1995

Rabies--Epidemiology, Prevention, and Future Research

John W. Krebs
Centers for Disease Control and Prevention

Mark L. Wilson
Yale University

James E. Childs
Centers for Disease Control and Prevention

RABIES—EPIDEMIOLOGY, PREVENTION, AND FUTURE RESEARCH

JOHN W. KREBS, MARK L. WILSON, AND JAMES E. CHILDS

Viral and Rickettsial Zoonoses Branch, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333 (JWK, JEC)
Department of Epidemiology and Public Health, School of Medicine, Yale University, 60 College Street, New Haven, CT 06520-8034 (MLW)

Rabies is caused by a single-stranded, negative-sense RNA virus, maintained in nature by a variety of animal reservoirs. Rabies virus infects the central nervous system, resulting in progressive encephalopathy and ultimately death in an infected human. Globally, the risk of contracting rabies for humans is greatest in regions of the developing world where dog rabies is enzootic. Where rabies in dogs has been eliminated or otherwise controlled through vaccination programs, the disease can be maintained by wildlife. Wildlife primarily involved in maintenance of transmission cycles are carnivores and bats. Persons having frequent contact with wildlife, such as mammalogists, are at greater risk than the general population for exposure to rabid animals. Rabies prevention can be achieved by elimination of exposure and by vaccination through preexposure prophylaxis and postexposure treatment. Preexposure rabies prophylaxis affords a measure of protection for unrecognized rabies exposures and simplifies postexposure treatment. Postexposure treatment is recommended following exposure to a potentially rabid animal and involves treatment of wound and administration of rabies vaccine as well as rabies immune globulin for individuals not previously vaccinated. Future research on rabies is necessary to define the effects of infection on wildlife populations and to evaluate the potential for intervening in wildlife transmission using oral rabies vaccines.

Key words: rabies, *Lyssavirus,* Rhabdoviridae, zoonoses

The antiquity of rabies is illustrated by the ancient origins of terms describing this disease. The Latin word "rabies" is believed to derive from the Sanskrit "rabhas," meaning "to do violence." Early recognition of the infectivity of the saliva of rabid dogs led Roman writers to describe the infectious material as a poison, for which the Latin word was "virus" (Steele and Fernandez, 1991). *Lyssavirus,* the genus to which rabies and rabies-related viruses belong, owes its name to the Greek "lyssa" or "lytta," meaning "madness." The first recorded description of canine rabies apparently was made by Democritus ca. 500 B.C. Aristotle, writing of rabies in his *Natural History of Animals,* described dogs suffering from a madness causing irritability and how following their bite other animals became diseased. Little has changed in the epidemiology of rabies, as dogs and other carnivores remain the common sources of human infection in most areas of the world where the virus is enzootic.

CHARACTERISTICS OF LYSSAVIRUSES

Rabies and rabies-like illnesses are caused by a number of different neurotropic viruses belonging to the genus *Lyssavirus* in the family Rhabdoviridae. The rabies virion consists of single-stranded, negative-sense RNA contained within a bullet-shaped, bilayered envelope. The genome encodes five structural proteins. Three of these, the transcriptase, nucleoprotein, and phosphoprotein complex with the genome

Journal of Mammalogy, Vol. 76, No. 3 (Aug., 1995), pp. 681-694

to form an inner nucleocapsid. The matrix protein forms the inner side of the bilayered lipid envelope and the glycoprotein forms the outer layer and spike-like projections, the target of virus neutralizing antibody (Wunner et al., 1988).

Members of the genus *Lyssavirus* have been subdivided into serotypes or genotypes (GT) on the basis of studies of neutralization and monoclonal antibodies or genetic characterization. The classical strains of rabies virus belong to serotype 1 (also GT 1). Other rabies-related viruses include Lagos bat, Mokola, and Duvenhage viruses, constituting GT 2, 3, and 4, respectively. Serotype 5 originally was proposed to accommodate European bat lyssaviruses (EBLV 1 and 2). However, these eventually were shown to be genetically different and have been proposed as GT 5 and 6, respectively (Baer and Smith, 1991; Bourhy et al., 1993).

Classical rabies viruses are present worldwide with the exception of some islands and areas inaccessible or inhospitable to wildlife that might serve as hosts. The known distribution of GT 2-6 is described from only a few isolates and, thus far, is confined to Africa, Europe, and the former Soviet Union. Fatal rabies-like human illnesses have been associated with several of these other lyssaviruses, including Mokola virus (GT 3), isolated from insectivores (*Suncus*), rodents, and domestic dogs and cats in East, West, and southern Africa (Familusi et al., 1972; Foggin, 1983; Ogunkoya et al., 1990; Saluzzo et al., 1984; Shope et al., 1970); Duvenhage virus (GT 4), isolated from a man bitten by a bat (species unknown) in Pretoria, South Africa (Meredith et al., 1971); Yuli virus, isolated from a boy bitten by a bat (species unknown) in the former Soviet Union (Selimov et al., 1989) appears most similar to EBLV 1 (GT 5; C. E. Rupprecht and J. S. Smith, pers. comm.), isolated from *Eptesicus serotinus* in Holland (Nieuwenhuijs et al., 1992); EBLV 2 (GT 6), isolated from a Swiss researcher of bats in Finland (similar isolates have since been obtained from *Myotis dasycneme*—King and Turner, 1993). While not known to be responsible for any human deaths, Lagos bat virus (GT 2) was isolated from *Eidolon helvum* in Nigeria (Bougler and Porterfield, 1958).

Viral Transmission

Rabies virus is transmitted by its introduction into wounds or cuts in skin or mucous membranes, most commonly by bites. Transmission of rabies virus also may occur, under unusual circumstances, via nonbite exposures. The nonbite exposures of apparent highest risk are those from large amounts of aerosolized rabies virus, organs (i.e., corneas) transplanted from patients who died of rabies, and contact of saliva or nervous tissue from a rabid animal with mucous membranes or scratches (Centers for Disease Control and Prevention, 1991).

Two cases of rabies have been attributed to airborne exposures in laboratories (Centers for Disease Control and Prevention, 1977; Winkler et al., 1973), and two cases of rabies have been attributed to airborne exposures in a bat-infested cave in Texas (Constantine, 1967). The only documented cases of rabies caused by human-to-human transmission occurred in eight recipients of transplanted corneas. Investigations revealed that each of the donors had died of an illness compatible with or proven to be rabies (Centers for Disease Control and Prevention, 1980, 1981; Gode and Bhide, 1988; Houff et al., 1979; World Health Organization, 1994). The eight cases occurred in Thailand (two cases), Iran (two cases), India (two cases), United States (one case), and France (one case). Stringent guidelines for acceptance of donor corneas have reduced this risk. Although bites inflicted by infected humans theoretically could transmit rabies, possible cases are poorly documented (Helmick et al., 1987).

