Macaque Models of Human Infectious Disease

Murray B. Gardner and Paul A. Luciw

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

Murray B. Gardner, MD, is an emeritus professor and Paul A. Luciw, PhD, a professor in the Center for Comparative Medicine and Department of Pathology and Laboratory Medicine at the University of California in Davis. Dr. Luciw is also a professor at the California National Primate Research Center in Davis.

Address correspondence and reprint requests to Dr. Murray B. Gardner, Center for Comparative Medicine, University of California, Road 98 and Hutchison Drive, Davis, CA 95616 or email mbgardner@ucdavis.edu.

[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.

References

Abe K, Kurata T, Teramoto Y, Shiga J, Shikata T. 1993. Lack of susceptibility of various primates and woodchucks to hepatitis C virus. J Med Primatol 22:433-434.

Abe S, Ota Y, Koike S, Kurata T, Horie H, Nomura T, Hashizume S, Nomoto A. 1995. Neurovirulence test for oral live poliovaccines using poliovirus-sensitive transgenic mice. Virology 206:1075-1083.

Adams RJ, Bishop JL. 1980. An oral disease resembling noma in six rhesus monkeys (*Macaca mulatta*). Lab Anim Sci 30:85-91.

Aggarwal R, Kamili S, Spelbring J, Krawczynski K. 2001. Experimental studies on subclinical hepatitis E virus infection in cynomolgus macaques. J Infect Dis 184:1380-1385.

Agy MB, Schmidt A, Florey MJ, Kennedy BJ, Schaefer G, Katze MG, Corey L, Morton WR, Bosch ML. 1997. Serial in vivo passage of HIV-1 infection in *Macaca nemestrina*. Virology 238:336-343.

Ahmed RK, Biberfeld G, Thorstensson R. 2005. Innate immunity in experimental SIV infection and vaccination. Mol Immunol 42:251-258.

Ajariyakhajorn C, Mammen MP Jr, Endy TP, Gettayacamin M, Nisalak A, Nimmannitya S, Libraty DH. 2005. Randomized, placebo-controlled trial of nonpegylated and pegylated forms of recombinant human alpha interferon 2a for suppression of dengue virus viremia in rhesus monkeys. Antimicrob Agents Ch 49:4508-4514.

Albrecht P, Burnstein T, Klutch MJ, Hicks HT, Ennis FA. 1977. Subacute sclerosing panencephalitis: Experimental infection in primates. Science 195:64-66.

Allen AM, Palmer AE, Tauraso NM, Shelokov A. 1968. Simian hemorrhagic fever. II. Studies in pathology. Am J Trop Med Hyg 17:413-421.

Allen TM, O'Connor DH, Jing P, Dzuris JL, Mothe BR, Vogel TU, Dunphy E, Liebl ME, Emerson C, Wilson N, Kunstman KJ, Wang X, Allison DB, Hughes AL, Desrosiers RC, Altman JD, Wolinsky SM, Sette A, Watkins DI. 2000. Tat-specific cytotoxic T lymphocytes select for SIV escape variants during resolution of primary viraemia. Nature 407:386-390.

Apetrei C, Robertson DL, Marx PA. 2004. The history of SIV and AIDS: Epidemiology, phylogeny and biology of isolates from naturally SIV infected nonhuman primates (NHP) in Africa. Front Biosci 9:225-254.

Apetrei C, Kaur A, Lerche NW, Metzger M, Pandrea I, Hardcastle J, Falkenstein S, Bohm R, Koehler J, Traina-Dorge V, Williams T, Staprans S, Plauche G, Veazey RS, McClure H, Lackner AA, Gormus B, Robertson DL, Marx PA. 2005. Molecular epidemiology of simian immunodeficiency virus SIVsm in US primate centers unravels the origin of SIVmac and SIVstm. J Virol 79:8991-9005.

Arroyo J, Miller C, Catalan J, Myers GA, Ratterree MS, Trent DW, Monath TP. 2004. ChimeriVax-West Nile virus live-attenuated vaccine: Preclinical evaluation of safety, immunogenicity, and efficacy. J Virol 78:12497-12507.

Ayash-Rashkovsky M, Chenine AL, Steele LN, Lee SJ, Song R, Ong H, Rasmussen RA, Hofmann-Lehmann R, Else JG, Augostini P, McClure HM, Secor WE, Ruprecht RM. 2007. Coinfection with *Schistosoma mansoni* reactivates viremia in rhesus macaques with chronic simian-human immunodeficiency virus clade C infection. Infect Immun 75: 1751-1756.

Baas T, Baskin CR, Diamond DL, Garcia-Sastre A, Bielefeldt-Ohmann H, Tumpey TM, Thomas MJ, Carter VS, Teal TH, Van Hoeven N, Proll S, Jacobs JM, Caldwell ZR, Gritsenko MA, Hukkanen RR, Camp DG 2nd, Smith RD, Katze MG. 2006. Integrated molecular signature of disease: Analysis of influenza virus-infected macaques through functional genomics and proteomics. J Virol 80:10813-10828.

Baer GM, Shaddock JH, Moore SA, Yager PA, Baron SS, Levy HB. 1977. Successful prophylaxis against rabies in mice and Rhesus monkeys: The interferon system and vaccine. J Infect Dis 136:286-291.

Bai Y, Narayan K, Dail D, Sondey M, Hodzic E, Barthold SW, Pachner AR, Cadavid D. 2004. Spinal cord involvement in the nonhuman primate model of Lyme disease. Lab Invest 84:160-172.

Banish LD, Sims R, Sack D, Montali RJ, Phillips L Jr, Bush M. 1993. Prevalence of shigellosis and other enteric pathogens in a zoologic collection of primates. JAVMA 203:126-132.

Bannantine JP, Rockey DD. 1999. Use of primate model system to identify *Chlamydia trachomatis* protein antigens recognized uniquely in the context of infection. Microbiology 145 (Pt 8):2077-2085.

Barker LF, Maynard JE, Purcell RH, Hoofnagle JH, Berquist KR, London WT. 1975. Viral hepatitis, type B, in experimental animals. Am J Med Sci 270:189-195.

Barnett SW, Murthy KK, Herndier BG, Levy JA. 1994. An AIDS-like condition induced in baboons by HIV-2. Science 266:642-646.

Barouch DH, Kunstman J, Kuroda MJ, Schmitz JE, Santra S, Peyerl FW, Krivulka GR, Beaudry K, Lifton MA, Gorgone DA, Montefiori DC, Lewis MG, Wolinsky SM, Letvin NL. 2002. Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. Nature 415:335-339.

Barry PA, Lockridge KM, Salamat S, Tinling SP, Yue Y, Zhou SS, Gospe SM Jr, Britt WJ, Tarantal AF. 2006. Nonhuman primate models of intrauterine cytomegalovirus infection. ILAR J 47:49-64.

Baskerville A, Fitzgeorge RB, Broster M, Hambleton P. 1983. Histopathology of experimental Legionnaires' disease in guinea pigs, rhesus monkeys and marmosets. J Pathol 139:349-362.

Baskin CR, Garcia-Sastre A, Tumpey TM, Bielefeldt-Ohmann H, Carter VS, Nistal-Villan E, Katze MG. 2004. Integration of clinical data,

pathology, and cDNA microarrays in influenza virus-infected pigtail macaques (*Macaca nemestrina*). J Virol 78:10420-10432.

Baze WB, Bernacky BJ. 2002. Campylobacter-induced fetal death in a rhesus monkey. Vet Pathol 39:605-607.

Bennett AM, Slomka MJ, Brown DW, Lloyd G, Mackett M. 1999. Protection against herpes B virus infection in rabbits with a recombinant vaccinia virus expressing glycoprotein D. J Med Virol 57:47-56.

Berendt RF, McDonough WE, Walker JS. 1974. Persistence of *Diplococcus pneumoniae* after influenza virus infection in *Macaca mulatta*. Infect Immun 10:369-374.

Blanchard JL, Baskin GB, Watson EA. 1986. Generalized amyloidosis in rhesus monkeys. Vet Pathol 23:425-430.

Blaney JE Jr, Matro JM, Murphy BR, Whitehead SS. 2005. Recombinant, live-attenuated tetravalent dengue virus vaccine formulations induce a balanced, broad, and protective neutralizing antibody response against each of the four serotypes in rhesus monkeys. J Virol 79:5516-5528.

Bonecini-Almeida Mda G, Galvao-Castro B, Pessoa MH, Pirmez C, Laranja F. 1990. Experimental Chagas' disease in rhesus monkeys. I. Clinical, parasitological, hematological and anatomo-pathological studies in the acute and indeterminate phase of the disease. Mem Inst Oswaldo Cruz 85:163-171.

Bons N, Mestre-Frances N, Charnay Y, Salmona M, Tagliavini F. 1996. Spontaneous spongiform encephalopathy in a young adult rhesus monkey. C R Acad Sci III 319:733-736.

Boonjakuakul JK, Canfield DR, Solnick JV. 2005. Comparison of *Helicobacter pylori* virulence gene expression in vitro and in the Rhesus macaque. Infect Immun 73:4895-4904.

Breitschwerdt EB, Kordick DL. 2000. Bartonella infection in animals: Carriership, reservoir potential, pathogenicity, and zoonotic potential for human infection. Clin Microbiol Rev 13:428-438.

Brooks JI, Rud EW, Pilon RG, Smith JM, Switzer WM, Sandstrom PA. 2002. Cross-species retroviral transmission from macaques to human beings. Lancet 360:387-388.

Brown KE, Young NS. 1997. The simian parvoviruses. Rev Med Virol 7:211-218.

Brown KE, Liu Z, Gallinella G, Wong S, Mills IP, O'Sullivan MG. 2004. Simian parvovirus infection: A potential zoonosis. J Infect Dis 190: 1900-1907.

Bruce AG, Bakke AM, Bielefeldt-Ohmann H, Ryan JT, Thouless ME, Tsai CC, Rose TM. 2006. High levels of retroperitoneal fibromatosis (RF)-associated herpesvirus in RF lesions in macaques are associated with ORF73 LANA expression in spindleoid tumour cells. J Gen Virol 87(Pt 12):3529-3538.

Brusasca PN, Peters RL, Motzel SL, Klein HJ, Gennaro ML. 2003. Antigen recognition by serum antibodies in nonhuman primates experimentally infected with *Mycobacterium tuberculosis*. Comp Med 53:165-172.

Bukreyev A, Rollin PE, Tate MK, Yang L, Zaki SR, Shieh WJ, Murphy BR, Collins PL, Sanchez A. 2007. Successful topical respiratory tract immunization of primates against Ebola virus. J Virol 81:6379-6388.

Cadavid D, Bai Y, Dail D, Hurd M, Narayan K, Hodzic E, Barthold SW, Pachner AR. 2003. Infection and inflammation in skeletal muscle from nonhuman primates infected with different genospecies of the Lyme disease spirochete *Borrelia burgdorferi*. Infect Immun 71:7087-7098.

Cadavid D, Bai Y, Hodzic E, Narayan K, Barthold SW, Pachner AR. 2004. Cardiac involvement in nonhuman primates infected with the Lyme disease spirochete *Borrelia burgdorferi*. Lab Invest 84:1439-1450.

Campos M, Pal S, O'Brien TP, Taylor HR, Prendergast RA, Whittum-Hudson JA. 1995. A chlamydial major outer membrane protein extract as a trachoma vaccine candidate. Invest Ophthalmol Vis Sci 36:1477-1491.

Capone S, Meola A, Ercole BB, Vitelli A, Pezzanera M, Ruggeri L, Davies ME, Tafi R, Santini C, Luzzago A, Fu TM, Bett A, Colloca S, Cortese R, Nicosia A, Folgori A. 2006a. A novel adenovirus type 6 (Ad6)-based hepatitis C virus vector that overcomes preexisting anti-ad5 immunity and induces potent and broad cellular immune responses in rhesus macaques. J Virol 80:1688-1699.

Capone S, Zampaglione I, Vitelli A, Pezzanera M, Kierstead L, Burns J, Ruggeri L, Arcuri M, Cappelletti M, Meola A, Ercole BB, Tafi R, Santini C, Luzzago A, Fu TM, Colloca S, Ciliberto G, Cortese R, Nicosia A, Fattori E, Folgori A. 2006b. Modulation of the immune response induced by gene electrotransfer of a hepatitis C virus DNA vaccine in nonhuman primates. J Immunol 177:7462-7471.

Capuano SV 3rd, Croix DA, Pawar S, Zinovik A, Myers A, Lin PL, Bissel S, Fuhrman C, Klein E, Flynn JL. 2003. Experimental *Mycobacterium tuberculosis* infection of cynomolgus macaques closely resembles the various manifestations of human M. tuberculosis infection. Infect Immun 71:5831-5844.

Carbone M, Pass HI. 2006. Evolving aspects of mesothelioma carcinogenesis: SV40 and genetic predisposition. J Thorac Oncol 1:169-171.

Carlson CS, O'Sullivan MG, Jayo MJ, Anderson DK, Harber ES, Jerome WG, Bullock BC, Heberling RL. 1997. Fatal disseminated cercopithecine herpesvirus 1 (herpes B infection in cynomolgus monkeys (*Macaca fascicularis*). Vet Pathol 34:405-414.

Carlson JR, Chang WL, Zhou SS, Tarantal AF, Barry PA. 2005. Rhesus brain microvascular endothelial cells are permissive for rhesus cytomegalovirus infection. J Gen Virol 86(Pt 3):545-549.

Carvalho CM, Andrade MC, Xavier SS, Mangia RH, Britto CC, Jansen AM, Fernandes O, Lannes-Vieira J, Bonecini-Almeida MG. 2003. Chronic Chagas' disease in rhesus monkeys (*Macaca mulatta*): Evaluation of parasitemia, serology, electrocardiography, echocardiography, and radiology. Am J Trop Med Hyg 68:683-691.

Caulfield MJ, Smith JG, Wang S, Capen RC, Blondeau C, Lentsch S, Arminjon F, Sabouraud A. 2000. Immunogenicity of a hexavalent combination vaccine in rhesus monkeys. Vaccine 19:902-907.

Chan SY, Bernard HU, Ratterree M, Birkebak TA, Faras AJ, Ostrow RS. 1997. Genomic diversity and evolution of papillomaviruses in rhesus monkeys. J Virol 71:4938-4943.

Chapman WL Jr, Crowell WA. 1977. Amyloidosis in rhesus monkeys with rheumatoid arthritis and enterocolitis. JAVMA 171:855-858.

Chattopadhyay S, Jiang J, Chan TC, Manetz TS, Chao CC, Ching WM, Richards AL. 2005. Scrub typhus vaccine candidate Kp r56 induces humoral and cellular immune responses in cynomolgus monkeys. Infect Immun 73:5039-5047.

Chege GK, Steele AD, Hart CA, Snodgrass DR, Omolo EO, Mwenda JM. 2005. Experimental infection of nonhuman primates with a human rotavirus isolate. Vaccine 23:1522-1528.

Chen TH, Elberg SS. 1976. Priming of *Macaca cynomolgus philippinensis* with purified antigen of *Brucella melitensis* before injection of Rev. I vaccine. J Infect Dis 134:294-296.

Chen Z, Zhang L, Qin C, Ba L, Yi CE, Zhang F, Wei Q, He T, Yu W, Yu J, Gao H, Tu X, Gettie A, Farzan M, Yuen KY, Ho DD. 2005. Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J Virol 79:2678-2688.

Chen ZW. 2004. Immunology of AIDS virus and mycobacterial coinfection. Curr HIV Res 2:351-355.

Chenine AL, Buckley KA, Li PL, Rasmussen RA, Ong H, Jiang S, Wang T, Augostini P, Secor WE, Ruprecht RM. 2005. *Schistosoma mansoni* infection promotes SHIV clade C replication in rhesus macaques. AIDS 19:1793-1797.

Choi YK, Simon MA, Kim DY, Yoon BI, Kwon SW, Lee KW, Seo IB, Kim DY. 1999. Fatal measles virus infection in Japanese macaques (*Macaca fuscata*). Vet Pathol 36:594-600.

Chomel BB, Kasten RW, Floyd-Hawkins K, Chi B, Yamamoto K, Roberts-Wilson J, Gurfield AN, Abbott RC, Pedersen NC, Koehler JE. 1996. Experimental transmission of *Bartonella henselae* by the cat flea. J Clin Microbiol 34:1952-1956.

Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. 1989. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 244:359-362.

Chopra HC, Mason MM. 1970. A new virus in a spontaneous mammary tumor of a rhesus monkey. Cancer Res 30:2081-2086.

Christe KL, McChesney MB, Spinner A, Rosenthal AN, Allen PC, Valverde CR, Roberts JA, Lerche NW. 2002. Comparative efficacy of a

canine distemper-measles and a standard measles vaccine for immunization of rhesus macaques (*Macaca mulatta*). Comp Med 52:467-472.

Coalson JJ, Archer LT, Hall NK, Kern JD, Benjamin BA, Beller-Todd B, Hinshaw LB. 1979. Prolonged shock in the monkey following live E coli organism infusion. Circ Shock 6:343-355.

Coban C, Philipp MT, Purcell JE, Keister DB, Okulate M, Martin DS, Kumar N. 2004. Induction of *Plasmodium falciparum* transmission-blocking antibodies in nonhuman primates by a combination of DNA and protein immunizations. Infect Immun 72:253-259.

Cohen DW, Goldman HM. 1960. Oral disease in primates. Ann N Y Acad Sci 85:889-909.

Cohen JK, Kilpatrick AM, Stroud FC, Paul K, Wolf F, Else JG. 2007. Seroprevalence of West Nile virus in nonhuman primates as related to mosquito abundance at two national primate research centers. Comp Med 57:115-119.

Contreras G, Furesz J. 1992. Possible influence of measles virus infection of cynomolgus monkeys on the outcome of the neurovirulence test for oral poliovirus vaccine. Biologicals 20:27-33.

Cosgriff TM, Morrill JC, Jennings GB, Hodgson LA, Slayter MV, Gibbs PH, Peters CJ. 1989. Hemostatic derangement produced by Rift Valley fever virus in rhesus monkeys. Rev Infect Dis 11 (Suppl 4):S807-S814.

Courgnaud V, Van Dooren S, Liegeois F, Pourrut X, Abela B, Loul S, Mpoudi-Ngole E, Vandamme A, Delaporte E, Peeters M. 2004. Simian T cell leukemia virus (STLV) infection in wild primate populations in Cameroon: Evidence for dual STLV type 1 and type 3 infection in agile mangabeys (*Cercocebus agilis*). J Virol 78:4700-4709.

Custer DM, Thompson E, Schmaljohn CS, Ksiazek TG, Hooper JW. 2003. Active and passive vaccination against hantavirus pulmonary syndrome with Andes virus M genome segment-based DNA vaccine. J Virol 77:9894-9905.

Cypess RH, Lubiniecki A, DeSeau V, Siebert JR. 1977. Observations on trichinosis in the rhesus monkey. J Med Primatol 6:23-32.

Daddario-DiCaprio KM, Geisbert TW, Geisbert JB, Stroher U, Hensley LE, Grolla A, Fritz EA, Feldmann F, Feldmann H, Jones SM. 2006a. Cross-protection against Marburg virus strains by using a live, attenuated recombinant vaccine. J Virol 80:9659-9666.

Daddario-DiCaprio KM, Geisbert TW, Stroher U, Geisbert JB, Grolla A, Fritz EA, Fernando L, Kagan E, Jahrling PB, Hensley LE, Jones SM, Feldmann H. 2006b. Postexposure protection against Marburg haemorrhagic fever with recombinant vesicular stomatitis virus vectors in nonhuman primates: An efficacy assessment. Lancet 367:1399-1404.

Dalgard DW, Hardy RJ, Pearson SL, Pucak GJ, Quander RV, Zack PM, Peters CJ, Jahrling PB. 1992. Combined simian hemorrhagic fever and Ebola virus infection in cynomolgus monkeys. Lab Anim Sci 42:152-157.

Daniel MD, Kirchhoff F, Czajak SC, Sehgal PK, Desrosiers RC. 1992. Protective effects of a live attenuated SIV vaccine with a deletion in the nef gene. Science 258:1938-1941.

Darwin C. 1839. Narrative of the Surveying Voyages of His Majesty's Ships Adventure and Beagle between the Years 1826 and 1836. London: H. Colburn.

De Swart RL, Kuiken T, Timmerman HH, van Amerongen G, Van Den Hoogen BG, Vos HW, Neijens HJ, Andeweg AC, Osterhaus AD. 2002. Immunization of macaques with formalin-inactivated respiratory syncytial virus (RSV) induces interleukin-13-associated hypersensitivity to subsequent RSV infection. J Virol 76:11561-11569.

De Swart RL, Kuiken T, Fernandez-de Castro J, Papania MJ, Bennett JV, Valdespino JL, Minor P, Witham CL, Yuksel S, Vos H, van Amerongen G, Osterhaus AD. 2006. Aerosol measles vaccination in macaques: Preclinical studies of immune responses and safety. Vaccine 24:6424-6436.

De Waal L, Wyatt LS, Yuksel S, van Amerongen G, Moss B, Niesters HG, Osterhaus AD, de Swart RL. 2004. Vaccination of infant macaques with a recombinant modified vaccinia virus Ankara expressing the respiratory syncytial virus F and G genes does not predispose for immunopathology. Vaccine 22:923-926.

Dean CH, Alarcon JB, Waterston AM, Draper K, Early R, Guirakhoo F, Monath TP, Mikszta JA. 2005. Cutaneous delivery of a live, attenuated chimeric flavivirus vaccine against Japanese encephalitis (Chimeri-Vax)-JE) in nonhuman primates. Hum Vaccin 1:106-111.

Dezzutti CS, Frazier DE, Olsen RG. 1990. Efficacy of an HTLV-1 subunit vaccine in prevention of a STLV-1 infection in pigtail macaques. Dev Biol Stand 72:287-96.

Di Giulio DB, Eckburg PB. 2004. Human monkeypox: An emerging zoonosis. Lancet Infect Dis 4:15-25.

DiNapoli JM, Yang L, Suguitan A Jr, Elankumaran S, Dorward DW, Murphy BR, Samal SK, Collins PL, Bukreyev A. 2007. Immunization of primates with a Newcastle disease virus-vectored vaccine via the respiratory tract induces a high titer of serum neutralizing antibodies against highly pathogenic avian influenza virus. J Virol 81:11560-11568.

Dittmer DP, Gonzalez CM, Vahrson W, DeWire SM, Hines-Boykin R, Damania B. 2005. Whole-genome transcription profiling of rhesus monkey rhadinovirus. J Virol 79:8637-8650.

Djavani MM, Crasta OR, Zapata JC, Fei Z, Folkerts O, Sobral B, Swindells M, Bryant J, Davis H, Pauza CD, Lukashevich IS, Hammamieh R, Jett M, Salvato MS. 2007. Early blood profiles of virus infection in a monkey model for lassa fever. J Virol 81:7960-7973.

Doi SQ, Kimbason T, Reindel J, Dubois A. 2005. Molecular characterization of *Helicobacter pylori* strains isolated from cynomolgus monkeys (*M. fascicularis*). Vet Microbiol 108:133-139.

Donnelly JJ, Taylor HR, Young E, Khatami M, Lok JB, Rockey JH. 1986. Experimental ocular onchocerciasis in cynomolgus monkeys. Invest Ophthalmol Vis Sci 27:492-499.

Dubois A, Fiala N, Heman-Ackah LM, Drazek ES, Tarnawski A, Fishbein WN, Perez-Perez GI, Blaser MJ. 1994. Natural gastric infection with *Helicobacter pylori* in monkeys: A model for spiral bacteria infection in humans. Gastroenterology 106:1405-1417.

Dubois A, Fiala N, Weichbrod RH, Ward GS, Nix M, Mehlman PT, Taub DM, Perez-Perez GI, Blaser MJ. 1995. Seroepizootiology of *Helicobacter pylori* gastric infection in nonhuman primates housed in social environments. J Clin Microbiol 33:1492-1495.

Dubois A, Lee CK, Fiala N, Kleanthous H, Mehlman PT, Monath T. 1998. Immunization against natural *Helicobacter pylori* infection in nonhuman primates. Infect Immun 66:4340-4346.

Dutta S, Kaushal DC, Ware LA, Puri SK, Kaushal NA, Narula A, Upadhyaya DS, Lanar DE. 2005. Merozoite surface protein 1 of *Plasmodium vivax* induces a protective response against *Plasmodium cynomolgi* challenge in rhesus monkeys. Infect Immun 73:5936-5944.

Earl PL, Americo JL, Wyatt LS, Eller LA, Whitbeck JC, Cohen GH, Eisenberg RJ, Hartmann CJ, Jackson DL, Kulesh DA, Martinez MJ, Miller DM, Mucker EM, Shamblin JD, Zwiers SH, Huggins JW, Jahrling PB, Moss B. 2004. Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox. Nature 428:182-185.

Edghill-Smith Y, Bray M, Whitehouse CA, Miller D, Mucker E, Manischewitz J, King LR, Robert-Guroff M, Hryniewicz A, Venzon D, Meseda C, Weir J, Nalca A, Livingston V, Wells J, Lewis MG, Huggins J, Zwiers SH, Golding H, Franchini G. 2005a. Smallpox vaccine does not protect macaques with AIDS from a lethal monkeypox virus challenge. J Infect Dis 191:372-381.

Edghill-Smith Y, Golding H, Manischewitz J, King LR, Scott D, Bray M, Nalca A, Hooper JW, Whitehouse CA, Schmitz JE, Reimann KA, Franchini G. 2005b. Smallpox vaccine-induced antibodies are necessary and sufficient for protection against monkeypox virus. Nat Med 11:740-747.

Ekanayake DK, Rajapakse RP, Dubey JP, Dittus WP. 2004. Seroprevalence of *Toxoplasma gondii* in wild toque macaques (*Macaca sinica*) at Polonnaruwa, Sri Lanka. J Parasitol 90:870-871.

Engel G, Hungerford LL, Jones-Engel L, Travis D, Eberle R, Fuentes A, Grant R, Kyes R, Schillaci M. 2006. Risk assessment: A model for predicting cross-species transmission of simian foamy virus from macaques (*M. fascicularis*) to humans at a monkey temple in Bali, Indonesia. Am J Primatol 68:934-948.

Escalante AA, Barrio E, Ayala FJ. 1995. Evolutionary origin of human and

primate malarias: Evidence from the circumsporozoite protein gene. Mol Biol Evol 12:616-626.

Escalante AA, Cornejo OE, Freeland DE, Poe AC, Durrego E, Collins WE, Lal AA. 2005. A monkey's tale: The origin of *Plasmodium vivax* as a human malaria parasite. Proc Natl Acad Sci U S A 102:1980-1985.

Espana C, Gajdusek DC, Gibbs CJ Jr, Osburn BI, Gribble DH, Cardinet GH, Chanock RM. 1975. Transmission of Creutzfeldt-Jakob disease to the stumptail macaque (*Macaca arctoides*). Proc Soc Exp Biol Med 149:723-724.

Estep RD, Powers MF, Yen BK, Li H, Wong SW. 2007. Construction of an infectious rhesus rhadinovirus bacterial artificial chromosome for the analysis of Kaposi's sarcoma-associated herpesvirus-related disease development. J Virol 81:2957-2969.

Fallon PG, Gibbons J, Vervenne RA, Richardson EJ, Fulford AJ, Kiarie S, Sturrock RF, Coulson PS, Deelder AM, Langermans JA, Thomas AW, Dunne DW. 2003. Juvenile rhesus monkeys have lower type 2 cytokine responses than adults after primary infection with *Schistosoma mansoni*. J Infect Dis 187:939-945.

Farber JM, Daley E, Coates F, Beausoleil N, Fournier J. 1991. Feeding trials of *Listeria monocytogenes* with a nonhuman primate model. J Clin Microbiol 29:2606-2608.

Feichtinger H, Li SL, Kaaya E, Putkonen P, Grunewald K, Weyrer K, Bottiger D, Ernberg I, Linde A, Biberfeld G. 1992. A monkey model for Epstein Barr virus-associated lymphomagenesis in human acquired immunodeficiency syndrome. J Exp Med 176:281-286.

Fernandez KR, Hansen LM, Vandamme P, Beaman BL, Solnick JV. 2002. Captive rhesus monkeys (*Macaca mulatta*) are commonly infected with *Helicobacter cinaedi*. J Clin Microbiol 40:1908-1912.

Fisher-Hoch SP, McCormick JB, Auperin D, Brown BG, Castor M, Perez G, Ruo S, Conaty A, Brammer L, Bauer S. 1989. Protection of rhesus monkeys from fatal Lassa fever by vaccination with a recombinant vaccinia virus containing the Lassa virus glycoprotein gene. Proc Natl Acad Sci U S A 86:317-321.

Fisher-Hoch SP, Mitchell SW, Sasso DR, Lange JV, Ramsey R, McCormick JB. 1987. Physiological and immunologic disturbances associated with shock in a primate model of Lassa fever. J Infect Dis 155:465-474.

Fisher-Hoch SP, Hutwagner L, Brown B, McCormick JB. 2000. Effective vaccine for lassa fever. J Virol 74:6777-6783.

Fitzgeorge RB, Baskerville A, Lander KP. 1981. Experimental infection of Rhesus monkeys with a human strain of *Campylobacter jejuni*. J Hyg (Lond) 86:343-351.

Focher F, Lossani A, Verri A, Spadari S, Maioli A, Gambino JJ, Wright GE, Eberle R, Black DH, Medveczky P, Medveczky M, Shugar D. 2007. Sensitivity of monkey B virus (*Cercopithecine herpesvirus* 1) to antiviral drugs: Role of thymidine kinase in antiviral activities of substrate analogs and acyclonucleosides. Antimicrob Agents Ch 51:2028-2034.

Fogg MH, Garry D, Awad A, Wang F, Kaur A. 2006. The BZLF1 homolog of an Epstein-Barr-related gamma-herpesvirus is a frequent target of the CTL response in persistently infected rhesus macaques. J Immunol 176:3391-3401.

Foley JE, Lerche NW, Dumler JS, Madigan JE. 1999. A simian model of human granulocytic ehrlichiosis. Am J Trop Med Hyg 60:987-993.

Foucault C, Brouqui P, Raoult D. 2006. *Bartonella quintana* characteristics and clinical management. Emerg Infect Dis 12:217-223.

Fritz DL, Jaax NK, Lawrence WB, Davis KJ, Pitt ML, Ezzell JW, Friedlander AM. 1995. Pathology of experimental inhalation anthrax in the rhesus monkey. Lab Invest 73:691-702.

Frolova MP, Isachkova LM, Shestopalova NM, Pogodina VV. 1985. Experimental encephalitis in monkeys caused by the Powassan virus. Neurosci Behav Physiol 15:62-69.

Fultz PN, McGinn T, Davis IC, Romano JW, Li Y. 1999. Coinfection of macaques with simian immunodeficiency virus and simian T cell leukemia virus type I: Effects on virus burdens and disease progression. J Infect Dis 179:600-611.

Gajdusek DC, Gibbs CJ Jr. 1971. Transmission of two subacute spongiform encephalopathies of man (Kuru and Creutzfeldt-Jakob disease) to new world monkeys. Nature 230:588-591.

Gallinella G, Zuffi E, Gentilomi G, Manaresi E, Venturoli S, Bonvicini F, Cricca M, Zerbini M, Musiani M. 2003. Relevance of B19 markers in serum samples for a diagnosis of parvovirus B19-correlated diseases. J Med Virol 71:135-139.

Gao W, Tamin A, Soloff A, D'Aiuto L, Nwanegbo E, Robbins PD, Bellini WJ, Barratt-Boyes S, Gambotto A. 2003. Effects of a SARS-associated coronavirus vaccine in monkeys. Lancet 362:1895-1896.

Gardner MB. 1996. The history of simian AIDS. J Med Primatol 25:148-157.

Gardner MB, Luciw P, Lerche N, Marx P. 1988. Nonhuman primate retrovirus isolates and AIDS. Adv Vet Sci Comp Med 32:171-226.

Gardner MB, Jennings M, Carlson JR, Lerche N, McGraw T, Luciw P, Marx P, Pedersen N. 1989. Postexposure immunotherapy of simian immunodeficiency virus (SIV) infected rhesus with an SIV immunogen. J Med Primatol 18:321-328.

