Title

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Journal

ILAR Journal, 49(2)

ISSN

1084-2020

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Publication Date

2008

DOI

10.1093/ilar.49.2.220

Peer reviewed

# Macaque Models of Human Infectious Disease

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## Abstract

Macaques have served as models for more than 70 human infectious diseases of diverse etiologies, including a multitude of agents—bacteria, viruses, fungi, parasites, prions. The remarkable diversity of human infectious diseases that have been modeled in the macaque includes global, childhood, and tropical diseases as well as newly emergent, sexually transmitted, oncogenic, degenerative neurologic, potential bioterrorism, and miscellaneous other diseases. Historically, macaques played a major role in establishing the etiology of yellow fever, polio, and prion diseases. With rare exceptions (Chagas disease, bartonellosis), all of the infectious diseases in this review are of Old World origin. Perhaps most surprising is the large number of tropical (16), newly emergent (7), and bioterrorism diseases (9) that have been modeled in macaques. Many of these human diseases (e.g., AIDS, hepatitis E, bartonellosis) are a consequence of zoonotic infection. However, infectious agents of certain diseases, including measles and tuberculosis, can sometimes go both ways, and thus several human pathogens are threats to nonhuman primates including macaques. Through experimental studies in macaques, researchers have gained insight into pathogenic mechanisms and novel treatment and vaccine approaches for many human infectious diseases, most notably acquired immunodeficiency syndrome (AIDS), which is caused by infection with human immunodeficiency virus (HIV). Other infectious agents for which macaques have been a uniquely valuable resource for biomedical research, and particularly vaccinology, include influenza virus, paramyxoviruses, flaviviruses, arenaviruses, hepatitis E virus, papillomavirus, smallpox virus, *Mycobacteria*, *Bacillus anthracis*, *Helicobacter pylori*, *Yersinia pestis*, and *Plasmodium* species. This review summarizes the extensive past and present research on macaque models of human infectious disease.

**Key Words:** comparative medicine; human pathogens; infectious disease; macaque

## Introduction

Macaques represent the major nonhuman primate (NHP[1]) resource for biomedical research. The National Institutes of Health (NIH)–supported National Primate Research Centers (NPRCs) provide an effective infrastructure to supply and house NHPs—about 40,000 total and mostly macaques (*Macaca*)—for the benefit of research into human disease. Other NHP species from Africa (e.g., African green and sooty mangabey monkeys, baboons, and chimpanzees) and the New World (e.g., marmosets, spider and owl monkeys) are also housed in NPRCs and other facilities and have contributed significantly to research on AIDS and other infectious diseases. When applicable, we mention these other NHP species in the relevant infectious disease section.

The 16 species of macaques are found primarily in southern Asia (Napier and Napier 1985). They are omnivorous, adaptable to almost any ecological niche, and adapt well to captivity. The species most commonly used in biomedical research are rhesus macaques (*M. mulatta;* from India, but no longer imported); cynomolgus, long-tailed, or crab-eating macaques (*M. fascicularis;* from southern Asia); and pigtail macaques (*M. nemestrina;* from Southeast Asia). The NIH National Center for Research Resources (NCRR) plans to increase the number of macaque breeding colonies, including specific pathogen-free (SPF) animals, and set up a database to enable researchers to locate animals with particular characteristics (NCRR 2004-2008).

By experimentally inducing infectious diseases in such a closely related primate or occasionally studying naturally occurring infection, investigators hope, of course, to gain valuable insight, relevant to humans, into disease mechanisms so as to develop improved therapies, diagnostics, and vaccines. The opportunity is at hand to better achieve these goals because of the recent availability of the sequence of the macaque genome (Rhesus Macaque Genome Sequencing and Analysis Consortium 2007) and of the genomes of many infectious pathogens and their insect vectors. In particular, much new information can be obtained about the agent-host relationship through the use of macaque-specific nucleic acid and protein assays.

In this article we review the various human infectious diseases for which macaques have served as models over

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[1]Abbreviations used in this article: AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; CNS, central nervous system; HIV/SIV, human/simian immunodeficiency virus; IL, interleukin; NHP, nonhuman primate; PCR, polymerase chain reaction

the past century. These models represent diverse pathogens including bacteria, viruses, fungi, parasites, and prions. The categorization of specific agents in Table 1 is based on a recent survey that explores the origins of human infectious diseases (Wolfe et al. 2007). Under each broad category, the diseases are ordered according to viral, bacterial, and parasitic etiology, and according to historical precedent or related infectious agents and diseases. We have also included several NHP infectious agents that produce disease similar to related human pathogens.

Many pathogens of humans are zoonoses (diseases transmitted from animals to humans), and several zoonotic pathogens are transmitted directly from human to human. In particular, zoonotic infections are the major source of emerging and reemerging diseases worldwide (Murphy 1998; Palmer et al. 2005; Wolfe et al. 2005). Furthermore, some human pathogens, called anthropozoonoses, can spread accidentally to NHPs.

For most of the macaque models of infectious pathogens described in this review, we mention important historical events or current relevance to human disease and focus on the most up-to-date research accomplishments. Because of space limitations, we describe primarily recent and novel examples of infectious disease modeling in captive macaque species. Accordingly, cited references are representative and by no means comprehensive. We refer readers to other published resources for further information on human infectious agents, including viruses (Graffe 1991; Knipe et al. 2006), bacteria (Mandell et al. 2005), and parasites (Marquardt et al. 2000), as well as for the historical impact of these pathogens (Karlen 1995; Oldstone 1998). Our goal is to focus on the macaque as an immensely valuable resource for a wide spectrum of comparative infectious disease research that benefits both humans and animals.

## Global Diseases

Several infectious diseases of viral or bacterial etiology are distributed worldwide and either are the cause of current epidemics or have the potential for worldwide spread.

**Table 1 Human infectious diseases and agents studied in the macaque model[a]**

Global Diseases
- Acquired immunodeficiency syndrome
- Influenza
- Hepatitis
- Tuberculosis
- Gastritis, gastric cancer

Childhood diseases
- Polio
- Measles
- Chickenpox
- Respiratory syncytial virus
- Metapneumovirus
- Cytomegalovirus
- Herpes simplex virus
- Human herpesvirus 6

Tropical diseases
- Yellow fever
- Dengue fever
- Japanese encephalitis
- Rift valley fever
- Arenaviruses (lassa fever, lymphocytic choriomeningitis virus)
- Typhus
- Leprosy
- Buruli ulcer
- Malaria
- Schistosomiasis
- Chagas disease
- African sleeping sickness
- Ascariasis
- Lymphatic filariasis
- Onchocerciasis

Sexually transmitted diseases
- Syphilis
- Chlamydia
- Papillomavirus

Newly emergent diseases
- West Nile virus
- Hantaviruses
- Severe acute respiratory syndrome
- Granulocytic ehrlichiosis
- Lyme disease
- Bartonellosis
- Melioidosis

Potential bioterrorism agents
- Smallpox
- Monkeypox
- Rabies
- Marburg virus
- Ebola virus
- Anthrax
- Tularemia
- Plague
- Brucellosis

Transmissible spongiform encephalopathies
- Kuru
- Creutzfeldt-Jakob disease
- Bovine spongiform encephalopathy

Oncogenic viruses
- Simian T lymphotropic virus
- Simian type D retrovirus
- Simian foamy virus
- Epstein-Barr virus
- Kaposi's sarcoma herpesvirus

Other infectious diseases
- Rotavirus
- Norwalk virus
- Tick-borne encephalitis
- Simian hemorrhagic fever virus
- Simian parvovirus
- Polyomavirus
- Q fever
- *Escherichia coli*
- *Campylobacter*
- *Listeria*
- Legionnaires disease
- Bacillary dysentery (shigellosis)
- Streptococcal pneumonia
- Streptococcal pharyngitis
- Chronic enterocolitis
- Trichinosis
- Toxoplasmosis
- Periodontal disease

[a]Under the broad categories, diseases are ordered according to viral, bacterial, and parasitic etiology, and according to historical precedent or related infectious agents and diseases. This list includes several nonhuman primate agents that produce disease similar to related human pathogens.

## Acquired Immunodeficiency Syndrome (AIDS)/Simian Immunodeficiency Virus (SIV) *(Retroviridae)*

The founders of the National Primate Research Centers could not have envisioned a more suitable example of the value of NHPs in biomedical research than that of simian acquired immunodeficiency syndrome (SAIDS) as a model for human AIDS[1]. SAIDS was initially (1983-1985) the designation for a fatal immunosuppressive disease induced by an indigenous type D retrovirus in many macaques (Letvin and King 1984; Gardner et al. 1988). Simian immunodeficiency virus (SIV[1]), a lentivirus closely related to human immunodeficiency virus (HIV[1]), was discovered in just a few macaques with immunosuppression and lymphomas at the New England center (Apetrei et al. 2005; Letvin et al. 1985). SIV does not occur in Asian macaques in the wild, but was acquired in captive macaques by accidental or purposeful cross-species infection from sooty mangabeys or African green monkeys (Apetrei et al. 2004). In their natural African hosts, which number about 36 different Cercopithecine species, SIV strains are asymptomatic and transmitted mainly through wounds or bites acquired in fights and through sexual contact.

The major difference in the host-virus relationship between African monkeys and Asian macaques is the presence in the latter of a much stronger anti-SIV immune response associated with T and B cell activation and a loss of $CD4^+$ T lymphocytes. In the different species of macaques tested, SIV (mainly of sooty mangabey origin) causes an AIDS-like disease with remarkable similarities to HIV-1/AIDS (Gardner et al. 2004; Letvin et al. 1985). However, the SIV-induced macaque disease usually has a much shorter incubation period (2 months to 3 years) than does HIV-induced AIDS in humans. SIV from sooty mangabeys is also responsible for spreading by contact to humans in western Africa to cause HIV-2-associated AIDS, which is still largely confined to West Africa (Apetrei et al. 2004; Hirsch et al. 1989). Similarly but more dramatically, the HIV-1 pandemic almost certainly arose by cross-species spread of SIV from chimpanzees via the bushmeat trade (Keele et al. 2006; Van Heuverswyn and Peeters 2007).

The value of the macaque model for AIDS research is highlighted by the lack of persistent infection and development of signs of immunodeficiency in macaques experimentally infected with HIV-1 (Agy et al. 1997). Although certain strains of HIV-2 induce SAIDS in macaques (McClure et al. 2000), infection of these animals with pathogenic strains and clones of SIV has been the experimental system of choice for comparative research on HIV/AIDS (Levy 2007 provides comprehensive coverage of HIV and AIDS). In every aspect of their molecular makeup, pathogenesis, and pathology, SIV and HIV are similar in the respective susceptible host (Lackner and Veazey 2007). The macaque model first demonstrated the importance of the gastrointestinal tract in acute infection as a focus of SIV replication (Heise et al. 1993) and T cell depletion (Smit-McBride et al. 1998; Veazey et al. 1998). Opportunistic infections and tumors also are virtually identical in AIDS and SAIDS. Included among the opportunistic infections are cytomegalovirus (CMV), simian vacuolating virus 40 (SV40), avian mycobacteria, pneumocystis, and cryptosporidia. Opportunistic tumors include B cell lymphoma and retroperitoneal fibromatosis; the latter is the counterpart of Kaposi's sarcoma (see the sections on simian type D retrovirus and on Kaposi's sarcoma herpesvirus).

Worth mentioning are two exceptions where HIV has induced AIDS in captive NHPs other than macaques. A single chimpanzee among many inoculated with HIV-1 developed an AIDS-like condition after 10 years (Novembre et al. 1997), and several baboons exhibited an AIDS-like condition 18 to 24 months after inoculation with HIV-2 (Barnett et al. 1994). Also noteworthy is the induction of SAIDS in captive macaques after serial passage of SIV derived from naturally infected African green monkeys (Goldstein et al. 2005). In addition, a single captive sooty mangabey naturally infected with SIV developed SAIDS at 18 years of age (Ling et al. 2004). Clearly, however, infection of macaque species with SIV of initial sooty mangabey origin remains the animal model of choice for AIDS research.

Investigators have used macaque models to compare different routes of SIV challenge with SIVs of different cell tropisms, including mucosal membranes (Haase 2005; Miller et al. 1989), and to study both mutated versions and recombinants of this virus (Kestler 1991; Mankowski et al. 1997; Marthas et al. 1993). Pediatric AIDS has been modeled in newborn and infant macaques infected with SIV (Klumpp et al. 1993; Marthas et al. 1995). Accordingly, the macaque model now plays a prominent role for evaluating antiviral therapies ( North et al. 2006; Van Rompay 2005) and vaccines for AIDS (McMichael 2006; Nathanson and Mathieson 2000). Although HIV-1 does not productively infect macaques, chimeric viruses, designated simian/human immunodeficiency viruses (SHIV), bearing HIV-1 envelope (Reimann et al. 1996) or reverse transcriptase genes (Uberla et al. 1995), do so and can induce SAIDS. Recently, an HIV-1 derivative with 7% SIV genetic content has been shown to establish infection in nemestrina macaques (Igarashi et al. 2007). Thus, it is possible to test therapies and vaccines targeted to HIV gene products in the macaque.

The SIV/SAIDS model has revealed the molecular pathways of infected T lymphocytes that are affected by products of certain viral genes, such as *nef* and *vif*, and has provided information about the role of *env* glycoprotein in determining cell tropism and cytopathology. Additional studies of immune responses in macaques have defined epitopes of the *env* glycoprotein that are targeted by neutralizing antibodies or antibody-dependent cell cytotoxicity (Hessell et al. 2007). Investigators have gained a better understanding of the viral-specific epitopes expressed on infected cells that serve as targets of cytotoxic T lymphocytes, and of the point mutations in these epitopes that allow the

virus to escape this cellular immune surveillance (Allen et al. 2000; Barouch et al. 2002). This model has provided deeper insight into cellular processes that restrain virus replication, knowledge that might lead to improved therapy.