Human and Animal Disease

Rabies virus preferentially infects nervous tissue. After inoculation, virions may

remain temporarily inactive or initiate attachment to the plasma membrane of peripheral nerve cells. There is evidence of replication of the rabies virus in skeletal muscle cells near the site of inoculation prior to infection of nerve cells (Balachandran and Charlton, 1994). The nervous-tissue pathway of infection may shield the virus from the immune system, thus, accounting for the lack of early antibody response. The virus spreads by retrograde axoplasmic flow until it reaches the spinal cord and then rapidly disseminates through the central nervous system. There then begins a reverse dissemination of virus along peripheral nerves to sites throughout the body, including the salivary glands, where it is shed in the saliva.

The incubation period of rabies in humans is variable; well-documented incubation periods range from <10 days to >6 years (Fishbein, 1991; Smith et al., 1991). In most cases, however, the first symptoms of rabies are noted within 30-90 days of exposure. Initial symptoms can include pain or paresthesia (abnormal touch sensation, such as burning) at the site of the wound, followed by fever, headache, malaise, and apprehension. As disease progresses, changes in mental status may occur including disorientation, agitation, hallucination, and, rarely in humans, aggression. Physical manifestations may appear in the form of difficulty swallowing, hypersalivation, priapism (persistent erection of the penis), muscle spasms, and ultimately paralysis. Hydrophobia occurs in fewer than one-half of all human cases. The progress of the disease, once symptoms appear, is relentlessly downhill. Death may occur in ≤1 week, following the development of initial symptoms, usually as a result of respiratory failure. Ventilatory support may prolong survival, but, in spite of experimental use of interferon and other antiviral drugs, no effective treatment exists once the infected individual becomes symptomatic (Fishbein, 1991).

Although almost universally fatal, there have been four well-documented instances of survival from rabies of persons whose infections had progressed to clinical disease. All four persons had received vaccine either prior to exposure or during the incubation period, and at least two remain affected by sequelae (Alvarez et al., 1994; Centers for Disease Control and Prevention, 1977; Hattwick et al., 1972; Porras et al., 1976).

Natural History and Epizootiology

Rabies is a zoonotic disease, maintained and transmitted to humans by animal hosts. Human infections are of no importance to virus maintenance because humans do not normally contribute to the transmission cycle (Helmick et al., 1987). Mammalian carnivores play the essential role as hosts for rabies virus in terrestrial cycles of the disease. In most developing countries where rabies is enzootic, the domestic dog is the primary reservoir for the disease and the source for most human exposures. The extent of rabies infection among wildlife in developing countries is unknown because of the overwhelming importance of canine rabies and incomplete surveillance among wildlife. Most developed countries have brought dog rabies under control through effective pet-vaccination programs. In these countries, the disease, when present, is maintained among wildlife with only occasional transmission to domestic animals and humans.

Across much of Europe, the red fox (*Vulpes vulpes*) is the main reservoir while the raccoon dog (*Nyctereutes procyonoides*) and the gray wolf (*Canis lupus*) are reservoirs in more northern regions of Eurasia (Wandeler et al., 1994). In Africa, jackals (*Canis*) and mongooses (*Cynictis penicillata*) as well as other carnivores are responsible for maintenance and transmission among wildlife (King et al., 1994). In North America, raccoons (*Procyon lotor*), skunks (primarily *Mephitis mephitis*), foxes (primarily *V. vulpes*), and bats (several species)

are the major reservoirs (Smith, 1989). Less is known about terrestrial wildlife reservoirs in Central and South America due to the importance of dog rabies. Mongooses (*Herpestes auropunctatus*), introduced on some islands in the Caribbean (e.g., Puerto Rico), have provided wildlife reservoirs for rabies. Globally, rabies in bats is widespread and, although transmission cycles are distinct from those of terrestrial rabies, can spread to terrestrial mammals. Rabies in vampire bats (primarily *Desmodus rotundus*), which affects cattle and occasionally humans, is of special concern in regions of Central and South America (Lopez et al., 1992; Pawan, 1936).

Characterization of rabies-viral isolates by molecular-typing methods indicates that infections within broad geographic regions of the United States can be linked to distinct viral variants, each primarily maintained by intraspecific transmission within a dominant reservoir (Smith, 1989). Infections among the diverse remaining mammalian species of these regions generally are regarded as spill-over from the dominant reservoir species. The expected distribution of the variants affecting terrestrial species of animals has been established (Rupprecht and Smith, 1994; Fig. 1). Overlaying the disease in terrestrial animals are independent reservoirs for rabies in several species of insectivorous bats. The finding of a single variant in rabid raccoons from the southeastern states and the mid-Atlantic and northeastern states is compatible with the suggestion that transport of infected raccoons from a long-standing focus of rabies in the southeastern states was responsible for the more recent epizootic in the mid-Atlantic and northeastern states (Jenkins et al., 1988). Rabies in skunks (mainly *M. mephitis*) can be identified in three regions in the northcentral states, California, and the southcentral states. Rabies in foxes is recognized in four regions. Although the number of cases of rabies in gray foxes (*Urocyon cinereoargenteus*) in Arizona and Texas is small, distinctive variants identify reservoirs for rabies in these animals as independent of the more frequently reported disease in skunks in the same area (Krebs et al., 1994). The geographically-separate regions of rabies in Arctic (*Alopex lagopus*) and red foxes in Alaska and red foxes in the counties of New York and Vermont that border Canada are part of a much larger area of enzootic rabies extending across Canada from the Northwest Territories to Ontario. An epizootic of rabies in coyotes and affecting dogs in southern Texas is unrelated to other reservoirs for rabies in Texas (Clark et al., 1994). European isolates of rabies are predominantly the red-fox-rabies-viral variant. The distribution of dog-rabies-viral variants throughout Africa and North and South America reflects their common origin and introduction via transportation of infected dogs by European colonizers (Smith and Seidel, 1993). Countries and other geographic entities, many of which are islands, reportedly free of terrestrial rabies at the time of this publication include Australia, New Zealand, Papua New Guinea, Japan, Hawaii, Taiwan, United Kingdom, Ireland, mainland Norway, Sweden, Portugal, most of Pacific Oceania, and some Atlantic and Caribbean islands.

