is thought to have begun in southeastern China's Guangdong province in November 2002, with subsequent spread to the special administrative region of Hong Kong by February 2003, and other countries including Vietnam, Singapore, Taiwan, Canada, and the United States. Epidemiologic investigation showed that the disease disproportionately affected healthcare workers and other close contacts of patients such as family members.

Through an NIAID-supported contract with Dr. Robert Webster at St. Jude Children's Research Hospital in Memphis, researchers at Hong Kong University and their colleagues at four local hospitals were the first to report to the World Health Organization the isolation of a virus that was linked conclusively to SARS patients. Using a high-powered microscope, researchers examined

List of NIAID Emerging and Re-emerging Diseases 2005

Group I—Pathogens Newly Recognized in the Past Two Decades

Acanthamebiasis
 Australian bat Lyssavirus
 Babesia, atypical
Bartonella henselae
 Coronaviruses/Severe Acute Respiratory Syndrome (SARS)
 Ehrlichiosis
Encephalitozoon cuniculi
Encephalitozoon hellem
Enterocytozoon bieneusi
Helicobacter pylori
 Hendra or equine morbilli virus
 Hepatitis C
 Hepatitis E
 Human herpesvirus 8
 Human herpesvirus 6
 Influenza
 Lyme borreliosis
 Microsporidia
 Parvovirus B19

Group II—Re-emerging Pathogens

Coccidioides immitis
 Enterovirus 71

Prion diseases
Streptococcus, group A
Staphylococcus aureus

Group III—Agents with Bioterrorism Potential

■ CDC—Category A

Bacillus anthracis (anthrax)
Clostridium botulinum
Francisella tularensis (tularemia)
 Variola major (smallpox) and other poxviruses
 Viral hemorrhagic fevers
 Arenaviruses
 LCM, Junin virus, Machupo virus, Guanarito virus
 Lassa Fever
 Bunyaviruses
 Hantaviruses
 Rift Valley fever
 Flaviruses
 Dengue
 Filoviruses
 Ebola
 Marburg
Yersinia pestis

a culture from a lung biopsy sample and found virus particles whose surfaces were studded with an array of proteins resembling a crown around the virus—a “coronavirus.” The researchers then used antibody tests and other molecular tools to confirm that that this deadly coronavirus (Co-V) was present in at least 35 of the SARS patients they were studying.

Before the emergence of SARS (also called SARS-CoV), human coronaviruses were predominantly associated with up to 30 percent of common colds. Coronaviruses are the largest single-stranded RNA viruses known, and are divided into three serogroups. Recent data indicate that SARS is the prototype strain for a new fourth group of coronaviruses.

In response to the need for rapidly increased research on the SARS coronavirus, in FY 2003, NIAID awarded administrative supplements to

grantees to expand activities on the basic biology and immunology of coronaviruses. NIAID’s grant program supports basic research on animal coronaviruses and the SARS coronavirus. NIAID also supports contracts to develop diagnostics, vaccines, and therapeutics for SARS. In addition, NIAID supports epidemiologic work on SARS and conducts SARS research within its intramural program. Recent accomplishments include:

- **Animal Models.** NIAID Division of Intramural Research (DIR) scientists and their collaborators developed several animal models for SARS, including mouse, hamster, and nonhuman primate models, which allow the evaluation of vaccines, immunotherapies, and antiviral drugs. Using these models, DIR scientists have collaborated with colleagues at NIH, at academic institutions, and in industry to evaluate the immunogenicity

List of NIAID Emerging and Re-emerging Diseases 2005 (cont'd)