Gardner MJ, Hall N, Fung E, White O, Berriman M, Hyman RW, Carlton JM, Pain A, Nelson KE, Bowman S, Paulsen IT, James K, Eisen JA, Rutherford K, Salzberg SL, Craig A, Kyes S, Chan MS, Nene V, Shallom SJ, Suh B, Peterson J, Angiuoli S, Pertea M, Allen J, Selengut J, Haft D, Mather MW, Vaidya AB, Martin DM, Fairlamb AH, Fraunholz MJ, Roos DS, Ralph SA, McFadden GI, Cummings LM, Subramanian GM, Mungall C, Venter JC, Carucci DJ, Hoffman SL, Newbold C, Davis RW, Fraser CM, Barrell B. 2002. Genome sequence of the human malaria parasite *Plasmodium falciparum*. Nature 419:498-511.

Gardner MB, Carlos MP, Luciw PA. 2004. Simian retroviruses. In: Wormser GP, ed. AIDS and Other Manifestations of HIV Infection, 4th ed. Amsterdam: Elsevier Academic Press.

Gaynor AM, Nissen MD, Whiley DM, Mackay IM, Lambert SB, Wu G, Brennan DC, Storch GA, Sloots TP, Wang D. 2007. Identification of a novel polyomavirus from patients with acute respiratory tract infections. PLoS Pathog 3:e64.

Geisbert TW, Pushko P, Anderson K, Smith J, Davis KJ, Jahrling PB. 2002. Evaluation in nonhuman primates of vaccines against Ebola virus. Emerg Infect Dis 8:503-507.

Geisbert TW, Hensley LE, Jahrling PB, Larsen T, Geisbert JB, Paragas J, Young HA, Fredeking TM, Rote WE, Vlasuk GP. 2003a. Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: A study in rhesus monkeys. Lancet 362:1953-1958.

Geisbert TW, Young HA, Jahrling PB, Davis KJ, Larsen T, Kagan E, Hensley LE. 2003b. Pathogenesis of Ebola hemorrhagic fever in primate models: Evidence that hemorrhage is not a direct effect of virus-induced cytolysis of endothelial cells. Am J Pathol 163:2371-2382.

Geisbert TW, Jones S, Fritz EA, Shurtleff AC, Geisbert JB, Liebscher R, Grolla A, Stroher U, Fernando L, Daddario KM, Guttieri MC, Mothe BR, Larsen T, Hensley LE, Jahrling PB, Feldmann H. 2005. Development of a new vaccine for the prevention of Lassa fever. PLoS Med 2:e183.

Ghedin E, Wang S, Spiro D, Caler E, Zhao Q, Crabtree J, Allen JE, Delcher AL, Guiliano DB, Miranda-Saavedra D, Angiuoli SV, Creasy T, Amedeo P, Haas B, El-Sayed NM, Wortman JR, Feldblyum T, Tallon L, Schatz M, Shumway M, Koo H, Salzberg SL, Schobel S, Pertea M, Pop M, White O, Barton GJ, Carlow CK, Crawford MJ, Daub J, Dimmic MW, Estes CF, Foster JM, Ganatra M, Gregory WF, Johnson NM, Jin J, Komuniecki R, Korf I, Kumar S, Laney S, Li BW, Li W, Lindblom TH, Lustigman S, Ma D, Maina CV, Martin DM, McCarter JP, McReynolds L, Mitreva M, Nutman TB, Parkinson J, Peregrin-Alvarez JM, Poole C, Ren Q, Saunders L, Sluder AE, Smith K, Stanke M, Unnasch TR, Ware J, Wei AD, Weil G, Williams DJ, Zhang Y, Williams SA, Fraser-Liggett C, Slatko B, Blaxter ML, Scott AL. 2007. Draft genome of the filarial nematode parasite *Brugia malayi*. Science 317:1756-1760.

Gheit T, Sekkat S, Cova L, Chevallier M, Petit MA, Hantz O, Lesenechal M, Benslimane A, Trepo C, Chemin I. 2002. Experimental transfection of *Macaca sylvanus* with cloned human hepatitis B virus. J Gen Virol 83(Pt 7):1645-1649.

Gibbs CJ Jr, Gajdusek DC. 1973. Experimental subacute spongiform virus encephalopathies in primates and other laboratory animals. Science 182:67-68.

Giddens WE Jr, Tsai CC, Morton WR, Ochs HD, Knitter GH, Blakley GA. 1985. Retroperitoneal fibromatosis and acquired immunodeficiency syndrome in macaques: Pathologic observations and transmission studies. Am J Pathol 119:253-263.

Goldstein S, Ourmanov I, Brown CR, Plishka R, Buckler-White A, Byrum R, Hirsch VM. 2005. Plateau levels of viremia correlate with the degree of CD4+-T-cell loss in simian immunodeficiency virus SIVagm-infected pigtail macaques: Variable pathogenicity of natural SIVagm isolates. J Virol 79:5153-5162.

Gonder JC, Kishimoto RA, Kastello MD, Pedersen CE Jr, Larson EW. 1979. Cynomolgus monkey model for experimental Q fever infection. J Infect Dis 139:191-196.

Gonder JC, Kenyon RH, Pedersen CE Jr. 1980. Epidemic typhus infection in cynomolgus monkeys (*Macaca fascicularis*). Infect Immun 30:219-223.

Good RC. 1968. Biology of the mycobacterioses: Simian tuberculosis: Immunologic aspects. Ann N Y Acad Sci 154:200-213.

Gormus BJ, Xu K, Baskin GB, Martin LN, Bohm RP Jr, Blanchard JL, Mack PA, Ratterree MS, Meyers WM, Walsh GP. 1998. Experimental leprosy in rhesus monkeys: Transmission, susceptibility, clinical and immunological findings. Lepr Rev 69:235-245.

Gormus BJ, Baskin GB, Xu K, Ratterree MS, Mack PA, Bohm RP Jr, Meyers WM, Walsh GP. 2002. Anti-leprosy protective vaccination of rhesus monkeys with BCG or BCG plus heat-killed *Mycobacterium leprae*: Lepromin skin test results. Lepr Rev 73:254-261.

Goverdhan MK, Kulkarni AB, Gupta AK, Tupe CD, Rodrigues JJ. 1992. Two-way cross-protection between West Nile and Japanese encephalitis viruses in bonnet macaques. Acta Virol 36:277-283.

Graczyk TK, Cranfield MR, Kempske SE, Eckhaus MA. 1995. Fulminant *Streptococcus pneumoniae* meningitis in a lion-tailed macaque (*Macaca silenus*) without detected signs. J Wildl Dis 31:75-78.

Graff J, Nguyen H, Yu C, Elkins WR, St Claire M, Purcell RH, Emerson SU. 2005. The open reading frame 3 gene of hepatitis E virus contains a cis-reactive element and encodes a protein required for infection of macaques. J Virol 79:6680-6689.

Graffe A. 1991. A History of Experimental Virology. Berlin: Springer-Verlag.

Graham BS, Mascola JR. 2005. Lessons from failure: Preparing for future HIV-1 vaccine efficacy trials. J Infect Dis 191:647-649.

Gray WL. 2004. Simian varicella: A model for human varicella-zoster virus infections. Rev Med Virol 14:363-381.

Gray WL, Oakes JE. 1984. Simian varicella virus DNA shares homology with human varicella-zoster virus DNA. Virology 136:241-246.

Gray WL, Starnes B, White MW, Mahalingham R. 2001. The DNA sequence of the simian varicella virus genome. Virology 284:124-130.

Green LC, Didier PJ, Bowers LC, Didier ES. 2004. Natural and experimental infection of immunocompromised rhesus macaques (*Macaca mulatta*) with the microsporidian *Enterocytozoon bieneusi* genotype D. Microbes Infect 6:996-1002.

Groen J, Gerding M, Koeman JP, Roholl PJ, van Amerongen G, Jordans HG, Niesters HG, Osterhaus AD. 1995. A macaque model for hantavirus infection. J Infect Dis 172:38-44.

Guirakhoo F, Pugachev K, Zhang Z, Myers G, Levenbook I, Draper K, Lang J, Ocran S, Mitchell F, Parsons M, Brown N, Brandler S, Fournier C, Barrere B, Rizvi F, Travassos A, Nichols R, Trent D, Monath T. 2004. Safety and efficacy of chimeric yellow fever-dengue virus tetravalent vaccine formulations in nonhuman primates. J Virol 78:4761-4775.

Haagmans BL, Kuiken T, Martina BE, Fouchier RA, Rimmelzwaan GF, van Amerongen G, van Riel D, de Jong T, Itamura S, Chan KH, Tashiro M, Osterhaus AD. 2004. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat Med 10:290-293.

Haase AT. 2005. Perils at mucosal front lines for HIV and SIV and their hosts. Nat Rev Immunol 5:783-792.

Habis A, Baskin G, Simpson L, Fortgang I, Murphey-Corb M, Levy LS. 2000. Rhesus lymphocryptovirus infection during the progression of SAIDS and SAIDS-associated lymphoma in the rhesus macaque. AIDS Res Hum Retrov 16:163-171.

Hambleton P, Stephenson JR, Baskerville A, Wiblin CN. 1983. Pathogenesis and immune response of vaccinated and unvaccinated rhesus monkeys to tick-borne encephalitis virus. Infect Immun 40:995-1003.

Hansen SG, Strelow LI, Franchi DC, Anders DG, Wong SW. 2003. Complete sequence and genomic analysis of rhesus cytomegalovirus. J Virol 77:6620-6636.

Hawley HB, Yamada T, Mosher DF, Fine DP, Berendt RF. 1977. Disseminated intravascular coagulopathy during experimental pneumococcal sepsis: Studies in normal and asplenic rhesus monkeys. J Med Primatol 6:203-218.

Heise C, Vogel P, Miller CJ, Halsted CH, Dandekar S. 1993. Simian immunodeficiency virus infection of the gastrointestinal tract of rhesus macaques: Functional, pathological, and morphological changes. Am J Pathol 142:1759-1771.

Hepler RW, Kelly R, McNeely TB, Fan H, Losada MC, George HA, Woods A, Cope LD, Bansal A, Cook JC, Zang G, Cohen SL, Wei X, Keller PM, Leffel E, Joyce JG, Pitt L, Schultz LD, Jansen KU, Kurtz M. 2006. A recombinant 63-kDa form of *Bacillus anthracis* protective antigen produced in the yeast *Saccharomyces cerevisiae* provides protection in rabbit and primate inhalational challenge models of anthrax infection. Vaccine 24:1501-1514.

Heppner DG Jr, Kester KE, Ockenhouse CF, Tornieporth N, Ofori O, Lyon JA, Stewart VA, Dubois P, Lanar DE, Krzych U, Moris P, Angov E, Cummings JF, Leach A, Hall BT, Dutta S, Schwenk R, Hillier C, Barbosa A, Ware LA, Nair L, Darko CA, Withers MR, Ogutu B, Polhemus ME, Fukuda M, Pichyangkul S, Gettyacamin M, Diggs C, Soisson L, Milman J, Dubois MC, Garcon N, Tucker K, Wittes J, Plowe CV, Thera MA, Duombo OK, Pau MG, Goudsmit J, Ballou WR, Cohen J. 2005. Towards an RTS,S-based, multi-stage, multi-antigen vaccine against falciparum malaria: Progress at the Walter Reed Army Institute of Research. Vaccine 23:2243-2250.

Heraud JM, Edghill-Smith Y, Ayala V, Kalisz I, Parrino J, Kalyanaraman VS, Manischewitz J, King LR, Hryniewicz A, Trindade CJ, Hassett M, Tsai WP, Venzon D, Nalca A, Vaccari M, Silvera P, Bray M, Graham BS, Golding H, Hooper JW, Franchini G. 2006. Subunit recombinant vaccine protects against monkeypox. J Immunol 177:2552-2564.

Herchenroder O, Renne R, Loncar D, Cobb EK, Murthy KK, Schneider J, Mergia A, Luciw PA. 1994. Isolation, cloning, and sequencing of simian foamy viruses from chimpanzees (SFVcpz): High homology to human foamy virus (HFV). Virology 201:187-199.

Herzog C, Riviere J, Lescoutra-Etchegaray N, Charbonnier A, Leblanc V, Sales N, Deslys JP, Lasmezas CI. 2005. PrPTSE distribution in a primate model of variant, sporadic, and iatrogenic Creutzfeldt-Jakob disease. J Virol 79:14339-14345.

Hessell AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR. 2007. Fc receptor but not complement binding is important in antibody protection against HIV. Nature 449:101-104.

Hevey M, Negley D, Pushko P, Smith J, Schmaljohn A. 1998. Marburg virus vaccines based upon alphavirus replicons protect guinea pigs and nonhuman primates. Virology 251:28-37.

Hicks JT, Sullivan JL, Albrecht P. 1977. Immune responses during measles infection in immunosuppressed Rhesus monkeys. J Immunol 119: 1452-1456.

Higashi K, Asada H, Kurata T, Ishikawa K, Hayami M, Spriatna Y, Sutarman Y, Yamanishi K. 1989. Presence of antibody to human herpesvirus 6 in monkeys. J Gen Virol 70 (Pt 12):3171-3176.

Hirano M, Ding X, Tran HT, Li TC, Takeda N, Sata T, Nakamura S, Abe K. 2003. Prevalence of antibody against hepatitis E virus in various species of nonhuman primates: Evidence of widespread infection in Japanese monkeys (*Macaca fuscata*). Jpn J Infect Dis 56:8-11.

Hirsch VM, Olmsted RA, Murphey-Corb M, Purcell RH, Johnson PR. 1989. An African primate lentivirus (SIVsm) closely related to HIV-2. Nature 339:389-392.

Hoffman SJ, Polack FP, Hauer DA, Singh M, Billeter MA, Adams RJ, Griffin DE. 2003. Vaccination of rhesus macaques with a recombinant

measles virus expressing interleukin-12 alters humoral and cellular immune responses. J Infect Dis 188:1553-1561.

Honko AN, Sriranganathan N, Lees CJ, Mizel SB. 2006. Flagellin is an effective adjuvant for immunization against lethal respiratory challenge with *Yersinia pestis*. Infect Immun 74:1113-1120.

Hooper JW, Thompson E, Wilhelmsen C, Zimmerman M, Ichou MA, Steffen SE, Schmaljohn CS, Schmaljohn AL, Jahrling PB. 2004. Smallpox DNA vaccine protects nonhuman primates against lethal monkeypox. J Virol 78:4433-4443.

Hooper JW, Custer DM, Smith J, Wahl-Jensen V. 2006. Hantaan/Andes virus DNA vaccine elicits a broadly cross-reactive neutralizing antibody response in nonhuman primates. Virology 347:208-216.

Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, Savioli L. 2007. Control of neglected tropical diseases. N Engl J Med 357:1018-1027.

Hubbert WT. 1969. Melioidosis: Sources and potential. Wildl Dis 5:208-212.

Huff JL, Hansen LM, Solnick JV. 2004. Gastric transcription profile of *Helicobacter pylori* infection in the rhesus macaque. Infect Immun 72:216-226.

Hull RN. 1971. B virus vaccine. Lab Anim Sci 21:1068-1071.

Hunsmann G, Schneider J, Schmitt J, Yamamoto N. 1983. Detection of serum antibodies to adult T cell leukemia virus in nonhuman primates and in people from Africa. Int J Cancer 32:329-332.

Hutin YJ, Williams RJ, Malfait P, Pebody R, Loparev VN, Ropp SL, Rodriguez M, Knight JC, Tshioko FK, Khan AS, Szczeniowski MV, Esposito JJ. 2001. Outbreak of human monkeypox, Democratic Republic of Congo, 1996 to 1997. Emerg Infect Dis 7:434-438.

Igarashi T, Iyengar R, Byrum RA, Buckler-White A, Dewar RL, Buckler CE, Lane HC, Kamada K, Adachi A, Martin MA. 2007. Human immunodeficiency virus type 1 derivative with 7% simian immunodeficiency virus genetic content is able to establish infections in pig-tailed macaques. J Virol 81:11549-11552.

Ilyinskii PO, Daniel MD, Horvath CJ, Desrosiers RC. 1992. Genetic analysis of simian virus 40 from brains and kidneys of macaque monkeys. J Virol 66:6353-6360.

Inoue S, Morita K, Matias RR, Tuplano JV, Resuello RR, Candelario JR, Cruz DJ, Mapua CA, Hasebe F, Igarashi A, Natividad FF. 2003. Distribution of three arbovirus antibodies among monkeys (*Macaca fascicularis*) in the Philippines. J Med Primatol 32:89-94.