Knowledge of the circulation of rabies variants in bats is less well developed than our knowledge of terrestrial variants. Rabies-viral variants circulating in bats are antigenically and genetically distinct from those associated with terrestrial carnivores and indicate independent transmission cycles of rabies (Smith, 1989). Rabies has been reported in >50 species of bats in the Western Hemisphere. In the southeastern and mid-Atlantic regions of the United States, the red bat (*Lasiurus borealis*) and other solitary species are found rabid most commonly. The yellow bat (*Lasiurus intermedius*) and the Seminole bat (*Lasiurus seminolus*) also are important vectors in the southeastern states (Baer and Smith, 1991). In the Rocky Mountain, plains, and northcentral states, the hoary bat (*Lasiurus cinereus*) and the big brown bat (*Eptesicus*

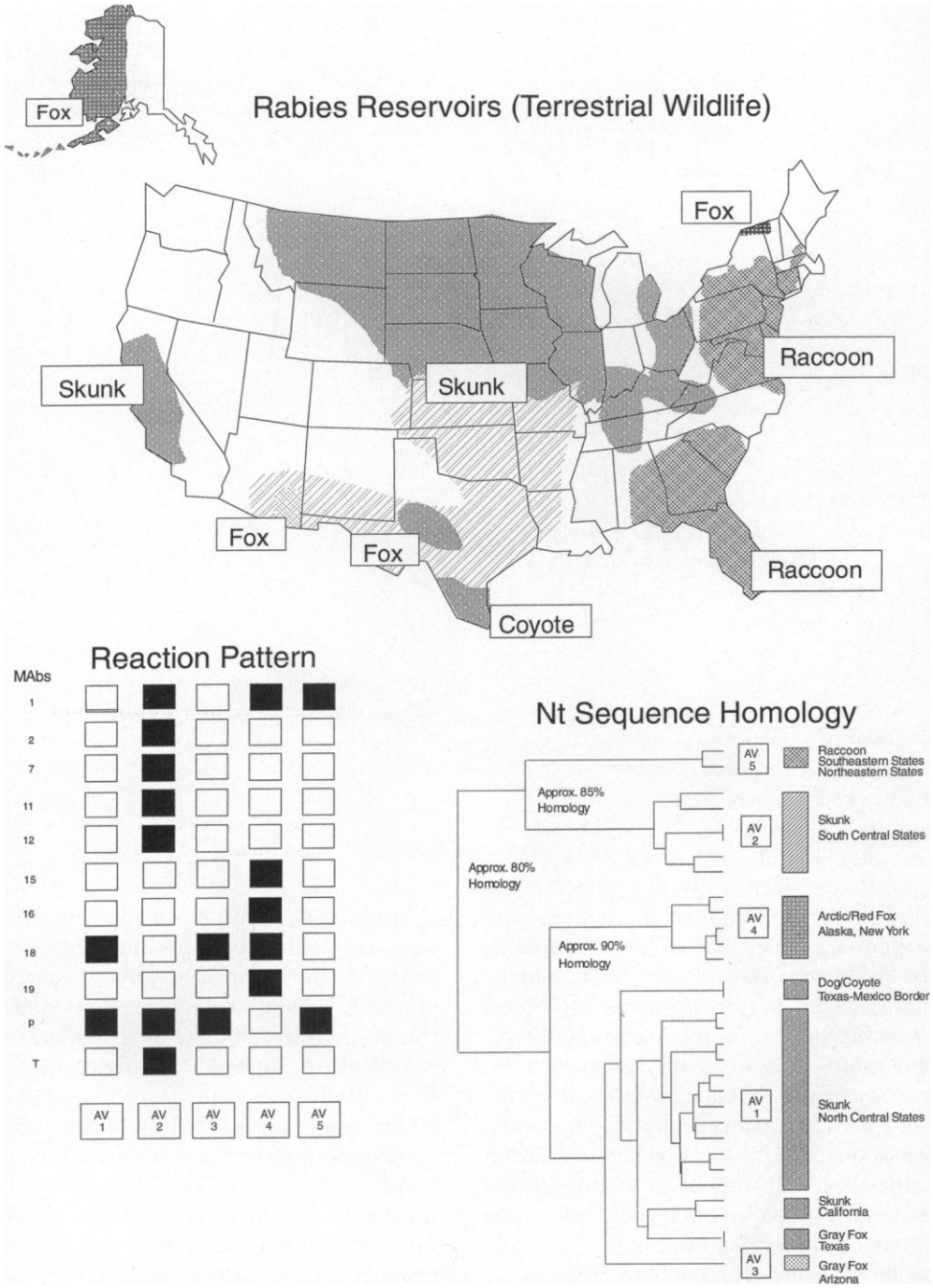

FIG. 1.—Distribution of antigenic and genetic variants of rabies virus and the major species of terrestrial wildlife affected in the United States, 1993. Antigenic analysis was performed with a panel of monoclonal antibodies (MAbs) reactive with the rabies nucleoprotein. Filled boxes indicate a negative reaction by indirect immunofluorescent testing of infected brain material. Nucleotide (Nt) sequence of the nucleoprotein gene was obtained by direct sequencing of the cDNA product from a polymerase-chain reaction.