■ CDC—Category B

Brucella species (brucellosis)
Burkholderia pseudomallei (melioidosis)
Burkholderia mallei (glanders)
Coxiella burnetii (Q fever)
 Epsilon toxin of *Clostridium perfringens*
 Food-borne and Waterborne Pathogens
 Bacteria
 Campylobacter jejuni
 Diarrheagenic *E. coli*
 Listeria monocytogenes
 Pathogenic vibrios
 Salmonella
 Shigella species
 Yersinia enterocolitica
 Protozoa
 Cryptosporidium parvum
 Cyclospora cayatanensis
 Entamoeba histolytica
 Giardia lamblia
 Microsporidia
 Toxoplasma
 Viruses (calciviruses, hepatitis A)
 Additional viral encephalitides
 California encephalitis
 Eastern equine encephalitis

Japanese encephalitis virus
 Kyasanur Forest virus
 LaCrosse virus
 Venezuelan equine encephalitis
 Western equine encephalitis
 West Nile virus
 Ricin toxin (from *Ricinus communis*)
 Staphylococcal enterotoxin B
 Typhus fever (*Rickettsia prowazekii*)

■ CDC—Category C

Emerging infectious disease threats such as Nipah virus, additional hantaviruses, and the following pathogens:

Influenza
 Other rickettsias
 Multidrug-resistant tuberculosis
 Rabies
 Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)
 Tick-borne encephalitis viruses
 Tick-borne hemorrhagic fever viruses
 Crimean-Congo hemorrhagic fever virus
 Yellow fever

Pathogens that naturally emerge with, or are engineered for, increased virulence, increased transmission, and/or the ability to evade the immune response.

and efficacy of inactivated, subunit, vectored, and DNA vaccines against SARS as well as several candidate immunotherapies.³⁰

- **Therapeutics.** To date, NIAID screening contracts have evaluated more than 20,000 chemicals for anti-SARS-CoV activity. These NIAID-supported investigators have screened more than 1,400 compounds, including all U.S. Food and Drug Administration (FDA)-approved antiviral drugs. Four compounds, thus far, have shown activity and will be studied further. In addition, NIAID is supporting the development of therapeutic strategies such as antisense oligonucleotides that inhibit viral RNA and humanized monoclonal antibodies.
- **Vaccines.** NIAID is partnering with academia and industry to develop vaccines for SARS, using a variety of different vaccine approaches, including SARS vaccines with adjuvants, virus-like particle vaccines, and recombinant protein and bacterial-vector based vaccines.
- **Diagnostics.** NIAID is supporting research on a variety of different diagnostics approaches for SARS, including polymerase chain reaction- and microarray-based tests, antigen identification for serodiagnosis, and identification of genomic and proteomics targets.
- **Surveillance and Epidemiology.** NIAID has expanded its Pandemic Preparedness in Asia contract with St. Jude Children's Research Hospital (Dr. Robert Webster, Principal Investigator) to expand efforts to identify the animal reservoirs for coronaviruses in Asia, establish cell-based laboratory assays to assess the immune response in infected patients, and

conduct seroepidemiologic studies of family members and other close contacts of SARS patients to assess the rates of asymptomatic infections.

For more information on SARS research updates and opportunities, visit www.niaid.nih.gov/dmid/sarsapps.htm and www.niaid.nih.gov/factsheets/sars.htm.

West Nile Virus

In the early summer of 1999, a mysterious cluster of cases of encephalitis (inflammation of the brain) and related deaths appeared in New York City, raising the concern of public health officials. Within a short time, researchers identified the cause of the outbreak as West Nile virus (WNV), a flavivirus family virus common in Africa, West Asia, and the Middle East, but never before observed in North America. Symptoms of WNV infection are usually mild, including fever, headache, body aches, skin rash, and swollen lymph glands. If WNV enters the brain, however, it can cause life-threatening encephalitis or meningitis (inflammation of the lining of the brain and spinal cord). These more severe complications of the disease most often affect elderly or immunocompromised individuals.