Ivanoff B, Tayot JL, Creach O, Fontanges R. 1978. Experimental cholera in monkeys. Bull Soc Pathol Exot Filiales 71:240-248.

Jahrling PB, Peters CJ. 1984. Passive antibody therapy of Lassa fever in cynomolgus monkeys: Importance of neutralizing antibody and Lassa virus strain. Infect Immun 44:528-533.

Jahrling PB, Peters CJ, Stephen EL. 1984. Enhanced treatment of Lassa fever by immune plasma combined with ribavirin in cynomolgus monkeys. J Infect Dis 149:420-427.

Jahrling PB, Hensley LE, Martinez MJ, Leduc JW, Rubins KH, Relman DA, Huggins JW. 2004. Exploring the potential of variola virus infection of cynomolgus macaques as a model for human smallpox. Proc Natl Acad Sci U S A 101:15196-15200.

Jainkittivong A, Langlais RP. 1998. Herpes B virus infection. Oral Surg Oral Med O 85:399-403.

Ji XH, Sun KY, Feng YH, Yin GQ. 2004. Changes of inflammation-associated cytokine expressions during early phase of experimental endotoxic shock in macaques. World J Gastroenterol 10:3026-3033.

Johnson DR, Azuolas J, Lavender CJ, Wishart E, Stinear TP, Hayman JA, Brown L, Jenkin GA, Fyfe JAM. 2007. *Mycobacterium ulcernas* in mosquitos captured during outbreak of Buruli ulcer, Southeastern Australia. Emerg Inf Dis 13:1653-1660.

Johnson PD, Stinear T, Small PL, Pluschke G, Merritt RW, Portaels F, Huygen K, Hayman JA, Asiedu K. 2005. Buruli ulcer (*M. ulcerans* infection): New insights, new hope for disease control. PLoS Med 2:e108.

Jones-Engel L, Engel GA, Schillaci MA, Rompis A, Putra A, Suaryana KG, Fuentes A, Beer B, Hicks S, White R, Wilson B, Allan JS. 2005. Primate-to-human retroviral transmission in Asia. Emerg Infect Dis 11:1028-1035.

Jones-Engel L, Engel GA, Schillaci MA, Lee B, Heidrich J, Chalise M, Kyes RC. 2006. Considering human-primate transmission of measles virus through the prism of risk analysis. Am J Primatol 68:868-879.

Kamili S, Spelbring J, Carson D, Krawczynski K. 2004. Protective efficacy of hepatitis E virus DNA vaccine administered by gene gun in the cynomolgus macaque model of infection. J Infect Dis 189:258-264.

Kang G, Pulimood AB, Koshi R, Hull A, Acheson D, Rajan P, Keusch GT, Mathan VI, Mathan MM. 2001. A monkey model for enterohemorrhagic *Escherichia coli* infection. J Infect Dis 184:206-210.

Kao LM, Bush K, Barnewall R, Estep J, Thalacker FW, Olson PH, Drusano GL, Minton N, Chien S, Hemeryck A, Kelley MF. 2006. Pharmacokinetic considerations and efficacy of levofloxacin in an inhalational anthrax (postexposure) rhesus monkey model. Antimicrob Agents Ch 50:3535-3552.

Karlen A. 1995. Man and Microbes. New York: Touchstone.

Kasa TJ, Lathrop GD, Dupuy HJ, Bonney CH, Toft JD. 1977. An endemic focus of *Trypanosoma cruzi* infection in a subhuman primate research colony. JAVMA 171:850-854.

Kawai HF, Koji T, Iida F, Kaneko S, Kobayashi K, Nakane PK. 1999. Shift of hepatitis E virus RNA from hepatocytes to biliary epithelial cells during acute infection of rhesus monkey. J Viral Hepat 6:287-297.

Kawai S, Matsumoto J, Aikawa M, Matsuda H. 2003. Increased plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell molecule-1 (sVCAM-1) associated with disease severity in a primate model for severe human malaria: *Plasmodium coatneyi*-infected Japanese macaques (*Macaca fuscata*). J Vet Med Sci 65:629-631.

Keele BF, Van Heuverswyn F, Li Y, Bailes E, Takehisa J, Santiago ML, Bibollet-Ruche F, Chen Y, Wain LV, Liegeois F, Loul S, Ngole EM, Bienvenue Y, Delaporte E, Brookfield JF, Sharp PM, Shaw GM, Peeters M, Hahn BH. 2006. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. Science 313:523-526.

Kelly DJ, Chulay JD, Mikesell P, Friedlander AM. 1992. Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. J Infect Dis 166:1184-1187.

Kennedy FM, Astbury J, Needham JR, Cheasty T. 1993. Shigellosis due to occupational contact with nonhuman primates. Epidemiol Infect 110: 247-251.

Kenyon RH, Rippy MK, McKee KT Jr, Zack PM, Peters CJ. 1992. Infection of *Macaca radiata* with viruses of the tick-borne encephalitis group. Microb Pathog 13:399-409.

Kestler HW 3rd, Ringler DJ, Mori K, Panicali DL, Sehgal PK, Daniel MD, Desrosiers RC. 1991. Importance of the *nef* gene for maintenance of high virus loads and for development of AIDS. Cell 65:651-662.

Kinsey MD, Formal SB, Dammin GJ, Giannella RA. 1976. Fluid and electrolyte transport in rhesus monkeys challenged intracecally with *Shigella flexneri* 2a. Infect Immun 14:368-371.

Kishimoto RA, Gonder JC, Johnson JW, Reynolds JA, Larson EW. 1981. Evaluation of a killed phase I *Coxiella burnetii* vaccine in cynomolgus monkeys (*Macaca fascicularis*). Lab Anim Sci 31:48-51.

Klingstrom J, Plyusnin A, Vaheri A, Lundkvist A. 2002. Wild-type Puumala hantavirus infection induces cytokines, C-reactive protein, creatinine, and nitric oxide in cynomolgus macaques. J Virol 76:444-449.

Klumpp SA, Novembre FJ, Anderson DC, Simon MA, Ringler DJ, McClure HM. 1993. Clinical and pathologic findings in infant rhesus macaques infected with SIVsmm by maternal transmission. J Med Primatol 22:169-176.

Knipe DM, Howley PM, Griffin DE, Lamb RA. 2006. Fields Virology, 5th ed. Philadelphia: Lippincott Williams & Wilkins.

Kobasa D, Jones SM, Shinya K, Kash JC, Copps J, Ebihara H, Hatta Y, Kim JH, Halfmann P, Hatta M, Feldmann F, Alimonti JB, Fernando L, Li Y, Katze MG, Feldmann H, Kawaoka Y. 2007. Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. Nature 445:319-323.

Kobune F, Takahashi H, Terao K, Ohkawa T, Ami Y, Suzaki Y, Nagata N,

Sakata H, Yamanouchi K, Kai C. 1996. Nonhuman primate models of measles. Lab Anim Sci 46:315-320.

Kodama M, Murakami K, Sato R, Okimoto T, Nishizono A, Fujioka T. 2005. *Helicobacter pylori*-infected animal models are extremely suitable for the investigation of gastric carcinogenesis. World J Gastroenterol 11:7063-7071.

Koehler JE, Sanchez MA, Tye S, Garrido-Rowland CS, Chen FM, Maurer T, Cooper JL, Olson JG, Reingold AL, Hadley WK, Regnery RR, Tappero JW. 2003. Prevalence of Bartonella infection among human immunodeficiency virus-infected patients with fever. Clin Infect Dis 37:559-566.

Kornegay RW, Giddens WE Jr, Van Hoosier GL Jr, Morton WR. 1985. Subacute nonsuppurative hepatitis associated with hepatitis B virus infection in two cynomolgus monkeys. Lab Anim Sci 35:400-404.

Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, Laman JD, de Jong T, van Doornum G, Lim W, Ling AE, Chan PK, Tam JS, Zambon MC, Gopal R, Drosten C, van der Werf S, Escriou N, Manuguerra JC, Stohr K, Peiris JS, Osterhaus AD. 2003. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 362:263-270.

Kuiken T, van den Hoogen BG, van Riel DA, Laman JD, van Amerongen G, Sprong L, Fouchier RA, Osterhaus AD. 2004. Experimental human metapneumovirus infection of cynomolgus macaques (*Macaca fascicularis*) results in virus replication in ciliated epithelial cells and pneumocytes with associated lesions throughout the respiratory tract. Am J Pathol 164:1893-1900.

Kunz E, Matz-Rensing K, Stolte N, Hamilton PB, Kaup FJ. 2002. Reactivation of a *Trypanosoma cruzi* infection in a rhesus monkey (*Macaca mulatta*) experimentally infected with SIV. Vet Pathol 39:721-725.

Kutok JL, Klumpp S, Simon M, MacKey JJ, Nguyen V, Middeldorp JM, Aster JC, Wang F. 2004. Molecular evidence for rhesus lymphocryptovirus infection of epithelial cells in immunosuppressed rhesus macaques. J Virol 78:3455-3461.

Kwang HS, Pedersen NC, Lerche NW, Osborn KG, Marx PA, Gardner MB. 1987. Viremia, antigenemia, and serum antibodies in rhesus macaques infected with simian retrovirus type 1 and their relationship to disease course. Lab Invest 56:591-597.

Lackner AA, Veazey RS. 2007. Current concepts in AIDS pathogenesis: Insights from the SIV/macaque model. Ann Rev Med 58:461-476.

Lake-Bakaar DM, Abele G, Lindborg B, Soike KF, Datema R. 1988. Pharmacokinetics and antiviral activity in simian varicella virus-infected monkeys of (R,S)-9-[4-hydroxy-2-(hydroxymethyl) butyl]guanine, an anti-varicella-zoster virus drug. Antimicrob Agents Ch 32: 1807-1812.

Langermans JA, Andersen P, van Soolingen D, Vervenne RA, Frost PA, van der Laan T, van Pinxteren LA, van den Hombergh J, Kroon S, Peekel I, Florquin S, Thomas AW. 2001. Divergent effect of bacillus Calmette-Guerin (BCG) vaccination on *Mycobacterium tuberculosis* infection in highly related macaque species: Implications for primate models in tuberculosis vaccine research. Proc Natl Acad Sci U S A 98:11497-11502.

Lapin B, Andreevna L. 1963. Comparative Pathology in Monkeys. Springfield IL: Thomas.

Lasmezas CI, Fournier JG, Nouvel V, Boe H, Marce D, Lamoury F, Kopp N, Hauw JJ, Ironside J, Bruce M, Dormont D, Deslys JP. 2001. Adaptation of the bovine spongiform encephalopathy agent to primates and comparison with Creutzfeldt-Jakob disease: Implications for human health. Proc Natl Acad Sci U S A 98:4142-4147.

Lasmezas CI, Comoy E, Hawkins S, Herzog C, Mouthon F, Konold T, Auvre F, Correia E, Lescoutra-Etchegaray N, Sales N, Wells G, Brown P, Deslys JP. 2005. Risk of oral infection with bovine spongiform encephalopathy agent in primates. Lancet 365:781-783.

Le Bras J, Larouze B, Geniteau M, Andrieu B, Dazza MC, Rodhain F. 1984. Malaria, arbovirus and hepatitis infections in *Macaca fascicularis* from Malaysia. Lab Anim 18:61-64.

Leong YK, Awang A. 1990. Experimental group A rotaviral infection in cynomolgus monkeys raised on formula diet. Microbiol Immunol 34: 153-162.

Leroy EM, Rouquet P, Formenty P, Souquiere S, Kilbourne A, Froment JM, Bermejo M, Smit S, Karesh W, Swanepoel R, Zaki SR, Rollin PE. 2004. Multiple Ebola virus transmission events and rapid decline of central African wildlife. Science 303:387-390.

Letvin NL. 2006. Progress and obstacles in the development of an AIDS vaccine. Nat Rev Immunol 6:930-939.

Letvin NL, King NW. 1984. Clinical and pathologic features of an acquired immune deficiency syndrome (AIDS) in macaque monkeys. Adv Vet Sci Comp Med 28:237-265.

Letvin NL, Daniel MD, Sehgal PK, Desrosiers RC, Hunt RD, Waldron LM, MacKey JJ, Schmidt DK, Chalifoux LV, King NW. 1985. Induction of AIDS-like disease in macaque monkeys with T cell tropic retrovirus STLV-III. Science 230:71-73.

Levine PH, Leiseca SA, Hewetson JF, Traul KA, Andrese AP, Granlund DJ, Fabrizio P, Stevens DA. 1980. Infection of rhesus monkeys and chimpanzees with Epstein-Barr virus. Arch Virol 66:341-351.

Levy JA. 2007. HIV and the Pathogenesis of AIDS, 3rd ed. Washington: ASM Press.

Li Q, Dong C, Wang J, Che Y, Jiang L, Wang J, Sun M, Wang L, Huang J, Ren D. 2003. Induction of hepatitis C virus-specific humoral and cellular immune responses in mice and rhesus by artificial multiple epitopes sequence. Viral Immunol 16:321-333.

Li BJ, Tang Q, Cheng D, Qin C, Xie FY, Wei Q, Xu J, Liu Y, Zheng BJ, Woodle MC, Zhong N, Lu PY. 2005a. Using siRNA in prophylactic and therapeutic regimens against SARS coronavirus in Rhesus macaque. Nat Med 11:944-951.

Li SW, Zhang J, Li YM, Ou SH, Huang GY, He ZQ, Ge SX, Xian YL, Pang SQ, Ng MH, Xia NS. 2005b. A bacterially expressed particulate hepatitis E vaccine: Antigenicity, immunogenicity and protectivity on primates. Vaccine 23:2893-2901.

Lichtenwalner AB, Patton DL, Van Voorhis WC, Sweeney YT, Kuo CC. 2004. Heat shock protein 60 is the major antigen which stimulates delayed-type hypersensitivity reaction in the macaque model of *Chlamydia trachomatis* salpingitis. Infect Immun 72:1159-1161.

Lindsley HB, Kysela S, Steinberg AD. 1974. Nucleic acid antibodies in African trypanosomiasis: Studies in Rhesus monkeys and man. J Immunol 113:1921-1927.

Line AS, Paul-Murphy J, Aucoin DP, Hirsh DC. 1992. Enrofloxacin treatment of long-tailed macaques with acute bacillary dysentery due to multiresistant *Shigella flexneri* IV. Lab Anim Sci 42:240-244.

Ling B, Apetrei C, Pandrea I, Veazey RS, Lackner AA, Gormus B, Marx PA. 2004. Classic AIDS in a sooty mangabey after an 18-year natural infection. J Virol 78:8902-8908.

Linial ML. 1999. Foamy viruses are unconventional retroviruses. J Virol 73:1747-1755.

Lockridge KM, Sequar G, Zhou SS, Yue Y, Mandell CP, Barry PA. 1999. Pathogenesis of experimental rhesus cytomegalovirus infection. J Virol 73:9576-9583.

Lockridge KM, Zhou SS, Kravitz RH, Johnson JL, Sawai ET, Blewett EL, Barry PA. 2000. Primate cytomegaloviruses encode and express an IL-10-like protein. Virology 268:272-280.

Lodmell DL, Ray NB, Parnell MJ, Ewalt LC, Hanlon CA, Shaddock JH, Sanderlin DS, Rupprecht CE. 1998. DNA immunization protects nonhuman primates against rabies virus. Nat Med 4:949-952.

Lodmell DL, Parnell MJ, Bailey JR, Ewalt LC, Hanlon CA. 2002. Rabies DNA vaccination of nonhuman primates: Post-exposure studies using gene gun methodology that accelerates induction of neutralizing antibody and enhances neutralizing antibody titers. Vaccine 20:2221-2228.

Loomis-Huff JE, Eberle R, Lockridge KM, Rhodes G, Barry PA. 2001. Immunogenicity of a DNA vaccine against herpes B virus in mice and rhesus macaques. Vaccine 19:4865-4873.

Lowenstine LJ, Pedersen NC, Higgins J, Pallis KC, Uyeda A, Marx P, Lerche NW, Munn RJ, Gardner MB. 1986. Seroepidemiologic survey of captive Old-World primates for antibodies to human and simian retroviruses, and isolation of a lentivirus from sooty mangabeys (*Cercocebus atys*). Int J Cancer 38:563-574.