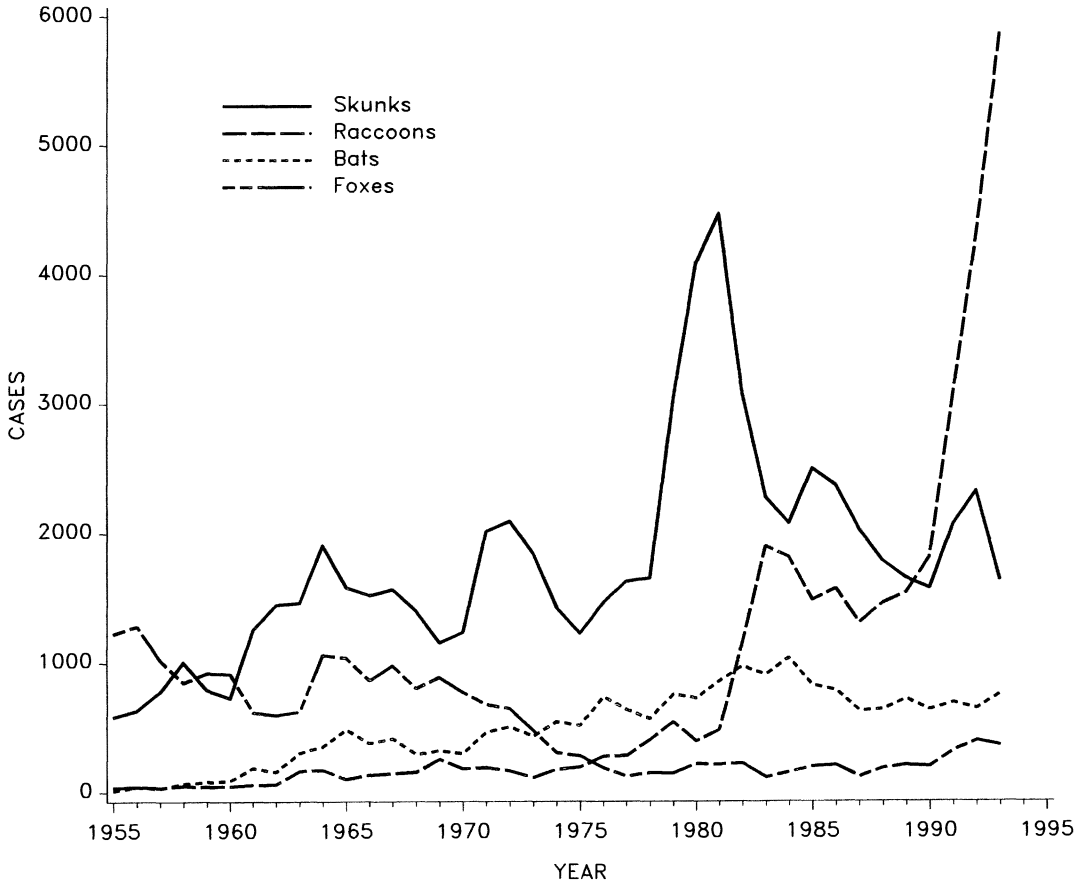

FIG. 2.—Cases of rabies in wild animals in the United States, 1955–1993.

fuscus) are important vector species. The Brazilian free-tailed bat (*Tadarida brasiliensis*) is an important vector in the southwestern states. In the northeastern states, the big brown bat is most commonly reported rabid. The silver-haired bat (*Lasionycteris noctivagans*) is an important vector in the Pacific Northwest; rabies-viral variants associated with this species have been identified with a number of human-rabies cases over a much broader geographic area (see section on epidemiology).

In the Eastern Hemisphere, reports of bats infected with rabies-like viruses are fewer. Only 14 cases of infection with rabies-related viruses were reported in four species of bats during a 31-year period in Europe (Baer and Smith, 1991). These and subsequent cases spurred the examination of more bats, resulting in the discovery of more infected individuals during the past 10 years. There have been only scattered reports of "rabid" bats from Asia and bats infected with rabies-related viruses from Africa (Bougler and Porterfield, 1958; Pal et al., 1980).

The relative contribution of the different carnivores and bats to the maintenance of rabies in the United States has changed dramatically since before the 1950s when dog rabies predominated. Foxes (*U. cinereoargenteus* and *V. vulpes*) were the most frequently reported rabid species of wildlife until 1958, when reports of rabid skunks (primarily *M. mephitis*) first exceeded the declining annual numbers of cases reported in foxes (Fig. 2). From 1961 through 1989, the annual numbers of rabid skunks ex-

ceeded those of other wildlife. Beginning in 1990 and continuing until the present, raccoons have been the predominant species reported rabid. Following the first reported case of bat rabies in the United States in 1953, the numbers of rabid bats increased and peaked at 1,038 in 1984 but, since then, have decreased, varying between 600 and 800 annually (Krebs et al., 1994).

During 1993, 49 states, the District of Columbia, and Puerto Rico reported 9,495 cases of rabies in animals and three cases in humans to the Centers for Disease Control and Prevention. Greater than 93% (8,889 cases) were among wildlife; 6.4% (606 cases) were domestic animals. This was the largest annual total of cases of rabies in wildlife ever reported by the Centers for Disease Control and Prevention and indicates the continuing problem of rabies in wildlife in the United States (Krebs et al., 1994). Canine rabies was enzootic in coyotes and unvaccinated dogs in 17 counties of southern Texas in 1994 (Clark et al., 1994; Texas State Health Department, pers. comm.). The rabies virus variant involved has been present in the Texas-Mexico border area since at least 1978. In late 1993, this variant was found in a rabid dog on a hunting compound in Alabama where translocated coyotes from Texas had been released (J. S. Smith, pers. comm.). This event is similar to the introduction of the raccoon-rabies variant into the mid-Atlantic states during the early to mid-1970s. Individuals such as wildlife rehabilitators who transport animals, especially carnivores, must be aware of the potential for introducing rabies and other zoonoses into areas where these diseases are not enzootic.

Cats continue to be the domestic species most commonly reported rabid. This may be attributable to the lack of legislation in some states requiring vaccination of cats for rabies and the difficulty of enforcing laws where they exist. Other factors, such as high population densities of cats in suburban locations presumably place these animals at greater risk for contacting wildlife in rabies-enzootic areas.

Rodents and lagomorphs are among those animals least likely to be reported rabid, contributing <1% to the total cases reported in 1993. Woodchucks (*Marmota monax*) are the sole exception to this statement, accounting for >92% (59/64) of all cases reported in this group in 1993 (Krebs et al., 1994).

Epidemiology

Worldwide, most human rabies occurs in developing countries where canine rabies is endemic. Because effective rabies vaccines are available, most human deaths are preventable but occur because public health resources and access to preventive treatment are limited. Cases of rabies are substantially underreported in most developing countries. This is exemplified by the fact that only 261 laboratory-confirmed and 1,065 clinically-diagnosed cases of human rabies were reported to the World Health Organization for 1991 (World Health Organization, 1993). However, unofficial estimates of human-rabies deaths of 2,000 in Bangladesh, 4,500 in China, 6,500 in Pakistan, and 25,000 in India were provided by national representatives at the Workshop on Rabies Control in Asian Countries in Samarkand (central Asia) on 19–21 September 1989. Rabies represents a serious public health problem in many regions of the world.

In contrast, cases of human rabies in developed nations have become increasingly rare. While the numbers of human-rabies cases in the United States exceeded 100/year during the early 1900s, an annual average of less than one indigenously-acquired case of human rabies has been reported over the past 30 years. However, control of rabies requires a complex and expensive system of operations at local, state, and federal levels. It has been estimated that the cost of rabies control in this country exceeds $300 million annually (Fishbein and Arcangeli, 1987).

