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Overview of Simian Viruses and Recognized Virus Diseases and Laboratory Support for the Diagnosis of Viral Infections

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Introduction

A phylogenetic relationship to the human is often suggested as the reason for selecting a particular simian host, such as the chimpanzee, for studies on human diseases. It is thought that the use of another primate permits the extrapolation of more meaningful data than those derived from other species of animals. However, there is more to selecting an appropriate nonhuman primate model than phylogenetic relatedness. Two widely separated species, the chimpanzee and, with a few exceptions, the marmoset, are highly susceptible to hepatitis A, while the rhesus monkey is not. Therefore, care in selection of the most appropriate model for the study of a particular disease is vital to the success of any research program.

Historically, the nonhuman primate has often been misused in medical research through failure to recognize these animals not as "test tubes" but as biological entities, with a full range of individual responses to internal and external influences. Fortunately, the scientific community is becoming more concerned about the use and abuse of these animals in research. An awareness that nonhuman primates differ among the species in their responses to human disease agents and to their own particular infectious agents is becoming apparent.

The influence of viruses and viral diseases on the health of nonhuman primate colonies and ultimately on the success of research programs has not been extensively studied. Investigators often fail to recognize infection, particularly latent infection and subclinical disease, and overt disease is frequently handled by disposal of the animal without attempt to discover the cause and epidemiology. Among the many viruses harbored by nonhuman primates, *Herpesvirus simiae* (B virus) has generated the most interest, and that because of its extreme danger to humans, not to other animals.

This report will attempt to provide an awareness of the influence of viruses and their diseases, as well as the importance of their detection, on the health of colonies necessary for "self-sustaining populations" of nonhuman primates.

Simian Viruses and Diseases of Monkeys and Apes

The presence of an extensive virus population (Hull, 1968; Kalter et al., 1980), counterparts of human viruses (Matthews, 1982), in nonhuman primates is now

K. Benirschke (ed.), *Primates*

well established (Table 46.1). That many of these viruses are associated with a variety of diseases both in the host of origin and in alien hosts is also well recognized (Andrews, 1976; Hull, 1968; Kalter and Herberling, 1976; Kalter, 1983). Several of these simian agents are lethal for primates, both human and nonhuman; othersare oncogenic; and still others are capable of producing an assortment of clinical ailments. Nonhuman primates are equally susceptible to the viruses that cause infection/disease in humans, often with the same end result—death.

Nonhuman primate viruses, distinct from other animal viruses, have been recognized since Sabin and Wright (1934) described the presence of a herpesvirus (herpes B) in a fatal human case following a monkey bite. A number of investigators have since demonstrated antigenically distinct viruses in simian tissue (principally kidney cells) as well as in feces, throat washings, and spinal fluid (Herberling and Cheever, 1960; Hull et al., 1956; Hull, 1968; Kalter, 1960; Malherbe and Harwin, 1957). Although these viruses are antigenically distinct from the recognized human and other animal virus isolates, in general they conform to the biological criteria used to classify a virus (Kalter et al., 1980). The majority of the simian viruses may be included in existing virus families, notably Picornaviridae (picornaviruses, principally the enteroviruses). Adenoviridae (adenoviruses), and Herpesviridae (herpesviruses), and all are capable of infecting various species of primates including humans. The most notorious, however, are the herpesviruses, present in most simian species and associated with human and nonhuman primate fatalities as well as with oncogenesis. Retroviruses of nonhuman primates are well described and have also gained a certain amount of notoriety, not only because retroviruses are frequently responsible for tumor production in many animal species but also because recent findings have indicated that there is a close relationship between simian retroviruses responsible for simian acquired immunodeficiency syndrome (SAIDS) and the human disease AIDS. Other distinctive simian viruses exist but are found less frequently than the above viruses (Kalter et al., 1980).

In addition, viruses have been recovered from nonhuman primates that are either identical to or so closely related antigenically to the human agents that differentiation is impossible or of little consequence. These viruses are, in essence, primate (human and nonhuman) viruses. Included among these viruses are influenza viruses (Orthomyxoviridae), measles virus (Paramyxoviridae), reoviruses and rotaviruses (Reoviridae), monkeypox virus (Poxviridae), yellow fever virus (Togaviridae), rabies virus (Rhabdoviridae), and others. Several viruses originally isolated from nonhuman primates (respiratory syncytial virus, SV 5) have been reclassified as animal (human?) viruses rather than simian viruses. Unclassified viruses such as Marburg virus may or may not be simian in origin but are associated with diseases attributed to monkey contact. The various arboviruses (Togaviridae, Bunyaviridae, and other vector-transmitted viruses) are primate (human and nonhuman) viruses and generally not host restrictive. Disease occurs in both human and nonhuman primates as a result of infection with viruses derived from both human and nonhuman primates as well as from other animal sources. The full extent of infectivity of many of these viruses is not known.

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TABLE 46.1. Natural viral diseases of nonhuman primates.

Disease	Species	Virus	References
Adenovirus diseases			
Conjunctivitis–rhinorrhea	Patas monkey; *Macaca* sp.	SV17	Tyrrell et al. (1960); Bullock (1965)
Pneumoenteritis	African green monkey, baboon	V340, V404; V340	Kim et al. (1967); Eugster et al. (1969)
Conjunctivitis, upper respiratory infection, cough, nasal discharge	Rhesus	SV15	Landon and Bennett (1969)
Cough, skin lesions	Chimpanzee	Cytomegalovirus	Muchmore (1971)
Necrotizing pneumonia	Rhesus; stump-tailed macaque	SV11; SV15	Valerio (1971); España (1971)
Necrotizing viral, pancreatitis	Rhesus	"Adeno"; Ad. 31	Chandler et al. (1974); McClure et al. (1971)
Pneumonia	Rhesus; African green monkey, baboon, Bonnet monkey, cynomolgus, pig-tailed macaque	SV20; SV11	Moe et al. (1977); Boyce et al. (1978)
Viuria	Chimpanzee	Adenovirus	Asher et al. (1978)
Conjunctivitis–pneumonia	Rhesus	SV37	Vasileva et al. (1978)
Diarrhea	Rhesus	SV20, SV17, SV32	Stuker et al. (1979)
Aspiration pneumonia	Japanese macaque	"Adenovirus"	Umemura et al. (1985)
Arbovirus diseases			
Yellow fever	Red howler monkey; marmoset	Yellow fever	Balfour (1914); Anderson and Downs (1955); Laemmert and Castro-Ferreira (1945)
	Howler, marmoset		Vargas-Mendez and Elton (1953)
Kyasnur Forest disease	Langur, Bonnet monkey	Kyasanur Forest disease virus	Work and Trapido (1957); Webb (1969)
Dengue	"Monkeys" (Cercopithecus?)	Dengue	Monath et al. (1974)
Herpesvirus disease			
Salivary gland disease	Chimpanzee	Cytomegalovirus (CMV)	Vogel and Pinkerton (1955)
Generalized cytomegalovirus	Gorilla	CMV	Tsuchiya et al. (1970)
Genital malformations	Squirrel monkey	CMV	Ordy et al. (1981)
Herpesvirus	Rhesus	Herpes B (HBV, B virus)	Keeble et al. (1958)
B virus	Rhesus; cynomolgus; macaques	HBV	Pille (1960); Hartley (1964); Zwartouw et al. (1984)
Herpesvirus	Macaques	HBV	Roberts et al. (1984)
Herpesvirus (genital infection)	Rhesus	HBV	Zwartouw and Boulter (1984)
Respiratory disease	Bonnet monkey	HBV	España (1973)
Disseminated herpes	Rhesus	HBV	McClure et al. (1973)
Cerebral infarction	Rhesus	Herpesvirus	Daniel et al. (1975)