WNV is transmitted to humans by mosquitoes, which pick up the virus from infected birds. Although the route by which WNV entered the United States is not known, it is thought that the virus may have been introduced by an infected bird that was imported into the country, by an infected mosquito that stowed away on a shipment or transport vehicle entering the country, or by an infected human returning from a country where the virus is common. Since WNV first appeared in the United States, there have been annual outbreaks of the disease, and it has spread across the United States. Experts believe WNV has now become established in North America as a seasonal epidemic that flares up in the summer and continues into the fall.

Because WNV is now well-established in the United States, scientists and health experts at NIAID, along with public health officials, have continued to enhance research on WNV and other arthropod-borne viruses. There are currently no drugs to treat the virus and no vaccines available to prevent infection in humans. However, NIAID supports a robust WNV research portfolio that is aimed toward increased understanding of WNV and developing vaccines, diagnostics, and therapeutics for WNV. The following points summarize key research in several different areas:

- **Basic research.** NIAID conducts basic research on WNV, which leads to a better understanding of the host, pathogen, and environmental factors that influence disease emergence. Basic research determines which flavivirus proteins contribute to the virus's ability to cause disease, and examines how protective immune responses are elicited within the central nervous system during acute flavivirus encephalitis.
- **Animal models.** A golden hamster model has been developed by NIAID-supported researchers and is used for screening drugs and for examining factors that contribute to immunity. This model has proven useful in evaluating strategies for preventing the complications associated with this emerging infectious disease.
- **Vaccines.** NIAID provided initial support via a 3-year, fast-track grant (2000–2003) to Acambis, Inc. to develop a live, attenuated recombinant vaccine for WNV. The resulting chimeric vaccine (a vaccine composed of parts from two or more different organisms) is derived from the well-established Yellow Fever 17D vaccine, in which the envelope genes of the Yellow Fever vaccine virus were replaced with those of the West Nile virus. The WNV vaccine candidate demonstrated good safety, efficacy, and protection against

disease in animal models. The company that developed the vaccine is conducting a phase I clinical trial of the vaccine in humans (started in November 2003), with excellent results so far with regard to safety and immunogenicity. In addition, the NIAID Vaccine Research Center is partnering with industry to develop a DNA vaccine for WNV. A clinical trial of this vaccine began in April 2005.

- **Therapeutics.** NIAID is supporting *in vitro* screening of chemical compounds for possible antiviral activity against several viruses, including WNV, through the NIAID Collaborative Antiviral Testing Group contracts. More than 2,000 compounds had been screened (as of July 2005). A small number (approximately 1 to 2 percent) demonstrated some antiviral activity *in vitro* and are undergoing further testing *in vivo* in mice and hamster models of disease. One of the compounds appears to be particularly effective in the hamster model of WNV disease. NIAID also is supporting research on immunotherapeutics.
- **Center Programs.** NIAID supports the World Reference Center for Emerging Viruses and Arboviruses, which provides basic/applied research capability on arboviruses (including WNV) and other emerging viruses; provides technical support/expertise for investigations of virus outbreaks throughout the world; enables the collection, generation, maintenance, and distribution of a repository of viral and other reference materials; provides a forum to train investigators in virus identification and characterization techniques; and provides clinical trial support.
- **Research Centers.** NIAID also supports two Emerging Viral Diseases Research Centers, which provide broad-based, interactive, multidisciplinary research teams with the scientific expertise needed to study the

emergence of a wide variety of zoonotic and arthropod-borne viral pathogens and other emerging viral threats. Both center contracts also provide the capacity to redirect funds and resources in the event of an urgent public health threat from either natural disease or bioterrorist release. These contracts cover several important areas of research, including basic biology of the virus, WNV ecology and pathogenic/epidemic potential, diagnosis, prevention, and therapy.

- **Insect vectors.** NIAID supports research aimed at better understanding the insect vectors of WNV transmission in affected areas. Such an understanding will allow improved monitoring and surveillance for the vectors and the viruses they transmit.

For more information on West Nile virus and NIAID's research portfolio in this area, see www.niaid.nih.gov/publications/wnile/default.htm and www.niaid.nih.gov/factsheets/westnile.htm.

