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NON-CIRCULATING

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 Guidelines for Prevention of Herpesvirus
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 Monkey Handlers

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GUIDELINES FOR PREVENTION OF HERPESVIRUS SIMIAE (B VIRUS) INFECTION IN MONKEY HANDLERS*

The report of a case of encephalitis caused by B virus in a monkey handler in 1932 indicated that B virus can be highly pathogenic for humans. Seventeen additional cases of B virus infection in humans were described through 1973** and four cases, including the first known case of person-to-person transmission of the virus, occurred in Pensacola, Florida, in 1987. Twenty of the 22 cases resulted in encephalitis; 15 of these patients died. This extreme degree of morbidity and mortality has given the impression that B virus infection in humans nearly always results in severe or fatal disease. The frequency of mild or asymptomatic B virus infection, however, has never been adequately assessed.

The occurrence of the four 1987 cases of B virus infection prompted CDC to convene a working group to discuss guidelines for preventing B virus infection in monkey handlers. In formulating these guidelines, the working group recognizes that other methods of caring for nonhuman primates and preventing transmission of pathogenic agents from animal to human and from human to animal have been described. The purpose of the working group was to supplement existing methods with specific guidelines intended to minimize transmission of B virus infection from macaque monkeys to humans.

Herpesvirus simiae (B virus) is a member of the herpes group of viruses that is enzootic in rhesus (*Macaca mulatta*), cynomolgus (*M. fascicularis*), and other Asiatic monkeys of the genus *Macaca*. As with herpes simplex virus 1 infection in humans, primary infection with B virus in macaques may result in gingivostomatitis with characteristic buccal mucosal lesions, but it probably occurs frequently without such signs. Subsequently, the virus remains latent in the host and may reactivate spontaneously or in times of stress, resulting in shedding of virus in saliva and/or genital secretions. In captivity, as well as in the wild, sexually mature macaques are more likely to have been exposed to the virus and more likely than immature animals to be shedding virus at any given time.

Although it is commonly believed that transmission to humans occurs by exposure to contaminated monkey saliva through bites or scratches, such exposure has not been consistently documented. Except for one instance of person-to-person transmission, however, all cases of B virus infection in humans have occurred in persons exposed to monkeys or monkey tissues.

B virus-related disease is characterized by a variety of symptoms, which generally occur within one month of exposure. These symptoms include vesicular skin lesions at or near the site of inoculation, localized neurologic symptoms, and ultimately, encephalitis.

*Reprinted from: CDC. MMWR 1987;36(41):680-2,687-9, with editorial comment.

**In this review, Palmer reports a total of 24 cases from 1932 to 1973, citing a reference from CDC. Documentation of B virus infection, however, was established in only 17 of these cases; an 18th case, which occurred in 1958, was omitted in Palmer's review.

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A unique feature of the 1987 Pensacola cases was the occurrence of mild disease in two of the four patients. Both of these persons received acyclovir (9-[2-hydroxyethoxymethyl]-guanine) in the early stages of disease. They became culture-negative, and their lesions healed during therapy. Whether their infections would have become more severe without therapy is not known. Both *in vivo* and *in vitro* efficacy of acyclovir (Southwest Foundation for Biomedical Research, unpublished data) against B virus has been demonstrated.

The working group recognizes that B virus infection may occur in persons not handling live macaques. One case of B virus infection occurred following the persons's exposure to contaminated cell cultures of simian origin, and one case occurred after the patient had cleaned a monkey skull. Although transmission of infection has not been documented for persons working with B virus in the laboratory, such work is potentially hazardous. Guidelines concerning appropriate biocontainment measures for working with B virus are published elsewhere. The guidelines described herein pertain only to the risk associated with the care and maintenance of living macaques.

The working group also recognizes that the paucity of information regarding the transmissibility of B virus, the efficacy of measures to prevent transmission, and the chemotherapy of B virus infection have rendered these guidelines difficult to formulate. These guidelines are therefore based on the available information, much of which is anecdotal and much of which is based on theoretical considerations from knowledge of other herpes viruses.

The risk of acquiring B virus infection from macaques appears to be very low. Persons who have handled macaques since B virus infection was first reported in humans number in the thousands, yet only 22 well-documented cases of infection have been described. The reasons for such an apparently low rate of transmission may include infrequent B virus shedding by macaques, cross-reactive immunity against B virus stimulated by herpes simplex virus infection, and undetected asymptomatic infection. Nevertheless, the consequences of symptomatic infection are such that these guidelines are warranted, especially since such infections appear preventable.

GUIDELINES FOR PREVENTION OF B VIRUS INFECTION IN MONKEY HANDLERS:

1. Macaque monkeys should be used for research purposes only when clearly indicated.
2. When feasible, monkeys that are required for research purposes should be free of B virus infection and should be maintained under conditions that are appropriate to assure their B virus-free status. The possibility of acquiring and maintaining such a B virus-free colony should be explored by each animal facility.
3. All macaque monkeys not known to be free of B virus infection should be regarded as infected because viral shedding is intermittent and can occur in the absence of visible lesions. Direct handling of macaques should be minimized as much as possible. Capturing, restraining, or otherwise handling fully awake macaques by hand is not recommended. Rather, such procedures should be accomplished using acceptable physical and chemical restraint methods. Macaques that are handled regularly should be housed in squeeze-back cages that permit physical restraint of the animal before handling. When a number of animals are caged together, tunnels or chutes should be provided whenever feasible so that individual monkeys can be separated and restrained before handling. When feasible, chemical restraint by injection (eg, ketamine HCl) may be used before removing the animal from the cage, particularly for larger animals or for animals that are otherwise difficult to handle. Behavioral conditioning of macaques is a practical and useful adjunct to the application of these restraint procedures and is particularly recommended where several animals are caged together.