TABLE 46.1. (Continued).

Disease	Species	Virus	References
Oral lesions	Rhesus	Herpesvirus	Vizoso (1975)
Chickenpox	Apes; African green monkey	Varicella	Heuschele (1960); Lehner et al. (1984)
Exanthema (fatal)	Vervet	LVMV (Varicella)	Clarkson et al. (1967)
Herpesvirus	Patas monkey	PMHV (Varicella)	McCarthy et al. (1968)
Macular rash, pruritis	Apes	Varicella	McClure and Keeling (1971)
Chicken pox	Gorilla	Varicella-Zoster	White et al. (1972)
Varicella	Stump-tailed macaque;	Medical Lake Macaque (MLM);	Blakely et al. (1973);
	Patas	Delta herpes	Gard and London (1983)
Generalized rash, vesiculations, anorexia	Patas *Cercopithecus* sp. *Cercocebus* sp.	Delta herpes	Allen et al. (1974)
"Smallpox"	Chimpanzee	Varicella	Marennikova et al. (1974)
Generalized Herpes (fatal)	Patas	Delta herpes	Wolf et al. (1974)
Herpesvirus (fatal)	Marmoset;	*Herpesvirus tamarinus* (herpes M)	Holmes et al. (1964)
	Spider monkey	SMV (SMHV, herpes T)	Hull et al. (1972)
Herpesvirus	Marmoset; owl monkey; squirrel monkey	Marmoset herpes; herpes T	Melnick et al. (1964); Hunt and Melendez (1966); Daniel et al. (1967)
Pruritis	Owl monkey	Herpes T (HVT)	Emmons et al. (1968)
Encephalitis (resp. distress)	Owl monkey	Herpes T	Tate et al. (1971)
Herpesvirus	Marmoset; owl monkey; gibbon	HVT; herpes simples; *H. hominis*	Morita et al. (1979); Melendez et al. (1969); Smith et al. (1969)
Encephalitis (fatal)	Gibbon	*H. hominis*	Emmons and Linnette (1970)
Genital herpes	Chimpanzee	HSV-2	McClure et al. (1980)
Herpesvirus (generalized)	Gorilla	*H. hominis* (HSV-1)	Heldstab et al. (1981)
Encephalitis (fatal)	Gibbon	Herpesvirus	Ramsey et al. (1982)
Malignant lymphoma	Rhesus	Herpes-like	Stowell et al. (1971)
Lymphoma	Owl monkey	*H. hominis* (HVS)	Rabin et al. (1975)
Malignant lymphoma	Baboon	HVP (lymphotropic baboon herpesvirus)	Agrba et al. (1980)
Vesicular disease (fatal)	Macaques	"Herpes-type"	Lourie et al. (1971)

TABLE 46.1. (Continued).

Disease	Species	Virus	References
Lymphoma	Owl monkey	*H. Saimiri* (HVS)	Hunt et al. (1973)
Herpesvirus (fatal)	Patas, colobus	HVS-HSV	Loomis et al. (1981)
Generalized infection	Marmosets	*H. saimiri*	Benirschke (1983)
Myelitis and paralysis	African green monkey	SA8	Malherbe and Harwin (1957)
Pneumonia	Gelada	Herpes virus	Ochoa et al. (1982)
Orthomyxovirus diseases			
Grippe	Chimpanzee	"Influenza"	Mouquet (1926)
Death	Cebus	"Influenza"	Ratcliffe (1942)
"Influenza"	Cercopithecoid	"Influenza"	Panthier et al. (1949)
Fever, malaise	Baboon	A_2/Hong Kong/68	Kalter et al. (1969)
Respiratory disease	Gibbon	A_2/Hong Kong/68	Johnsen et al. (1971)
Papovavirus diseases			
Progressive multifocal leukoencephalopathy (PML)	Rhesus	SV40	Holmberg et al. (1977)
Paramyxovirus diseases in nonhuman primates			
Papular and desquamative exanthem	Orangutan	"Measles"	Fox and Weidman (1923)
Measles	Cynomolgus; rhesus; colobus; silver-leaf monkey (*Presbytis cristatus*)	Measles	Ruckle (1956); Shishido (1966); Potkay et al. (1966); Hall et al. (1972); Yamanouchi et al. (1973); Colman and Clarke (1975); Hime et al (1975); Remfry (1976); Montrey et al. (1980)
Giant cell pneumonia	Rhesus	Measles	Manning et al. (1968)
Measles (fatal)	Marmoset	Measles	Levy and Mirkovic (1971)
Endometritis, cervicitis, abortion	Rhesus	Measles	Renne et al. (1973)
Gastroenterocolitis	Marmoset	Measles	Fraser et al. (1978)
Encephalitis	Rhesus, pig-tailed macaque		Steele et al. (1982)
Coryza	Chimpanzee	"CCA"[1] (chimpanzee coryza agent)	Morris et al. (1956)
Pneumonia	Patas	Paraflu-3	Churchill (1963)
Upper respiratory infection	Gibbon	Paraflu-3	Martin and Kaye (1983)
Pneumonia	Chimpanzee	Paraflu-3	Jones et al. (1984)
Acute respiratory disease	Marmoset	Paraflu-1	Flecknell et al. (1983)
Mumps (parotiditis)	Rhesus	Mumps	Bloch (1937)
Gastroenterocolitis	Marmoset	"Measles"(?) SV5	Gibson et al. (1980)
Respiratory disease	Cynomolgus	Murayana	Nishikawa et al. (1977)

TABLE 46.1. (Continued).