An important anti-HIV drug, tenofovir, was developed in the SAIDS model (Van Rompay 2005) and is now in early trials with the goal of preventing the sexual transmission of HIV in Africa. Strong vaccine protection against SIV challenge was first shown with a live attenuated SIV deleted of the *nef* gene (Daniel et al. 1992); however, a low level of virulence, particularly in newborn macaques, proved that this vaccine strategy would be too unsafe for humans (Whitney and Ruprecht 2004). Many versions of SIV and SHIV vaccines, including whole inactivated virus, live attenuated recombinant virus, and viral DNA, in various combinations and with different adjuvants, remain to be tested in this model. In short, if experimental conditions are optimal and the immunizing and challenge virus are homologous, some degree of vaccine protection, albeit not sterilizing, is possible; however, long-lasting protection against heterologous strains remains an elusive goal.

The SIV macaque model did point the way to the eventual failure in humans of nonneutralizing antibodies induced by a recombinant *env* vaccine that was intended to protect against HIV-1 infection (Graham and Mascola 2005). The model also correctly predicted the failure of therapeutic (i.e., postexposure) HIV vaccines to lower virus load or delay disease (Gardner et al. 1989). However, it remains possible that therapeutic vaccination may be beneficial when given early after infection, preferably when the drugs have markedly reduced viral load. Whether or not an effective HIV-1 vaccine is ultimately developed, the macaque model of AIDS will be required for validation of the immunogenicity, safety, and efficacy of future candidate formulations (Letvin 2006; McMichael 2006).

Questions about long-term antiviral therapy, development of viral resistance, reservoirs of residual virus production or latent virus, and testing of novel antiviral drugs will continue to rely on this animal resource. A deeper understanding of the pathogenesis of AIDS and of the correlates of protective innate and adaptive immunity will depend on this immensely valuable animal model of simian AIDS (Ahmed et al. 2005).

## Influenza/Influenza Virus *(Orthomyxoviridae)*

Although F.M. Burnet showed in the early 1940s that macaques were susceptible to influenza A virus (Graffe 1991, 121), the principal animal models for extensive immunization trials and strain typing remained ferrets and mice. Recently, researchers have used macaques to compare the pathogenesis of highly virulent influenza strains, such as the reconstructed 1918 pandemic strain and the pathogenic bird flu strain (H5N1), with a nonvirulent conventional strain (H1N1) (Rimmelzwaan et al. 2001). Genomics and proteomics technologies, with macaque-specific reagents, have shown dramatic differences in gene expression in pulmonary lesions induced by the H5N1 influenza virus and tightly co-regulated genes expressed in peripheral white blood cells that might prove a marker of early infection (Baas et al. 2006). Apparent cytokine storms, triggered by alveolar damage from H5N1 virus replication in the lungs, induced an acute respiratory distress syndrome and multiple organ dysfunction at remote sites that were free of virus (Rimmelzwaan et al. 2003). A similar transcriptome approach revealed that the virulent 1918 strain of influenza virus induced a lethal respiratory infection associated with an atypical innate immune response and an abnormal antiviral response (Kobasa et al. 2007). A better understanding of the virus-host interaction in the macaque will aid development of interventions to modulate the host's innate immune response to virulent influenza virus and facilitate early diagnosis. A novel live vaccine, incorporating the H5N1 hemagglutinin influenza virus gene in an avian Newcastle disease virus vector and given via the respiratory tract to African green monkeys, has induced high levels of H5N1 neutralizing antibodies and is therefore considered a candidate for clinical evaluation in humans (DiNapoli et al. 2007).

## Hepatitis A/Hepatitis A Virus (HAV) *(Picornaviridae)*

Natural infection with HAV, associated with mild clinical disease, has been detected in newly caught macaques (Le Bras et al. 1984; Shevtsova et al. 1988). Whether of rhesus or human origin, HAV also causes experimental infection with little or no evidence of mild hepatitis in macaques (Mao et al. 1981). However, newly captured monkeys can be very sensitive to HAV and its associated acute and chronic liver disease, presumably due to the stress of acclimatization. There is no compelling need to advance a macaque model as an efficacious HAV vaccine has been licensed since 1992.

## Hepatitis B/Hepatitis B Virus (HBV) *(Hepadnaviridae)*

Natural infection with HBV-like virus, associated with mild hepatitis, has been observed in recently imported cynomolgus macaques from Indonesia (Kornegay et al. 1985). Rhesus macaques can be experimentally infected with human HBV with no evidence of liver damage (Barker et al. 1975; Zuckerman et al. 1975). However, macaques from Morocco (*M. sylvanus*) developed liver pathology after intrahepatic inoculation with a replication-competent HBV DNA plasmid construct (Gheit et al. 2002). Highly effective HBV vaccines have been licensed since 1982, so there is no need for an animal model for this virus.

## Hepatitis C/Hepatitis C Virus (HCV) *(Flaviviridae)*

HCV, the major cause of post-transfusion hepatitis, was isolated and cloned in 1989 (Choo et al. 1989). Mutations in the HCV genome allow this virus to avoid immune surveillance; the outcome is chronic infection and difficulty in producing an effective vaccine. Cynomolgus, rhesus, and Japanese macaques are resistant to experimental HCV infection (Abe et al. 1993); therefore, the chimpanzee, which is susceptible, remains the animal model of choice for HCV vaccine research. However, researchers are using the macaque model for HCV immunogenicity studies, particularly in an effort to define vaccine regimens that produce stronger cellular immune responses (Capone et al. 2006a,b; Li et al. 2003; Rollier et al. 2005).

## Hepatitis E/Hepatitis E Virus (HEV) *(Hepeviridae)*

HEV is an emerging human pathogen endemic to Southwest and Central Asia, the Middle East, North Africa, and Mexico. This virus, which spreads by the fecal-oral route, causes a significant number of acute hepatitis cases in humans, including epidemics with high (20%) mortality. Generally, however, most patients recover, and chronic HEV infection does not develop. Natural HEV infection occurs asymptomatically in Japanese macaques (*M. fuscata*) and may be transmissible to humans (Hirano et al. 2003). Cynomolgus and rhesus macaques are quite susceptible to human HEV subclinical infection (Aggarwal et al. 2001; Graff et al. 2005; Kawai et al. 1999) and have been extensively used in recent years to demonstrate the protective efficacy of several antiviral recombinant and DNA vaccines (Kamili et al. 2004; Li et al. 2005b; Purcell et al. 2003; Zhang et al. 2002).

## Hepatitis G/Hepatitis G Virus (HGV) *(Flaviviridae)*

HGV, isolated in 1995-1996, is distantly related to HCV. It is readily transmitted by blood transfusion, with a carrier rate of 2-5% in the general NHP population. Rhesus macaques are susceptible to experimental infection and disease with HGV or genomic RNA (Ren et al. 2005; Xu et al. 2001). However, because there is no evidence that HGV is harmful to humans, there is no need to develop anti-HGV vaccines, tests, or drugs.

## Tuberculosis (TB) *(Mycobacterium tuberculosis)*

The resurgence of *Mycobacterium tuberculosis (M.tb.)* as a major global cause of death has been accelerated by the HIV epidemic and the appearance of multidrug-resistant *M.tb.* strains. Improved diagnostics, drugs, and vaccines are needed.

Macaques are highly susceptible to human *M.tb.* (as well as bovine and avian *Mycobacteria*) and manifest the complete spectrum of clinical and pathologic manifestations of human TB—extending from active, progressive disease to latency and healing (Capuano et al. 2003; Walsh et al. 1996). Natural outbreaks of human, bovine, or avian TB have occurred repeatedly over the years in captive macaques (Zumpe et al. 1980). Fifty years ago, macaques were used to demonstrate the efficacy of the bacillus Calmette-Guerin (BCG) vaccine, an attenuated strain of *M. bovis*, and to evaluate other vaccine approaches and test new drugs against lethal challenge with *M.tb.* (Good 1968; Schmidt 1956). Although researchers have confirmed these results in recent years (Langermans et al. 2001), neither the BCG vaccine nor drugs have curtailed the global spread of TB. But with modern macaque-specific reagents on hand, this model is being resurrected. Interferon gamma release from antigen-specific T cells provides a useful immunologic correlate of protection against *M.tb.* infection (Baskin et al. 2004).

The macaque model is helping to better define immunodominant antigens, conserved in different *M.tb.* strains, that induce maximum protection when given alone or together with BCG (Brusasca et al. 2003; McShane et al. 2004). Such antigens could become the basis for better diagnostics and vaccines. The macaque model can also be useful for the study of coinfection with SIV, the counterpart of HIV. Macaques experimentally coinfected with SIV and BCG exhibit a fatal disseminated disease characterized by BCG granulomas in multiple organs (Chen 2004; Shen et al. 2002). Because HIV-infected human infants vaccinated with BCG also experience a high risk of developing disseminated BCG disease (von Reyn 2006), the World Health Organization (WHO) does not recommend BCG vaccination for HIV-infected children (WHO 2007). An SIV-induced compromise of adaptive T cell responses may contribute to this tuberculosis-like disease (Zhou et al. 2003). Understanding *M.tb.* pathogenesis in the macaque can lead to better management and control of the human TB epidemic.

## Gastritis/Gastric Cancer *(Helicobacter pylori)*

The macaque is a superior animal model for investigating the pathogenesis of *H. pylori*–associated gastritis and gastric cancer (Kodama et al. 2005). About half of the world's population is infected with *H. pylori*, a bacterium that grows only in the stomach and is acquired orally in childhood. About 3% of those infected exhibit gastritis and stomach ulcers, and about 1% progress to stomach cancer. *H. pylori* secretes urease, which converts urea to ammonia and reduces gastric acidity, thus enhancing gastric colonization. *H. pylori* injects a toxin (*cagA* gene product) in gastric

epithelial cells, leading to their disorganization (Saadat et al. 2007). Antibiotics are effective in eliminating the bacterium from the host, thereby preventing complications.

The macaque has proven to be a suitable model for understanding the biology and molecular pathogenesis of *H. pylori*. Macaques are naturally infected with several strains closely related to that of humans and are also highly susceptible to the human strain (Doi et al. 2005; Dubois et al. 1994, 1995; Solnick et al. 1999, 2003). They develop gastritis and antral erosions indistinguishable from those that occur in humans (Reindel et al. 1999; Shuto et al. 1993). Macaques also exhibit atrophic gastritis, a precursor to adenocarcinoma in humans. Captive rhesus monkeys are frequently colonized with a related species, *H. cinaedi*, either asymptomatically or in association with chronic colitis and hepatitis (Fernandez et al. 2002).

A modification of the *H. pylori* outer membrane protein expression that occurs during experimental infection (Solnick et al. 2004) may facilitate epithelial adherence and promote chronic infection. Analysis of the gastric transcriptional profile has revealed an expected upregulation of cell structural elements and inflammatory and immune responses, as well as a novel downregulation of heat shock protein (Huff et al. 2004). These studies also demonstrated an increased expression of virulence genes thought to encode the *H. pylori* type IV structural pilus and its accessory proteins (Boonjakuakul et al. 2005). A predominant Th1-type immune response is induced early after infection and may be associated with apoptosis of gastric lymphocytes and epithelial cells (Mattapallil et al. 2000; Tanaka et al. 2005). Researchers have evaluated the result of short-term antibiotic treatment on *H. pylori* infection and intestinal microflora in macaques (Tanaka et al. 2005); several vaccination strategies, including recombinant *H. pylori* urease, partially protect macaques against infection with this agent (Dubois et al. 1998).

## Childhood Diseases

This section covers viral diseases commonly acquired in childhood.

### Poliomyelitis/Poliovirus *(Picornaviridae)*

Macaques have played a major role in poliomyelitis (polio) research, particularly vaccine development (Graffe 1991). The first indication that the poliomyelitis agent was a filterable virus came in 1908-1909 when the disease, known since prehistory, was experimentally induced in macaques by inoculation of filtered spinal cord from an infected individual. Humans are the only known natural host for poliovirus, and it was not until 1949 that the virus could be grown in tissue cultures of nonhuman primate kidney cells (African green monkey Vero cells).

In order to type different strains of poliovirus, about 30,000 rhesus macaques were used over a 3-year period for experimental infection. The serotyping drew on about 100 "wild" virus strains from numerous anatomical sources. Monkey sera were typed by virus neutralization assays, and by 1951 scientists had identified three predominant immulogical types of virus, with type 1 the most prevalent and most virulent. Such cell cultures also allowed the demonstration of viremia in monkeys and humans in 1951-1952. Based on this research in the NHP model, the Salk inactivated (1955) vaccine as well as the Koprowski and later Sabin (1962) attenuated polio vaccines were tested for immunogenicity, safety, and efficacy in many thousands of human children and were proven to be protective and safe.

Simian vacuolating virus 40 (SV40), a polyomavirus, was discovered in 1959 as a contaminant of inactivated poliovirus vaccine prepared in macaque cell cultures. However, there is no conclusive evidence to implicate SV40 virus of polio vaccine origin in any human disease (Shah 2007). The detection of SV40-related sequences by polymerase chain reaction (PCR[1]) in some mesotheliomas and meningiomas suggests an association with a related agent in certain human cancers (Carbone and Pass 2006; White et al. 2005). There is no evidence of HIV or SIV in polio vaccine stocks used in the first US polio immunization campaigns (Rizzo et al. 2001). In an example of reverse zoonosis, in 1957 a polio type 2 outbreak, presumably of human origin, affected six monkeys in the NHP colony in Sukhumie, Russia (Lapin and Andreevna 1963).