Lukashevich IS, Djavani M, Rodas JD, Zapata JC, Usborne A, Emerson C, Mitchen J, Jahrling PB, Salvato MS. 2002. Hemorrhagic fever occurs

after intravenous, but not after intragastric, inoculation of rhesus macaques with lymphocytic choriomeningitis virus. J Med Virol 67:171-186.

Lukashevich IS, Tikhonov I, Rodas JD, Zapata JC, Yang Y, Djavani M, Salvato MS. 2003. Arenavirus-mediated liver pathology: Acute lymphocytic choriomeningitis virus infection of rhesus macaques is characterized by high-level interleukin-6 expression and hepatocyte proliferation. J Virol 77:1727-1737.

Lusso P, Secchiero P, Crowley RW. 1994. In vitro susceptibility of *Macaca nemestrina* to human herpesvirus 6: A potential animal model of coinfection with primate immunodeficiency viruses. AIDS Res Hum Retrov 10:181-187.

Lusso P, Crowley RW, Malnati MS, Di Serio C, Ponzoni M, Biancotto A, Markham PD, Gallo RC. 2007. Human herpesvirus 6A accelerates AIDS progression in macaques. Proc Natl Acad Sci U S A 104:5067-5072.

MacMillan JG, Rice RM, Jerrells TR. 1985. Development of antigen-specific cell-mediated immune responses after infection of cynomolgus monkeys (*Macaca fascicularis*) with *Rickettsia tsutsugamushi*. J Infect Dis 152:739-749.

Maddison SE, Slemenda SB, Hillyer GV, Chandler FW, Kagan IG. 1979. Immune responses to *Schistosoma mansoni* in rhesus monkeys with multiple chronic and early primary infections. Infect Immun 25:249-254.

Majer M, Behrens F, Weinmann E, Mauler R, Maass G, Baumeister HG, Luthardt T. 1978. Diarrhea in newborn cynomologus monkeys infected with human rotavirus. Infection 6:71-72.

Mandell GL, Bennett JE, Dolin R. 2005. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier.

Mankowski JL, Flaherty MT, Spelman JP, Hauer DA, Didier PJ, Amedee AM, Murphey-Corb M, Kirstein LM, Munoz A, Clements JE, Zink MC. 1997. Pathogenesis of simian immunodeficiency virus encephalitis: Viral determinants of neurovirulence. J Virol 71:6055-6060.

Mansfield KG, Westmoreland SV, DeBakker CD, Czajak S, Lackner AA, Desrosiers RC. 1999. Experimental infection of rhesus and pigtail macaques with macaque rhadinoviruses. J Virol 73:10320-10328.

Mansfield KG, Lin KC, Newman J, Schauer D, MacKey J, Lackner AA, Carville A. 2001. Identification of enteropathogenic *Escherichia coli* in simian immunodeficiency virus-infected infant and adult rhesus macaques. J Clin Microbiol 39:971-976.

Mao JS, Go YY, Huang HY, Yu PH, Huang BZ, Ding ZS, Chen NL, Yu JH, Xie RY. 1981. Susceptibility of monkeys to human hepatitis A virus. J Infect Dis 144:55-60.

Marchevsky RS, Freire MS, Coutinho ES, Galler R. 2003. Neurovirulence of yellow fever 17DD vaccine virus to rhesus monkeys. Virology 316: 55-63.

Marquardt WH, Demaree RS, Grieve RB. 2000. Parasitology and Vector Biology. San Diego: Harcourt/Academic.

Marra CM, Handsfield HH, Kuller L, Morton WR, Lukehart SA. 1992. Alterations in the course of experimental syphilis associated with concurrent simian immunodeficiency virus infection. J Infect Dis 165: 1020-1025.

Marra CM, Castro CD, Kuller L, Dukes AC, Centurion-Lara A, Morton WR, Lukehart SA. 1998. Mechanisms of clearance of *Treponema pallidum* from the CSF in a nonhuman primate model. Neurology 51:957-961.

Marthas ML, Ramos RA, Lohman BL, Van Rompay KK, Unger RE, Miller CJ, Banapour B, Pedersen NC, Luciw PA. 1993. Viral determinants of simian immunodeficiency virus (SIV) virulence in rhesus macaques assessed by using attenuated and pathogenic molecular clones of SIVmac. J Virol 67:6047-6055.

Marthas ML, van Rompay KK, Otsyula M, Miller CJ, Canfield DR, Pedersen NC, McChesney MB. 1995. Viral factors determine progression to AIDS in simian immunodeficiency virus-infected newborn rhesus macaques. J Virol 69:4198-4205.

Marx PA, Pedersen NC, Lerche NW, Osborn KG, Lowenstine LJ, Lackner AA, Maul DH, Kwang HS, Kluge JD, Zaiss CP, Sharpe V, Spinner AP, Allison AC, Gardner MB. 1986. Prevention of simian acquired immune deficiency syndrome with a formalin-inactivated type D retrovirus vaccine. J Virol 60:431-435.

Mason RA, Tauraso NM, Spertzel RO, Ginn RK. 1973. Yellow fever vaccine: Direct challenge of monkeys given graded doses of 17D vaccine. Appl Microbiol 25:539-544.

Masters CL, Alpers MP, Gajdusek DC, Gibbs CJ Jr, Kakulas BA. 1976. Experimental kuru in the gibbon and sooty mangabey and Creutzfeldt-Jakob disease in the pigtail macaque, with a summary of the host range of the subacute spongiform virus encephalopathies. J Med Primatol 5:205-209.

Mattapallil JJ, Dandekar S, Canfield DR, Solnick JV. 2000. A predominant Th1 type of immune response is induced early during acute *Helicobacter pylori* infection in rhesus macaques. Gastroenterology 118:307-315.

Matz-Rensing K, Floto A, Schrod A, Becker T, Finke EJ, Seibold E, Splettstoesser WD, Kaup FJ. 2007. Epizootic of tularemia in an outdoor housed group of cynomolgus monkeys (*Macaca fascicularis*). Vet Pathol 44:327-334.

Maul DH, Zaiss CP, MacKenzie MR, Shiigi SM, Marx PA, Gardner MB. 1988. Simian retrovirus D serogroup 1 has a broad cellular tropism for lymphoid and nonlymphoid cells. J Virol 62:1768-1773.

McArthur-Vaughan K, Gershwin LJ. 2002. A rhesus monkey model of respiratory syncytial virus infection. J Med Primatol 31:61-73.

McClure J, Schmidt JM, Ray-Cuille MA, Bannick J, Misher L, Tsai C-C, Anderson DM, Morton WR, Hu SL. 2000. Derivation and characterization of a highly pathogenic isolate of human immunodeficient virus type 2 that causes rapid CD4+ cell depletion in *Macaca nemestrina.* J Med Primatol 29:114-126.

McElroy AK, Bray M, Reed DS, Schmaljohn CS. 2002. Andes virus infection of cynomolgus macaques. J Infect Dis 186:1706-1712.

McMichael AJ. 2006. HIV vaccines. Ann Rev Immunol 24:227-255.

McNeely TB, Staub JM, Rusk CM, Blum MJ, Donnelly JJ. 1998. Antibody responses to capsular polysaccharide backbone and O-acetate side groups of *Streptococcus pneumoniae* type 9V in humans and rhesus macaques. Infect Immun 66:3705-3710.

McShane H, Pathan AA, Sander CR, Keating SM, Gilbert SC, Huygen K, Fletcher HA, Hill AV. 2004. Recombinant modified vaccinia virus Ankara expressing antigen 85A boosts BCG-primed and naturally acquired antimycobacterial immunity in humans. Nat Med 10:1240-1244.

Meisenhelder JE, Thompson PE. 1963. Comparative observations on experimental *Schistosoma Mansoni* infections in African green and rhesus monkeys. J Parasitol 49:568-570.

Men R, Wyatt L, Tokimatsu I, Arakaki S, Shameem G, Elkins R, Chanock R, Moss B, Lai CJ. 2000. Immunization of rhesus monkeys with a recombinant of modified vaccinia virus Ankara expressing a truncated envelope glycoprotein of dengue type 2 virus induced resistance to dengue type 2 virus challenge. Vaccine 18:3113-3122.

Mense MG, Borschel RH, Wilhelmsen CL, Pitt ML, Hoover DL. 2004. Pathologic changes associated with brucellosis experimentally induced by aerosol exposure in rhesus macaques (*Macaca mulatta*). Am J Vet Res 65:644-652.

Mett V, Lyons J, Musiychuk K, Chichester JA, Brasil T, Couch R, Sherwood R, Palmer GA, Streatfield SJ, Yusibov V. 2007. A plant-produced plague vaccine candidate confers protection to monkeys. Vaccine 25:3014-3017.

Meyer KF, Smith G, Foster L, Brookman M, Sung M. 1974. Live, attenuated *Yersinia pestis* vaccine: Virulent in nonhuman primates, harmless to guinea pigs. J Infect Dis 129 Suppl:S85-S12.

Miller CJ, Alexander NJ, Sutjipto S, Lackner AA, Gettie A, Hendrickx AG, Lowenstine LJ, Jennings M, Marx PA. 1989. Genital mucosal transmission of simian immunodeficiency virus: Animal model for heterosexual transmission of human immunodeficiency virus. J Virol 63: 4277-4284

Miyoshi I, Fujishita M, Taguchi H, Matsubayashi K, Miwa N, Tanioka Y. 1983. Natural infection in nonhuman primates with adult T cell leukemia virus or a closely related agent. Int J Cancer 32:333-336.

Moghaddam A, Rosenzweig M, Lee-Parritz D, Annis B, Johnson RP, Wang F. 1997. An animal model for acute and persistent Epstein-Barr virus infection. Science 276:2030-2033.

Monath TP, Levenbook I, Soike K, Zhang ZX, Ratterree M, Draper K, Barrett AD, Nichols R, Weltzin R, Arroyo J, Guirakhoo F. 2000. Chimeric yellow fever virus 17D-Japanese encephalitis virus vaccine: Dose-response effectiveness and extended safety testing in rhesus monkeys. J Virol 74:1742-1751.

Monath TP, Liu J, Kanesa-Thasan N, Myers GA, Nichols R, Deary A, McCarthy K, Johnson C, Ermak T, Shin S, Arroyo J, Guirakhoo F, Kennedy JS, Ennis FA, Green S, Bedford P. 2006. A live, attenuated recombinant West Nile virus vaccine. Proc Natl Acad Sci U S A 103:6694-6699.

Mone J, Whitehead E, Leland M, Hubbard G, Allan JS. 1992. Simian T-cell leukemia virus type I infection in captive baboons. AIDS Res Hum Retrov 8:1653-1661.

Mooser H, Weyer F. 1953. Experimental infection of Macacus rhesus with *Rickettsia quintana* (trench fever). Proc Soc Exp Biol Med 83:699-701.

Morrill JC, Peters CJ. 2003. Pathogenicity and neurovirulence of a mutagen-attenuated Rift Valley fever vaccine in rhesus monkeys. Vaccine 21:2994-3002.

Morrill JC, Jennings GB, Cosgriff TM, Gibbs PH, Peters CJ. 1989. Prevention of Rift Valley fever in rhesus monkeys with interferon-alpha. Rev Infect Dis 11 Suppl 4:S815-S825.

Morris SA, Tanowitz HB, Wittner M, Bilezikian JP. 1990. Pathophysiological insights into the cardiomyopathy of Chagas' disease. Circulation 82:1900-1909.

Morton WR, Bronsdon M, Mickelsen G, Knitter G, Rosenkranz S, Kuller L, Sajuthi D. 1983. Identification of *Campylobacter jejuni* in *Macaca fascicularis* imported from Indonesia. Lab Anim Sci 33:187-188.

Mulder JB. 1971. Shigellosis in nonhuman primates: A review. Lab Anim Sci 21:734-738.

Mumphrey SM, Changotra H, Moore TN, Heimann-Nichols ER, Wobus CE, Reilly MJ, Moghadamfalahi M, Shukla D, Karst SM. 2007. Murine norovirus 1 infection is associated with histopathological changes in immunocompetent hosts, but clinical disease is prevented by STAT1-dependent interferon responses. J Virol 81:3251-3263.

Murphey-Corb M, Martin LN, Rangan SR, Baskin GB, Gormus BJ, Wolf RH, Andes WA, West M, Montelaro RC. 1986. Isolation of an HTLV-III-related retrovirus from macaques with simian AIDS and its possible origin in asymptomatic mangabeys. Nature 321:435-437.

Murphy FA. 1998. Emerging zoonoses. Emerg Infect Dis 4:429-435.

Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, Zanardi LR, Setia S, Fair E, LeBaron CW, Wharton M, Livengood JR. 2001. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 344:564-572.

Myint KS, Raengsakulrach B, Young GD, Gettayacamin M, Ferguson LM, Innis BL, Hoke CH Jr, Vaughn DW. 1999. Production of lethal infection that resembles fatal human disease by intranasal inoculation of macaques with Japanese encephalitis virus. Am J Trop Med Hyg 60: 338-342.

Nagata N, Iwasaki T, Ami Y, Harashima A, Hatano I, Suzaki Y, Yoshii K, Yoshii T, Nomoto A, Kurata T. 2001. Comparison of neuropathogenicity of poliovirus type 3 in transgenic mice bearing the poliovirus receptor gene and cynomolgus monkeys. Vaccine 19:3201-3208.

Nagle RB, Ward PA, Lindsley HB, Sadun EH, Johnson AJ, Berkaw RE, Hildebrandt PK. 1974. Experimental infections with African Trypanosomes. VI. Glomerulonephritis involving the alternate pathway of complement activation. Am J Trop Med Hyg 23:15-26.

Nakamura H, Hayami M, Ohta Y, Ishikawa K, Tsujimoto H, Kiyokawa T, Yoshida M, Sasagawa A, Honjo S. 1987. Protection of cynomolgus monkeys against infection by human T cell leukemia virus type-I by immunization with viral env gene products produced in *Escherichia coli*. Int J Cancer 40:403-407.

Nakao E, Hotta S. 1973. Immunogenicity of purified, inactivated chikungunya virus in monkeys. B World Health Organ 48:559-562.

Napier JR, Napier PH. 1985. The Natural History of the Primates. Cambridge MA: MIT Press.

Narasimhan S, Caimano MJ, Liang FT, Santiago F, Laskowski M, Philipp MT, Pachner AR, Radolf JD, Fikrig E. 2003. *Borrelia burgdorferi* transcriptome in the central nervous system of nonhuman primates. Proc Natl Acad Sci U S A 100:15953-15958.

Nathanson N, Mathieson BJ. 2000. Biological considerations in the development of a human immunodeficiency virus vaccine. J Infect Dis 182: 579-589.

NCRR [National Center for Research Resources]. 2004-2008. Strategic Plan: Challenges and Critical Choices. Bethesda: National Institutes of Health.

Neal DE Jr, Dilworth JP, Kaack MB, Didier P, Roberts JA. 1990. Experimental prostatitis in nonhuman primates: II. Ascending acute prostatitis. Prostate 17:233-239.

Nene V, Wortman JR, Lawson D, Haas B, Kodira C, Tu ZJ, Loftus B, Xi Z, Megy K, Grabherr M, Ren Q, Zdobnov EM, Lobo NF, Campbell KS, Brown SE, Bonaldo MF, Zhu J, Sinkins SP, Hogenkamp DG, Amedeo P, Arensburger P, Atkinson PW, Bidwell S, Biedler J, Birney E, Bruggner RV, Costas J, Coy MR, Crabtree J, Crawford M, Debruyn B, Decaprio D, Eiglmeier K, Eisenstadt E, El-Dorry H, Gelbart WM, Gomes SL, Hammond M, Hannick LI, Hogan JR, Holmes MH, Jaffe D, Johnston JS, Kennedy RC, Koo H, Kravitz S, Kriventseva EV, Kulp D, Labutti K, Lee E, Li S, Lovin DD, Mao C, Mauceli E, Menck CF, Miller JR, Montgomery P, Mori A, Nascimento AL, Naveira HF, Nusbaum C, O'Leary S, Orvis J, Pertea M, Quesneville H, Reidenbach KR, Rogers YH, Roth CW, Schneider JR, Schatz M, Shumway M, Stanke M, Stinson EO, Tubio JM, Vanzee JP, Verjovski-Almeida S, Werner D, White O, Wyder S, Zeng Q, Zhao Q, Zhao Y, Hill CA, Raikhel AS, Soares MB, Knudson DL, Lee NH, Galagan J, Salzberg SL, Paulsen IT, Dimopoulos G, Collins FH, Birren B, Fraser-Liggett CM, Severson DW. 2007. Genome sequence of *Aedes aegypti*, a major arbovirus vector. Science 316:1718-1723.