Disease	Species	Virus	References
Picornavirus diseases			
Poliomyelitis (paralytic)	Chimpanzee	?	Goldman (1935); Müller (1935)
	Gorilla, orangutan	Polio 1	Guilloud and Kline (1966); Allmond et al. (1967); Guilloud et al. (1969)
Poliomyelitis	Chimpanzee	Polio	Howe and Bodian (1944); Melnick and Horstmann (1947)
	Colobus	Polio-1	Guillous and Kline (1966)
Myocarditis	Gibbon, chimpanzee	EMC	Schmidt (1948); Gainer (1967); Gaskin et al. (1980); Helwig and Schmidt (1945)
Myocarditis, pulmonary edema	Night monkey (*Aotes trivirgatus*), squirrel monkey	EMC	Roca-Garcia and SanMartin-Barber (1957)
Fever, diarrhea, respiratory disease	Chimpanzee	"Coxsackie-B5"	Kelly et al. (1978)
Diarrhea	Rhesus	SV6, SV48	Heberling (1972)
Neurologic	Rhesus, vervet	SV16	Kaufmann et al. (1973)
Hepatitis	Chimpanzee	HAV	Hillis (1967)
Poxvirus diseases			
"smallpox"	Cebus	"Smallpox"	Bleyer (1922)
Pox-infection	Orangutan	"Variola-like"	Gispen (1949)
Pox-infection (fatal)	Orangutan, chimpanzee, gorilla, "Cercopithecus," marmoset	"Monkeypox"	Peters (1966)
Pox-infection	Cynomolgus, rhesus; vervet, chimpanzee	"Monkeypox" Monkeypox (Variola?)	vonMagnus et al. (1959); Prier et al. (1960); Sauer et al. (1960); McConnel et al. (1962); Gispen and Kapsenberg (1967); Marennikova et al. (1972)
Subcutaneous tumors	Rhesus, baboon	? (YABA)	Bearcroft and Jamieson (1958)
Pox-like skin lesions	Rhesus (other macaques)	Tanapox (Yaba-like, Orteca, 1211)	Nicholas and McNulty (1968); Crandell et al. (1969); España (1968)
Molluscum contagiosum	Chimpanzee	Molluscum contagiosum	Douglas et al. (1967); Schmidt and Butler (1971)
Rabies (Rhabdovirus)			
Respiratory infection	Rhesus	Rabies	Boulger (1966)
Rabies	"Monkey," cebus, cynomolgus, squirrel monkey, "Micoleone" (golden lion marmoset)	Rabies	Richardson and Humphrey (1971)
	Chimpanzee		Miot et al. (1973)

TABLE 46.1. (Continued).

Disease	Species	Virus	References
Reovirus–rotavirus diseases			
Rhinitis	Chimpanzee	REO-1	Sabin (1959)
Diarrhea[2]	Chimpanzee; rhesus	Rotavirus; rotavirus (SA11)	Ashley et al. (1978); Stuker et al. (1980)
Retrovirus diseases			
Mammary tumor (adenocarcinoma)	Rhesus	MPMV (Mason Pfizer monkey virus)	Jensen et al. (1970)
Leukemia	Woolly monkey, gibbon	SSV/SSAV[3] GALV[3]	Theilen et al. (1971); Kawakami et al. (1972)
Leukemia–lymphosarcomas	Baboon, *M. arctoides*	? ("BILN")	Lapin et al. (1973)
Lymphoma	Baboon; stump-tailed macaque	Foamy virus 1	Rabin et al. (1976); Schnitzer (1981)
Pelvic endometriosis	Pig-tailed macaque		DiGiacomo et al. (1977)
SAIDS; lymphoma; lymphoma–retroperitoneal fibromatosis	Macaques	Type D (MPMV, SRV-1, SRV-2); HTLV-III (STLV-III)	Stowell et al. (1971); Manning and Griesemer (1974); Giddens et al. (1983); Henrickson et al. (1983); Letvin et al. (1983); Marx et al. (1984)
Miscellaneous diseases			
Marburg	African green monkey	Marburg	Martini et al. (1968)
Simian Hemorrhagic fever	Macaques	SHF	Lapin and Shevtsova (1966); Palmer et al. (1968); Allen et al. (1968)
Rubella	African green monkey	Rubella (Togaviridae)	Cabasso and Stebbins (1965)
Subacute Sclerosing Panencephalitis-like	Baboon	?	Kim et al. (1970)
Neurologic disease	Rhesus	Picornavirus	Kaufmann (1972)
Perinatal telencephalic leukoencephalopathy	Chimpanzee	?	Brack (1973)

[1] Respiratory syncytial virus.
[2] The significance of finding other viruses in stool samples, from both normal animals and those with diarrhea, emphasizes the need for further study.
[3] Closely related viruses—see text.

diseases. While this phylogenetic relationship appears to exist to a certain extent, variations in susceptibility to viruses among simian species must be considered. This difference in susceptibility is exemplified by certain marmoset species (with few exceptions) that phylogenetically are far removed from chimpanzees but are along with the chimpanzee both highly susceptible to hepatitis A.

Virus diseases of primates may be grouped according to the source of infection: natural, with which we are primarily concerned, or experimental. Experimental infectious disease studies also need consideration, particularly if they are not adequately controlled, allowing "in-house" epidemics to occur. Simian hemorrhagic fever was spread through several animal colonies by failure to sterilize adequately syringes or tattooing needles.

"Natural" infections in primate colonies have resulted from contact with rodents (gibbon ape leukemia) and humans (influenza, respiratory syncytial virus–croup). To develop and maintain primate colonies with minimal losses resulting from viruses, one must guard against the introduction of agents from the wild (newly imported animals) but also against the spread of a virus derived from the accidental infection of an animal in the colony by another animal (human?) source. A mechanism for monitoring the animals is necessary for early detection of an alien agent to prevent its spread.

With encroaching human populations, human contact with wild groups of animals needs consideration. These naive animals are highly susceptible to infectious agents by virtue of lack of previous contact (immunization). More often than not, such contact will have little effect on these groups of animals other than immunization. However, one bad experience, such as occurred with the introduction of measles into secluded human populations, can do much to endanger further an already endangered group of animals.