No human infection or cases of "wild" polio have occurred in this country since 1979, and the Americas were declared polio-free in 1994. However, polio is still a concern in some poor, underdeveloped countries in Africa and Asia. Use of the macaque is therefore still necessary for monitoring the potential neurovirulence of the live attenuated Sabin polio vaccine, which is now administered primarily in developing countries (Rezapkin et al. 1999). (Because reversion to virulence remains a problem with this live attenuated vaccine, it is no longer given in the United States.) A transgenic mouse carrying the human polio virus receptor gene (CD155) has been developed for neurogenic virulence testing (Abe et al. 1995; Nagata et al. 2001), but the global drive to eradicate polio will probably continue to depend on the macaque model to test for neurogenic virulence of the oral vaccine. Importantly, the macaque has been used recently in poliovirus pathogenicity studies (Samuel et al. 1993) and in efforts to develop a hexavalent vaccine against inactivated poliovirus, influenza, hepatitis B, diphtheria, tetanus, and pertussis (Caulfield et al. 2000).

### Measles *(Paramyxoviridae)*

Despite the availability of a licensed vaccine since 1963, measles is the leading cause of vaccine-preventable childhood mortality worldwide, responsible for an estimated 345,000 deaths in 2005. Inadvertent transmission of either this virus (from humans) or the closely related distemper

virus (from dogs) to captive macaques has caused numerous outbreaks with significant morbidity and mortality (Choi et al. 1999; Jones-Engel et al. 2006; Willy et al. 1999). Experimental inoculation of "wild" measles virus strains in macaques produces a disease that closely mimics human measles in its clinical and pathologic manifestations, including immunosuppression and occasional central nervous system (CNS[1]) complications (Albrecht et al. 1977; Kobune et al. 1996). Undetected CNS infection of macaques with measles virus may have affected the results of neurovirulence tests done with some oral poliovirus vaccines (Contreras and Furesz 1992). This animal model has been particularly valuable for studying measles virus pathogenesis in the normal and immunocompromised host (Hicks et al. 1977; Polack et al. 1999; Zhu et al. 1997b). Cellular immunity appears more important than humoral immunity in clearance of the virus (Pahar et al. 2005; Permar et al. 2003).

During the past decade, investigators have taken advantage of this excellent disease model to test new vaccine strategies. Adult macaques, immunized with either the human measles virus vaccine (Attenuvax) or the canine distemper virus vaccine, were protected against challenge infection by human measles virus (Christe et al. 2002). Because maternal measles virus antibody can interfere with the active immune response, experiments were done in infant macaques to compare several recombinant vaccines given in the presence or absence of preexisting immunity. At least partial protection against challenge infection and disease was achieved in infant macaques in the presence of maternal antibody to measles virus by vaccination with (1) replication-competent or -defective vaccinia virus expressing measles virus hemagglutinin and fusion proteins (Stittelaar et al. 2000; Zhu et al. 2000), (2) recombinant BCG expressing the measles virus nucleoprotein (Zhu et al. 1997a), or (3) a measles virus DNA vaccine (Premenko-Lanier et al. 2004). Addition of interleukin (IL[1])-12 to a recombinant measles virus vaccine altered the T helper type 2 immune response but did not improve the immunosuppression associated with challenge infection (Hoffman et al. 2003). Very recently, a live attenuated measles virus vaccine given by aerosol administration has been efficacious in macaques (De Swart et al. 2006).

The goal of the Global Initiative Against Measles is to reduce measles mortality through the use of the current vaccine in countries with high measles deaths, such as India, Indonesia, and Pakistan. The macaque model is essential for defining an effective antimeasles vaccine regimen to achieve this goal.

## Chickenpox/Varicella Zoster (VZV)/Simian Varicella Virus (SVV) *(Herpesviridae)*

Simian varicella virus (SVV) shares 70-75% genetic identity with human varicella (chickenpox) and herpes zoster (shingles) virus (VZV) (Gray and Oakes 1984). Simian varicella virus (SVV) causes a highly contagious disease, often fatal, in Old World monkeys, including macaques (Wenner et al. 1975). It is not known whether these monkeys are the natural host for the virus, nor is there any evidence that SVV infects humans.

SVV infection of macaques is very similar in clinical symptoms and pathogenesis to VZV infection in humans and therefore provides an excellent model (Gray 2004). Like VZV, SVV establishes lifelong latent infection in neural ganglia, where it may be reactivated (e.g., after gamma irradiation). Antiviral therapy has been effective in limiting fatalities in SVV epizootics (Lake-Bakaar et al. 1988). The entire SVV genome has been cloned, sequenced, and transfected into Vero cells to yield infectious virus, allowing site-specific mutagenesis and insertion of foreign genes to study pathogenesis and viral latency and to develop vaccines (Gray et al. 2001). The current live attenuated VZV vaccine is generally safe in humans but there are some concerns about duration of efficacy and safety; macaques offer an opportunity to evaluate new attenuated VZV vaccines as well as subunit or DNA vaccines.

## Respiratory Syncytial Virus (RSV) *(Paramyxoviridae)*

Respiratory syncytial virus (RSV) is a major cause of severe respiratory disease in infant and elderly humans. Young macaques are susceptible to experimental RSV infection and exhibit mild clinical disease (McArthur-Vaughan and Gershwin 2002; Simoes et al. 1999). An inactivated RSV vaccine, developed in the 1960s, caused enhanced disease after natural infection. Researchers reproduced this immunopathological phenomenon in macaques and showed that it was caused by antibody-dependent enhancement of RSV replication (Ponnuraj et al. 2003). A vaccine-induced IL-13-mediated hypersensitivity to subsequent RSV infection also contributed, at least in part, to this adverse reaction (De Swart et al. 2002). The macaque model is now proving helpful for assessing the safety of novel RSV vaccines designed to prevent the immunopathology that occurs after RSV infection (De Waal et al. 2004).

## Metapneumovirus *(Paramyxoviridae)*

This newly discovered human paramyxovirus is a causative agent of acute lower respiratory tract infection in very young children, the elderly, and immunocompromised patients. The virus is ubiquitous, acquired early in life, and readily cultured in rhesus monkey kidney cells. Very recently, experimental infection of macaques with metapneumovirus induced an asymptomatic infection with transient protective immunity against reinfection with the homologous virus strain (Kuiken et al. 2004; van den Hoogen et al. 2007).

### Cytomegalovirus (CMV) *(Herpesviridae)*

Cytomegalovirus (CMV[1]) infection of macaques closely resembles that of humans in its prevalence and natural history. Congenital CMV infection in humans is the leading infectious cause of birth defects in newborns. As in humans, macaque CMV is generally present after puberty as an asymptomatic lifelong infection (Vogel et al. 1994). Naïve rhesus macaques experimentally infected with rhesus CMV seroconverted and became infected but remained healthy (Lockridge et al. 1999).

Rhesus CMV has been completely sequenced and its proteins are 60% similar to human CMV proteins (Hansen et al. 2003). Rhesus CMV encodes an IL-10-like protein that has immunosuppressive properties (Lockridge et al. 2000; Spencer et al. 2002). Reactivation of CMV, with associated inflammation, occurs in immunosuppressed humans and macaques, most dramatically evident in human and simian AIDS. Naïve macaques experimentally infected with rhesus CMV and SIV show an augmented SIV pathogenesis (Sequar et al. 2002). Rhesus CMV has a strong affinity for endothelial cells encoded by a viral cyclooxygenase-2 homologue (Carlson et al. 2005; Rue et al. 2004). A macaque model of intrauterine rhesus CMV infection exhibits a range of developmental abnormalities similar to those observed in humans congenitally infected with CMV (Barry et al. 2006; Tarantal et al. 1998).

Development of an effective CMV vaccine to prevent congenital infection is a high public health priority. Initial results indicate that a rhesus CMV DNA vaccine targeting the glycoprotein B, phosphoprotein pp65, and viral IL-10 induces low levels of neutralizing antibody and decreases viral load after challenge (Yue et al. 2007). Further work in this macaque model requires improving the level of vaccine protection.

### Herpes B Virus *(Herpesviridae)*

B virus, an alphaherpesvirus that is now completely sequenced (Perelygina et al. 2003), is the macaque counterpart of herpes simplex virus (HSV) in humans. Like HSV, B virus produces a ubiquitous lifelong infection in macaques and is present in almost all colony-bred animals in enzootically infected populations by the time they reach sexual maturity (Jainkittivong and Langlais 1998). Reactivation of the virus is usually asymptomatic but may occasionally cause a "cold sore," gingivitis, or even fatal systemic infection (Carlson et al. 1997). Interestingly, coinfection of macaques with SIV (or simian type D retrovirus) seldom causes activation of latent B virus despite the frequent activation of other latent herpesviruses (e.g., CMV and Epstein-Barr virus).

Among 35 herpesviruses identified in nonhuman primates, B virus is the only one known to be pathogenic for humans. About 40 cases of zoonotic B virus infection have been reported over about four decades, with a high incidence of encephalitis and death (Ostrowski et al. 1998). Rapid treatment with antiviral medications prevents disease complications, and new antiviral drugs are in development (Focher et al. 2007).

A vaccine that could prevent or limit B virus infection in macaques would lessen the occupational risk for individuals that handle these animals. To that end an inactivated B virus vaccine was tested for immunogenicity in macaques in the 1960s (Hull 1971), and in the 1990s a vaccinia virus expressing glycoprotein D given to rabbits conferred good protection against B virus challenge infection (Bennett et al. 1999). Most recently, the immunogenicity of a DNA vaccine against B virus has been tested in mice and uninfected rhesus macaques (Loomis-Huff et al. 2001); a low level of B virus neutralizing antibodies was induced in the monkeys that were not challenged. Future vaccine combinations will include live vectors, such as vaccinia virus, aimed at eliciting cell-mediated immunity, which is important for protecting against B virus.

### Human Herpesvirus 6 (HHV-6) *(Herpesviridae)*

This lymphotropic herpesvirus causes roseola infantum in humans. To determine whether HHV-6 might accelerate progression to AIDS in HIV-infected people, researchers coinfected pigtail macaques with HHV-6 and SIV. HHV-6 infection alone in this species was asymptomatic (Yalcin et al. 1992), but in the presence of SIV it appeared to accelerate AIDS progression (Lusso et al. 2007; Yalcin et al. 1992). Also, in vitro infection of macaque T lymphocytes with HHV-6 increased the levels of SIV replication (Lusso et al. 1994). This macaque model may help in investigations of both viral and host factors that influence the interaction between HHV-6 and HIV in progression to AIDS. Based on serology, a related but as yet unidentified herpesvirus may be present in squirrel monkeys and a few macaques (Higashi et al. 1989).

## Tropical Diseases

Many infectious diseases, of viral or parasitic etiology and often involving both an animal reservoir and insect vector, are mostly confined to tropical areas of the world.

### Yellow Fever *(Flaviviridae)*

Yellow fever virus was the first described human pathogen transmitted by an insect (*Aedes aegypti* mosquito). In 1927 researchers found that rhesus macaques were susceptible to the experimental induction of classical yellow fever from filtered human blood and used this animal model to successfully apply Koch's postulates to a virus infection for the first time in virology (Stokes et al. 1928, 2001). Almost 100 years later, the complete genome sequence of *Ae. aegypti* has just been reported (Nene et al. 2007). The natural

sources of yellow fever virus are monkeys, originally from tropical West Africa. With the spread of infected humans and *Aedes* mosquitoes, the virus has adapted to the Americas. Interestingly, yellow fever virus has never been reported in Asia, despite the presence of *Ae. aegypti*. Mosquito control led to eradication of the virus in Cuba and Panama at the beginning of the 20th century.

The first yellow fever vaccine was made in 1939 from the brains of experimentally infected macaques (Graffe 1991). Later an attenuated live vaccine (17D) was prepared in chick embryos, and its neurotropic and immunogenic properties were tested in macaques (Mason et al. 1973). This 17D seed virus is the source of the current human vaccine, which has proven to be stable, safe, and efficacious when given as a single dose. However, occasional cases of fatal hemorrhagic fever have recently been associated with the 17D vaccine (Vasconcelos et al. 2001). Therefore, for quality control, testing of the potential neurovirulence of this vaccine continues in rhesus monkeys (Marchevsky et al. 2003). The 17D yellow fever vaccine strain also now provides the vector for recombinant, chimeric vaccines against other flaviviruses, such as the Japanese encephalitis, Chikungunya, West Nile, and dengue viruses. All of these vaccines have relied on rhesus monkeys for proof of efficacy and for neurovirulence safety testing (as discussed below).

## Dengue *(Flaviviridae)*

Epidemic dengue has become more common since the 1980s and is now second only to malaria as the most important mosquito-borne (*Ae. aegypti*) disease affecting humans. The global distribution of dengue is expanding and is now comparable to that of malaria. Each year 50 to 100 million cases of dengue fever occur and about 500,000 of them exhibit severe dengue hemorrhagic fever, which has a case fatality rate of about 5%.

The dengue agent belongs to one of four virus serotypes of the genus *Flavivirus*. There is no cross protection between serotypes and epidemics can be caused by multiple serotypes. Hemorrhagic fever is associated with superinfection with a dengue virus serotype distinct from the serotype of primary infection, possibly via the mechanism of antibody-dependent enhancement of virus uptake and replication. Investigators have documented natural asymptomatic infections of macaques in Southeast Asia with dengue and other flaviviruses (e.g., Japanese encephalitis, Chikungunya, and Sindbis viruses), suggesting possible sylvatic transmission cycles (Inoue et al. 2003; Peiris et al. 1993). No licensed vaccine for dengue is available but there has recently been progress with several recombinant live attenuated dengue virus vaccines in macaques.