Ni YS, Chan TC, Chao CC, Richards AL, Dasch GA, Ching WM. 2005. Protection against scrub typhus by a plasmid vaccine encoding the 56-KD outer membrane protein antigen gene. Am J Trop Med Hyg 73:936-941.

Nigam P, Earl PL, Americo JL, Sharma S, Wyatt LS, Edghill-Spano Y, Chennareddi LS, Silvera P, Moss B, Robinson HL, Amara RR. 2007. DNA/MVA HIV-1/AIDS vaccine elicits long-lived vaccinia virus-specific immunity and confers protection against a lethal monkeypox challenge. Virology 366:73-83.

Noguchi H, Battistini TS. 1926. Etiology of Oroya fever: I. Cultivation of *Bartonella bacilliformis*. J Ex Med 43:841-864.

North TW, Van Rompay KK, Higgins J, Matthews TB, Wadford DA, Pedersen NC, Schinazi RF. 2005. Suppression of virus load by highly active antiretroviral therapy in rhesus macaques infected with a recombinant simian immunodeficiency virus containing reverse transcriptase from human immunodeficiency virus type 1. J Virol 79:7349-7354.

Novembre FJ, Saucier M, Anderson DC, Klumpp SA, O'Neil SP, Brown CR 2nd, Hart CE, Guenthner PC, Swenson RB, McClure HM. 1997. Development of AIDS in a chimpanzee infected with human immunodeficiency virus type 1. J Virol 71:4086-4091.

O'Rourke LG, Pitulle C, Hegarty BC, Kraycirik S, Killary KA, Grosenstein P, Brown JW, Breitschwerdt EB. 2005. *Bartonella quintana* in cynomolgus monkey (*Macaca fascicularis*). Emerg Infect Dis 11:1931-1934.

O'Sullivan MG, Anderson DC, Fikes JD, Bain FT, Carlson CS, Green SW, Young NS, Brown KE. 1994. Identification of a novel simian parvovirus in cynomolgus monkeys with severe anemia: A paradigm of human B19 parvovirus infection. J Clin Invest 93:1571-1576.

O'Sullivan MG, Anderson DK, Goodrich JA, Tulli H, Green SW, Young NS, Brown KE. 1997. Experimental infection of cynomolgus monkeys with simian parvovirus. J Virol 71:4517-4521.

Oldstone MBA. 1998. Viruses, Plagues, and History. Oxford UK: Oxford University.

Olson LC, Skinner SF, Palotay JL, McGhee GE. 1986. Encephalitis associated with *Trypanosoma cruzi* in a Celebes black macaque. Lab Anim Sci 36:667-670.

Ostrow RS, McGlennen RC, Shaver MK, Kloster BE, Houser D, Faras AJ. 1990. A rhesus monkey model for sexual transmission of a papillomavirus isolated from a squamous cell carcinoma. Proc Natl Acad Sci U S A 87:8170-8174.

Ostrow RS, Coughlin SM, McGlennen RC, Johnson AN, Ratterree MS, Scheffler J, Yaegashi N, Galloway DA, Faras AJ. 1995. Serological and molecular evidence of rhesus papillomavirus type 1 infections in tissues from geographically distinct institutions. J Gen Virol 76 (Pt 2):293-299.

Ostrowski SR, Leslie MJ, Parrott T, Abelt S, Piercy PE. 1998. B virus from pet macaque monkeys: An emerging threat in the United States? Emerg Infect Dis 4:117-121.

Oswald WB, Geisbert TW, Davis KJ, Geisbert JB, Sullivan NJ, Jahrling PB, Parren PW, Burton DR. 2007. Neutralizing antibody fails to impact the course of Ebola virus infection in monkeys. PLoS Pathog 3:e9.

Pachner AR, Delaney E, Zhang WF, O'Neill T, Major E, Frey AB, Davidson E. 1999. Protection from Lyme neuroborreliosis in nonhuman primates with a multiantigenic vaccine. Clin Immunol 91:310-313.

Pachner AR, Dail D, Narayan K, Dutta K, Cadavid D. 2002. Increased expression of B-lymphocyte chemoattractant, but not pro-inflammatory cytokines, in muscle tissue in rhesus chronic Lyme borreliosis. Cytokine 19:297-307.

Pachner AR, Dail D, Bai Y, Sondey M, Pak L, Narayan K, Cadavid D. 2004. Genotype determines phenotype in experimental Lyme borreliosis. Ann Neurol 56:361-370.

Pahar B, Li J, McChesney MB. 2005. Detection of T cell memory to measles virus in experimentally infected rhesus macaques by cytokine flow cytometry. J Immunol Methods 304:174-183.

Palmer AE, Allen AM, Tauraso NM, Shelokov A. 1968. Simian hemorrhagic fever. I. Clinical and epizootiologic aspects of an outbreak among quarantined monkeys. Am J Trop Med Hyg 17:404-412.

Palmer S, Brown D, Morgan D. 2005. Early qualitative risk assessment of the emerging zoonotic potential of animal diseases. BMJ 331:1256-1260.

Patton DL. 1985. Immunopathology and histopathology of experimental chlamydial salpingitis. Rev Infect Dis 7:746-753.

Patton DL, Sweeney YT, Balkus JE, Hillier SL. 2006. Vaginal and rectal topical microbicide development: Safety and efficacy of 1.0% Savvy (C31G) in the pigtail macaque. Sex Transm Dis 33:691-695.

Patton DL, Sweeney YT, Stamm WE. 2005. Significant reduction in inflammatory response in the macaque model of chlamydial pelvic inflammatory disease with azithromycin treatment. J Infect Dis 192:129-135.

Paul SD, Singh KR. 1968. Experimental infection of *Macaca radiata* with Chikungunya virus and transmission of virus by mosquitoes. Indian J Med Res 56:802-811.

Peeling RW, Patton DL, Cosgrove Sweeney YT, Cheang MS, Lichtenwalner AB, Brunham RC, Stamm WE. 1999. Antibody response to the chlamydial heat-shock protein 60 in an experimental model of chronic pelvic inflammatory disease in monkeys (*Macaca nemestrina*). J Infect Dis 180:774-779.

Peiris JS, Dittus WP, Ratnayake CB. 1993. Seroepidemiology of dengue and other arboviruses in a natural population of toque macaques (*Macaca sinica*) at Polonnaruwa, Sri Lanka. J Med Primatol 22:240-245.

Percy DH, Egwu IN, Jonas AM. 1972. Experimental *Brucella canis* infection in the monkey (*Macaca arctoides*). Can J Comp Med 36:221-225.

Perelygina L, Zhu L, Zurkuhlen H, Mills R, Borodovsky M, Hilliard JK. 2003. Complete sequence and comparative analysis of the genome of herpes B virus (*Cercopithecine herpesvirus* 1) from a rhesus monkey. J Virol 77:6167-6177.

Permar SR, Klumpp SA, Mansfield KG, Kim WK, Gorgone DA, Lifton MA, Williams KC, Schmitz JE, Reimann KA, Axthelm MK, Polack FP, Griffin DE, Letvin NL. 2003. Role of CD8(+) lymphocytes in control and clearance of measles virus infection of rhesus monkeys. J Virol 77:4396-4400.

Persson GR, Engel LD, Whitney CW, Weinberg A, Moncla BJ, Darveau RP, Houston L, Braham P, Page RC. 1994. *Macaca fascicularis* as a model in which to assess the safety and efficacy of a vaccine for periodontitis. Oral Microbiol Immun 9:104-111.

Peters CJ, Reynolds JA, Slone TW, Jones DE, Stephen EL. 1986. Prophylaxis of Rift Valley fever with antiviral drugs, immune serum, an interferon inducer, and a macrophage activator. Antiviral Res 6:285-297.

Peters CJ, Jones D, Trotter R, Donaldson J, White J, Stephen E, Slone TW Jr. 1988. Experimental Rift Valley fever in rhesus macaques. Arch Virol 99:31-44.

Petschow BW, Litov RE, Young LJ, McGraw TP. 1992. Response of colostrum-deprived cynomolgus monkeys to intragastric challenge exposure with simian rotavirus strain SA11. Am J Vet Res 53:674-678.

Philipp MT, Aydintug MK, Bohm RP Jr, Cogswell FB, Dennis VA, Lanners HN, Lowrie RC Jr, Roberts ED, Conway MD, Karacorlu M, Peyman GA, Gubler DJ, Johnson BJ, Piesman J, Gu Y. 1993. Early and early disseminated phases of Lyme disease in the rhesus monkey: A model for infection in humans. Infect Immun 61:3047-3059.

Philipp MT, Lobet Y, Bohm RP Jr, Roberts ED, Dennis VA, Gu Y, Lowrie RC Jr, Desmons P, Duray PH, England JD, Hauser P, Piesman J, Xu K. 1997. The outer surface protein A (OspA) vaccine against Lyme disease: Efficacy in the rhesus monkey. Vaccine 15:1872-1887.

Philipp MT, Purcell JE, Martin DS, Buck WR, Plauche GB, Ribka EP, DeNoel P, Hermand P, Leiva LE, Bagby GJ, Nelson S. 2006. Experimental infection of rhesus macaques with *Streptococcus pneumoniae*: A possible model for vaccine assessment. J Med Primatol 35:113-122.

Phipps AJ, Premanandan C, Barnewall RE, Lairmore MD. 2004. Rabbit and nonhuman primate models of toxin-targeting human anthrax vaccines. Microbiol Mol Biol Rev 68:617-629.

Pialoux G, Gauzere BA, Jaureguiberry S, Strobel M. 2007. Chikungunya, an epidemic arbovirosis. Lancet Infect Dis 7:319-327.

Pletnev AG, Bray M, Hanley KA, Speicher J, Elkins R. 2001. Tick-borne Langat/mosquito-borne dengue flavivirus chimera, a candidate live attenuated vaccine for protection against disease caused by members of the tick-borne encephalitis virus complex: Evaluation in rhesus monkeys and in mosquitoes. J Virol 75:8259-8267.

Pogodina VV, Levina LS, Fokina GI, Koreshkova GV, Malenko GV, Bochkova NG, Rzhakhova OE. 1981. Persistence of tick-borne encephalitis virus in monkeys. III. Phenotypes of the persisting virus. Acta Virol 25:352-360.

Polack FP, Auwaerter PG, Lee SH, Nousari HC, Valsamakis A, Leiferman KM, Diwan A, Adams RJ, Griffin DE. 1999. Production of atypical measles in rhesus macaques: Evidence for disease mediated by immune complex formation and eosinophils in the presence of fusion-inhibiting antibody. Nat Med 5:629-634.

Ponnuraj EM, Springer J, Hayward AR, Wilson H, Simoes EA. 2003. Antibody-dependent enhancement, a possible mechanism in augmented pulmonary disease of respiratory syncytial virus in the Bonnet monkey model. J Infect Dis 187:1257-1263.

Premenko-Lanier M, Rota PA, Rhodes GH, Bellini WJ, McChesney MB. 2004. Protection against challenge with measles virus (MV) in infant macaques by an MV DNA vaccine administered in the presence of neutralizing antibody. J Infect Dis 189:2064-2071.

Pung OJ, Spratt J, Clark CG, Norton TM, Carter J. 1998. *Trypanosoma cruzi* infection of free-ranging lion-tailed macaques (*Macaca silenus*) and ring-tailed lemurs (*Lemur catta*) on St. Catherine's Island, Georgia, USA. J Zoo Wildl Med 29:25-30.

Punkosdy GA, Dennis VA, Lasater BL, Tzertzinis G, Foster JM, Lammie PJ. 2001. Detection of serum IgG antibodies specific for Wolbachia surface protein in rhesus monkeys infected with *Brugia malayi*. J Infect Dis 184:385-389.

Purcell RH, Nguyen H, Shapiro M, Engle RE, Govindarajan S, Blackwelder WC, Wong DC, Prieels JP, Emerson SU. 2003. Pre-clinical immunogenicity and efficacy trial of a recombinant hepatitis E vaccine. Vaccine 21:2607-2615.

Puri SK, Dutta GP. 2005. *Plasmodium cynomolgi*: Gametocytocidal activity of the anti-malarial compound CDRI 80/53 (elubaquine) in rhesus monkeys. Exp Parasitol 111:8-13.

Quinn TC, Taylor HR, Schachter J. 1986. Experimental proctitis due to rectal infection with *Chlamydia trachomatis* in nonhuman primates. J Infect Dis 154:833-841.

Raengsakulrach B, Nisalak A, Gettayacamin M, Thirawuth V, Young GD, Myint KS, Ferguson LM, Hoke CH Jr, Innis BL, Vaughn DW. 1999. Safety, immunogenicity, and protective efficacy of NYVAC-JEV and

ALVAC-JEV recombinant Japanese encephalitis vaccines in rhesus monkeys. Am J Trop Med Hyg 60:343-349.

Raether W, Seidenath H. 1976. Trypanocidal effect of diamidine 98/202 in experimental *Trypanosoma rhodesiense* infection of the stumptailed macaque (*Macaca arctoides*). Tropenmed Parasitol 27:238-244.

Ransom JP, Krueger AP. 1954. Chronic pneumonic plague in *Macaca mulatta*. Am J Trop Med Hyg 3:1040-1054.

Ratterree MS, da Rosa AP, Bohm RP Jr, Cogswell FB, Phillippi KM, Caillouet K, Schwanberger S, Shope RE, Tesh RB. 2003. West Nile virus infection in nonhuman primate breeding colony, concurrent with human epidemic, southern Louisiana. Emerg Infect Dis 9:1388-1394.

Reed DS, Hensley LE, Geisbert JB, Jahrling PB, Geisbert TW. 2004. Depletion of peripheral blood T lymphocytes and NK cells during the course of ebola hemorrhagic fever in cynomolgus macaques. Viral Immunol 17:390-400.

Reimann KA, Li JT, Veazey R, Halloran M, Park IW, Karlsson GB, Sodroski J, Letvin NL. 1996. A chimeric simian/human immunodeficiency virus expressing a primary patient human immunodeficiency virus type 1 isolate env causes an AIDS-like disease after in vivo passage in rhesus monkeys. J Virol 70:6922-6928.

Reindel JF, Fitzgerald AL, Breider MA, Gough AW, Yan C, Mysore JV, Dubois A. 1999. An epizootic of lymphoplasmacytic gastritis attributed to *Helicobacter pylori* infection in cynomolgus monkeys (*Macaca fascicularis*). Vet Pathol 36:1-13.

Ren H, Zhu FL, Cao MM, Wen XY, Zhao P, Qi ZT. 2005. Hepatitis G virus genomic RNA is pathogenic to *Macaca mulatta*. World J Gastroenterol 11:970-975.

Renne R, Dittmer D, Kedes D, Schmidt K, Desrosiers RC, Luciw PA, Ganem D. 2004. Experimental transmission of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) to SIV-positive and SIV-negative rhesus macaques. J Med Primatol 33:1-9.

Rezapkin GV, Fan L, Asher DM, Fibi MR, Dragunsky EM, Chumakov KM. 1999. Mutations in Sabin 2 strain of poliovirus and stability of attenuation phenotype. Virology 258:152-160.

Rhesus Macaque Genome Sequencing and Analysis Consortium. 2007. Evolutionary and biomedical insights from the rhesus macaque genome. Science 316:222-234.

Riemenschneider J, Garrison A, Geisbert J, Jahrling P, Hevey M, Negley D, Schmaljohn A, Lee J, Hart MK, Vanderzanden L, Custer D, Bray M, Ruff A, Ivins B, Bassett A, Rossi C, Schmaljohn C. 2003. Comparison of individual and combination DNA vaccines for B anthracis, Ebola virus, Marburg virus and Venezuelan equine encephalitis virus. Vaccine 21:4071-4080.

Rimmelzwaan GF, Kuiken T, van Amerongen G, Bestebroer TM, Fouchier RA, Osterhaus AD. 2001. Pathogenesis of influenza A (H5N1) virus infection in a primate model. J Virol 75:6687-6691.

Rimmelzwaan GF, Kuiken T, van Amerongen G, Bestebroer TM, Fouchier RA, Osterhaus AD. 2003. A primate model to study the pathogenesis of influenza A (H5N1) virus infection. Avian Dis 47(3 Suppl):931-933.