Lyme Disease

Lyme disease is an infection caused by the corkscrew-shaped bacteria *Borrelia burgdorferi*, which are transmitted by the bite of deer ticks (*Ixodes scapularis*) and Western black-legged ticks (*Ixodes pacificus*).

Typically, the first symptom of Lyme disease is a red rash known as erythema migrans. The telltale rash starts as a small red spot at the site of the tick bite and expands over time, forming a circular or oval-shaped rash. As infection spreads, rashes can appear at different sites on the body. Erythema migrans is often accompanied by symptoms such as fever, headache, stiff neck, body aches, and fatigue. After several months of *B. burgdorferi* infection, slightly more than half of people not treated with antibiotics develop recurrent attacks of painful and swollen joints, most commonly in the knees. About 10 to 20 percent of untreated people develop chronic arthritis. Lyme disease can also affect the nervous

system, causing such symptoms as stiff neck, Bell's palsy, and numbness in the limbs. Less commonly, untreated people can develop heart problems, hepatitis, and severe fatigue.

In 2004, the U.S. Centers for Disease Control and Prevention (CDC) reported 19,804 cases of Lyme disease throughout the United States. Five states—New York, Pennsylvania, Massachusetts, Connecticut, and New Jersey—accounted for nearly 75 percent of all reported cases.³¹

The major goals of the NIAID Lyme disease research program are to develop better means of diagnosing, treating, and preventing this disease. To accomplish these objectives, the NIAID Lyme disease research portfolio includes a broad range of activities that are essential to increasing understandings of the disease. The studies include both intramural and extramural research on animal models of disease, microbial physiology, molecular and cellular mechanisms of pathogenesis, mechanisms of protective immunity, vectors and disease transmission, efficacy of different modes of antibiotic therapy, and development of more sensitive and reliable diagnostic tests for both early (acute) and late (chronic) Lyme disease.

Intramural Research Highlights. NIAID intramural investigators are studying Lyme disease on the NIH campus in Bethesda, Maryland, and at the Rocky Mountain Laboratories (RML) in Hamilton, Montana, where NIAID scientists discovered the etiologic agent *B. burgdorferi* in the early 1980s. RML scientists are using microarray technology to identify genes associated with unique aspects of the pathogenicity of Lyme disease and other relapsing fever microorganisms.

On the NIH campus, NIAID clinical investigators seek to better understand the natural history of Lyme disease and possible causes for persisting symptoms. To this end, three clinical studies currently are ongoing at the

NIH Clinical Center: one to evaluate and treat patients with classic Lyme disease; another to conduct a comprehensive clinical, microbiologic, and immunologic assessment of patients who have suspected chronic Lyme disease despite previous antibiotic therapy; and a third to use gene microarrays to examine the host response in skin biopsies from patients with erythema migrans, the circular skin rash associated with Lyme disease.

Lyme borreliosis and ehrlichiosis will continue to be areas of high priority for basic research for NIAID, especially with regard to (1) the characterization and treatment of acute and chronic infection; (2) the influence of co-infection with other vector-borne pathogens on the diagnosis, treatment, and severity of Lyme disease; and (3) the development of rapid, sensitive, and specific diagnostic tests and preventive strategies (e.g., vaccines and vector control measures).

Influenza

The “flu” is an infection of the respiratory system caused by an influenza virus. Seasonal influenza outbreaks are a leading cause of infectious disease mortality in the United States, causing approximately 36,000 deaths each year. An annual influenza vaccine is the primary means of limiting the impact of the seasonal influenza.



Child receiving a nasal vaccine for influenza.

