Since rabies is a statistically 100% fatal disease, the focus is to prevent human rabies by administering rabies post-exposure prophylaxis if exposure occurs. Additional efforts should be made to prevent additional human exposure through rabies education, animal quarantine and animal vaccination.

Biology, Transmission, and Pathogenesis

Rabies Virus

The rabies virus belongs to the order Mononegavirales, viruses with a nonsegmented, negative-stranded RNA genome. Within this group, viruses with a distinct "bullet" shape are classified in the Rhabdoviridae family, which includes at least three genera of animal viruses, Lyssavirus, Ephemerovirus, and Vesiculovirus. The genus Lyssavirus includes rabies virus, Lagos bat virus, Mokola virus, Duvenhage virus, European bat virus 1 & 2, and Australian bat virus. The most common is the rabies virus. The rabies virus is only cause of rabies in the US. The virus can be further classified by slight variation within species that it infects, such as the raccoon variant, canine variant, and bat variant of the rabies virus.

Although the rabies virus can infect a variety of cell types, it primarily targets neurons. The cycle of viral infection is depicted in Figure 1: Transmission of Rabies Through the CNS, on page 9. The virus spreads by retrograde axonal transport from the peripheral nerves to the neuronal cell body. After replication in the cell body of the primary neuron, infection proceeds via retrograde axonal transport and transsynaptic spread through several neurons. Transsynaptic spread is the ability of the virus to use synaptic junctions to propagate within the CNS. Neuronal infection by the rabies virus causes abnormalities in the function of neurotransmitters affecting serotonin, GABA, and muscarinic acetylcholine transmission. Cells of the salivary gland are infected next, which in turn shed virus into the oral cavity. This accounts for the presence of the virus in saliva.

Susceptibility

ALL mammals (animals that are warm-blooded, have hair, fur, or mammary glands) are susceptible to rabies, but there are varying degrees of susceptibility. Birds and reptiles cannot be infected with the rabies virus.

Table 1 Levels of Rabies Susceptibility

Level of Susceptibility	Animals
Most Susceptible	Foxes, coyotes, jackals, and wolves
Highly Susceptible	Skunks, raccoons, bats, ferrets, and cattle
Moderately Susceptible	Dogs and cats (domesticated), sheep, goats, horses, and subhuman primates

Opossums are relatively resistant to rabies and considered a low risk for infection. Experiments have shown that the viral exposure dose required to infect opossums is 80,000 times that needed to infect a fox. Rodents and rabbits are also a relatively low risk for transmitting the rabies virus and seem somewhat refractory to rabies infection. Experimentally infected rodents generally

excrete little or no virus in saliva making the likelihood for transmission negligible. The fox rabies and raccoon rabies viral strains are not well adapted to rodents, other than woodchucks or groundhogs – large rodents which may share habitat with raccoons and foxes and have the capability of surviving an attack from a rabid animal. The Advisory Committee on Immunization Practices of the US Public Health Service states that:

"Small rodents (i.e., squirrels, chipmunks, rats, mice, hamsters, guinea pigs, and gerbils) and lagomorphs (including rabbits and hares) are rarely infected with rabies and have not been known to transmit rabies to humans."

Only an unprovoked, aggressive attack by a rodent or rabbit with clinical evidence of rabies infection should normally be considered for investigation and rabies treatment/prophylaxis. Domesticated rodents purchased from pet shops, raised in controlled captive breeding, and never exposed to carnivorous animals or bats pose no risk of rabies by biting (i.e., guinea pigs, hamsters, gerbils, mice, and white rats).

Any wild animal, especially wild carnivores and bats, must be considered to be rabid. Since wild animals can have extended incubation periods, they cannot be considered free of rabies even if purchased from a pet shop, acquired as a baby, and/or held for a long period of time. The period of viral shedding in the saliva prior to or after the onset of clinical symptoms is not known for these animals; therefore, an appropriate observation period following an exposure cannot be ascertained.

Animals can acquire the virus not only from bites and scratches with saliva contamination, but also through in-utero infections, nursing, or from eating a dead rabid animal. Although rare, aerosol transmission to humans in bat caves and laboratories and infection via transplanted organs have also been documented.

The public should be warned not to handle wild animals or bats under any circumstances, including injured or sick animals. A disabled animal's chances for survival are much greater with professional assistance from animal control or wildlife management experts. Wild animals that bite humans must not be held for observation, but humanely sacrificed and submitted to the lab for rabies examination.

Transmission

Transmission of rabies virus usually begins when infected saliva of a host is passed to an uninfected animal. Various routes of transmission have been documented and include contamination of mucous membranes (i.e., eyes, nose, and mouth), aerosol transmission, and corneal transplantations. The most common mode of rabies virus transmission is through a bite and/or virus-containing saliva of an infected host.

Following primary infection, the virus enters an eclipse phase in which it cannot be easily detected within the host. This phase may last for several days or months. Investigations have shown both direct entry of virus into peripheral nerves at the site of infection and indirect entry after viral replication in non-neural tissue (i.e., muscle cells). During the eclipse phase, the host immune defenses may confer cell-mediated immunity against viral infection because rabies virus is a good antigen. The uptake of virus into peripheral nerves is important for progressive infection to occur.

After uptake into peripheral nerves, rabies virus is transported to the central nervous system (CNS) via retrograde axoplasmic flow. Typically this occurs via sensory and motor nerves at the initial site of infection. The incubation period (see Figure 14) is the time from exposure to onset of clinical signs of disease. The incubation period may vary from a few days to several years, but is typically 1 to 3 months. Dissemination of virus within the CNS is rapid, and includes early involvement of limbic system neurons. Active cerebral infection is followed by passive centrifugal spread of virus to peripheral nerves. The amplification of infection within the CNS occurs through cycles of viral replication and cell-to-cell transfer of progeny virus. Centrifugal spread of virus may lead to the invasion of highly innervated sites of various tissues, including the salivary glands. During this period of cerebral infection, the classic behavioral changes associated with rabies develop.

Pathology of rabies infection is typically defined by encephalitis and myelitis. Perivascular infiltration with lymphocytes, polymorphonuclear leukocytes, and plasma cells can occur throughout the entire CNS. Rabies infection frequently causes cytoplasmic eosinophilic inclusion bodies (Negri bodies) in neuronal cells, especially pyramidal cells of the hippocampus and Purkinje cells of the cerebellum. These inclusions have been identified as areas of active viral replication by the identification of rabies viral antigen. Several factors may affect the outcome of rabies exposure. These include the virus variant, the dose of virus inoculums, the route and location of exposure, as well as individual host factors, such as age and host immune defenses.

Figure 1 Transmission of Rabies Through the CNS