The full spectrum of virus diseases that occur among simian populations in the wild is unknown. Very few studies have been conducted on simian species in their native habitat. The majority of information available on virus diseases of nonhuman primates has been derived from captive animals or those in contact with humans or other species of animals. Trapping conditions are still deplorable in many instances and probably are the major source of infection and disease, but contact with other animal species does occur under natural conditions. Attempts to analyze data obtained from studies on wild populations of animals are clouded by the diverse conditions under which the different species live. The need for food and water results in migration patterns producing contacts impossible to determine. Even those animal populations that are stationary are in contact with other populations that are migratory. Under these conditions, precise origins of diseases are purely speculative.

In spite of these difficulties, serological studies and the isolation of viruses from animals immediately following capture have provided some information of value. Serological surveys furnish data regarding past infections; isolation data offer little in the way of past history, usually indicating only current infections. An important exception is the isolation of an agent from tissues, e.g., herpesviruses from ganglia, in the case of latent infections.

Antibody studies suggest widespread distribution of virus infections among wild populations. Clinical disease, however, has been reported rarely (Kalter and Heberling, 1971). With few exceptions, little is known about fatal virus diseases occurring in the wild. Animals that die are rarely found and rapidly disappear

from the scene. Animals that are found, again with few exceptions, are rarely studied for specific cause of death, particularly with regard to viruses.

Verifiable reports of fatal virus diseases occurring in nonhuman primates in the wild are, therefore, few. High rates of fatalities among simians as a result of viruses have been reported, usually coincidental with human deaths, caused by yellow fever virus, Kyasanur Forest virus, and Marburg virus. The first two diseases were actually occurrences in the wild; the latter deaths were seen in the laboratory. Deaths caused by poxviruses (monkeypox), rabies, measles (rubeola), retroviruses (gibbon ape leukemia virus, SAIDS), picornaviruses (poliovirus, coxsackievirus), and others have been reported to occur as a result of natural infections. It is not clear what the impact of these viruses would be in colonies reared under controlled laboratory conditions.

Information on captive animals is more readily available than on those in nature. Review of documented captive animal disease outbreaks indicates that the majority are nosocomial. Mishandling, mixing of species or groups of animals, and breakdown in appropriate procedures account for most occurrences. As a result, disease caused by human agents spread by personnel either directly or indirectly occurs more frequently than diseases caused by simian viruses.

Only those virus diseases that occur naturally rather than experimentally will be discussed. It should be emphasized that the majority of these infections/diseases are more debilitating than fatal; nonetheless, the loss of time and the disruption of programs emphasize the need for proper handling procedures to sustain populations.

Viruses

In reviewing the major virus diseases observed in nonhuman primates as a result of "natural" infections, no attempt will be made to provide details on any particular disease or diseases. My intent is to emphasize the extensive occurrence of natural viral diseases that have been recognized and indicate the potential effect such occurrences could have on "self-sustaining" populations. I will also discuss measures necessary to prevent these diseases or minimize their spread. Serological assays of simian sera indicate widespread contact among simian species with all the following viruses and their various serotypes (Kalter and Heberling, 1971).

Adenoviruses (Adenoviridae)

This virus family (Adenoviridae) is the one most frequently isolated from simians. Over 20 serotypes are recognized, and one or another of these may be recovered from normal as well as sick animals at any time. As a result, association with disease is difficult to determine and requires careful laboratory support. Mainly present in the respiratory and intestinal tract of all simian species, adenoviruses may also be found in various tissues and conjunctival fluids. Cross-reactions with human adenoviruses are common (Willimzik et al., 1981), making differentiation between human and nonhuman strains difficult. As seen in Table 46.1, diseases similar to those occurring in humans are found in nonhuman primates as a result of the adenoviruses.

Arboviruses (Togaviridae, Bunyaviridae, etc.)

The use of nonhuman primates as sentinel animals for the detection of arboviruses indicates their susceptibility. A wide range in susceptibility to these viruses exists among primates. It might be assumed, because of the widespread prevalence and the large number of viruses included among the arboviruses, that infection/disease would be extensive. However, deaths as a result of arboviruses occur infrequently, and clinical disease, although it undoubtedly occurs, is also apparently infrequent (Table 46.1). It is noteworthy to recognize that monkeys play an important role in the maintenance of yellow fever in nature. This is a rare role for nonhuman primates to play in the epidemiology of infection.

Herpesviruses (Herpesviridae)

One of the most ubiquitous of virus families, the herpesviruses are also one of the most important in terms of infection/disease. As a natural infection, the herpesviruses are rapidly disseminated. In captivity, the herpesviruses are also responsible for infection, disease, and death. Undoubtedly, herpesviruses as a group are of greatest concern for nonhuman primates as well as to users of nonhuman primates. Herpesviruses are responsible for every conceivable type of clinical condition, extending from inapparent to mild localized disease to death. Any program designed to maintain self-sustaining populations must give thought to control of this group of viruses. A large number of herpesviruses are recognized, and although many are considered host specific, crossing of species barriers is common. When this occurs, it is frequently associated with a clinical pattern more severe than that seen in the original host. For this reason, B virus has probably become the simian virus of greatest concern among primate investigators.

Herpesviruses in their native hosts, while not innocuous, are probably of little concern in terms of colony management; however, in colonies of mixed populations or where human contact is not controlled, herpesviruses must be considered a major threat in maintenance of the colony. As Hunt (this volume) emphasizes, the cytomegaloviruses do not appear to be of any clinical consequence. However, until more is known about the full pathogenic potential of this virus(es), the frequency of occurrence in primates should make it suspect as a potential pathogen. There is also increasing concern regarding the oncogenic capabilities of the herpesviruses (Table 46.1).

Influenza Viruses (Orthomyxoviridae)

It is now apparent that all primates respond to infection with strains of influenza A viruses. This response may be clinical or subclinical. Clinical disease is similar to that seen in the human, with virus shed into the environment. Deaths appear to be associated with secondary bacterial infection. Serological studies indicate widespread distribution of antibody to influenza A, with greater numbers of positives seen to the newer strains (Kalter and Heberling, 1978). Vaccines apparently are effective but, in view of the lack of severe disease, the need for vaccination may be questioned. Although antibody to influenza virus B is detected, these seropositives are few, and it would appear that this virus is probably inconsequential as a disease factor. Epizootics in gibbons with type A (A_2/Hong Kong/68)

have been reported (Johnson et al., 1971). Reports of isolated cases in nonhuman primates are also known (Table 46.1).