Rhesus monkeys are quite susceptible to experimental infection with dengue virus and have provided an important animal model for pathogenesis, treatment, and vaccine development. Using DNA microarrays, PCR, and multiplex cytokine detection, researchers have shown transcriptional activation of innate antiviral immune responses (but no upregulation of certain cytokine genes) 5 days after infection with dengue virus type 1 (Sariol et al. 2007). Attempts to suppress dengue virus type 2 early viremia in rhesus monkeys with recombinant human alpha interferon showed a temporary suppression of viremia but no effect on total viral burden (Ajariyakhajorn et al. 2005). A recombinant modified vaccinia virus expressing the envelope glycoprotein of dengue type 2 virus protected rhesus monkeys against homologous viral challenge (Men et al. 2000). A recombinant, modified live chimeric yellow fever/dengue type 2 virus vaccine (ChimeriVax) protected rhesus monkeys against challenge with wild-type dengue type 2 virus (Guirakhoo et al. 2004); protection correlated with the production of neutralizing antibody. This vaccine is now in phase 1 clinical trials. Most recently, tetravalent live attenuated dengue virus vaccines given to rhesus macaques provided complete protection against viremia from dengue type 2 challenge but only partial protection against the other three serotypes (Blaney et al. 2005; Sun et al. 2006). Interference among the four vaccine viruses will require further dose adjustments to identify an optimal formulation for humans.

The availability of infectious cDNA clones of several flaviviruses has made possible the construction of other new live chimeric flavivirus vaccines bearing attenuating mutations in which the protective antigens of various highly virulent as well as attenuated flaviviruses may prove useful in immunizing against diverse flaviviruses of public health significance. For example, a yellow fever virus chimera expressing the envelope genes of Japanese encephalitis virus (another flavivirus) protected macaques against homologous virus challenge (see below); and a live dengue virus chimera bearing the envelope glycoprotein gene of an avirulent tick-borne flavivirus (Langat virus) protected rhesus monkeys against infection with highly virulent, closely related tick-borne flaviviruses (Pletnev et al. 2001).

## Chikungunya Virus *(Togaviridae)*

Spread by mosquitoes (*A. aegypti*, *A. albopictus)*, chikungunya virus has caused significant outbreaks of disease, with similarities to dengue, in Tanganyika, northern India, Malaysia, and recently in Italy (Pialoux et al. 2007). The name is derived from the Makonde (Tanganyika) word meaning “that which bends up” in reference to the stooped posture that develops as a result of the disease’s arthritic symptoms. Macaques are susceptible to experimental infection and have therefore been used to study mosquito transmission of the virus (Paul and Singh 1968) and the feasibility of developing inactivated (Nakao and Hotta 1973) or attenuated (Turell and Malinoski 1992) viral vaccines. Because of the rapid reemergence of chikungunya virus, the relative lack of knowledge of mechanisms of pathogenesis, and lack of effective vaccines and therapies, ma-

caques will be very valuable for addressing critical issues in the virus-host relationship and for developing interventions.

## Japanese Encephalitis *(Flaviviridae)*

Japanese encephalitis virus (JEV) is one of the most important causes of viral encephalitis worldwide and is spreading throughout most of China, Southeast Asia, and the Indian subcontinent. That a filterable agent was responsible for fatal encephalitis was first shown in 1933 by experimental transmission of JEV to macaques (Karlen 1995). This virus was later shown to be transmitted between wild and domestic birds and pigs by Culex mosquitoes. Formalin-killed and attenuated live vaccines have been in use for many years, and the killed vaccine was given during the Second World War to protect American troops in Asia. Rhesus macaques are highly susceptible to a lethal infection that resembles fatal human disease by intranasal inoculation with JEV (Myint et al. 1999). In recent years, macaques have been used to test several recombinant flavivirus vaccines, including JEV and West Nile virus (Dean et al. 2005; Monath et al. 2000; Raengsakulrach et al. 1999). In another study investigators showed that bonnet macaques immunized with the JEV vaccine were protected against West Nile virus, whereas the West Nile virus immunization only reduced the severity of JEV disease (Goverdhan et al. 1992).

## Rift Valley Fever *(Bunyaviridae)*

This mosquito-borne tropical disease virus causes major morbidity and mortality in livestock and humans in sub-Saharan Africa. Rhesus macaques are quite susceptible to experimental infection, and about 20% develop a severe hemorrhagic disease (Peters et al. 1988). They have been used to show the beneficial effects of antiviral drugs and alpha interferon treatment in protection against viremia, hemorrhage, and liver damage soon after infection (Cosgriff et al. 1989; Morrill et al. 1989; Peters et al. 1986). Both formalin-killed and mutagen-attenuated vaccines showed partial protection against challenge infection and disease in rhesus monkeys (Morrill and Peters 2003). This animal model is also suitable for developing both new methods of rapid diagnosis and therapies for the disseminated intravascular coagulation (DIC) and hemorrhage that occur in the severe disease.

## Arenaviruses/Lassa Fever and Lymphocytic Choriomeningitis (LCM) Virus *(Arenaviridae)*

Among the numerous arenaviruses, only four are known to cause disease in humans; of these, infection with LCM virus (LCMV) and Lassa virus has been modeled in macaques. LCM virus, acquired from rodents, originated in the Old World but is now worldwide in distribution. About 5% of common house mice (*Mus musculus*) carry LCMV asymptomatically and pet hamsters can become infected through contact with wild mice. Human infection may be asymptomatic or result in a mild febrile illness or acute meningitis, especially with laboratory exposure to guinea pig–passaged LCMV. Congenital infection can cause hydrocephalus and fetal death. Person-to-person transmission has not been reported. In contrast, Lassa virus is localized to West Africa, also acquired from rodents, and capable of causing severe, often fatal, disease in a minority of infected humans. Lassa fever virus can spread between humans and is manifested by hepatitis, diffuse hemorrhages, and CNS damage.

Experimental infection of rhesus monkeys with LCM virus, given intravenously, results in uniformly fatal hemorrhagic fever with encephalopathy (Walker et al. 1982), whereas virus given intragastrically induces a spectrum of clinical outcomes characteristic of Lassa virus infection in humans (Lukashevich et al. 2002). Macaques infected by the intragastric route were protected from lethal disease when challenged later by the intravenous route; this protection correlated best with strong cell-mediated immunity (Rodas et al. 2004). In the last 5 years research has established the LCMV infection of macaques as a surrogate for Lassa virus infection of humans (Djavani et al. 2007). The transcriptome of macaques experimentally infected with LCM virus showed a weak inflammatory response, upregulation of IL-6 expression, evidence of hepatocyte proliferation, and blood changes indicative of major alterations in eicosanoid, immune response, and hormone response pathways (Lukashevich et al. 2003). Research in the early 1980s showed that rhesus monkeys were also susceptible to lethal infection with Lassa virus and that ribavirin treatment and immune plasma were beneficial (Jahrling et al. 1984). These studies showed that shock in the macaque model of Lassa fever is due to biochemical dysfunction of platelets and endothelial cells, which leads to leakage of plasma and hemorrhage (Fisher-Hoch et al. 1987).

Passive antibody therapy, alone or combined with ribavirin, was effective in cynomolgus macaques against infection with Lassa virus (Jahrling and Peters 1984). In 1989, it was reported that rhesus monkeys were protected from fatal Lassa fever by vaccination with a recombinant vaccinia virus containing the Lassa virus glycoprotein (Fisher-Hoch et al. 1989). Further work with macaques has confirmed the efficacy and safety of this vaccine and established suitability for evaluation in humans (Fisher-Hoch et al. 2000). Researchers recently reported a new and very effective vaccine for prevention of experimental Lassa fever in macaques by immunizing with vesicular stomatitis virus as a carrier for the genetic material of Lassa virus (Geisbert et al. 2005).

## Leprosy *(Mycobacterium leprae)*

Naturally occurring leprosy has been documented in chimpanzees, sooty mangabeys, and wild-caught cynomolgus macaques (Valverde et al. 1998). Experimental infection of

rhesus macaques with *M. leprae* caused clinical leprosy in about 50% of them (Gormus et al. 1998; Wolf et al. 1985). Coinfection with SIV increased susceptibility with impaired response to *M. leprae* antigens, probably because of a loss of $CD4^+$ T cells. BCG vaccination protected rhesus monkeys from experimental leprosy (Gormus et al. 2002). Experimental attempts to transmit *M. leprae* from sooty mangabeys to rhesus macaques in the early 1980s led to the inadvertent transmission of SIV and the induction of SAIDS (Murphey-Corb et al. 1986).

## Buruli Ulcer *(Mycobacterium ulcerans)*

Buruli ulcer, a so-called neglected tropical disease (Hotez et al. 2007), is caused by *Mycobacterium ulcerans* and presents as disfiguring skin ulcers. Together with tuberculosis and leprosy, this mycobacterial disease has become a major health problem in over 30 countries, particularly in central Africa. *M. ulcerans* was first identified in the environment in the 1990s using PCR amplification methods on aquatic insects obtained from endemic areas of Africa. Thus, transmission may occur by biting water bugs of the insect order *Hemiptera* (Johnson et al. 2005). In southeastern Australia, a recent outbreak of Buruli ulcer was probably transmitted by mosquitoes (Johnson et al. 2007). No specific vaccine is available, but cross-protective efficacy against *M. ulcerans* experimental infection has been achieved in mice by vaccination with either BCG or plasmid DNA encoding antigen 85 (Ag85A) of *M. tuberculosis* (Tanghe et al. 2001). However, the lack of an experimental animal model that replicates the spectrum of human disease features, in particular the extensive ulceration, prompted a study on the intradermal inoculation of a cynomolgus monkey with *M. ulcerans* (Walsh et al. 2007). The inoculation sites developed ulcers within 2 to 4 weeks with the size and rate of progression proportional to the number of organisms delivered. The macaque may thus provide a valuable model for further vaccine development against *M. ulcerans*.

## Typhus *(Rickettsiae)*

Louse-borne *rickettsiae* (*R. prowazekii* and *R. tsutsugamushi*, the causes of epidemic typhus and scrub typhus, respectively) have affected the course of human history because of epidemics in armies and other crowded populations with poor hygiene. A live attenuated vaccine against *R. prowazekii* has been developed, but its use in humans is accompanied by a substantial incidence of side effects, including a mild form of typhus. Cynomolgus macaques are susceptible to experimental epidemic typhus infection (Gonder et al. 1980), and have served as a model for the development of a scrub typhus vaccine made from either the recombinant outer membrane protein (Chattopadhyay et al. 2005) or its DNA (Ni et al. 2005). Infected macaques develop an *R. tsutsugamushi* antigen-specific cell-mediated immune response (MacMillan et al. 1985). The vaccine made from the outer membrane protein of *R. tsutsugamushi* induced humoral and cellular immune responses but was not as effective as an attenuated live vaccine in preventing infection in macaques; however, this vaccine was able to reduce inflammation at the site of inoculation (Chattopadhyay et al. 2005).

## Malaria *(Plasmodia)*

Considering that the worldwide incidence of malaria is over 300 million clinical cases, with 1.3 million deaths annually, the need for protective measures, including vaccines, remains imperative. Increasing drug resistance among malarial parasites adds to the difficulty of malaria control. Of the four species of such parasites that infect humans, *P. falciparum*, of avian origin, causes most deaths in Africa, and *P. vivax*, of macaque origin, accounts for more than 50% of infections outside Africa and 10% of those in Africa (Escalante et al. 1995, 2005). Macaques are susceptible to experimental infection with the sporozoites of *P. falciparum* and *P. vivax* as well as those of about 10 related indigenous plasmodium species (e.g., *P. cynomolgi, P. fragile, P. coatneyi*) (Kawai et al. 2003). Both natural and experimental infections can cause clinical malaria, and various antimalarial drugs successfully eliminate the parasitemia (Puri and Dutta 2005; Wengelnik et al. 2002). Experimental studies of pathogenesis or vaccinology use *P. falciparum, P. vivax*, or the indigenous macaque *Plasmodium* species. In 2002 researchers published the complete genome sequence of *Anopheles gambiae*, the primary mosquito vector of malaria in Africa (Gardner et al. 2002).

Three general types of malarial vaccines are in research and development: (1) those that target the circumsporozoite (CS) protein (expressed on the extracellular sporozoite and the intracellular hepatic stage of the parasite) to induce sterile immunity; (2) those that target the blood-stage merozoites to reduce disease burden; and (3) those that target zygote development in the mosquito host to block transmission. Most vaccine research has focused on blocking the initial infection, using irradiated killed sporozoites, CS surface proteins recombined with hepatitis B virus surface (or core) antigen, adenovirus recombinants, or naked DNA in various combinations and protocols (Heppner et al. 2005; Walsh et al. 2006; Wu et al. 2006). Most experiments have used mice or humans, but macaques have also been used for immunogenicity, efficacy, and safety testing as well as in vaccine tests aimed at recombinant surface proteins of the merozoite or zygote stages (Coban et al. 2004; Dutta et al. 2005). Each of these three vaccine approaches has shown a degree of efficacy in mice, macaques, and humans, but not of a sufficient magnitude to support widespread clinical application. Recently, the transcriptional profile of host gene expression in whole white blood cells was tested in a rhesus monkey model of human *P. vivax* malaria. The results indicate a downregulation of genes involved in RNA

processing during the initial liver stage of infection and an upregulation of defense response genes (Ylostalo et al. 2005). The macaque model may yet direct research efforts toward better vaccines and novel targeted therapies.

## Schistosomiasis *(Schistosomia mansoni)*

Several *Schistosomia* species (parasitic trematodes) infect about 250 million people in tropical and subtropical countries. Although mortality is low, schistosomiasis can be very debilitating in about 5% of infected individuals. Snails are the intermediate host for *cercariae*, which infect mammals by penetrating the skin and migrating hematogenously to many organs where the worms and their eggs cause inflammation. *S. mansoni* primarily affects the liver. Interestingly, *S. haematobium* causes squamous cell carcinoma of the bladder in Egypt.