An alarming trend in the epidemiology

of human rabies in the United States is the lack of information regarding the exposing event. From 1980 to 1994, 24 laboratory-confirmed cases of human rabies have been reported in the United States (two additional infections diagnosed in United States citizens working abroad occurred after dog bites). No history of animal bite was reported for 18 of the 24 cases (Centers for Disease Control and Prevention, 1994; Krebs et al., 1994; Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, pers. obser.). Ten of these 24 infections were believed to have been acquired outside the United States, and dog-rabies-viral variants were implicated by epidemiologic or genetic evidence. For 11 of 14 domestically-acquired cases, rabies-viral variants associated with bats were implicated by molecular typing (Centers for Disease Control and Prevention, 1994; Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, pers. obser.). All but three of these 11 variants were of the type associated with the silver-haired bat, a species rarely submitted for rabies testing (Childs et al., 1994). In only one of these 11 cases was the exposure attributable to bat bite.

The involvement of bat variants of rabies in eight of the last 10 indigenously-acquired infections of human rabies and >78% of all indigenously-acquired cases in humans since 1980 indicates the potential for human disease, even with effective barriers that prevent transmission from terrestrial animals (Centers for Disease Control and Prevention, 1994; Krebs et al., 1994; Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, pers. obser.). When occupational contact with bats is unavoidable, rabies preexposure prophylaxis is advised (Table 1).

Prevention

Vaccination of pet animals provides a barrier to transmission of rabies to humans. This has provided a major mechanism for prevention by breaking the link between rabies cycles in wildlife and transmission to domestic animals; the latter providing a ready means to pass the infection on to humans.

One of the most exciting developments in recent decades is the demonstration that wildlife also can be vaccinated against rabies. Successful use of oral rabies vaccines (attenuated viruses or genetically engineered recombinants) delivered in edible baits is changing the geographic distribution of rabies. In Europe and Canada, the incidence of rabies in red foxes has decreased as a result of targeted use of oral rabies vaccines (Muller, 1994; Wilhelm and Schneider, 1990). In the United States, trials are being conducted, or are planned, in Massachusetts, New Jersey, and New York) to vaccinate wild raccoons. The goal is to create immune barriers to prevent or slow the dissemination of rabies. Results of earlier trials designed to evaluate vaccine safety, efficacy, ecologic impact, and physical bait variables have been favorable (Rupprecht et al., 1992, 1993). Approval and licensing of such vaccines may provide authorities with new mechanisms to deal with rabies in raccoons and other wildlife. For example, officials in New York are considering several applications of oral vaccines to control rabies in red foxes at the border with Canada and have initiated programs using oral vaccine to interrupt rabies transmission among raccoons in two counties where the disease is now enzootic in this species. Similarly, the United States Department of Agriculture is funding a collaborative project to interrupt the transmission cycle of rabies in coyotes in southern Texas through the use of an oral rabies vaccine.

Rabies is the only disease for which vaccination is effectively applied after exposure. Although each possible exposure to rabies should be evaluated by a physician, local or state public health officials can provide additional information concerning the need for prophylaxis. In the United States, the following factors should be considered before specific antirabies treatment is initi-

TABLE 1.—*Recommended rabies-preexposure-prophylaxis guide, United States, modified from that of the Advisory Committee on Immunization Practices.*

Risk category	Nature of risk	Typical populations	Preexposure recommendations
Continuous	Virus present continuously, often in high concentrations; aerosol, mucous membrane, bite, or nonbite exposure; specific exposures may go unrecognized	Rabies research laboratory workers; rabies biologics production workers	Primary course[a]; serologic testing every 6 months; booster vaccination when antibody level falls below acceptable level[b]
Frequent	Exposure usually episodic, with source recognized, but exposure also may be unrecognized; aerosol, mucous membrane, bite, or nonbite exposure	Rabies diagnostic laboratory workers, mammalogists, spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies epizootic areas; travelers visiting foreign areas of enzootic rabies for >30 days	Primary course[a]; serologic testing or booster vaccination every 2 years[b]
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized; mucous membrane, bite, or nonbite exposure	Veterinarians and animal-control and wildlife workers in areas of low rabies enzootic icity; veterinary students	Primary course[a]; no serologic testing or booster vaccination
Rare (population at large)	Exposures always episodic; mucous membrane, or bite with source unrecognized	United States population at large, including persons in rabies epizootic areas	No vaccination necessary

[a] IM (intramusuclar = HDCV (human diploid cell vaccine) or RVA (rabies vaccine, adsorbed), 1.0 ml (deltoid area), one each on days 0, 7, and 21 or 28. ID (intradermal) = HDCV, 0.1 ml, one each on days 0, 7, and 21 or 28.

[b] Minimum acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by RFFIT (rapid focus fluorescence inhibition test). Booster dose (IM = HDCV or RVA, 1.0 ml in deltoid area, day 0 only; or ID = HDCV, 0.1 ml, day 0 only) should be administered if the titer falls below this level.

ated. Postexposure treatment is only necessary following a "true" exposure. The most important exposure is animal bite, which includes any penetration of the skin by teeth. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment (Hattwick, 1974). Nonbite exposures include contact of saliva or other potentially infectious material (such as brain tissue) from a rabid animal with scratches, abrasions, open wounds, or mucous membranes and should be considered for treatment. Other contacts, such as petting a rabid animal and contact with the blood, urine, or feces of a rabid animal, do not constitute exposures and are not indications for prophylaxis.

All bites by carnivores (especially raccoons, skunks, and foxes) and bats must be considered possible exposures. Postexposure prophylaxis (Table 2) should be initiated unless the exposure occurred in a country or region known to be free of terrestrial rabies or in a part of the continental United States known to be free of terrestrial rabies and the results of testing of brain tissue from the animal responsible for the exposure will be available within 48 h. If the animal has been tested and shown not to be rabid, treatment is unnecessary and can be discontinued. Bat rabies exists in areas that are considered free of terrestrial rabies, and all bites or scratches from bats should be considered potential exposures.

Signs of rabies in wild carnivores cannot be interpreted reliably; therefore, any such animal that bites or scratches a person should be killed at once (without unnecessary damage to the head) and the brain sub-

TABLE 2.—*Recommended rabies-postexposure-prophylaxis schedule, United States, modified from that of the Advisory Committee on Immunization Practices.*

Vaccination status	Treatment	Regimen[c]
Not previously vaccinated	Local wound	All wounds should be thoroughly cleansed with soap and water
	HRIG[b]	20 IU/kg body weight; if anatomically feasible, up to one-half the dose should be administered around the wound(s) and the rest should be administered intramuscularly in the gluteal area; no more than the recommended dose should be given
	Vaccine	HDCV or RVA[d], 1.0 ml, intramuscular (deltoid area[e]), one each on days 0, 3, 7, 14, and 28
Previously vaccinated[a]	Local wound	All wounds should be thoroughly cleansed with soap and water
	HRIG	HRIG should not be administered
	Vaccine	HDCV or RVA, 1.0 ml, intramuscular (deltoid area[e]), one each on days 0 and 3.