Parainfluenza Viruses (Paramyxoviridae

Several of the human parainfluenza viruses are responsible for disease in nonhuman primates. A certain amount of confusion exists in classification of these viruses because there have been isolations made from simians that suggest "true" simian viruses exists. Indeed, several have been found to be primate viruses that infect both human and nonhuman primates. Infection with the various parainfluenza viruses, mumps, measles (rubeola), and respiratory syncytial virus (chimpanzee coryza agent, CCA) has been reported. The exact relationship of two simian isolates, SV 5 and SV 41, to simians is still in need of study.

Papovaviruses (Papovaviridae)

Two virus genera, *Papillomavirus* and *Polyomavirus*, make up this virus family. The viruses included herein are of interest not so much for what they have done, but for their potential. Present in a number of different animal species including human and nonhuman primates, many of these viruses have the ability to produce tumors or transform cells. In spite of this recognized capability, only limited pathogenicity has been demonstrated. SV 40, one of the first simian viruses recognized (Rustigian et al., 1955), is present in *Macaca* sp. kidney cells. This virus has been widely distributed to humans, inadvertently incorporated into the poliovaccine. No adverse effects have been recorded as a result of this administration although some 30 years have passed since it was first given to humans. Holmberg et al. (1977) were able to isolate SV 40 following the immunological suppression of macaques with progressive multifocal leukoencephalopathy (PML). Inasmuch as these viruses are associated with latency (Norkin, 1982), are they activated when the individual is stressed or immunologically impaired?

Picornaviruses (Picornaviridae)

This family of viruses (Picornaviridae) originally included only the enteroviruses (polio-, coxsackie-, and echoviruses) but now includes the rhinoviruses and hepatitis A virus (HAV) derived from humans plus a number of animal viruses sharing the same biological characteristics (foot and mouth disease virus, encephalomyocarditis virus [see Hunt, this volume], and a number of insect viruses). Counterparts of the human enteroviruses are also present in various animal species including simians, rodents, cattle, swine, and others. These and the adenoviruses are the most numerous of the isolates encountered in routine primate virus isolation attempts. Antibody studies (Kalter, 1967) indicate that infection with the enteroviruses is widespread among nonhuman primates. In terms of disease, however, they are relatively unimportant although disease caused by one or another of these viruses has been recorded. Encephalomyocarditis virus evidently can be a major problem in primate colonies (Gaskin et al., 1980). Rhinoviruses do not appear to be highly pathogenic (Dick and Dick, 1974), but only limited information is available on this large group of viruses.

Poxviruses (Poxviridae)

A widely distributed virus group, most of these are restrictive to their natural host. Antigenic crossing among viruses in each genus makes differentiation of the viruses difficult. Several poxvirus genera exist in the family Poxviridae; infection of primates is generally with members of the vaccinia subgroup (Orthopoxvirus) (vaccinia-variola-monkeypox viruses). There is concern over poxvirus transmission, and human infection with monkeypox following contact with an infected chimpanzee has been reported (Mutombo et al., 1983). The extent of natural infection with this virus among nonhuman primates is not known. Unclassified Poxviridae (Yaba virus, Tanapox virus, molluscum contagiosum virus) are also known to be infectious for one or another nonhuman primate.

Reoviruses (Reoviridae)

Reoviruses isolated from nonhuman primates (SV 12 and SV 59) are so closely related antigenically to the recognized human reovirus types 1 and 2 that they are considered counterparts of the human types. In general, these viruses are of low pathogenicity although antibody surveys indicate widespread occurrence of all three reovirus types. Sabin (1959) did report the occurrence of a zoonoses of rhinitis in chimpanzees from which a type 2 reovirus was isolated. Reovirus association with diarrhea is suspected but not demonstrated. Another member of the family Reoviridae, the rotaviruses, are known to cause gastroenteritis in different animal species. It is apparent that all primates as well as other animal species may develop gastroenteritis following infection with one or another of the rotavirus types. SA 11, previously isolated from African green monkeys (Malherbe and Strickland-Cholmley, 1967) is a rotovirus antigenically related to an agent isolated from an abattoir. This virus has not been found in nonhuman primates with any frequency. Recently, however, Stuker et al. (1980) have reported a similar virus in macaques with diarrhea.

Retroviruses–Oncornaviruses (Retroviridae)

Tumors and tumor viruses as detailed by others in this volume (Hunt, Rabin and Benveniste) occur in nonhuman primates with great frequency. Although at one time it was thought that nonhuman primates did not develop malignancies, it is now recognized that these occur in simians as in humans. As indicated (see Herpesviruses), tumor induction is not restricted to the retroviruses. However, this family (Retroviridae) of viruses, which includes a number of RNA viruses, has been associated with oncogenesis in many animal species. Tumor induction in primates with retroviruses as a natural infection of primates (leukemia in gibbons, SAIDS in rhesus) has initiated extensive studies on the origin of these viruses, their relationship to each other, and their potential to induce tumors. It is still unclear what "diseases" the primate endogenous C-type retroviruses are capable of causing. They are apparently present in all vertebrate tissue (placentas) and as pseudotypes do cause metastatic disease (Kalter et al., 1975, 1977). Also, the relationship of such viruses as the AIDS–SAIDS viruses; the woolly monkey SSV–gibbon ape viruses (GALV) and other retroviruses to oncon-

genesis and their natural hosts is still unclear. The woolly monkey agent had been recovered from one monkey in contact with a gibbon ape that subsequently died of "leukemia."

Rabies (Rhabdoviridae)

This virus, frequently overlooked as a cause of deaths in nonhuman primates, does occur and is a disease that must be considered in colony management, particularly those that are "open" in which contact with wild animals is possible. The disease, similar to that seen in humans, has been reported in a variety of nonhuman primates (Richardson and Humphrey, 1971).

Miscellaneous Viruses

A number of diseases have been ascribed to one or another exotic virus (or suspected virus) either in nature or as the result of experimental studies. Infection resulting from experimental studies obviously does not concern those interested in colony management other than to suggest a possible etiology or cast suspicion when attempting to define an unknown outbreak. For example, lymphocytic choriomeningitis (LCM) virus (*Arenavirus*) has not been reported to cause natural disease of primates. However, the presence of this virus in rodents (natural host) as well as experimental studies (Armstrong et al., 1936) would strongly suggest that this disease could occur in any simian population.