In the past, new, highly virulent strains of influenza to which the human population had little or no prior immunity occasionally have emerged and have led to global outbreaks, or influenza “pandemics.” The most famous of these was the influenza pandemic of 1918–1919 (often referred to as Spanish influenza). The global death toll for this pandemic was between 20–25 million with perhaps billions of people infected. Other influenza pandemics occurred in 1957 and 1968 and were known as the Asian flu and Hong Kong flu, respectively. Although it has been many years since the last influenza pandemic, scientists and public health officials have been aware of the potential for future outbreaks of deadly strains of influenza and have increased their vigilance and preparedness in light of the current influenza outbreak occurring in Asia.

In 1997, a strain of influenza virus that usually only infects birds, called H5N1 avian influenza or “bird flu,” sickened and killed both poultry and humans in Hong Kong. The virus disappeared from Hong Kong after the mass culling of more than 1 million domestic birds, but reappeared in poultry and humans in Vietnam in 2003. As of mid-July 2006, the H5N1 influenza strain had spread to more than 50 countries, where it infected over 200 people and had killed more than half of them. Public health officials are concerned that this avian virus could mutate and develop the ability to spread from person to person, which could result in a fast-moving global pandemic.

NIAID, which supports a robust portfolio of research on influenza, has been very active in research to enhance understandings of avian influenza viruses and develop vaccines against strains of influenza that could be potential pandemic threats. NIAID currently supports influenza research in the following major areas:

- **Basic biology.** NIAID supports basic research on virus structure and function,

viral pathogenesis, and the host response to infection.

- **Surveillance/epidemiology.** NIAID supports research to better understand the natural history and emergence of influenza viruses with pandemic potential and to evaluate community-based strategies for interrupting the spread of influenza. One example of this crucial work to understand and monitor avian influenza viruses is NIAID’s Influenza Pandemic Preparedness in Asia contract, which supports surveillance and research on the avian virus as it unfolds in Asia, tracing its epidemiology, gathering viral samples, and conducting molecular and genetic research to characterize the virus and assist in the development of vaccines and therapeutics.
- **Drug discovery and evaluation.** NIAID supports the development of novel drugs against influenza and the evaluation of these new agents in both *in vitro* screening assays and animal models. To date, NIAID has screened more than 2,000 compounds for activity against influenza. NIAID also supports development of antiviral drugs against influenza.
- **Enhanced vaccine production strategies.** NIAID supports research on technologies that will enable more rapid production of influenza vaccines, including reverse genetics-based seed strain production, mammalian cell culture of seed virus strains, and a baculovirus expression system for production of vaccine components.
- **Vaccine development and evaluation.** Developing new influenza vaccines and strategies has been a major focus of the NIAID influenza program. These strategies include supporting the development of live-attenuated and recombinant vaccines, immunomodulators and adjuvants, cell

culture-based vaccines, and basic research aimed at optimizing the immune response. NIAID is also exploring common epitope or “universal” flu vaccines, a strategy that could result in flu vaccines that provide broad immunity against many strains of influenza viruses. NIAID also supports the production and clinical testing of vaccines against avian influenza subtypes of high pandemic potential. For example, NIAID’s Vaccine and Treatment Evaluation Units have recently completed a clinical trial of a candidate H5N1 avian influenza vaccine in healthy adults. Preliminary data indicate that the vaccine is generally safe and stimulates an immune response. Future plans include testing this H5N1 vaccine in the elderly and in children, populations often most vulnerable to influenza.

In addition, NIAID’s Division of Intramural Research is capitalizing on its decades of research and development of live-attenuated vaccines to develop avian influenza vaccines under a cooperative research and development agreement (CRADA) with MedImmune, Inc. Under the CRADA, DIR and MedImmune scientists will produce and test multiple live-attenuated intranasal vaccines against potential pandemic flu strains, starting with the H5N1 strain (see page 147).

Also, DIR scientists are continuing work begun several years ago following the emergence of an H9N2 avian flu strain in Hong Kong and China that caused several human infections. A live-virus vaccine developed by DIR and CDC scientists against this H9N2 avian virus has completed phase 1 clinical testing for safety and efficacy.