[a] Any person with a history of preexposure vaccination with HDCV or RVA; prior postexposure prophylaxis with HDCV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

[b] Human rabies immune globulin.

[c] These regimens are applicable for all age groups, including children.

[d] HDCV = human diploid cell vaccine; RVA = rabies vaccine, adsorbed.

[e] The deltoid area is the preferred site of vaccination for adults and older children. For young children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

mitted for rabies testing. If the test results are negative, it can be assumed that the saliva contains no rabies virus, and the bitten person need not be treated. If the biting animal is particularly rare or valuable and the risk of rabies small, postexposure treatment can be administered to the bite victim in lieu of killing the animal for rabies testing (National Association of State Public Health Veterinarians, 1995).

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are, with the exception of woodchucks, almost never found to be rabid and have not been known to cause rabies in humans in the United States. In all cases involving rodents, the state or local health department should be consulted before a decision is made to initiate postexposure antirabies prophylaxis.

Management of animals other than dogs and cats depends on the species, the circumstances of the bite, and the epizootiology of rabies in the area. If the period of rabies-viral shedding for the species is unknown, the animal may be killed and tested rather than confined and observed, when it bites a human (Centers for Disease Control and Prevention, 1991; National Association of State Public Health Veterinarians, 1995).

The likelihood that a domestic animal is infected with rabies varies from region to region. In areas where canine rabies is not enzootic (including virtually all of the United States and its territories, with the exception of southern Texas), a healthy domestic dog or cat that bites a person should be confined and observed for 10 days. Human treatment can be delayed pending the outcome of this confinement. If signs suggestive of rabies develop, the animal should be humanely killed and tested for rabies. Any stray or unwanted dog or cat that bites a person should be killed immediately and the head submitted for rabies examination (Centers for Disease Control and Prevention, 1991; National Association of State Public Health Veterinarians, 1995).

As discussed earlier, exposures to dogs in

canine-rabies-enzootic areas outside the United States carry a much higher risk; some authorities, therefore, recommend that postexposure rabies treatment be initiated immediately following such exposures (Table 2). Treatment can be discontinued if the dog or cat remains healthy during the 10-day observation period.

Preexposure rabies prophylaxis (traditional vaccination) is recommended for persons, such as mammalogists, whose activities bring them into frequent contact with rabies virus or potentially rabid wildlife, especially raccoons, skunks, foxes, and bats (Table 1). It should be considered for persons visiting foreign areas for >30 days, where canine rabies is enzootic (Table 1). Persons visiting locations considered especially hazardous or engaged in vocations that increase their risk of exposure should consider preexposure prophylaxis regardless of the duration of their visit.

Opportunities for Research

Despite the descriptive epidemiology of rabies in various species, our understanding of many aspects of the basic biology of infection and transmission of the rabies virus in wildlife is incomplete. Fundamental questions concerning the pathogenicity, immune response, transmission dynamics, and epizootiology of rabies remain unanswered. These questions have not been studied in part because most human exposures are recognized and successfully treated. Consequently, public health and conservation efforts to reduce human exposure and to prevent animal disease, respectively, are seriously hampered by a lack of knowledge ranging from the molecular to the macrogeographic.

As previously outlined, wildlife rabies in the United States has been characterized mainly by compiling reported positive test results from animals submitted to testing facilities. Which animals are submitted and tested depends largely on public and municipal initiative, compromising the quality of such data. While these data are useful in documenting trends over time or space, they are of limited analytical value to ecologic and epidemiologic research. Additional effort is required to estimate the incidence of disease, rather than counting the number of positive tests. Without systematic sampling or surveillance of large groups of both healthy and sick animals, it becomes difficult to analyze the impact of rabies on animal populations. Well-designed surveys of wildlife populations would be useful in determining the prevalence of infection, evaluating demographic differences in disease, and characterizing transmission dynamics.

Although certain aspects of rabies-viral infection and pathogenesis in dogs and cats have been well-documented, at least three basic areas of research into wildlife rabies await further study. How does transmission occur? What impacts do infections have on various wildlife populations? How is virus circulation maintained? Existing dogma provides that most intraspecific transmission of rabies virus in foxes, skunks, raccoons, and bats occurs via bite. While this is a sound working hypothesis, little has been done to rigorously explore the possibility that grooming, nursing, or more casual contact among these animals could transmit virus. We know even less about how infection alters the natural behavior of wildlife species, hence, their ability to pass on rabies virus. As an example, neither the population density of raccoons nor the proportion that are being infected has been defined in most settings. Similarly, strain-specific variation in the periods of incubation and infectiousness of rabies-viral variants needs further study. Why rabies variants associated with silver-haired bats have been implicated in the majority of the cases of indigenously-acquired human rabies in the United States is unclear. Information on the ecology and behavior of this species of bat is sparse. Efforts to understand and alter the transmission dynamics of rabies virus as well as its spread to other species would benefit enormously from such knowledge.

Secondly, the range of outcomes of natural rabies-viral infection in wildlife species is not well understood. For most species, the proportion of individuals that survive infection and develop antibody or remain chronically infected is unknown. The existence, among wildlife, of individuals that survive infection and become chronic carriers, as has been demonstrated for dogs (Fekadu et al., 1992), is undocumented and, presumably, extremely rare. However, evidence suggests that not all infected raccoons die of rabies, a phenomenon that could have a major impact on population-level processes (Bigler et al., 1973; Brown et al., 1990; Carey and McLean, 1983). Natural herd immunity would rise, and previously-infected immune survivors could lower the rate of transmission. Various hypotheses have been advanced to explain why incidence of rabies decreases following an initial period of intense transmission. If the mortality rate is high, decreased incidence may result from declines in population density and fewer exposed animals; furthermore, decreased contacts would occur as the number of infectious and uninfected animals is reduced.

Finally, how and why does enzootic rabies persist? Perhaps small, unrecognized foci of transmission persist through a process of contagion, like that which occurs during epizootics. Enzootic raccoon rabies has persisted in the southeastern United States a half-century after its emergence, and periodic epizootic activity has been reported in the mid-Atlantic states during the past 2 decades. Yet, fox rabies never became enzootic in the Southeast following major enzootics in the 1960s. We lack the data necessary to explain many of these phenomena convincingly.