Marburg disease is an infrequent simian disease of concern to colony managers. It is still not clear where or how this "one-time" outbreak originated. Neither is it known what role the African green monkey played in the spread of this disease other than that it served as the carrier of the agent bringing it into Frankfurt-Marburg, Germany, and into Belgrade, Yugoslavia (Martini and Siegert, 1971). It is important to recognize that the animals in Germany were used shortly after arrival and that there was no unusual mortality recorded. The animals in Belgrade were held for 6 weeks, and here the death rate was higher than usual (35%). It was originally believed that no unusual deaths among monkeys were observed in Uganda, the source of the monkeys. However, a recent report suggests that this was not the case (Smith, 1982). A retrospective report by Smith suggests that there were sick animals as well as humans in the area, but investigations into this relationship were not done.

Simian hemorrhagic fever (SHF) is another disease that has occurred unexpectedly, with high mortality rates (100% of animals with clinical disease), in primate colonies in the United States, Soviet Union, and England. This disease outbreak was primarily in *Macaca* spp., which appears to be the only genus susceptible to this virus. The epidemiology of the disease within colonies is not clear, but contaminated syringes as well as reuse of needles for tatooing without appropriate sterilization was suspected (Shevtsova, 1967; Lapin et al., 1967; Tauraso et al., 1968; Palmer et al., 1968, Wood et al., 1970).

These diseases and others that occur in areas from which laboratory primates are collected require consideration. Included also are such viruses as Lassa fever (*Arenavirus*), members of the Tacaribe complex such as Junin virus (Argentine hemorrhagic fever), and Machupo virus (Bolivian hemorrhagic fever). Other hemorrhagic fevers caused by various viruses, some classified and others not,

include dengue (group B *Flavivirus*), Omsk hemorrhagic fever and Kyasanur Forest disease (Flavivirus). Crimean–Congo hemorrhagic fever viruses are in the family Bunyaviridae (*Nairovirus*), as is Rift Valley fever virus. Undoubtedly, there are others yet to be detected. Isolated reports suggest that these diseases do occur in monkeys and apes.

Mention has been made of chimpanzee infection with HAV (hepatitis A virus). Two unclassified hepatitis viruses—HBV (hepatitis B) and NANB (non A and non B hepatitis)—are infectious for chimpanzees, at least experimentally. Are simians independently susceptible to these viruses in nature or only as a result of human contact? The occurrence of HAV in chimpanzees was recognized when humans contracted the disease as a result of contact with infected animals (Hillis, 1961).

Gastroenteritis is a major problem in colony management. What is the etiology of this disease? It is evident that this syndrome is caused by many different viruses, some of which have been determined, others suspected, and still others yet to be determined. Thus, in addition to the rotaviruses, adenoviruses, reoviruses, picornaviruses, coronaviruses, calciviruses, astraviruses, orbiviruses, and others, one may ask, What is the role of other nonviral agents either in conjunction with viruses or acting independently in causation of diarrhea—parasites, bacteria, fungi, chemicals and other physiological insults?

Last we may question the influence of "slow" or exotic viruses on colony maintenance. Nonhuman primates have been useful in defining the etiology of several human diseases thought to be caused by exotic viruses. The majority of these diseases are considered members of the subacute spongiform virus encephalopathy group (scrapie and transmissible mink encephalopathy in animals, kuru and Creutzfeldt-Jakob's disease in humans). As suggested by Amyx et al. (1983), these and other human and animal diseases of this type may be caused by exotic viruses or conventional viruses. Included here are multiple sclerosis, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Pick's disease, Huntington's chorea, and other similar diseases. Frauchiger and Fankhauser (1970) emphasize that naturally occurring diseases of the central nervous system are rarely, if ever, seen in nonhuman primates. On the other hand, reports are seen to the contrary! Is PML as reported by Holmberg et al. (1977) in rhesus monkeys an indication of simian exotic disease counterparts? Kim et al. (1970) have reported a subacute sclerosing panencephalitis-like syndrome in adult baboons; the etiology, however, was not determined. Similarly, Brack (1973) listed the occurrence of perinatal telencephalic leukoencephalopathy in chimpanzees.

Diagnosis and Detection

In attempting to define the role of viruses in self-sustaining populations of nonhuman primates, it is not only important clinically to recognize the existence of these viruses but to have methods for their detection. Diagnosis of virus diseases is necessary to maintain the well being of colony animals by prevention and control of the spread of these agents. Diagnosis is also helpful in order to apply specific therapy or preventive measures such as appropriate vaccines. In veterinary medicine as in human medicine, the clinician is faced with the dilemma of determining the etiology of zoonoses or the cause of an illness in an individual

animal. Clinical acumen is important, but when specific etiologies of respiratory diseases, intestinal disturbances, neurological disease, or exanthems are desired, the support of a diagnostic laboratory is highly desirable (see Appendix A of this volume).

It is important to recognize that diagnostic methodologies have markedly improved during the past few years, and, as will be demonstrated herein, a serologic diagnostic method has now been developed to provide information within hours after the collection of appropriate specimens. A similar procedure for the rapid identification of an isolate is also available. What are the diagnostic procedures that are in use, and how are they applied? In essence, the laboratory procedures used for veterinary medicine, as would be expected, are the same as used in human medicine.

Approaches to the Laboratory Diagnosis of Viral Infections

The final diagnosis of an illness is completed by the combined efforts of the clinical and laboratory personnel. The clinician, recognizing a diagnostic problem, provides the laboratory with the necessary suitable specimens collected at the most appropriate time in relation to the illness (Kalter, 1971). The laboratory in turn considers the most appropriate test or tests for the type of specimen provided: (1) the direct examination of the specimen for the presence of a virus or its antigen(s); (2) serologic determination of antibody either as: (a) an early globulin (IgM), (b) present in a single serum specimen indicating past exposure, (c) present in high titer suggestive of recent infection, or (d) preferably, the detection of an antibody rise in a convalescent serum over that found in an acute serum sample; (3) the isolation of an agent, its identification, and the demonstration of its relationship to the illness by observing an antibody rise to the isolate in the convalescent serum, and (4) the significance of the findings in terms of specificity of reaction, cross-reactions of antigens, compatibility with clinical findings, etc. The cross-reactions among such viruses as the adenoviruses or herpesviruses is well known. It is apparent that the satisfactory completion of the above necessitates the availability of suitable reagents. Sensitive and specific reagents are the *sine qua non* of the laboratory's capabilities.