Rivailler P, Jiang H, Cho YG, Quink C, Wang F. 2002. Complete nucleotide sequence of the rhesus lymphocryptovirus: Genetic validation for an Epstein-Barr virus animal model. J Virol 76:421-426.

Rivailler P, Carville A, Kaur A, Rao P, Quink C, Kutok JL, Westmoreland S, Klumpp S, Simon M, Aster JC, Wang F. 2004. Experimental rhesus lymphocryptovirus infection in immunosuppressed macaques: An animal model for Epstein-Barr virus pathogenesis in the immunosuppressed host. Blood 104:1482-1489.

Rizzo P, Matker C, Powers A, Setlak P, Heeney JL, Carbone M. 2001. No evidence of HIV and SIV sequences in two separate lots of polio vaccines used in the first US polio vaccine campaign. Virology 287: 13-17.

Roberts ED, Bohm RP Jr, Lowrie RC Jr, Habicht G, Katona L, Piesman J, Philipp MT. 1998. Pathogenesis of Lyme neuroborreliosis in the rhesus monkey: The early disseminated and chronic phases of disease in the peripheral nervous system. J Infect Dis 178:722-732.

Roberts JA. 1975. Experimental pyelonephritis in the monkey. III. Pathophysiology of ureteral malfunction induced by bacteria. Invest Urol 13:117-120.

Rockx BH, Bogers WM, Heeney JL, van Amerongen G, Koopmans MP. 2005. Experimental norovirus infections in nonhuman primates. J Med Virol 75:313-320.

Rodas JD, Lukashevich IS, Zapata JC, Cairo C, Tikhonov I, Djavani M, Pauza CD, Salvato MS. 2004. Mucosal arenavirus infection of primates can protect them from lethal hemorrhagic fever. J Med Virol 72:424-435.

Rogers JV, Casbohm SL, Giannunzio LF, Sinnott LT, Rust SW, Brys AM, Durnford JM, Quinn CP, Robinson DM, Hunt RE, Estep JE, Sabourin CL. 2006. Transcriptional analysis of protective antigen-stimulated PBMC from nonhuman primates vaccinated with the anthrax vaccine absorbed. Vaccine 24:3609-3617.

Rollier C, Verschoor EJ, Paranhos-Baccala G, Drexhage JA, Verstrepen BE, Berland JL, Himoudi N, Barnfield C, Liljestrom P, Lasarte JJ, Ruiz J, Inchauspe G, Heeney JL. 2005. Modulation of vaccine-induced immune responses to hepatitis C virus in rhesus macaques by altering priming before adenovirus boosting. J Infect Dis 192:920-929.

Rout WR, Formal SB, Giannella RA, Dammin GJ. 1975. Pathophysiology of Shigella diarrhea in the rhesus monkey: Intestinal transport, morphological, and bacteriological studies. Gastroenterology 68:270-278.

Rubins KH, Hensley LE, Jahrling PB, Whitney AR, Geisbert TW, Huggins JW, Owen A, Leduc JW, Brown PO, Relman DA. 2004. The host response to smallpox: Analysis of the gene expression program in peripheral blood cells in a nonhuman primate model. Proc Natl Acad Sci U S A 101:15190-15195.

Rue CA, Jarvis MA, Knoche AJ, Meyers HL, DeFilippis VR, Hansen SG, Wagner M, Fruh K, Anders DG, Wong SW, Barry PA, Nelson JA. 2004. A cyclooxygenase-2 homologue encoded by rhesus cytomegalovirus is a determinant for endothelial cell tropism. J Virol 78:12529-12556.

Ruff K, Baskin GB, Simpson L, Murphey-Corb M, Levy LS. 2003. Rhesus rhadinovirus infection in healthy and SIV-infected macaques at Tulane National Primate Research Center. J Med Primatol 32:1-6.

Russell RG, Blaser MJ, Sarmiento JI, Fox J. 1989. Experimental *Campylobacter jejuni* infection in *Macaca nemestrina*. Infect Immun 57:1438-1444.

Saadat I, Higashi H, Obuse C, Umeda M, Murata-Kamiya N, Saito Y, Lu H, Ohnishi N, Azuma T, Suzuki A, Ohno S, Hatakeyama M. 2007. *Helicobacter pylori* CagA targets PAR1/MARK kinase to disrupt epithelial cell polarity. Nature 447:330-333.

Sale TA, Melski JW, Stratman EJ. 2006. Monkeypox: An epidemiologic and clinical comparison of African and US disease. J Am Acad Dermatol 55:478-481.

Samuel BU, Ponnuraj E, Rajasingh J, John TJ. 1993. Experimental poliomyelitis in bonnet monkey: Clinical features, virology and pathology. Dev Biol Stand 78:71-78.

Sariol CA, Munoz-Jordan JL, Abel K, Rosado LC, Pantoja P, Giavedoni L, Rodriguez IV, White LJ, Martinez M, Arana T, Kraiselburd EN. 2007. Transcriptional activation of interferon-stimulated genes but not of cytokine genes after primary infection of rhesus macaques with dengue virus type 1. Clin Vaccine Immunol 14:756-766.

Sato H, Une Y, Kawakami S, Saito E, Kamiya H, Akao N, Furuoka H. 2005. Fatal Baylisascaris larva migrans in a colony of Japanese macaques kept by a safari-style zoo in Japan. J Parasitol 91:716-719.

Schatzl H, Tschikobava M, Rose D, Voevodin A, Nitschko H, Sieger E, Busch U, von der Helm K, Lapin B. 1993. The Sukhumi primate monkey model for viral lymphomogenesis: High incidence of lymphomas with presence of STLV-I and EBV-like virus. Leukemia 7 Suppl 2:S86-S92.

Schiodt M, Lackner A, Armitage G, Lerche N, Greenspan JS, Lowenstine L. 1988. Oral lesions in rhesus monkeys associated with infection by simian AIDS retrovirus, serotype-I (SRV-1). Oral Surg Oral Med O 65:50-55.

Schmidt LH. 1956. Some observations on the utility of simian pulmonary tuberculosis in defining the therapeutic potentialities of isoniazid. Am Rev Tuberc 74(2 Part 2):138-153; discussion, 153-159.

Schmidtko J, Wang R, Wu CL, Mauiyyedi S, Harris NL, Della Pelle P, Brousaides N, Zagachin L, Ferry JA, Wang F, Kawai T, Sachs DH,

Cosimi BA, Colvin RB. 2002. Posttransplant lymphoproliferative disorder associated with an Epstein-Barr-related virus in cynomolgus monkeys. Transplantation 73:1431-1439.

Schou S, Hansen AK. 2000. Marburg and Ebola virus infections in laboratory nonhuman primates: A literature review. Comp Med 50:108-123.

Schou S, Holmstrup P, Kornman KS. 1993. Non-human primates used in studies of periodontal disease pathogenesis: A review of the literature. J Periodontol 64:497-508.

Schricker RL, Eigelsbach HT, Mitten JQ, Hall WC. 1972. Pathogenesis of tularemia in monkeys aerogenically exposed to *Francisella tularensis* 425. Infect Immun 5:734-744.

Schultz ER, Rankin GW Jr, Blanc MP, Raden BW, Tsai CC, Rose TM. 2000. Characterization of two divergent lineages of macaque rhadinoviruses related to Kaposi's sarcoma-associated herpesvirus. J Virol 74:4919-4928.

Semba RD, Donnelly JJ, Young E, Green WR, Scott AL, Taylor HR. 1991. Experimental ocular onchocerciasis in cynomolgus monkeys. IV. Chorioretinitis elicited by *Onchocerca volvulus* microfilariae. Invest Ophthalmol Vis Sci 32:1499-1507.

Sequar G, Britt WJ, Lakeman FD, Lockridge KM, Tarara RP, Canfield DR, Zhou SS, Gardner MB, Barry PA. 2002. Experimental coinfection of rhesus macaques with rhesus cytomegalovirus and simian immunodeficiency virus: Pathogenesis. J Virol 76:7661-7671.

Sestak K, Merritt CK, Borda J, Saylor E, Schwamberger SR, Cogswell F, Didier ES, Didier PJ, Plauche G, Bohm RP, Aye PP, Alexa P, Ward RL, Lackner AA. 2003. Infectious agent and immune response characteristics of chronic enterocolitis in captive rhesus macaques. Infect Immun 71:4079-4086.

Shah KV. 2007. SV40 and human cancer: A review of recent data. Int J Cancer 120:215-223.

Shen Y, Zhou D, Chalifoux L, Shen L, Simon M, Zeng X, Lai X, Li Y, Sehgal P, Letvin NL, Chen ZW. 2002. Induction of an AIDS virus-related tuberculosis-like disease in macaques: A model of simian immunodeficiency virus-mycobacterium coinfection. Infect Immun 70: 869-877.

Shevtsova ZV, Lapin BA, Doroshenko NV, Krilova RI, Korzaja LI, Lomovskaya IB, Dzhelieva ZN, Zairov GK, Stakhanova VM, Belova EG. 1988. Spontaneous and experimental hepatitis A in Old World monkeys. J Med Primatol 17:177-194.

Shuto R, Fujioka T, Kubota T, Nasu M. 1993. Experimental gastritis induced by *Helicobacter pylori* in Japanese monkeys. Infect Immun 61: 933-939.

Simoes EA, Hayward AR, Ponnuraj EM, Straumanis JP, Stenmark KR, Wilson HL, Babu PG. 1999. Respiratory syncytial virus infects the Bonnet monkey, *Macaca radiata*. Pediatr Dev Pathol 2:316-326.

Smit-McBride Z, Mattapallil JJ, McChesney M, Ferrick D, Dandekar S. 1998. Gastrointestinal T lymphocytes retain high potential for cytokine responses but have severe CD4(+) T cell depletion at all stages of simian immunodeficiency virus infection compared to peripheral lymphocytes. J Virol 72:6646-6656.

Smith MA, Clegg JA. 1985. Vaccination against *Schistosoma mansoni* with purified surface antigens. Science 227:535-538.

Smith MA, Takeuchi K, Brackett RE, McClure HM, Raybourne RB, Williams KM, Babu US, Ware GO, Broderson JR, Doyle MP. 2003. Nonhuman primate model for *Listeria monocytogenes*-induced stillbirths. Infect Immun 71:1574-1579.

Smith SL, Wang X, Godeny EK. 1997. Sequence of the 3' end of the simian hemorrhagic fever virus genome. Gene 191:205-210.

Soike KF, Gary GW, Gibson S. 1980. Susceptibility of nonhuman primate species to infection by simian rotavirus SA-11. Am J Vet Res 41:1098-1103.

Solnick JV, Canfield DR, Yang S, Parsonnet J. 1999. Rhesus monkey (*Macaca mulatta*) model of *Helicobacter pylori*: Noninvasive detection and derivation of specific-pathogen-free monkeys. Lab Anim Sci 49:197-201.

Solnick JV, Chang K, Canfield DR, Parsonnet J. 2003. Natural acquisition of *Helicobacter pylori* infection in newborn rhesus macaques. J Clin Microbiol 41:5511-5516.

Solnick JV, Hansen LM, Salama NR, Boonjakuakul JK, Syvanen M. 2004. Modification of *Helicobacter pylori* outer membrane protein expression during experimental infection of rhesus macaques. Proc Natl Acad Sci U S A 101:2106-2111.

Spencer JV, Lockridge KM, Barry PA, Lin G, Tsang M, Penfold ME, Schall TJ. 2002. Potent immunosuppressive activities of cytomegalovirus-encoded interleukin-10. J Virol 76:1285-1292.

Sprague LD, Neubauer H. 2004. Melioidosis in animals: A review on epizootiology, diagnosis and clinical presentation. J Vet Med B 51: 305-320.

Stephens RS, Kalman S, Lammel C, Fan J, Marathe R, Aravind L, Mitchell W, Olinger L, Tatusov RL, Zhao Q, Koonin EV, Davis RW. 1998. Genome sequence of an obligate intracellular pathogen of humans: *Chlamydia trachomatis*. Science 282:754-759.

Stittelaar KJ, Wyatt LS, de Swart RL, Vos HW, Groen J, van Amerongen G, van Binnendijk RS, Rozenblatt S, Moss B, Osterhaus AD. 2000. Protective immunity in macaques vaccinated with a modified vaccinia virus Ankara-based measles virus vaccine in the presence of passively acquired antibodies. J Virol 74:4236-4243.

Stittelaar KJ, van Amerongen G, Kondova I, Kuiken T, van Lavieren RF, Pistoor FH, Niesters HG, van Doornum G, van der Zeijst BA, Mateo L, Chaplin PJ, Osterhaus AD. 2005. Modified vaccinia virus Ankara protects macaques against respiratory challenge with monkeypox virus. J Virol 79:7845-7851.

Stittelaar KJ, Neyts J, Naesens L, van Amerongen G, van Lavieren RF, Holy A, De Clercq E, Niesters HG, Fries E, Maas C, Mulder PG, van der Zeijst BA, Osterhaus AD. 2006. Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection. Nature 439:745-748.

Stokes A, Bauer JH, Hudson NP. 1928. Transmission of yellow fever to *Macacus rhesus*: Preliminary note. J Am Assoc 90:253-254.

Stokes A, Bauer JH, Hudson NP. 2001. The transmission of yellow fever to *Macacus rhesus* (1928). Rev Med Virol 11:141-148.

Subekti DS, Tjaniadi P, Lesmana M, McArdle J, Iskandriati D, Budiarsa IN, Walujo P Suparto IH, Winoto I, Campbell JR, Porter KR, Sajuthi D, Ansari AA, Oyofo BA. 2002. Experimental infection of *Macaca nemestrina* with a Toronto Norwalk-like virus of epidemic viral gastroenteritis. J Med Virol 66:400-406.

Sun W, Nisalak A, Gettayacamin M, Eckels KH, Putnak JR, Vaughn DW, Innis BL, Thomas SJ, Endy TP. 2006. Protection of Rhesus monkeys against dengue virus challenge after tetravalent live attenuated dengue virus vaccination. J Infect Dis 193:1658-1665.

Suss J. 2003. Epidemiology and ecology of TBE relevant to the production of effective vaccines. Vaccine 21 Suppl 1:S19-S35.

Suss J, Gelpi E, Klaus C, Bagon A, Liebler-Tenorio EM, Budka H, Stark B, Muller W, Hotzel H. 2007. Tickborne encephalitis in naturally exposed monkey (*Macaca sylvanus*). Emerg Infect Dis 13:905-907.

Suzaki Y, Ami Y, Nagata N, Naito S, Kato H, Taneichi M, Takahashi M, Komiya T, Satoh S, Gondaira F, Sugiyama J, Nakano Y, Mori M, Komuro K, Uchida T. 2002. Protection of monkeys against Shiga toxin induced by Shiga toxin-liposome conjugates. Int Arch Allergy Imm 127:294-298.

Tanaka J, Fukuda Y, Shintani S, Hori K, Tomita T, Ohkusa T, Matsumoto T, Miwa H. 2005. Influence of antimicrobial treatment for *Helicobacter pylori* infection on the intestinal microflora in Japanese macaques. J Med Microbiol 54(Pt 3):309-314.

Tanghe A, Content J, Van Vooren JP, Portaels F, Huygen K. 2001. Protective efficacy of a DNA vaccine encoding antigen 85A from *Mycobacterium bovis* BCG against Buruli ulcer. Infect Immun 69:5403-5411.

Tarantal AF, Salamat MS, Britt WJ, Luciw PA, Hendrickx AG, Barry PA. 1998. Neuropathogenesis induced by rhesus cytomegalovirus in fetal rhesus monkeys (*Macaca mulatta*). J Infect Dis 177:446-450.

Taylor HR, Prendergast RA, Dawson CR, Schachter J, Silverstein AM. 1981. An animal model for cicatrizing trachoma. Invest Ophth Vis Sci 21:422-433.

Taylor HR, Young E, MacDonald AB, Schachter J, Prendergast RA. 1987. Oral immunization against chlamydial eye infection. Invest Ophth Vis Sci 28:249-258.

Tollis M, Dietzschold B, Volia CB, Koprowski H. 1991. Immunization of monkeys with rabies ribonucleoprotein (RNP) confers protective immunity against rabies. Vaccine 9:134-136.