Human-animal interactions resulting in rabies exposure are poorly defined. Descriptions of the circumstances of human exposure exist, but little systematic investigation of the ecology of rabid animal-human interactions has been published. Research that compares reported human exposures with comparable unexposed persons, examining human activity, physical environment, and animal behavior, would help define human risk of infectious contacts. Systematic studies of indirect contact with rabid wildlife through pets and of nonbite contact with potentially infectious materials also would be instructive. Efforts to more carefully document contact that may not be infectious should help reduce the expense and anxiety associated with certain suspected exposures.

Although an immunizing oral vaccine and attractive bait have been developed for raccoons, the design of applications and measurement of success in populations of raccoons are hindered without knowledge of the pathogenicity, immunogenicity, and demographic impact of natural rabies-viral infection. Because our knowledge in these realms is weak, neither the success nor failure of wildlife-vaccination trials will be easily interpretable. The amount, timing, and habitat distribution of vaccine baits as well as the proportion of the raccoon population that should be vaccinated to produce an impact need to be better defined. The knowledge gained from vaccination programs for European and Canadian foxes cannot be applied without modification to the control of raccoon rabies in the United States. The behavior, population density, and habitats of the two species differ considerably. The peridomestic tendencies of raccoons suggest that effective interventions could be attempted in diverse environments, each posing special logistical problems.

Ultimately, the objectives of any wildlife-vaccination campaign against rabies must be defined for each intervention. Should vaccination be aimed at decreasing transmission among wildlife, reducing wildlife disease and death, maintaining densities of wildlife populations, or lessening risk of human exposure? These goals are decidedly different and, in part, may be mutually inconsistent. There is obvious need for interaction with wildlife biologists and

mammalogists in the design and implementation of these interventions.

ACKNOWLEDGMENTS

We thank J. G. Olson, C. E. Rupprecht, and J. S. Smith for providing valuable comments on the manuscript. We also are grateful to J. O'Connor for editorial suggestions and grammatical corrections. Finally, we thank the state, territorial, and city health departments and laboratories and the World Health Organization for supplying data, without which this and other papers of such scope would not be possible.

LITERATURE CITED

ALVAREZ, L. H., ET AL. 1994. Partial recovery from rabies in a nine-year-old boy. Pediatric Infectious Disease, 13:1154–1155.

BAER, G. M., AND J. S. SMITH. 1991. Rabies in nonhematophagous bats. Pp. 341–366, *in* The natural history of rabies (G. M. Baer, ed.). CRC Press, Boca Raton, Florida, 620 pp.

BALACHANDRAN, A., AND K. CHARLTON. 1994. Experimental rabies infection of non-nervous tissues in skunks (*Mephitis mephitis*) and foxes (*Vulpes vulpes*). Veterinary Pathology, 31:93–102.

BIGLER, W. J., R. G. MCLEAN, AND H. A. TREVINO. 1973. Epizootiologic aspects of raccoon rabies in Florida. American Journal of Epidemiology, 98: 326–335.

BOUGLER, L. R., AND J. S. PORTERFIELD. 1958. Isolation of virus from Nigerian fruit bats. Transactions of the Royal Society of Tropical Medicine and Hygiene, 52:421–424.

BOURHY, H., B. KISSI, AND N. TORDO. 1993. Molecular diversity of the *Lyssavirus* genus. Virology, 194:70–81.

BROWN, C. L., C. E. RUPPRECHT, AND W. M. TZILKOWSKI. 1990. Adult raccoon survival in an enzootic rabies area of Pennsylvania. Journal of Wildlife Diseases, 26:346–350.

CAREY, A. B., AND R. G. MCLEAN. 1983. The ecology of rabies: evidence of co-adaptation. The Journal of Applied Ecology, 20:777–800.

CENTERS FOR DISEASE CONTROL AND PREVENTION. 1977. Rabies in a laboratory worker—New York. Morbidity and Mortality Weekly Report, 76:183–184.

———. 1980. Human-to-human transmission of rabies via a corneal transplant—France. Morbidity and Mortality Weekly Report, 29:25–26.

———. 1981. Human-to-human transmission of rabies via corneal transplant—Thailand. Morbidity and Mortality Weekly Report, 30:473–474.

———. 1991. Rabies prevention—United States, 1991, recommendations of the Immunizations Practices Advisory Committee (ACIP). Morbidity and Mortality Weekly Report, 40(RR-3):1–19.

———. 1994. Human rabies—California, 1994. Morbidity and Mortality Weekly Report, 43:455–457.

CHILDS, J. E., C. V. TRIMARCHI, AND J. W. KREBS. 1994. The epidemiology of bat rabies in New York State, 1988-1992. Epidemiology and Infection, 113:501–511.

CLARK, K. A., S. U. NEILL, J. S. SMITH, P. J. WILSON, V. W. WHADFORD, AND G. W. MCKIRAHAN. 1994. Epizootic canine rabies transmitted by coyotes in South Texas. Journal of the American Veterinary Medical Association, 204:536–540.

CONSTANTINE, D. G. 1967. Rabies transmission by air in bat caves. Public Health Service Publication, United States Government Printing Office, Washington, D.C., 1617:1–51.

FAMILUSI, J. B., B. O. OSUHKOYA, D. L. MOORE, G. E. KEMP, AND A. FABIYI. 1972. A fatal human infection with Mokola virus. The American Journal of Tropical Medicine and Hygiene, 21:959–963.

FEKADU, M., J. W. SUMNER, J. H. SHADDOCK, D. W. SANDERLIN, AND G. M. BAER. 1992. Sickness and recovery of dogs challenged with a street rabies virus after vaccination with a vaccinia virus recombinant expressing rabies virus N protein. Journal of Virology, 66:2601–2604.

FISHBEIN, D. B. 1991. Rabies in humans. Pp. 519–549, *in* The natural history of rabies (G. M. Baer, ed.). CRC Press, Boca Raton, Florida, 620 pp.

FISHBEIN, D. B., AND S. ARCANGELI. 1987. Rabies prevention in primary care. A four-step approach. Postgraduate Medicine, 82:83–90, 93–95.

FOGGIN, C. M. 1983. Mokola virus infection in cats and a dog in Zimbabwe. The Veterinary Record, 113:115.

GODE, G. R., AND N. K. BHIDE. 1988. Two rabies deaths after corneal grafts from one donor [letter]. The Lancet, 2:791.

HATTWICK, M. A. W. 1974. Human rabies. Public Health Reviews, 3:229–274.

HATTWICK, M. A. W., T. T. WEISS, C. J. STECHSULTE, AND G. M. BAER. 1972. Recovery from rabies: a case report. Annals of Internal Medicine, 76:931–942.

HELMICK, C. G., R. V. TAUXE, AND A. A. VERNON. 1987. Is there a risk to contacts of patients with rabies? Reviews of Infectious Diseases, 9:511–518.