Macaques are susceptible to experimental infection with *S. mansoni* (Maddison et al. 1979; Meisenhelder and Thompson 1963). Juvenile rhesus monkeys appear most susceptible to infection, perhaps because of a reduced type 2 cytokine response (Fallon et al. 2003). Rhesus monkeys have proven very useful for understanding the immunology of schistosomiasis because they develop a solid immunity to reinfection. Vaccination with a surface antigen gave partial protection against challenge in cynomolgus monkeys (Smith and Clegg 1985). In rhesus monkeys chronically infected with SHIV clade C, coinfection with *S. mansoni* reactivated viral replication and increased the expression of Th2-associated cytokine response (Ayash-Rashkovsky et al. 2007; Chenine et al. 2005). These findings suggest that parasite-infected humans may be more susceptible to HIV-1 infection.

## Chagas Disease *(Trypanosoma cruzi)*

Chagas disease occurs primarily in rural areas of South America and, interestingly, is absent in the Old World. Its pathogenic agent is a flagellate protozoan named *T. cruzi*, which is related to the agent of African sleeping sickness. The protozoa are transmitted to humans by the bites of triatomids ("kissing bugs"). A large natural reservoir for the organisms includes other infected humans, domestic animals, and wild animals such as rodents and monkeys. Infection has been described in both free-ranging and captive macaques (Kasa et al. 1977; Olson et al. 1986; Pung et al. 1998). Charles Darwin may have acquired this disease (i.e., cardiomyopathy) (Morris et al. 1990) from the bite of what he called "a great black bug of the Pampas" (a *Reduvius* vinchuca) (Darwin 1839). The acute phase exhibits a skin nodule at the site of the bite (usually on the head) and local lymphadenopathy. Chronic disease affects the nervous system, digestive system, and heart, and causes about 50,000 deaths annually, mostly from heart failure due to associated cardiomyopathy.

Both acute and chronic Chagas disease models have been established in rhesus (Bonecini-Almeida Mda et al. 1990; Carvalho et al. 2003). The acute phase includes parasitemia, circulating specific IgM and IgG antibodies, and hematologic alterations. Chronic disease occurs 15 to 19 years after infection, with severe cardiac damage. Scientists recently reported that SIV-induced immunosupression reactivated a previously unnoticed chronic infection of Chagas disease in a rhesus monkey (Kunz et al. 2002).

## African Sleeping Sickness *(Trypanosoma brucei* and *T.b. rhodesiense)*

African sleeping sickness is a major concern in 36 African countries, particularly in East and central/West Africa, where it is caused by subspecies of the protozoan *Trypanosoma brucei*: *T.b. gambiense* and *T.b. rhodesiense*, respectively. The disease is uniformly fatal if untreated. The eastern version is a zoonosis, with cattle as the main reservoir. Humans are the major reservoir for the western version, which is less virulent.

Rhesus macaques infected with *T.b. rhodesiense* developed a glomerulonephritis that was associated with activation of the alternate complement pathway (Nagle et al. 1974) and development of antibodies to nucleic acid (Lindsley et al. 1974). Stump-tailed macaques experimentally infected with *T.b. rhodesiense* showed neurologic signs (Raether and Seidenath 1976). There is no vaccine, but early treatment with a trypanocidal drug (diamidine) was effective in eliminating parasites from the blood.

## Ascariasis

Ascariasis has a global prevalence of approximately 800 million and is considered a major neglected tropical disease (Hotez et al. 2007). Fatal *Baylisascaris* larva migrans acquired from raccoon feces occurred spontaneously in a colony of Japanese macaques (Sato et al. 2005). Stump-tailed macaques experimentally infected with the nematode *Ascaris suum* have served as a model for allergic bronchitis, in particular because of the release of histamine, leukotrienes, and prostaglandins from bronchoalveolar mast cells (Wells et al. 1986).

## Lymphatic Filariasis

Lymphatic filariasis causes massive lymphedema or elephantiasis in approximately 25 million people throughout the tropics (Hotez et al. 2007). To investigate whether *Wolbachia* symbiotic bacteria in filarial nematodes contributed to the disease progression, researchers established a rhesus monkey model of filariasis and found that monkeys infected with the filarial *Brugia malayi* developed antibodies specific for *Wolbachia* surface protein as well as antifilarial

antibodies associated with lymphedema development (Punkosdy et al. 2001). These findings suggest that *Wolbachia* may be critical to the pathogenesis of elephantiasis. The draft genome of *B. malayi* predicts about 11,500 proteins whose analysis will provide insight into the molecular basis of the mutual relationship with *Wolbachia* endosymbiont (Ghedin et al. 2007). This information will serve as a basis for rational drug design against filariasis.

### Onchocerciasis

Onchocerciasis, or "river blindness," has been a major cause of blindness because of the associated chorioretinitis elicited by the *Onchocerca volvulus* microfilariae. Lesions resembling those of the human disease were induced by the injection of live *O. volvulus* microfilariae isolated from infected humans into the eyes of cynomolgus monkeys (Donnelly et al. 1986; Semba et al. 1991). In recent years, however, river blindness has been nearly eliminated by treatment with the antihelminthic drug ivermectin, thus negating the need for this animal model.

## Sexually Transmitted Diseases

This section focuses on bacterial and viral diseases that are sexually transmitted. (We discuss certain sexually transmitted pathogens, such as HIV and herpes simplex virus, elsewhere in this review; we refer readers to the sections on Global Diseases and Childhood Diseases, respectively.)

### Papillomavirus *(Papillomaviridae)*

Human papillomaviruses (HPV) are the cause of cervical cancer in humans and therefore the basis of a recently released vaccine against cervical cancer. About 50% of rhesus macaques from several different primate facilities are infected with indigenous papillomaviruses (Ostrow et al. 1995). PCR analysis of genital samples from female cynomolgus and rhesus monkeys also showed that they are natural hosts of genital papillomaviruses, which are genetically related to and have a genetic diversity similar to that of the HPVs (Chan et al. 1997). Cervical and vaginal epithelial neoplasms, associated with papillomavirus, were present in 5% of captive female cynomolgus macaques (Wood et al. 2004). Four viral types were associated with cervical intraepithelial neoplasia (CIN), which resembles human CIN. Transfer of cervical cells positive for one of these high-risk papillomavirus types, which are closely related to the highly oncogenic HPV16, to uninfected monkeys resulted in new cervical infections and the development of abnormal cytology (Wood et al. 2007). CIN and squamous cell carcinoma of the cervix resulted from sexual transmission of papillomavirus in a rhesus monkey (Ostrow et al. 1990). The macaque papillomavirus model should prove valuable for further research into the pathogenesis, therapy, and prevention of cervical cancer.

### Syphilis *(Treponema pallidum)*

After intrathecal inoculation with *T. pallidum*, rhesus macaques became infected but cleared the infection from the central nervous system (CNS), as happens in most humans with early syphilis (Marra et al. 1998). Local production of gamma interferon appeared to contribute to this process. Following intradermal inoculation, infected macaques developed primary and secondary syphilitic lesions and, in the presence of SIV coinfection, exhibited a delayed clearance of *T. pallidum* from the site of infection and an impaired humoral immune response to this agent (Marra et al. 1992).

### Chlamydia *(Chlamydia trachomatis)*

Chlamydia is the most common sexually transmitted disease in the United States, with almost 1 million cases reported annually to the Centers for Disease Control and Prevention (CDC). The causative microbe (*Chlamydia trachomatis*) is a gram-negative, obligate intracellular bacterium that passes from an infected mother to her baby in the birth canal and causes trachoma, a disease characterized by conjunctivitis leading to blindness in about half of the infants. Chlamydia is called a "silent disease" because most infected women and men have no symptoms. If untreated, infection causes pelvic inflammatory disease, which may lead to infertility or ectopic pregnancy. This agent also enhances the likelihood of infection with HIV. Now sequenced, the genome contains over 1 million base pairs coding for 894 open reading frames, including numerous potential virulence-associated proteins (Stephens et al. 1998).

Macaques have served as useful models for each aspect of *C. trachomatis* infection. Intraocular inoculation produces conjunctivitis and trachoma (Taylor et al. 1981), which are now either completely preventable with an oral vaccine of attenuated or killed bacteria (Taylor et al. 1987) or reduced in severity with a vaccine made from the major outer membrane protein (Campos et al. 1995). Vaccine protection appeared to correlate with induction of a cell-mediated immune response. Intrarectal or intratubal inoculation of macaques causes proctitis (Quinn et al. 1986) or salpigitis (Patton 1985), respectively, which have proven useful for understanding pathogenesis (Van Voorhis et al. 1997) and evaluation of systemic antibiotics (e.g., azithromycin) (Patton et al. 2005) and topical microbicides (Patton et al. 2006). Researchers have found that antibodies to a 60kDa *C. trachomatis* heat shock protein (Peeling et al. 1999) and two proteins including the heat shock protein 60, localized to the bacterial inclusion bodies (Bannantine and Rockey 1999), are markers of persistent infection and a delayed-type hypersensitivity reaction (Lichtenwalner et al. 2004).

## Newly Emergent Diseases

Certain infectious diseases of viral and bacterial etiology have exhibited a growing prevalence and distribution in the last 25 years for several reasons, including increased human exposure to animals and insects through expanding trade and travel. Growth of the human population, the AIDS pandemic, and the changing ecology are also significantly contributing to the emergence of infectious pathogens.

### West Nile Virus (WNV) *(Flaviviridae)*

West Nile virus (WNV), spread by mosquitoes, first appeared in the northeastern United States in 1998 and has gradually spread across the North American continent, causing approximately 20,000 reported human cases. The virus also infects birds and horses, often lethally, as well as macaques (Cohen et al. 2007; Ratterree et al. 2003), which have milder symptoms. A live attenuated recombinant vaccine has been constructed from an infectious clone of yellow fever virus (17D), in which the envelope genes of WNV replace those of 17D (Arroyo et al. 2004). Preclinical immunogenicity and efficacy tests in macaques showed that this vaccine induced strong WNV-specific neutralizing antibodies, T cell responses, and was efficacious and safe (Monath et al. 2006). The vaccine (ChimeriVax-WN02) is licensed for use in horses but not yet in humans.

### Hantaviruses *(Bunyaviridae)*

Hantaviruses, maintained in rodent reservoirs, cause two severe human diseases: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). Both diseases feature a vascular-leak syndrome with hemorrhagic manifestation and are often fatal. Approximately 20,000 cases are reported annually. Experimental hantavirus infection (Puumala, Andes, and Prospect Hill strains) of cynomolgus macaques results in a relatively mild form of HFRS (Groen et al. 1995; McElroy et al. 2002). Cytokine induction and viral RNA were monitored in the blood of these animals (Klingstrom et al. 2002). Passive transfer of neutralizing antibodies from rhesus macaques immunized with the HPS (Andes virus) DNA vaccine strongly protected highly susceptible hamsters against experimental infection with the Andes virus (Hooper et al. 2006). The DNA vaccine–induced antibodies also neutralized viruses that cause both HFRS and HPS (Custer et al. 2003).

### Severe Acute Respiratory Syndrome/SARS Coronavirus *(Coronaviridae)*

The emergence of SARS in 2002-2003 affected global health and caused major economic disruption. Macaques have been injected by various routes with the causative coronavirus (SARS-CoV), including an infectious molecular clone. Initial transmission of SARS-CoV to cynomolgus macaques helped to prove that this virus is the primary cause of SARS (Kuiken et al. 2003). A mild form of this disease was induced with minimal clinical symptoms, rapid clearance of virus, and resolution of the pneumonia. However, parameters of infection were sufficiently apparent that it was possible to show some benefit from therapy with siRNA, given either prophylactically or therapeutically (Li et al. 2005a). Pegylated alpha interferon also had a beneficial effect against SARS-CoV infection in macaques (Haagmans et al. 2004). An inactivated SARS-CoV vaccine (Zhou et al. 2005) and adenoviral (Gao et al. 2003) or vaccinia Ankara virus recombinant SARS-CoV (Chen et al. 2005) vaccines showed promising results against the homologous coronaviruses in macaques.

### Ehrlichiosis

*Ehrlichiae*, rickettsial agents classified in the family *Ehrlichiacae*, are obligate intracellular bacteria that share the tick vectors of other infectious pathogens such as *Borrelia burgdorferi*, the agent of Lyme disease. Rodents, particularly white-footed mice, and white-tailed deer are implicated as natural reservoirs for granulocytic ehrlichia. Human granulocytic ehrlichiosis was first described in 1994 and is now considered an emerging human infectious disease. Investigators have described a simian model in which rhesus macaques developed classical granulocytic ehrlichiosis after intravenous inoculation with horse blood infected with *Ehrlichia* from a human fatality (Foley et al. 1999). This animal model may be important for further study of the diagnosis, management and intervention, and pathogenesis of human granulocytic ehrlichiosis.

### Lyme Disease *(Borrelia burgdorferi)*

Lyme disease (*Borreliosis*) is a spirochete infection (*B. burgdorferi*) transmitted by the bite of a deer tick. An initial flu-like syndrome with rash and arthritis usually responds to treatment with antibiotics, especially if given early in the course of the illness. However, some patients that receive antibiotics develop a poorly understood chronic syndrome that features musculoskeletal, neurologic, psychiatric, and cardiac manifestations. A multiantigenic vaccine (Pachner et al. 1999) and an outer surface protein vaccine (Philipp et al. 1997) protected macaques from Lyme neuroborreliosis. A vaccine (Lymerix) against *B. burgdorferi* became available for humans in 1988 but was taken off the market in 1992 because of safety concerns (fear that it might be triggering an autoimmune reaction) and poor sales.