4. Macaque handlers should remove physically active animals from cages only with arm-length reinforced leather gloves. Handlers should be additionally protected with a long-sleeved garment to prevent scratches and a face shield (or surgical mask and goggles or glasses) to prevent exposure of eyes and mucous membranes to macaque secretions. In warm climates, where use of long-sleeved garments and leather gloves may be uncomfortable, supervisors may wish to rotate work schedules or have workers handle animals at cooler times of the day to minimize such discomfort in the daily work routine. If macaque handlers choose not to handle chemically restrained animals with arm-length leather gloves, latex or vinyl gloves should be worn to prevent direct contact with macaque secretions.
5. Cages and other equipment that may be contaminated with virus should be free of sharp edges and corners that may cause scratches or wounds to workers. Cages should be designed and arranged in animal housing areas so that the risk of workers being accidentally grabbed or scratched is minimized. Access to areas where macaques are maintained and used should be limited either to workers who are properly trained in procedures to avoid risk of infection or to those accompanied by such workers.
6. The routine screening of macaques for evidence of B virus infection is not recommended. Even animals previously found to be negative for virus or antibody might be positive at the time of a human exposure. Also, screening may increase the risk of infection to workers. In situations in which laboratory studies may cause immunosuppression of the animals, the investigator may elect to determine the infection status of the animals to be used, since virus shedding might be enhanced under such circumstances. Macaques with oral lesions suggestive of active B virus infection should be quarantined until the lesions have healed to reduce the risk of virus transmission to workers and other macaques.
7. Persons who handle macaques, including primate veterinarians and scientific investigators, should be trained in proper methods of restraint and in the use of protective clothing to help prevent bites and scratches. Such persons should be acquainted with standard operating procedures and other available training materials before handling animals. Training should be followed up with continual observation for lapses in these procedures as they occur. Macaque handlers should also be educated concerning the nature of B virus infection; the need to prevent bites, scratches, and other exposure to macaque secretions; and the need to clean wounds immediately. They should be educated concerning the early symptoms of B virus infection and the need to report injuries and/or symptoms suggestive of B virus infection to supervisors immediately. Animal handlers should be advised that persons who are immunosuppressed because of medication or underlying medical conditions may be at higher risk for B virus infection. A pre-employment serum sample should be obtained from all persons who work with macaques, and additional samples should be obtained annually to serve as a baseline for retrospective studies in the event of a suspected B virus infection. Such specimens should be aliquoted and frozen, preferably at -70°C .
8. All bite or scratch wounds incurred from macaques or from cages that might be contaminated with macaque secretions and that result in bleeding should be immediately and thoroughly scrubbed and cleansed with soap and water. Such incidents should be reported to the animal-care supervisor and recorded in a bite/scratch log. Superficial wounds that can be adequately cleansed probably require no further treatment. More extensive wounds should be referred to a medical consultant. Each animal-care facility should identify a medical consultant who will be on call to assist in such situations. Such consultants, in addition to having general knowledge concerning animal bites, should be knowledgeable concerning the hazard of B virus infection, its symptoms, and treatment. Following a bite or scratch, the animal handler should be instructed to report immediately any skin lesions or neurologic symptoms (such as itching, pain, or numbness) near the site of the wound or any other unusual illness. It is the responsibility of the supervisor, when no illness is reported, to determine the clinical status of the handler at weekly intervals for one month after the exposure. Symptoms suggestive of B virus infection should be reported

immediately to the medical consultant. When the possibility of B virus illness is seriously entertained, appropriate diagnostic studies should be performed and specific antiviral therapy should be instituted. (At the time of this writing, experimental and limited clinical data indicate acyclovir to be the drug of choice.) The physician may wish to consult the Viral Exanthems and Herpesvirus Branch, Division of Viral Diseases, CDC (Dr. Gary Holmes, [404] 329-1338) and, for laboratory assistance, the Southwest Foundation for Biomedical Research (Dr. Julia Hilliard, [512] 674-1410).

9. In some situations, prophylactic treatment with an antiviral agent may be considered in the absence of signs or symptoms suggestive of B virus infection. Such a situation might arise when an animal handler sustains a deep, penetrating wound that cannot be adequately cleansed. In such situations, studies to determine the B virus status of the animal should be considered, especially if the animal has clinical findings suggestive of B virus infection. These situations should be managed by the medical consultant, who may wish to consult the resource persons mentioned above. There is no evidence that pooled immune globulin is effective in preventing or ameliorating B virus infection. Neither hyperimmune human B virus globulin nor vaccine against B virus is currently available.

PDN Editorial Note: Macaques and cell cultures of simian origin are used in medical research laboratories and other facilities throughout Texas. Recent events indicate that B virus infections in humans may not be as rare or as fatal as previously believed. Thus, health care providers need to consider B virus infection in the differential diagnosis when patients present with apparent mild to severe herpes simplex infections. Information concerning occupational exposure of the patient or family members to monkeys or monkey cell lines should be obtained. B virus infection is potentially treatable with early recognition and intervention.

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1987 COMMUNICABLE DISEASE REPORTS DUE

The official statistical cut-off date for communicable disease reports from 1987 will be February 29, 1988. Please forward all reports of cases with dates of onset in 1987 to the Bureau of Epidemiology, 1100 W. 49th Street, Austin, Texas 78756-3180, before that date.

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