Tribe GW, Fleming MP. 1983. Biphasic enteritis in imported cynomolgus (*Macaca fascicularis*) monkeys infected with *Shigella*, *Salmonella* and *Campylobacter* species. Lab Anim 17:65-69.

Tulis JJ, Eigelsbach HT, Kerpsack RW. 1970. Host-parasite relationship in monkeys administered live tularemia vaccine. Am J Pathol 58:329-336.

Turell MJ, Malinoski FJ. 1992. Limited potential for mosquito transmission of a live, attenuated chikungunya virus vaccine. Am J Trop Med Hyg 47:98-103.

Uberla K, Stahl-Hennig C, Bottiger D, Matz-Rensing K, Kaup FJ, Li J, Haseltine WA, Fleckenstein B, Hunsmann G, Oberg B, Sodroski J. 1995. Animal model for the therapy of acquired immunodeficiency syndrome with reverse transcriptase inhibitors. Proc Natl Acad Sci U S A 92:8210-8214.

Urvater JA, McAdam SN, Loehrke JH, Allen TM, Moran JL, Rowell TJ, Rojo S, Lopez de Castro JA, Taurog JD, Watkins DI. 2000. A high incidence of Shigella-induced arthritis in a primate species: Major histocompatibility complex class I molecules associated with resistance and susceptibility, and their relationship to HLA-B27. Immunogenetics 51:314-325.

Valverde CR, Canfield D, Tarara R, Esteves MI, Gormus BJ. 1998. Spontaneous leprosy in a wild-caught cynomolgus macaque. Int J Leprosy 66:140-148.

van den Hoogen BG, Herfst S, de Graaf M, Sprong L, van Lavieren R, van Amerongen G, Yuksel S, Fouchier RA, Osterhaus AD, de Swart RL. 2007. Experimental infection of macaques with human metapneumovirus induces transient protective immunity. J Gen Virol 88(Pt 4):1251-1259.

van Gorder MA, Della Pelle P, Henson JW, Sachs DH, Cosimi AB, Colvin RB. 1999. Cynomolgus polyoma virus infection: A new member of the polyoma virus family causes interstitial nephritis, ureteritis, and enteritis in immunosuppressed cynomolgus monkeys. Am J Pathol 154: 1273-1284.

Van Heuverswyn F, Peeters M. 2007. The origins of HIV and implications for the global epidemic. Curr Infect Dis Rep 9:338-346.

Van Rompay KK. 2005. Antiretroviral drug studies in nonhuman primates: A valid animal model for innovative drug efficacy and pathogenesis experiments. AIDS Rev 7:67-83.

Van Voorhis WC, Barrett LK, Sweeney YT, Kuo CC, Patton DL. 1997. Repeated *Chlamydia trachomatis* infection of *Macaca nemestrina* fallopian tubes produces a Th1-like cytokine response associated with fibrosis and scarring. Infect Immun 65:2175-2182.

Vasconcelos D, Barnewall R, Babin M, Hunt R, Estep J, Nielsen C, Carnes R, Carney J. 2003. Pathology of inhalation anthrax in cynomolgus monkeys (*Macaca fascicularis*). Lab Invest 83:1201-1209.

Vasconcelos PF, Luna EJ, Galler R, Silva LJ, Coimbra TL, Barros VL, Monath TP, Rodrigues SG, Laval C, Costa ZG, Vilela MF, Santos CL, Papaiordanou PM, Alves VA, Andrade LD, Sato HK, Rosa ES, Froguas GB, Lacava E, Almeida LM, Cruz AC, Rocco IM, Santos RT, Oliva OF. 2001. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: A report of two cases. Lancet 358:91-97.

Veazey RS, DeMaria M, Chalifoux LV, Shvetz DE, Pauley DR, Knight HL, Rosenzweig M, Johnson RP, Desrosiers RC, Lackner AA. 1998. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. Science 280:427-431.

Virtaneva K, Porcella SF, Graham MR, Ireland RM, Johnson CA, Ricklefs SM, Babar I, Parkins LD, Romero RA, Corn GJ, Gardner DJ, Bailey JR, Parnell MJ, Musser JM. 2005. Longitudinal analysis of the group A Streptococcus transcriptome in experimental pharyngitis in cynomolgus macaques. Proc Natl Acad Sci U S A 102:9014-9019.

Voevodin A, Samilchuk E, Schatzl H, Boeri E, Franchini G. 1996. Interspecies transmission of macaque simian T-cell leukemia/lymphoma virus type 1 in baboons resulted in an outbreak of malignant lymphoma. J Virol 70:1633-1639.

Vogel P, Weigler BJ, Kerr H, Hendrickx AG, Barry PA. 1994. Seroepidemiologic studies of cytomegalovirus infection in a breeding population of rhesus macaques. Lab Anim Sci 44:25-30.

von Reyn CF. 2006. Routine childhood bacille Calmette Guerin immunization and HIV infection. Clin Infect Dis 42:559-561.

Waag DM, Byrne WR, Estep J, Gibbs P, Pitt ML, Banfield CM. 1999. Evaluation of cynomolgus (*Macaca fascicularis*) and rhesus (*Macaca mulatta*) monkeys as experimental models of acute Q fever after aerosol exposure to phase-I *Coxiella burnetii*. Lab Anim Sci 49:634-638.

Waag DM, England MJ, Tammariello RF, Byrne WR, Gibbs P, Banfield CM, Pitt ML. 2002. Comparative efficacy and immunogenicity of Q fever chloroform: Methanol residue (CMR) and phase I cellular (Q-Vax) vaccines in cynomolgus monkeys challenged by aerosol. Vaccine 20:2623-2634.

Walker DH, Johnson KM, Lange JV, Gardner JJ, Kiley MP, McCormick JB. 1982. Experimental infection of rhesus monkeys with Lassa virus and a closely related arenavirus, Mozambique virus. J Infect Dis 146: 360-368.

Walsh GP, Tan EV, Dela Cruz EC, Abalos RM, Villahermosa LG, Young LJ, Cellona RV, Nazareno JB, Horwitz MA. 1996. The Philippine cynomolgus monkey (*Macaca fasicularis*) provides a new nonhuman primate model of tuberculosis that resembles human disease. Nat Med 2:430-436.

Walsh DS, Gettayacamin M, Leitner WW, Lyon JA, Stewart VA, Marit G, Pichyangkul S, Gosi P, Tongtawe P, Kester KE, Holland CA, Kolodny N, Cohen J, Voss G, Ballou WR, Heppner DG Jr. 2006. Heterologous prime-boost immunization in rhesus macaques by two, optimally spaced particle-mediated epidermal deliveries of *Plasmodium falciparum* circumsporozoite protein-encoding DNA, followed by intramuscular RTS,S/AS02A. Vaccine 24:4167-4178.

Walsh DS, Dela Cruz EC, Abalos RM, Tan EV, Walsh GP, Portaels F, Meyers WM. 2007. Clinical and histologic features of skin lesions in a cynomolgus monkey experimentally infected with *Mycobacterium ulcerans* (Buruli ulcer) by intradermal inoculation. Am J Trop Med Hyg 76:132-134.

Watanabe T, Seiki M, Tsujimoto H, Miyoshi I, Hayami M, Yoshida M. 1985. Sequence homology of the simian retrovirus genome with human T cell leukemia virus type I. Virology 144:59-65.

Weinmann E, Majer M, Hilfenhaus J. 1979. Intramuscular and/or intralumbar postexposure treatment of rabies virus-infected cynomolgus monkeys with human interferon. Infect Immun 24:24-31.

Weiss RA. 1988. Foamy retroviruses: A virus in search of a disease. Nature 333:497-498.

Wells E, Harper ST, Jackson CG, Mann J, Eady RP. 1986. Characterization of primate bronchoalveolar mast cells. I. IgE-dependent release of histamine, leukotrienes, and prostaglandins. J Immunol 137:3933-3940.

Wengelnik K, Vidal V, Ancelin ML, Cathiard AM, Morgat JL, Kocken CH, Calas M, Herrera S, Thomas AW, Vial HJ. 2002. A class of potent antimalarials and their specific accumulation in infected erythrocytes. Science 295:1311-1314.

Wenner HA, Barrick S, Abel D, Seshumurty P. 1975. The pathogenesis of simian varicella virus in cynomolgus monkeys. P Soc Exp Biol Med 150:318-323.

Westerman LE, Xu J, Jiang B, McClure HM, Glass RI. 2005. Experimental infection of pigtail macaques with a simian rotavirus, YK-1. J Med Virol 75:616-625.

White MK, Gordon J, Reiss K, Del Valle L, Croul S, Giordano A, Dar binyan A, Khalili K. 2005. Human polyomaviruses and brain tumors. Brain Res Brain Res Rev 50:69-85.

Whitney JB, Ruprecht RM. 2004. Live attenuated HIV vaccines: Pitfalls and prospects. Curr Opin Infect Dis 17:17-26.

WHO [World Health Organization]. 2007. Global Advisory Committee on Vaccine Safety, 12-13 June 2007. Wkly Epidemiol Rec 82:252-259.

Williamson ED, Hodgson I, Walker NJ, Topping AW, Duchars MG, Mott JM, Estep J, Lebutt C, Flick-Smith HC, Jones HE, Li H, Quinn CP. 2005. Immunogenicity of recombinant protective antigen and efficacy against aerosol challenge with anthrax. Infect Immun 73:5978-5987.

Williamson ED, Flick-Smith HC, Waters E, Miller J, Hodgson I, Le Butt CS, Hill J. 2007. Immunogenicity of the rF1+rV vaccine for plague with identification of potential immune correlates. Microb Pathog 42: 11-21.

Willy ME, Woodward RA, Thornton VB, Wolff AV, Flynn BM, Heath JL, Villamarzo YS, Smith S, Bellini WJ, Rota PA. 1999. Management of a measles outbreak among Old World nonhuman primates. Lab Anim Sci 49:42-48.

Wobus CE, Thackray LB, Virgin HW 4th. 2006. Murine norovirus: A model system to study norovirus biology and pathogenesis. J Virol 80:5104-5112.

Wolf RH, Gormus BJ, Martin LN, Baskin GB, Walsh GP, Meyers WM, Binford CH. 1985. Experimental leprosy in three species of monkeys. Science 227:529-531.

Wolfe ND, Heneine W, Carr JK, Garcia AD, Shanmugam V, Tamoufe U, Torimiro JN, Prosser AT, Lebreton M, Mpoudi-Ngole E, McCutchan FE, Birx DL, Folks TM, Burke DS, Switzer WM. 2005. Emergence of unique primate T-lymphotropic viruses among central African bushmeat hunters. Proc Natl Acad Sci U S A 102:7994-7999.

Wolfe ND, Dunavan CP, Diamond J. 2007. Origins of major human infectious diseases. Nature 447:279-283.

Wong MM, Kozek WJ, Karr SL Jr, Brayton MA, Theis JH, Hendrickx AG. 1979. Experimental congenital infection of *Toxoplasma gondii* in *Macaca arctoides*. Asian J Infect Dis 3:61-67.

Wong SW, Bergquam EP, Swanson RM, Lee FW, Shiigi SM, Avery NA, Fanton JW, Axthelm MK. 1999. Induction of B cell hyperplasia in simian immunodeficiency virus-infected rhesus macaques with the simian homologue of Kaposi's sarcoma-associated herpesvirus. J Exp Med 190:827-840.

Wood CE, Borgerink H, Register TC, Scott L, Cline JM. 2004. Cervical and vaginal epithelial neoplasms in cynomolgus monkeys. Vet Pathol 41:108-115.

Wood CE, Chen Z, Cline JM, Miller BE, Burk RD. 2007. Characterization and experimental transmission of an oncogenic papillomavirus in female macaques. J Virol 81:6339-6345.

Wright GG, Hedberg MA, Slein JB. 1954. Studies on immunity in anthrax. III. Elaboration of protective antigen in a chemically defined, nonprotein medium. J Immunol 72:263-269.

Wu Y, Przysiecki C, Flanagan E, Bello-Irizarry SN, Ionescu R, Muratova O, Dobrescu G, Lambert L, Keister D, Rippeon Y, Long CA, Shi L, Caulfield M, Shaw A, Saul A, Shiver J, Miller LH. 2006. Sustained high-titer antibody responses induced by conjugating a malarial vaccine candidate to outer-membrane protein complex. Proc Natl Acad Sci U S A 103:18243-18248.

Wyatt RG, Sly DL, London WT, Palmer AE, Kalica AR, Van Kirk DH, Chanock RM, Kapikian AZ. 1976. Induction of diarrhea in colostrum-deprived newborn rhesus monkeys with the human reovirus-like agent of infantile gastroenteritis. Arch Virol 50:17-27.

Xu JZ, Yang ZG, Le MZ, Wang MR, He CL, Sui YH. 2001. A study on pathogenicity of hepatitis G virus. World J Gastroenterol 7:547-550.

Yalcin S, Mukai T, Kondo K, Ami Y, Okawa T, Kojima A, Kurata T, Yamanishi K. 1992. Experimental infection of cynomolgus and African green monkeys with human herpesvirus 6. J Gen Virol 73 (Pt 7):1673-1677.

Ylostalo J, Randall AC, Myers TA, Metzger M, Krogstad DJ, Cogswell FB. 2005. Transcriptome profiles of host gene expression in a monkey model of human malaria. J Infect Dis 191:400-409.

Yue Y, Kaur A, Eberhardt MK, Kassis N, Zhou SS, Tarantal AF, Barry PA. 2007. Immunogenicity and protective efficacy of DNA vaccines expressing rhesus cytomegalovirus glycoprotein B, phosphoprotein 65-2, and viral interleukin-10 in rhesus macaques. J Virol 81:1095-1109.

Zaucha GM, Jahrling PB, Geisbert TW, Swearengen JR, Hensley L. 2001. The pathology of experimental aerosolized monkeypox virus infection in cynomolgus monkeys (*Macaca fascicularis*). Lab Invest 81:1581-1600.

Zhang M, Emerson SU, Nguyen H, Engle R, Govindarajan S, Blackwelder WC, Gerin J, Purcell RH. 2002. Recombinant vaccine against hepatitis E: Duration of protective immunity in rhesus macaques. Vaccine 20: 3285-3291.

Zhang P, Chomel BB, Schau MK, Goo JS, Droz S, Kelminson KL, George SS, Lerche NW, Koehler JE. 2004. A family of variably expressed outer-membrane proteins (Vomp) mediates adhesion and autoaggregation in *Bartonella quintana*. Proc Natl Acad Sci U S A 101:13630-13635.

Zhou D, Lai X, Shen Y, Sehgal P, Shen L, Simon M, Qiu L, Huang D, Du GZ, Wang Q, Letvin NL, Chen ZW. 2003. Inhibition of adaptive Vgamma2Vdelta2+ T cell responses during active mycobacterial coinfection of simian immunodeficiency virus SIVmac-infected monkeys. J Virol 77:2998-3006.

Zhou J, Wang W, Zhong Q, Hou W, Yang Z, Xiao SY, Zhu R, Tang Z, Wang Y, Xian Q, Tang H, Wen L. 2005. Immunogenicity, safety, and protective efficacy of an inactivated SARS-associated coronavirus vaccine in rhesus monkeys. Vaccine 23:3202-3209.

Zhu YD, Fennelly G, Miller C, Tarara R, Saxe I, Bloom B, McChesney M. 1997a. Recombinant bacille Calmette-Guerin expressing the measles virus nucleoprotein protects infant rhesus macaques from measles virus pneumonia. J Infect Dis 176:1445-1453.

Zhu YD, Heath J, Collins J, Greene T, Antipa L, Rota P, Bellini W, McChesney M. 1997b. Experimental measles. II. Infection and immunity in the rhesus macaque. Virology 233:85-92.

Zhu Y, Rota P, Wyatt L, Tamin A, Rozenblatt S, Lerche N, Moss B, Bellini W, McChesney M. 2000. Evaluation of recombinant vaccinia virus: Measles vaccines in infant rhesus macaques with preexisting measles antibody. Virology 276:202-213.

Zuckerman AJ, Scalise G, Mazaheri MR, Kremastinou J, Howard CR, Sorensen K. 1975. Transmission of hepatitis B to the rhesus monkey. Dev Biol Stand 30:236-239.

Zumpe D, Silberman MS, Michael RP. 1980. Unusual outbreak of tuberculosis due to *Mycobacterium bovis* in a closed colony of rhesus monkeys (*Macaca mulatta*). Lab Anim Sci 30(2 Pt 1):237-240.