To better understand the pathogenesis of the chronic Lyme borreliosis syndrome, investigators have inoculated normal and immunosuppressed rhesus macaques with the causative spirochete and observed the animals for several

years. Different species of *B. burgdorferi* induced different patterns of infection, immunity, and inflammation (Pachner et al. 2004). The transcriptome of the spirochete in the central nervous system of macaques showed contrasting profiles depending on steroid treatment (Narasimhan et al. 2003). Researchers detected the spirochete, along with accompanying inflammation, months to years after inoculation, in the meninges, heart, and connective tissue elsewhere in the body, particularly in immunosuppressed monkeys (Bai et al. 2004; Cadavid et al. 2004, 2003; Philipp et al. 1993; Roberts et al. 1998). Increased expression of B lymphocyte (but not proinflammatory) cytokines was detected in the muscle tissue of chronically infected rhesus monkeys (Pachner et al. 2002).

### Bartonellosis

*Bartonella* species are arthropod vector–transmitted, bloodborne, intracellular bacteria that induce prolonged infection in the host. Several cell types, in particular erythrocytes, can harbor *Bartonella*. These agents are ubiquitous in nature with a substantial reservoir of persistent infection in domestic and wild animals, which can serve as a source of inadvertent human infection (Breitschwerdt and Kordick 2000). Infections in animals and humans may be asymptomatic or associated with chronic inflammatory diseases. Bacteremia with this agent is widespread in domestic and feral cats (Chomel et al. 1996), and zoonotic spread of *B. henselae* causes cat scratch disease. Other human diseases caused by *Bartonella* species are trench fever (*B. quintana*), Oroya fever (*B. bacilliformis*), bacillary angiomatosis (*B. quintana*), and bacterial endocarditis (*B. henselae*, *B. quintana*).

These species appear to be reemerging, often with few symptoms, as a persistent bacteremia in immunosuppressed and homeless individuals, particularly those infected with HIV-1 (Foucault et al. 2006; Koehler et al. 2003). There are reports of natural infection with *B. quintana* in captive-bred cynomolgus macaques (O'Rourke et al. 2005) and of its transmission to rhesus macaques (Mooser and Weyer 1953). In a 1926 study, *B. bacilliformis*, the agent of Oroya fever, was experimentally inoculated into young rhesus macaques in which it induced the same symptoms as observed in human cases of Oroya fever (Noguchi and Battistini 1926). A recently developed macaque model for *B. quintana* infection has revealed a relationship between changes in the outer membrane protein and different virulence properties during bloodstream infection (Zhang et al. 2004).

### Melioidosis *(Burkholderia pseudomallei)*

Melioidosis, a chronic infectious disease caused by the bacterium *Burkholderia pseudomallei*, is an emerging disease with a serious impact on animals and humans. In the past century, this agent has spread from East Asia to many previously unaffected parts of the world. Infection in humans and animals occurs by inoculation, ingestion, or inhalation of the organism, which is ubiquitous in the environment, particularly in soil. Many species of domestic farm and wild animals as well as nonhuman primates are commonly infected (in horses the disease is called glanders). A recent review summarizes the current studies of melioidosis outbreaks in animals, including nonhuman primates (Sprague and Neubauer 2004). In macaques, disease may include severe bronchopneumonia, multiple abscesses, and osteomyelitis. Detection of *B. pseudomallei* infection is a major challenge because of poor induction of antibodies. According to one reference (Hubbert 1969), a cynomolgus macaque was experimentally infected, but there has been no further research to develop the macaque model of this emerging pathogen.

## Potential Bioterrorism Agents

Several diseases with high morbidity and mortality, of viral or bacterial origin, pose a theoretical or real risk of exposure to large populations from inhalation or contaminated foodstuffs.

### Smallpox/Variola Virus *(Poxviridae)*

Although eradicated from the world in 1980 by vaccinia virus vaccination, smallpox virus retrieved from frozen stocks poses a significant threat as an agent of bioterrorism. Therefore, improved drugs and perhaps vaccines are urgently needed. With this purpose in mind, investigators recently exposed cynomolgus macaques to several strains of variola virus through aerosol and intravenous routes (Jahrling et al. 2004). Depending on the dose, the viruses induced either uniformly fatal disease resembling human smallpox or less severe systemic disease with lower mortality. High virus levels led to multisystem failure, depletion of T cells, and disseminated intravascular coagulation. cDNA microarrays of host gene expression in circulating white blood cells during infection showed upregulation of cytokines, including IL-6 and alpha interferon, which contributed to a cytokine storm (previously called toxemia) (Rubins et al. 2004).

### Monkeypox *(Poxviridae)*

Monkeypox virus (MPXV) causes a natural and experimental disease in cynomolgus macaques similar to human smallpox (Zaucha et al. 2001), and so this animal model can help to increase the effectiveness of antiviral drugs and candidate novel smallpox vaccines. Sporadic outbreaks of monkeypox also occur in humans in Africa and in the United States and thus are a public health concern. The reservoir is squirrels and other small mammals, and monkeys and humans are accidental hosts (Hutin et al. 2001;

Sale et al. 2006). In 2003, an outbreak of monkeypox in humans in the central United States was caused by contact with pet prairie dogs and other mammals that had been shipped from Gabon to Texas and then transported to pet distributors in the Chicago area (Di Giulio and Eckburg 2004). Vaccinia virus immunization (smallpox vaccine and modified vaccinia virus Ankara) affords long-lasting protection of macaques against monkeypox virus challenge (Earl et al. 2004; Heraud et al. 2006; Stittelaar et al. 2005). Vaccine protection is correlated with the induction of neutralizing antibody against monkeypox virus (Edghill-Smith et al. 2005b), but the smallpox vaccine does not protect macaques with SAIDS against a lethal monkeypox challenge (Edghill-Smith et al. 2005a). A smallpox DNA vaccine, consisting of four vaccinia virus genes, and a modified vaccinia Ankara DNA vaccine also protected macaques against otherwise lethal challenge with monkeypox virus (Hooper et al. 2004; Nigam et al. 2007). Treatment of macaques with antiviral compounds such as cidofovir, 24 hours after lethal intratracheal MPXV infection, was more effective at reducing mortality than vaccinia virus vaccination (Stittelaar et al. 2006).

## Rabies *(Rhabdoviridae)*

More than 40,000 people worldwide, mostly in developing countries, die annually from rabies. Because of the expense of the current vaccines derived from cell cultures and problems with stability, efforts are under way to develop a subunit or DNA vaccine. Macaques immunized with the rabies ribonucleoprotein were protected against challenge infection from a lethal dose of rabies virus (Tollis et al. 1991). Cynomolgus macaques immunized with DNA encoding the viral glycoprotein survived virus challenge, whereas nonvaccinated controls developed fatal rabies (Lodmell et al. 1998). Protection with both vaccines correlated with the induction of neutralizing antibodies. Very early (<6 hrs) postexposure treatment with interferon or a potent interferon inducer also significantly reduced mortality (Baer et al. 1977; Weinmann et al. 1979). Early (<6 days) postexposure DNA vaccination, given together with human rabies immunoglobulin, also reduced mortality.

## Marburg and Ebola Viruses *(Filoviridae)*

Marburg and Ebola viruses cause epidemics of hemorrhagic fever and are among the most virulent viruses that infect humans. The reservoir hosts in Africa are not known, although small mammals (possibly rodents or bats) are suspected. Wild nonhuman primates, including macaques, are, like humans, accidental hosts. These viruses are usually transmitted to humans through contact with an infected animal. A summary of Marburg and Ebola virus infections in laboratory NHPs is available (Schou and Hansen 2000). A total of 23 Marburg and Ebola virus outbreaks have been reported among humans and monkeys since the first documented outbreak in Marburg, Germany, in 1967. Most of the 1,100 human cases, with 800 deaths, occurred in Africa after contact with infected patients. In 1989, Ebola virus and simian hemorrhagic fever virus were isolated from a cynomolgus macaque imported to the United States from the Philippines. Human animal handlers became infected but did not get sick (Dalgard et al. 1992). In recent years, there have been several outbreaks of human and animal Ebola in Gabon and Republic of Congo. The epidemics were associated with different viral strains and high mortality of gorillas, chimpanzees, and duikers, and resulted from the handling of infected animal carcasses (Leroy et al. 2004).

Rhesus and cynomolgus macaques are highly susceptible to lethal infection with either Marburg or Ebola virus (Geisbert et al. 2003b). Ebola virus–infected monkeys have been studied to gain insight into the pathogenic mechanisms that lead to the profound lymphopenia, disseminated intravascular coagulation, and hemorrhagic and septic shock that are characteristic of filovirus infection of humans. The coagulation abnormalities are most likely triggered by immune-mediated mechanisms rather than by direct damage to endothelial cells. Lymphopenia is attributed to infection of dendritic cells, blocking their maturation and thus inhibiting activation of lymphocytes and triggering bystander apoptosis (Reed et al. 2004).

Release of tissue factor from monocyte/macrophages is a key event in triggering disseminated intravascular coagulation (DIC) in Ebola virus–infected macaques, and treatment with recombinant inhibitor of tissue factor helps to prevent DIC and prolong survival (Geisbert et al. 2003a). By contrast, treatment with recombinant alpha interferon or immunoglobulin has little benefit; neutralizing antibodies fail to protect or alter the course of Ebola virus infection in the monkeys (Oswald et al. 2007). Live attenuated recombinant vaccines protected macaques almost 100% against the Ebola and Marburg viruses. One of the vaccines was based on replication-competent vesicular stomatitis virus (VSV) expressing the envelope glycoprotein of the Marburg virus (Hevey et al. 1998). The vaccine induced cross protection against two heterologous strains of Marburg virus (Daddario-DiCaprio et al. 2006a) and also gave strong protection against lethal Marburg virus challenge if given within 30 minutes after virus inoculation (Daddario-DiCaprio et al. 2006b). Similar protection against both Ebola and Marburg virus was achieved using Venezuelan equine encephalitis (VEE) virus as a vector to express the glycoprotein and nucleoprotein of Ebola virus (Geisbert et al. 2002). A recombinant adenovirus carrying the Ebola virus glycoprotein was also protective. Most remarkably, macaques that received a combination DNA vaccine for Marburg virus, Ebola virus, VEE virus, and *B. anthracis* developed protective immunity against each agent (Riemenschneider et al. 2003). A recent report describes the protection of macaques against Ebola virus by topical immunization through the respiratory tract with a human

parainfluenza virus type 3 vaccine vector used to express the Ebola virus surface glycoprotein (Bukreyev et al. 2007).

### Anthrax *(Bacillus anthracis)*

Aerosolized *Bacillus anthracis* spores are considered the foremost infectious biological threat in the United States. It is therefore important to prepare and stockpile an anthrax vaccine. Because macaques are quite susceptible to experimental *B. anthracis* inhalation-induced disease, they represent an excellent model for testing vaccines and drugs (Fritz et al. 1995; Vasconcelos et al. 2003).

Studies 50 years ago showed that it was possible to protect rhesus macaques against inhalation challenge with *B. anthracis* spores by a cell-free vaccine containing alum-precipitated *B. anthracis* toxin-derived protective antigen (PA) (Wright et al. 1954). This vaccine (AVA) was used to immunize individuals at high risk of occupational exposure. More recently, investigators have evaluated vaccines composed of a recombinant form of the PA in rhesus macaques (Hepler et al. 2006; Phipps et al. 2004; Williamson et al. 2005); they found that the animals were fully protected against a lethal dose of aerosolized bacteria and that protection correlated significantly with neutralizing antibodies, which also conferred passive immunity to *B. anthracis* challenge of naïve macaques. A DNA vaccine for anthrax is also efficacious in macaques (Riemenschneider et al. 2003). Transcriptional profiles of about 200 genes in PA-stimulated peripheral blood mononuclear cells (PBMC) after anthrax vaccine gave a response representative of innate and adaptive immunity (Rogers et al. 2006). These studies predict that the PA-based vaccines should be efficacious in humans. This animal model has also been used for testing antibodies against inhalation anthrax given either alone or together with the vaccine (Kao et al. 2006; Kelly et al. 1992).

### Tularemia *(Francisella tularensis)*

*Francisella tularensis* is a zoonotic bacterium widespread in North America as well as parts of Europe and Asia. Squirrels and rabbits are the main reservoir and transmission to humans occurs by deerflies, mosquitoes, and ticks, or from the bite of an infected vertebrate. Tularemia is serious and often fatal. Outbreaks of naturally acquired tularemia have also been described in nonhuman primates, including macaques (Matz-Rensing et al. 2007). Rhesus macaques exposed to aerosol particles of *F. tularensis* develop the full-blown pneumonic form of tularemia, which is often fatal (Schricker et al. 1972). This macaque model was used 40 years ago to develop an efficacious live attenuated tularemia vaccine (Tulis et al. 1970). Long-lasting vaccine protection correlated with the presence of strong cell-mediated immunity against *F. tularensis*.

### Plague *(Yersinia pestis)*

Spread by rat fleas, this macrophage-tropic coccobacillus has been one of the great epidemic scourges of humanity, but the disease has largely disappeared in modern times due mostly to improved rodent control. However, direct human-to-human aerosol spread of *Yersinia pestis* presents a current bioterrorism threat and has prompted efforts to develop a plague vaccine. A case of chronic pneumonic plague in a rhesus monkey has been reported (Ransom and Krueger 1954). A live attenuated *Y. pestis* vaccine proved to be effective in macaques (Meyer et al. 1974). Recently, vaccination of cynomolgus macaques with flagellin, a toll-like receptor agonist and a fusion of the F1 and V antigens of *Y. pestis*, induced a strong antigen-specific IgG antibody response and was protective against lethal respiratory challenge with *Y. pestis* (Honko et al. 2006; Williamson et al. 2007). Immunization of cynomolgus macaques with recombinant *Y. pestis* F1 and V antigens made in plant vector systems provided complete protection against lethal challenge with *Y. pestis* (Mett et al. 2007).