HOUFF, S. A., ET AL. 1979. Human-to-human transmission of rabies virus by corneal transplant. The New England Journal of Medicine, 300:603–604.

JENKINS, S. R., B. D. PERRY, AND W. G. WINKLER. 1988. Ecology and epidemiology of raccoon rabies. Reviews of Infectious Diseases, 10, suppl. 4:S620–S625.

KING, A. A., AND G. S. TURNER. 1993. Rabies a review. Journal of Comparative Pathology, 108:1–39.

KING, A. A., C. D. MEREDITH, AND G. R. THOMSON. 1994. The biology of southern African lyssavirus variants. Pp. 267–295, *in* Lyssaviruses (C. E. Rupprecht, B. Dietzschold, and H. Koprowski, eds.). Springer-Verlag, Berlin, Germany, 352 pp.

KREBS, J. W., T. W. STRINE, J. S. SMITH, C. E. RUPPRECHT, AND J. E. CHILDS. 1994. Rabies surveillance in the United States during 1993. Journal of the American Veterinary Medical Association, 205: 1695–1709.

LOPEZ, A., P. MIRANDA, E. TEJADA, AND D. B. FISHBEIN. 1992. Outbreak of human rabies in the Peruvian jungle. Lancet, 339:408–411.

MEREDITH, C. D., A. P. ROSSOUW, AND H. VAN PRAGG KOCH. 1971. An unusual case of human rabies thought to be of chiropteran origin. South African Medical Journal, 45:767–769.

MULLER, W. W. 1994. Oral vaccination of foxes in Europe, 1992. Rabies Bulletin of Europe, 16:12–13.

NATIONAL ASSOCIATION OF STATE PUBLIC HEALTH VETERINARIANS. 1995. Compendium of animal rabies control, 1995. Journal of the American Veterinary Medical Association, 206:14–18.

NIEUWENHUIJS, J., J. HAAGSMA, AND P. LINA. 1992. Epidemiology and control of rabies in bats in The Netherlands. Reviews in Science and Technology, 11:1155–1161.

OGUNKOYA, A. B., G. W. BERAN, J. U. UMOH, N. E. GOMWALK, AND I. A. ABDULKADIR. 1990. Serological evidence of infection of dogs and man in Nigeria by lyssaviruses (family Rhabdoviridae). Transactions of the Royal Society of Tropical Medicine and Hygiene, 84:842–845.

PAL, S. R., ET AL. 1980. Rabies virus infection of a flying fox bat, *Pteropus poliocephalus* in Chandigarh, northern India. Tropical and Geographical Medicine, 32:265–267.

PAWAN, J. L. 1936. The transmission of paralytic rabies in Trinidad by the vampire bat. Annals of Tropical Medicine and Parasitology, 30:101–129.

PORRAS, C., J. J. BARBOZA, E. FUENZALIDA, H. L. ADAROS, A. M. OVIEDO, AND J. FURST. 1976. Recovery from rabies in man. Annals of Internal Medicine, 85: 44–48.

RUPPRECHT, C. E., AND J. S. SMITH. 1994. Raccoon rabies: the re-emergence of an epizootic in a densely populated area. Seminars in Virology, 5:155–164.

RUPPRECHT, C. E., C. A. HANLON, A. N. HAMIR, AND H. KOPROWSKI. 1992. Oral wildlife rabies vaccination: development of a recombinant rabies vaccine. Transactions of the North American Wildlife and Natural Resources Conference, 57:439–452.

RUPPRECHT, C. E., C. A. HANLON, M. NIEZGODA, J. R. BUCHANAN, D. DIEHL, AND H. KOPROWSKI. 1993. Recombinant rabies vaccine: efficacy assessment in free ranging animals. Onderstepoort Journal of Veterinary Research, 60:463–468.

SALUZZO, J. F., P. E. ROLLIN, C. DAUGET, J. P. DIGOUTTE, A. J. GEORGES, AND P. SUREAU. 1984. Premier isolement du virus mokola a partir d'un rongeur (*Lophuromys sikapusi*). Annals of Virology (Institute Pasteur), 135:57–66.

SELIMOV, M. A., A. G. TATAROV, A. D. BOTVINKIN, E. V. KLUEVA, L. G. KULIKOVA, AND N. A. KHISMATULINA. 1989. Rabies-related Yuli virus; identification with a panel of monoclonal antibodies. Acta Virology, 33:542–546.

SHOPE, R.E., ET AL. 1970. Two African viruses serologically and morphologically related to rabies virus. Journal of Virology, 6:690–692.

SMITH, J. S. 1989. Rabies virus epitopic variation: use in ecologic studies. Advances in Virus Research, 36: 215–253.

SMITH, J. S., AND H. D. SEIDEL. 1993. Rabies: a new look at an old disease. Progress in Medical Virology, 40:82–106.

SMITH, J. S., D. B. FISHBEIN, C. E. RUPPRECHT, AND K. CLARK. 1991. Unexplained rabies in three immigrants in the United States. a virologic investigation. The New England Journal of Medicine, 324:205–211.

STEELE, J. H., AND P. J. FERNANDEZ. 1991. History of rabies and global aspects. Pp. 1–24, *in* The natural history of rabies (G. M. Baer, ed.). CRC Press, Boca Raton, Florida, 620 pp.

WANDELER, A. I., S. A. NADIN-DAVIS, R. R. TINLINE, AND C. E. RUPPRECHT. 1994. Rabies epidemiology: some ecological and evolutionary perspectives. Pp. 297–324, *in* Lyssaviruses (C. E. Rupprecht, B. Dietzschold, and H. Koprowski, eds.). Springer-Verlag, Berlin, Germany, 352 pp.

WILHELM, U., AND L. G. SCHNEIDER. 1990. Oral immunization of foxes against rabies: practical experiences of a field trial in the Federal Republic of Germany. Bulletin of the World Health Organization, 68:87–92.

WINKLER, W. G., T. R. FASHINELL, L. LEFFINGWELL, P. HOWARD, AND P. CONOMY. 1973. Airborne rabies transmission in a laboratory worker. Journal of the American Medical Association, 226:1219–1221.

WORLD HEALTH ORGANIZATION. 1993. World survey of rabies. World Health Organization, Geneva, Switzerland, 27:1–37.

———. 1994. Veterinary public health. Two rabies cases following corneal transplantation. Weekly Epidemiological Record, 44:330.

WUNNER, W. H., J. K. LARSON, B. DIETZSCHOLD, AND C. L. SMITH. 1988. The molecular biology of rabies viruses. Reviews of Infectious Diseases, 10, suppl. 4:S771–S784.