Methodologies

Most laboratories depend upon several procedures for the satisfactory completion of their mission. However, as indicated previously, the specimen(s) provided will determine the laboratory's approach to the problem.

Electron Microscopy

Direct visualization of a virus requires use of the electron microscope. The size of viruses precludes the use of the light microscope. Direct visualization requires a distinctive morphological charactetistic of the virus. Electron microscopy is of value in examination of material obtained from skin lesions (exanthems), feces (diarrhea, hepatitis), and certain biopsy specimens. This approach is of value in detecting viruses that are difficult to grow, or do not grow, in culture (HAV, rotaviruses). Limiting features are the requirement for large quantities of virus

in the specimens as well as the inability to differentiate types within a virus family. Some specificity and sensitivity may be added by the application of an antibody (immunoelectron microscopy) to the system.

Serology

All too often, serological procedures are considered only in terms of classicial serological tests (complement fixation, neutralization, hemagglutination inhibition, etc.). Generally, serologic procedures, regardless of the test, require an acute and convalescent serum sample taken 2–3 weeks apart to detect antibody changes. A significant antibody rise (fourfold) is taken to indicate the host's response to the infectious agent. At times, additional serum samples must be collected to provide unequivocal information.

Serologic procedures are limited by the need to determine an antibody change. Exceptions occur where an antibody to an exotic agent is found or when IgM is present in an acute specimen.

Addition of serum to a procedure such a fluorescence microscopy when used for the direct visualization and identification of a virus or its antigens in a tissue(s) impression (immunofluorescence) is a rapid procedure. However, when used to detect antibody, the limitations inherent in any serologic test affect the results. The newer procedures that have been introduced such as enzyme immunoassays (EIA) or radioimmunoassays (RIA) are in essence similar to immunofluorescence. The virus or its antigens are detected by the presence of a homologous antibody. Detection of this reaction is done by labeling the antibody with an enzyme and detection of the enzyme-labeled antibody by a suitable substrate. In the RIA, instead of fluorescence or an enzyme, a labeled radioisotope (^{125}I) is used. The use of monoclonal antibody provides an enhanced specificity but in essence does not change the procedure.

Virus Isolation

Virus isolation studies are time consuming, often misleading and/or valueless, and more often than not are negative. Relating an isolate to the disease is nearly impossible unless a concomitant antibody rise to the agent is determined, and this, too, can be misleading because of contamination of the sample or unless Koch's postulates are established. Viruses are frequently encountered in body fluids or specimens that have no relationship to the illness under study. Laboratory expertise and cooperation with the clinician is required to resolve these findings.

To isolate an agent, it must be cultivated on a suitable medium—cell culture, animal, embryonate eggs. The choices are endless but the supply limited. Susceptibility varies, and maintenance of all the desired test systems is impossible. Host restrictions oftentimes require maintenance of a wide assortment of materials (cells, animals, etc.). Primary cells are considered preferable to secondary cells and newborn animals more desirable than older animals.

Newer Approaches

Attempts to unmask or free viruses from inhibiting substances, particularly fecal viruses by use of proteolytic enzymes, appear to be successful (Graham and Estes, 1980). Immunoassays (immunofluorescence, radioisotope, enzyme

immunoassays), molecular hybridization, and other molecular procedures are under study as substitutes for the classical approaches.

A simple, rapid, and sensitive method currently under study in our laboratory provides serologic data or isolation identification within 3–5 hours (Heberling and Kalter, 1985). This method, the "dot immunobinding assay" (DIA), utilizes nitrocellulose membranes for the rapid adsorption of virus proteins. As seen in Figure 46.1, positive reactions are indicated by the presence of a dark dot (original test color is red). Differentiation between B virus and herpes simplex is also detected as reflected by differences in staining intensity of the dot. Comparisons with SN titers are indicated by the results detailed in the various columns. The small, open circles are for space indication purposes only. Serum determination or identification is done by addition of labeled serum (antiglobulin), which in turn is made visible by use of a substrate dye against the antiglobulin. The results are highly sensitive and specific. Field studies may be done because equipment needs are minimal. Highly infectious viruses, such as *H. simiae*, may be inactivated with a psoralen–UV source.

Failure to Determine Etiology

There are a number of reasons why the laboratory fails in its attempts to define the precise etiology. This occurs most frequently in virus isolation studies because (1) specimens are mishandled (agent inactivated before specimen arrives

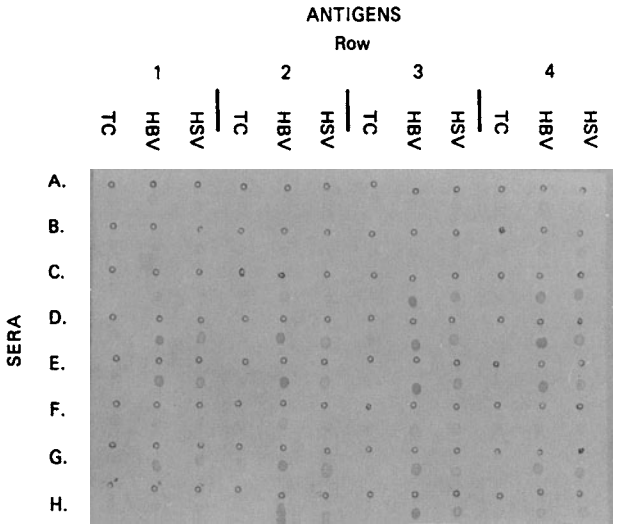

FIGURE 46.1. "DIA" testing of sera for antibody to B virus (HBV) and herpes simplex (HSV). Intensity of staining indicated the primary antigen. Open circles are for purposes of placement of antigen dots. Different rows indicate various serum titers (SN) used in test. T.C. is tissue culture control.

in laboratory), (2) specimens are taken at the wrong time in relation to illness, (3) an inappropriate specimen is collected, or (4) the laboratory uses the wrong procedures for isolation of the virus. Serologic studies are generally more rewarding but at times do not provide an answer because serum samples are not collected at appropriate times to demonstrate antibody, the selected procedure was inappropriate, or the laboratory procedure was not sufficiently sensitive to detect antibody.