- **Novel vaccine delivery systems.** NIAID-supported researchers are also helping to develop novel techniques to deliver influenza vaccines. For example, beginning in the mid-1970s, NIAID investigators were integral to the development and clinical evaluation of a

live influenza vaccine that can be delivered as a nasal spray. FluMist™ was licensed by the FDA in the summer of 2003, and was available for the first time during the 2003–2004 flu season. NIAID is currently exploring strategies to extend vaccine supplies using dose-sparing approaches such as immunizing people directly into the skin rather than in muscle, or adding substances called adjuvants to vaccines to increase their potency. These strategies could decrease the amount of vaccine required to elicit the desired level of immune response.

For more information on influenza, including weekly reports on flu activity, go to www.cdc.gov/flu/weekly/fluactivity.htm.

Prion Diseases

Fatal neurodegenerative diseases such as Creutzfeldt-Jakob disease (CJD) and bovine spongiform encephalopathy (also known as BSE or “mad cow” disease) are referred to as “prion diseases” because they are believed to be caused and transmitted by prion proteins, a new type of infectious agent discovered in the 1980s. Prion proteins enter cells and cause normal cellular proteins to adopt abnormal three-dimensional structures, which in turn leads to disease. In addition to CJD, which affects humans, scrapie and chronic wasting disease (CWD) are other prion diseases that affect animals. Since the onset of the BSE epidemic in the United Kingdom in the 1980s, the disease has resulted in the destruction of millions of animals in Europe. Because the BSE epidemic was temporally and geographically associated with the emergence of a variant form of CJD in humans, health officials believe the disease was spread to humans by infected beef. In May 2003, the finding of BSE in a single cow in Canada resulted in a ban on exportation of certain live ruminants and ruminant products from Canada to the United States. Since then, several other BSE-infected cows have been identified in the United States,

but there has been no evidence of transmission to humans in the United States.

Transmissible spongiform encephalopathy (TSE) research in DIR is conducted at the RML, where scientists are answering fundamental questions about the nature of infectious prions that are key to developing methods to prevent and treat prion-associated diseases. For example, RML investigators are working to determine how abnormal prions are formed and how they cause disease, the mechanisms of and barriers to cross-species transmission, and routes of TSE transmission. RML scientists made several important advances in 2005, including:

- Identification of the smallest and most efficient particles capable of initiating TSE diseases;³²
- Discovery of a molecule that might play a role in clinical manifestations of prion disease;³³
- Discovery of novel, potent abnormal prion inhibitors (called degenerate phosphorothioate oligonucleotides);³⁴ and
- Development of the first cultured cell line infected with CWD, and identification of the first inhibitors of CWD replication.

In addition, an important study to determine whether CWD prion protein can be transmitted to nonhuman primates via oral or intracerebral routes is now in its second year. RML scientists also are using a high-throughput screening method they developed in 2004 to find potential

TSE therapeutics, and studies of antibody and vaccine-based therapies for TSEs are ongoing.

NIAID also provides extramural grant support for investigator-initiated studies of CWD and other prion diseases that seek to better understand prion entry, trafficking, pathogenesis, and transmission, which could provide a basis for development of diagnostic and intervention strategies. In addition, NIH has initiated studies in response to the Department of Health and Humans Services' 2001 BSE/TSE Action Plan, including:

- NIAID support of a 7-year, \$8.4 million contract to Colorado State University to operate an emerging disease research center focused on CWD. The research center in Fort Collins investigates the mechanics of CWD infection in deer and elk, especially in the immune system's lymphoid tissues. Such studies underlie the search for improved diagnostics and therapies. In addition, studies of ecological factors in transmission and evaluation of CWD vaccination strategies in deer are ongoing.
- NIH evaluation of potential anti-TSE compounds in animal models. Through expansion of an NIAID contract with Utah State University, candidate compounds are evaluated for efficacy in transgenic animals that have a shortened time to death. This model was established at Utah State in collaboration with NIAID's RML.