### Brucellosis *(Brucella)*

*Brucella*, a small, non-spore-forming gram-negative coccobacillus, is a highly infectious biological warfare threat agent that causes severe human illness. This bacterium is a facultative intracellular parasite of macrophages. After aerosol exposure, rhesus macaques develop a disease similar to that of humans (Mense et al. 2004; Percy et al. 1972). Macaques immunized with a live attenuated strain of *B. melitensis*, after priming with purified antigen, were solidly protected from aerosol challenge with virulent *Brucella* (Chen and Elberg 1976). Protection correlated with induction of antibody to the bacterial outer membrane lipopolysaccharide and of a Th1 cytokine response.

## Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies are infectious prion diseases that affect the central nervous system and cause dementia. In the search for occult viruses, researchers in the 1960s and 1970s inoculated many nonhuman primates with CNS tissue preparations from humans that had unexplained neurodegenerative diseases. These experiments involved many macaques and sooty mangabeys housed at the California National Primate Research Center.[2] Blind

[2] Researchers subsequently realized that an unforeseen complication of the early experiments was the probable inadvertent transmission of SIV from healthy African-origin sooty mangabey carriers to Asian-origin macaques, a development that led to the discovery of simian AIDS 15 years later (Apetrei et al. 2005; Gardner 1996) (see the section on AIDS).

passages were carried out in an effort to amplify a putative human virus. Surprisingly, several of the human diseases—for example, kuru, restricted to New Guinea, and Creutzfeldt-Jakob disease (CJD), of worldwide distribution—were transmissible to chimpanzees, gibbon apes, and several species of New World monkeys and macaques (Espana et al. 1975; Gajdusek and Gibbs 1971; Gibbs and Gajdusek 1973; Masters et al. 1976). Each disease featured spongiform noninflammatory pathology in the brain and was similar in this respect to other transmissible spongiform encephalopathies that occur in sheep (scrapie), mink, deer, elk (chronic wasting disease, CWD), and cattle (bovine spongiform encephalopathy, BSE). Spontaneous spongiform encephalopathy has also been observed in a young adult rhesus monkey (Bons et al. 1996). These diseases are caused by abnormally folded protein aggregates, called prions. Other prion-associated spongiform encephalopathies that commonly occur in older humans, such as Alzheimer's disease, are not infectious.

In recent years, cynomolgus macaques have been inoculated with or fed brain homogenates from people with variant CJD or from cattle with BSE, as investigators analyzed the involvement of peripheral organs with the prion proteins (Herzog et al. 2005). The BSE agent readily adapted to macaques and exhibited the same molecular characteristics as the variant CJD agent (Lasmezas et al. 2001). Large amounts of the prion protein were present in lymphoid organs and smaller amounts in the nervous system. Lymphoid organs and blood thus represent a high risk for iatrogenic transmission of the infectious prions. One macaque developed variant CJD-like neurological disease 5 years after oral exposure to the BSE agent (Lasmezas et al. 2005). Prion disease research owes much of its progress to macaques used in the search for unconventional viruses.

## Oncogenic Viruses

Certain herpesviruses and retroviruses establish chronic infection, generally characterized by a latent state in the host. Several of these agents need a cofactor such as immunosuppression in the infected individual to cause cancer. This section includes several simian viruses that are indigenous to macaques and not infectious for humans but that are important models for closely related human diseases.

### Simian T Lymphotropic Virus (STLV) *(Retroviridae)*

Naturally occurring infection with several strains of STLV is highly prevalent in asymptomatic African and Asian nonhuman primates, including both wild macaques and those in primate centers and zoos (Hunsmann et al. 1983; Lowenstine et al. 1986; Miyoshi et al. 1983). The natural history and biology of STLV are very similar to those of human TLV (Watanabe et al. 1985). Both STLV and HTLV are ancient viruses, and HTLV apparently arose from contact with STLV-infected nonhuman primates in the distant past. Recent studies have documented human infection with multiple STLV-1-like viruses among central Africans exposed to monkeys either as house pets or through the bush meat trade (Wolfe et al. 2005); nearly 90% of bush meat was found infected with STLV (Courgnaud et al. 2004). No evidence has been found for the cross-species spread of STLV to primate handlers in the United States.

STLV-infected macaques do not serve as a practical model for HTLV infection because the latent period is long (4 to 5 decades) and the tumor incidence is low (<1%). Unlike HTLV, STLV has not been linked to lymphomas, immunosuppresion, or neurological diseases in macaques. Experimental coinfection of cynomolgus macaques with STLV and SIV showed no influence of STLV on the development of SAIDS (Fultz et al. 1999). Studies using cynomolgus macaques 20 years ago showed that protection against HTLV challenge infection was possible through immunization with recombinant HTLV-1 envelope protein (Nakamura et al. 1987). Cynomolgus macaques were also protected against STLV challenge by vaccination with HTLV *gag* and envelope subunits (Dezzutti et al. 1990). Vaccine protection correlated with the induction of antibodies to the envelope glycoprotein.

Interestingly, STLV infection of captive baboons at two primate facilities, the Sukhumi Primate Center in the Republic of Abkhazia and the Southwest Regional Primate Research Center in San Antonio, Texas, has been linked to a relatively high incidence of lymphoma (Mone et al. 1992; Voevodin et al. 1996). The Sukhumi outbreak of lymphomas has affected more than 300 baboons since 1967, and molecular studies indicate that the causative STLV strain was introduced into the baboons by cross-species transmission from rhesus macaques. Coinfection of these baboons with an EBV-related herpesvirus may be a cofactor in the pathogenesis of lymphoma (Schatzl et al. 1993). This could be a suitable animal model for HTLV-associated lymphomagenesis.

### Simian Type D Retrovirus (SRV) *(Retroviridae)*

Simian type D retrovirus is an indigenous retrovirus of macaques that can cause outbreaks of an immunosuppressive and fatal wasting disease in cohoused animals (Gardner et al. 2004). The prototype virus, Mason-Pfizer monkey virus (MPMV), was discovered in 1970 (Chopra and Mason 1970), but it wasn't until the early 1980s that the virus "reemerged" in macaques at several primate centers (Gardner et al. 1988; Letvin and King 1984). The associated disease was at first called simian AIDS (SAIDS), but this term is now confined to the SIV-induced disease in macaques and an occasional African NHP species (e.g., African green and sooty mangabey monkeys).

SRV differs from SIV both in its pathogenesis and in being more distantly related to HIV (SRV is not a lentivi-

rus). Unlike SIV and HIV, SRV causes a generalized infection of both T and B cells (Maul et al. 1988), is genetically stable, and can be controlled by neutralizing antibodies, whether induced naturally or by vaccines (Kwang et al. 1987; Marx et al. 1986). Many of the same opportunistic pathogens associated with SIV and HIV infection also exist in macaques with SIV infection. Interestingly, SRV-infected macaques are the major source of a Kaposi's sarcoma (KS)–like lesion called retroperitoneal fibromatosis (RF) (see the section on Kaposi's sarcoma). In contrast to SIV, SRV infection is not associated with B cell lymphomas or activation of latent EBV-like virus. Although humans do not harbor a type D retrovirus and are not susceptible to productive infection with SRV, we include it because it is an important model for retrovirus-induced immunosuppression and RF. Additionally, SRV must be eliminated in NHPs used for research, particularly in studies of SIV-induced SAIDS.

### Simian Foamy Viruses (SFV) *(Retroviridae)*

SFVs, members of the spumavirus group, are ubiquitous in macaques and other nonhuman primates in which they cause a persistent latent infection in the absence of any disease (Linial 1999; Weiss 1988). Humans do not harbor any spumaviruses, but they can become infected by contact with SFV carrier monkeys (a putative human foamy virus isolate was probably of chimpanzee origin; Herchenroder et al. 1994). Humans (e.g., animal health workers or African hunters) accidentally infected with SFV remain asymptomatic (Brooks et al. 2002; Engel et al. 2006; Jones-Engel et al. 2005).

### Epstein-Barr Virus (EBV)/ Lymphocryptovirus *(Herpesviridae)*

Macaques harbor a homologue of human EBV whose biology in macaques appears identical to that of EBV in humans (Moghaddam et al. 1997). The complete sequencing of both human EBV and the macaque EBV-related virus shows strong similarities (Rivailler et al. 2002). Like human EBV, the macaque virus generally causes a lifelong, asymptomatic, latent infection. Key aspects of human acute EBV infection are reproducible in the macaque model, including oral transmission, atypical lymphocytosis and lymphadenopathy, and activation of B cells, all features of infectious mononucleosis. Cytotoxic T cell responses are mostly responsible for containing virus replication (Fogg et al. 2006). As seen in humans with AIDS, the macaque EBV-like virus is activated in association with opportunistic B cell lymphomas that occur in the course of SIV-induced simian AIDS or with post-transplant immunosuppression (Habis et al. 2000; Schmidtko et al. 2002). Activated EBV in macaques also causes oral lesions (called hairy cell leukoplakia) that manifest in human AIDS (Kutok et al. 2004). Naïve macaques—whether immunocompetent or immunosuppressed, inoculated with human EBV (Levine et al. 1980) or the rhesus counterpart (Feichtinger et al. 1992; Moghaddam et al. 1997; Rivailler et al. 2004)—do not develop lymphomas in the relatively short observation period of 3 years or less.

### Kaposi's Sarcoma–Associated Herpesvirus *(Herpesviridae)*

Two distinct lineages of rhadinovirus—RV-1, or retroperitoneal fibrosis (RF)–associated herpesvirus (RFHV), and RV-2, or rhesus rhadinovirus (RRV), a more distantly related virus—are related to Kaposi's sarcoma (KS)–associated herpesvirus (KSHV, human herpesvirus 8), the causative virus of KS in humans (Schultz et al. 2000). RFHV, yet to be isolated and fully characterized as a replication-competent virus in vitro, is associated with a spontaneous disease in macaques called retroperitoneal fibromatosis (RF). Described in the 1980s in pigtail macaques (*M. nemestrina*) (Giddens et al. 1985), RF closely resembles human KS in its histopathology, except for the lack of skin manifestations. RF tumor cells contain multiple RV-1 genome copies, and the pattern of infectivity and latent antigen expression is similar to that of human KS (Bruce et al. 2006). Genomewide transcription patterns for RRV closely resemble the transcription profile for KSHV in infected fibroblasts (Dittmer et al. 2005). RRV is only infrequently detected by real-time PCR at low levels in peripheral blood of healthy macaques and more frequently in SIV-infected animals. However, RRV is not detected in SAIDS-associated lymphomas or lymphoid hyperplasia (Ruff et al. 2003). Experimental infection of macaques with RRV alone or together with SIV has induced generalized lymphadenopathy in a few animals, but as yet no RF lesions or lymphomas (Estep et al. 2007; Mansfield et al. 1999; Wong et al. 1999). If an infectious isolate or molecular clone of RFHV can eventually be derived, it will be interesting to determine whether this agent can induce RF in macaques. Because RRV replicates at very low levels and induces no specific pathology, it is unlikely to provide a useful animal model for disease (Renne et al. 2004).

## Other Infectious Diseases

A significant number of human diseases are caused by a diverse array of viral, bacterial, and parasitic pathogens.

### Rotaviruses *(Reoviridae)*

Group A rotaviruses are ubiquitous and infect most humans by the 3rd year of life. These viruses are the single most important cause of severe diarrhea in infants and young children worldwide. Nonhuman primates, including macaques, are naturally infected with simian rotavirus strains,

several of which (e.g., SA11, YK1) have been used for experimental infection of macaques (Soike et al. 1980; Westerman et al. 2005). In the natural simian host, diarrhea is usually not manifest and neonatal serum antibody of maternal origin is not associated with resistance to rotavirus infection or disease. However, intragastric challenge of newborn and infant cynomolgus macaques with the simian rotavirus strain SA11 does induce diarrhea (Petschow et al. 1992). Newborn macaques also are susceptible to experimental infection and diarrheal disease from human rotavirus isolates (Leong and Awang 1990; Majer et al. 1978; Wyatt et al. 1976). Baboons and vervet monkeys are similarly susceptible to experimental infection with human rotavirus but do not develop diarrhea (Chege et al. 2005). In 1998 a tetravalent rhesus-human reassortant rotavirus vaccine was licensed by the FDA as a live attenuated human vaccine; however, it was withdrawn when the incidence of intussusception in vaccinated infants increased above control (Murphy et al. 2001). Several human rotavirus vaccines are currently undergoing human trials.

## Norwalk Virus *(Noroviridae)*

About half of the US outbreaks of acute infectious nonbacterial gastroenteritis are due to Norwalk virus. Outbreaks occur in camps, schools, nursing homes, and on cruise ships and are associated with contaminated water and uncooked food. Antibodies against the virus are not protective. The human virus has not been cultured in vitro, but a murine norovirus isolate replicates in cell culture and has been useful for studies of pathogenesis in mice (Mumphrey et al. 2007; Wobus et al. 2006). Although neonatal pigtail macaques (*M. nemestrina*) and adult rhesus macaques are both susceptible to experimental infection with Norwalk virus (Rockx et al. 2005; Subekti et al. 2002), clinical gastroenteritis was not exhibited.