Prevention and Significance of Disease in Self-Sustaining Colonies

It is apparent that natural virus diseases, with some few exceptions, have not been a major factor nor do they pose a threat to development of a self-sustaining primate colony. The diseases that do occur have been mainly those associated with the day-to-day operation of a colony and are usually restricted to an individual animal. However, the exceptions are devastating, and Benirschke (1983) emphasizes the occurrence of such spontaneous diseases in primate colonies and the need to eliminate them in order to create self-sustaining colonies. Those incidents that have caused untoward effects have been the result of breakdowns in colony management and the result of human error (simian hemorrhagic fever) or contact with humans (hepatitis A). Marburg disease is a unique situation, and it is still not clear what the epidemiological factors were with regard to that outbreak.

Thus, development and maintenance of self-sustaining colonies require programs in which the human element is carefully controlled. Recommendations suggesting such a program have been well described in the literature (Gerone, 1983; Kalter, 1973, 1983; Kalter and Heberling, 1976). Simply stated, prevention is the function of a well-trained staff who follow established procedures and recognize that infectious diseases, by definition, are caused by infectious agents. Yes, Virginia, there is a germ theory. The following recommendations will do much to protect an animal colony:

1. Obtain animals from reputable dealers with knowledge and records of sources, methods of trapping, maintenance following trapping, personnel contacts, and baseline samples for reference.
2. Institute appropriate quarantine measures with routine health examinations and collection of appropriate samples from staff as well as animals for reference and/or immediate study from staff as well as animals.
3. Maintain a carefully controlled separation of species and, if possible, separation of new groups.
4. Develop a program for the complete study of all animals that die or become ill. Have a comprehensive program available for determining etiology—bacteriology, mycology, parasitology, virology, and pathology.
5. Include vaccination and routine examination for infectious agents whenever possible and practical.
6. Maintain complete records on all animals following arrival in colony.
7. Minimize contact with human and other animal populations. Develop a procedure for control of human contacts.

Inasmuch as many of the human diseases that are transmitted to the captured animals result from inadequate and poorly maintained trapping facilities in the countries of origin, the development of self-sustaining colonies will eliminate this threat. However, a word of caution is necessary concerning established colonies. *These animals will need to be maintained under carefully controlled conditions because they will undoubtedly be more susceptible to infectious agents than their counterparts who have survived previous contact with infectious diseases.* Another problem of laboratory-bred animals that will need consideration is the possibility of latent infections. This type of infection as well as those agents (endogenous) passed vertically from mother to offspring will continue to be a potential threat to any colony.

Future Considerations

Although thoughts of alternate approaches to that of using an intact animal may be appealing to some, conceptualization and realization of an artificial, biologically intact robot does not appear to be in the immediate future. As already demonstrated, other approaches, such as mathematical, computerized, or test-tube biologies, will obviate some use of intact animals. However, it does not appear that any of these surrogates will be capable of immunological, neurological, endocrinological, or other biophysiological responses to a foreign antigenic stimulus. An animal model, preferably employing a nonhuman primate that will provide meaningful data, will continue to be necessary to further our understanding of human diseases. In this regard, expanded studies on species still available in sufficient numbers are needed to provide the most appropriate host. Of the several hundred recognized simian species, some few dozen are used in most research laboratories. The rhesus monkey was not selected because of recognized susceptibility—it was simply available!

The host response of these animals is extremely variable. Infection may not cause an overt pathologic response other than immunologic, but the animals may be shedding viruses in their saliva, feces, urine, and other body fluids that will be infectious for others.

A negative aspect to the continued use of animals, either intact or as contributors of the cells for culture, is the remote possibility of contributing an unwanted pathogen that has been residing in the animal as a latent infection or as an endogenous virus. Hsiung (1968) emphasizes the lack of information on the pathogenesis, persistence, and epidemiology of latent virus infections in primates. As emphasized by Hsiung (1968) and reiterated herein, the presence of viruses within "normal" primate tissues is extremely common. The source of these viruses is generally unknown as is their potential for causing disease.

Nowhere is this potential problem brought to our attention more emphatically than by the presence of retroviruses in primate tissues. For a number of years since their omnipresence in the placentas of vertebrates was described, attempts to associate pathogenic qualities have been fruitless (Kalter, 1983). The recognition that, with some few exceptions, these viruses are difficult to isolate (although readily observed by electron microscopy) and that adult tissues show little if any evidence of their presence has apparently escaped understanding. However, morphologically and biologically similar agents are now recognized to

be associated with such primate diseases as AIDS, SAIDS, and various neoplastic diseases, and the possible relationship should be examined.

Thus, there is a realistic concern regarding the use of animal cells for direct employment as a source of vaccines or even for immortalization. As our molecular capabilities increase, what is the potential for removing that part of the genome responsible for carrying these endogenous agents? Molecular hybridization techniques utilizing various microbial cells could serve as a potential source of materials free of potential pathogens. Insertion of desired antigens would be valuable in eliminating the need for animal cells.

From the above, it would appear that there are a number of potential areas in need of exploration. Molecular studies should reduce the need for the large numbers of animals required for vaccine production. Complete elimination of animal colonies is inconceivable at present because no mechanism(s) exist to provide the information now offered by an intact animal. Colonies are needed in countries of origin as well as in those of utilization that provide animals of the highest quality. To do this, regulatory monitoring systems and support services must be provided. We have indicated a new rapid and specific virus diagnostic test that should do much to improve the quality of colony maintenance. Further study is required to expand and improve such procedures.

It is imperative that studies to determine the most appropriate simian species as models for specific human and nonhuman primate diseases be continued and supported. Gastroenteritis (diarrhea) is in need of a model system for understanding of the disease as well as prevention (vaccine development and evaluation), and as recently pointed out by Amyx et al. (1983), there is a need to establish primate models for the various exotic diseases now considered as possibly viral in etiology such as chronic encephalitis, Creutzfeldt–Jakob, schizophrenia, and hemorrhagic fever with renal syndrome. SAIDS–AIDS is also most appropriately studies in a nonhuman primate species, VandeBerg (1983) reiterated the need for nonhuman primate models and emphasized that little is known about the genetic aspects of viral diseases. Success with such diseases as poliomyelitis and hepatitis, in which the nonhuman primate has played such a positive role, should provide an impetus for expanded studies. Whitney (1983) cites several examples of nonprimate species serving as models in various research activities. Although this approach should be pursued, the immortal words of Koch should be kept in mind, "Meine Herren, vergessen Sie nie, dass die Mäuse keine Menschen sind" (Koprowski, 1958).

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