## Tick-Borne Encephalitis (TBE) *(Flaviviridae)*

Tick-borne encephalitis is a nontropical zoonotic disease of increasing incidence in Asia and Europe, especially Germany and Austria, where mass vaccination campaigns have been organized. This virus causes more than 10,000 cases of encephalitis annually. Rodents are the maintenance host, and TBE has been transmitted to dogs and horses as well as humans. TBE virus has been isolated from over 20 species of ticks, but the main vectors are *Ixodes persulcatus* and *I. ricinus*. Experimental infection of macaques results in viral persistence and encephalitis (Frolova et al. 1985; Kenyon et al. 1992; Pogodina et al. 1981). A naturally occurring case of TBE was reported in a macaque at a German monkey park (Suss et al. 2007). Using the rhesus monkey model of intranasal infection a commercial vaccine protected against a wild-type virus isolate and elicited an effective immune reaction without any evidence of immune enhancement (Hambleton et al. 1983). This effective vaccine is now available for individuals at risk (Suss 2003).

## Simian Hemorrhagic Fever Virus *(Arteriviridae)*

Simian hemorrhagic fever virus, first isolated in 1964 (Palmer et al. 1968) and now classified in the *Arteriviridae* family (Smith et al. 1997), can cause an acute severe disease with high mortality in macaques (Allen et al. 1968). Although not infectious for humans the macaque disease could be a model for studying the pathogenesis of viral hemorrhagic fevers in humans.

## Simian Parvovirus/Erythrovirus *(Parvoviridae)*

Human B-19 parvovirus is associated with several distinct clinical syndromes, including severe anemia, spontaneous abortion, and arthritis. Macaques are commonly infected, either naturally or experimentally, with simian parvovirus (SPV), which is closely related to human parvovirus B-19 (Brown and Young 1997; Brown et al. 2004; O'Sullivan et al. 1994). Experimental inoculation of SPV in naïve macaques induces temporary arrest of erythroid cell production, analogous to that observed in B-19 infection of humans (O'Sullivan et al. 1997). Similarly, mid-term SPV inoculation in macaque fetuses leads to fetal hydrops. PCR detection of parvovirus infection in monkeys has proven to be more sensitive and specific than serology (Gallinella et al. 2003). Although there is no proven human infection with SPV, it must be considered a potential zoonosis, especially given the ability of the virus to replicate in human bone marrow cells in vitro and the high level of viremia that develops in infected macaques.

## Polyomavirus (PV) *(Polyomaviridae)*

SV40, the prototype polyomavirus (PV) indigenous in macaques, is analogous to the BK and JC PVs in humans. In humans with AIDS and macaques with SAIDS, activation of JC or SV40 virus, respectively, causes demyelinating CNS disease, called progressive multifocal leukoencephalopathy. Genetic analysis of natural SV40 isolates from the brains and kidneys of several macaques revealed that the enhancer sequence organization is different from that of the laboratory strain of SV40 (Ilyinskii et al. 1992). Furthermore, another PV related to but distinct from SV40 was recently recovered from a number of cynomolgus macaques that were immunosuppressed to promote acceptance of renal allografts or xenografts (van Gorder et al. 1999). This virus, called CPV, caused interstitial nephritis in many of the grafted and native kidneys, as well as a late-onset ureteritis with stenosis in the graft recipients. CPV represents an excellent model for the BK polyomavirus-induced inter-

stitial nephritis and ureteral stenosis that occur in human renal transplant recipients. Researchers have recently discovered novel PVs in some human patients with acute respiratory tract infection (Gaynor et al. 2007).

## Q Fever *(Coxiella burnetii)*

A cynomolgus macaque model has been developed for study of this human disease (Gonder et al. 1979). Macaques were susceptible to experimental aerosol infection with *Coxiella burnetii* and developed the clinical signs and pulmonary pathology characteristic of Q fever infection in humans (Waag et al. 1999). A killed *C. burnetii* vaccine provided only partial protection against infection and disease (Kishimoto et al. 1981). More recently, the comparative efficacy of chloroform-methanol residue and cellular *C. burnetii* vaccines has been evaluated in this macaque model of Q fever (Waag et al. 2002).

## *Escherichia coli*

Toxigenic strains of *E. coli* (e.g., O157:H7) are important causes of human morbidity and mortality. For over 30 years, macaques have served as models to investigate the pathogenesis and treatment of experimental *E. coli* infection, including pyelonephritis (Roberts 1975), prostatitis (Neal et al. 1990), bloody diarrhea (Kang et al. 2001), and septic shock (Coalson et al. 1979). Immunization with Shiga toxin liposome conjugates protected macaques against lethal doses of *E. coli* Shiga toxin (Suzaki et al. 2002). Several recent macaque models of experimental, endotoxic shock and disseminated intravascular coagulation have monitored inflammatory cytokines and the effect of glucocorticoid treatment (Ji et al. 2004). Natural toxigenic *E. coli* infection has been described in SIV-infected infant and adult rhesus macaques with diarrhea (Mansfield et al. 2001). The rhesus *E. coli* isolate was genetically very similar to human isolates of the epsilon intimin subtype.

## Campylobacteriosis *(Campylobacter jejuni)*

This enteric bacterium is a close relative of the cholera bacillus (*Vibrio cholera*) and a common agent of infectious diarrhea. Asymptomatic infection is common in humans and captive macaques; diseased individuals may exhibit bloody diarrhea (Morton et al. 1983; Tribe and Fleming 1983). *Campylobacter* has also induced fetal death in a rhesus monkey (Baze and Bernacky 2002). Animals and contaminated food are sources of the bacteria. Rhesus and pigtail macaques are susceptible to experimental infection and colitis from a human strain of *Campylobacter* (Fitzgeorge et al. 1981; Russell et al. 1989). Interestingly, early efforts to infect rhesus monkeys with the related *V. cholera* were unsuccessful (Ivanoff et al. 1978).

## Listeriosis *(Listeria monocytogenes)*

Listeriosis, caused by the bacterium *Listeria monocytogenes*, is an important pathogen for humans and animals and can cause natural outbreaks in nonhuman primates. Hygienic food processing and storage remain the best preventive measures for both humans and nonhuman primates. Most human cases occur in immunocompromised individuals or as congenital infection, often leading to stillbirths. Various foodstuffs of vegetable or animal origin are the sources of infection. Cynomolgus macaques were used as a model for infection with *L. monocytogenes*, isolated from either humans or NHPs and administered orally (Farber et al. 1991). Systemic infection was documented with the shedding of this bacterium in the feces for several weeks. Animals that received $10^9$ bacteria suspended in sterile whole milk became ill with symptoms of septicemia, anorexia, and diarrhea. Given to pregnant macaques, the organism infected the fetus and caused stillbirths (Smith et al. 2003).

## Legionnaires Disease *(Legionella pneumophilia)*

A rhesus macaque model of aerosol infection with the *Legionella pneumophilia* was established in 1983 (Baskerville et al. 1983). Lung pathology similar to that seen in *L. pneumophilia*–infected humans was documented by light and electron microscopy. Guinea pigs and marmosets are equally susceptible to infection and pneumonia, so the macaque model has not been further developed.

## Bacillary Dysentery (Shigellosis) *(Shigella flexneri)*

Severe acute *Shigella* dysentery is among the most miserable of human diseases. There is no animal reservoir but epidemics occur in locales that lack effective sanitation. *Shigella* outbreaks also occur in captive macaque colonies where special eradication programs may be necessary for control (Banish et al. 1993; Line et al. 1992; Mulder 1971). This agent is an important occupational zoonosis (Kennedy et al. 1993). Researchers in the 1970s experimentally infected rhesus macaques with *S. flexneri* to investigate pathogenesis (Kinsey et al. 1976; Rout et al. 1975). Mucosal invasion of the colon was essential to the development of the fluid and electrolyte transport defect that led to the dysentery. In addition, jejunal transport abnormalities contributed to the diarrhea. Arthritis and amyloidosis in SIV-infected rhesus macaques have been associated with *S. flexneri* breakdown products in the intestine (Blanchard et al. 1986; Chapman and Crowell 1977; Urvater et al. 2000). This development may be analogous to the arthritis increasingly seen in HIV patients who are free of other risk factors for arthritis.

## Streptococcal Pneumonia *(Streptococcus pneumoniae)*

*Streptococcus pneumoniae* (also known as pneumococcus, diplococcus) has long been responsible for high rates of pneumonia, meningitis, and otitis media worldwide, particularly in young children and older adults. Over 30 years ago rhesus macaques were exposed to aerosols of influenza virus and *S. pneumonia*: the bacteria were cleared from the lower respiratory tissues but persisted in the upper respiratory tract (Berendt et al. 1974). Rhesus monkeys also served as a model for disseminated intravascular coagulation after experimental bloodstream infection (Hawley et al. 1977). In 1995 a fatal case of *S. pneumonia* meningitis was reported in a 3-month-old lion-tailed macaque (*M. silenes*) at the Baltimore Zoo (Graczyk et al. 1995). Since the early 1990s several pneumococcal polysaccharide vaccines have demonstrated effectiveness against infection in older children and adults, and subsequent immunogenicity studies in rhesus macaques led to the development of newer polysaccharide vaccines now available for children from 2 to 15 months of age (McNeely et al. 1998). However, adaptation of the adult vaccine is necessary to provide stronger and longer-lasting protection and higher efficacy in immunocompromised populations. To help answer this need, attempts are under way to develop a rhesus macaque model for pneumococcal vaccine assessment (Philipp et al. 2006).

## Streptococcal Pharyngitis *(Streptococcus pyogenes)*

Group A streptococcal pharyngitis and resultant rheumatic heart disease are still highly prevalent in developing countries. To better understand the pathogenesis of the acute pharyngitis and aid in the development of an effective streptococcal vaccine, cynomolgus macaques were experimentally infected with group A streptococcus (Virtaneva et al. 2005). Acute and asymptomatic phases of disease were identified and bacterial colonization and severe throat inflammation correlated with superantigens and prophage virulence gene expression. Temporal changes in the transcriptomes were linked to the phase of clinical disease and host defense response.

## Chronic Enterocolitis

Chronic enterocolitis is a leading cause of morbidity in captive macaques. A recent survey of fecal specimens from 100 immunocompetent rhesus macaques, with or without chronic diarrhea, revealed a multitude of potential enteric bacterial, protozoan, and parasitic pathogens (Sestak et al. 2003). Organisms associated with chronic diarrhea included *Campylobacter, Shigella, Yersinia*, adenovirus, and *Strongyloides*; other enteric pathogens, whether or not diarrhea was present, included *E. coli* carrying the Shiga toxin virulence gene, *Balantidium coli*, *Giardia lamblia*, *Enterocytozoon* (microsporidia), and *Trichuris trichiura* (whipworm). Microsporidia could be experimentally transmitted to SIV-infected rhesus monkeys (Green et al. 2004). Chronic diarrhea was associated with upregulation of certain cytokines (e.g., IL-1, IL-3, TNF [tumor necrosis factor]-alpha) and T lymphocytes ($CD4^+$, $CD69^+$) in the gut-associated lymphoid tissue.

## Trichinosis *(Trichinoma spiralis)*

This roundworm causes trichinosis, a common disease throughout the world that results from eating improperly cooked pork containing viable cysts of *T. spiralis*. In humans, the parasite larvae localize principally in skeletal muscles and evoke generalized myalgia. Rhesus monkeys experimentally infected 30 years ago with *T. spiralis* larvae developed trichinosis that showed clinical, pathological, and morphological similarities to the human disease (Cypess et al. 1977).

## Toxoplasmosis *(Toxoplasma gondii)*

Natural infection with *Toxoplasma gondii* has been noted in several species of Asian macaques, most recently in Toque macaques (*M. sinica*) from Sri Lanka (Ekanayake et al. 2004). Infection is closely linked to human environments where domestic cats are common. In a study of congenital *T. gondii* infection, researchers infected pregnant rhesus and stump-tailed macaques (*M. arctoides*) with these protozoa (Wong et al. 1979); no significant neonatal disease occurred despite CNS infection. Antiviral treatment with a combination of pyrimethamine and sulfadiazine was effective in eliminating the parasite in both the amniotic fluid and the neonate, whereas the parasite was detected in most of the untreated fetuses.

## Periodontal Disease

Various degrees of periodontal disease, from mild gingivitis to necrotizing ulcerative gingivitis (noma), associated with dental calculi, are present in macaques and other NHPs (Adams and Bishop 1980; Cohen and Goldman 1960; Schiodt et al. 1988). Noma is particularly associated with SRV (type D retrovirus)–induced immunosuppression. Experimental periodontitis can be induced in macaques by placement of periodontal silk ligatures or orthodontic elastic as well as by surgical removal of alveolar bone (Schou et al. 1993). The clinical, pathological, microbiological, and immunological characteristics of spontaneous and experimental periodontitis in macaques are similar to those of humans. Macaques manifest a subgingival flora resembling that found in humans, including members of *Actinobacillus*, *Porphyromonas*, *Bacteroides*, *Campylobacter*, and *Fuso-*

*bacterium*. In cynomolgus macaques, antibody titers and relative levels of *P. gingivalis* were inversely correlated, suggesting that a humoral immune response may be efficacious in reducing overgrowth with this bacterium (Persson et al. 1994). Thus the macaque model is highly suitable for developing vaccines against periodontitis.

## Summary

This survey illustrates the versatility of the macaque as an animal model for translational human infectious disease research. Additionally, natural infections of macaques with agents related to human pathogens extend the value of these animals. A further major benefit of this research is the alleviation of infectious disease for macaques as well as other primate species. Comparative studies in both human and macaque hosts are needed to address continuing problems caused by many infectious diseases that remain intractable. Factors such as increased travel, population growth, and changing ecology are giving rise to new and emerging infectious diseases. Recent advances in genomic, proteomic, metabolomic, and related technologies make macaque models all the more timely for studies aimed at improving the treatment and control of infectious diseases in humans and macaques alike—"one medicine" in action!

## Acknowledgments

We acknowledge Anita Moore, Angela Hatch, and Alex Borowsky for help in preparation of the typescript, and Steve Barthold for inspirational guidance. The following NIH grants support P.A.L. for research on infectious diseases in macaques: RR00169, RR022907, and U54-AI065359.

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