Death Raises Safety Issues For Primate Handlers

PROCEED WITH CAUTION: There is no way to tell if rhesus macaques such as these are releasing the deadly herpes B virus into body fluids, researchers warn. The death last December of a 22-year-old research assistant at Yerkes Regional Primate Research Center in Lawrenceville, Ga., has cast a pall over Yerkes and its parent institution, Emory University, and reminded scientists once again that their occupation can be deadly. Elizabeth Griffin died on December 10 of complications from a herpes B

By Barry Palevitz | March 2, 1998

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The death last December of a 22-year-old research assistant at Yerkes Regional Primate Research Center in Lawrenceville, Ga., has cast a pall over Yerkes and its parent institution, Emory University, and reminded scientists once again that their occupation can be deadly. Elizabeth Griffin died on December 10 of complications from a herpes B virus infection. She caught the virus when a body fluid from a rhesus monkey hit her in the eye on October 29. The news was especially shocking because it came on the heels of the death of Dartmouth University chemist Karen Wetterhahn last June from dimethylmercury poisoning (R. Lewis, *The Scientist*, Oct. 27, 1997, page 1).

Herpes B virus infection in humans is rare, the epidemiology roughly paralleling use of monkeys in research. "There was a major series of outbreaks in the 1950s when massive work was being done on polio virus. Then there was a spate of cases in the mid-1980s, reflecting the tremendous increase in use of monkeys to study retroviruses in the wake of the emergence of HIV," says Stephen Straus, chief of the laboratory of clinical investigation at the National Institute of Allergy and Infectious Diseases. More than 47,000 nonhuman primates, mostly macaques, were used in research in 1990, and that number is higher today, according to David Davenport, an associate professor of medicine and infectious diseases at the Michigan State University Kalamazoo Center for Medical Studies.

Griffin's death-the first in Yerkes' 68-year history-has sparked review of current guidelines for

monkey handling because the route of transmission was unusual (G.P. Holmes et al., *Clinical Infectious Diseases*, **20**:421-39, 1995). "This is a scary scenario. More than once earlier in my career, I had had inadequate eye protection, and macaques sneezed in my face," reports Christian Newcomer, director of the division of laboratory animal medicine at the University of North Carolina at Chapel Hill.

Herpes B infects 80 percent to 90 percent of adult macaques, including rhesus and cynomolgus monkeys. Although some monkeys develop lesions similar to herpes simplex "cold sores" in humans, most are asymptomatic. And, as is true of its simplex cousin, B virus likes nerves. It hides in trigeminal and sacral ganglia indefinitely, re-emerging during stress.

At any given time, only about 2 percent of monkeys "shed" virus-releasing it into saliva, conjunctival fluid, urine, and feces. Transmission to humans typically comes from bites and scratches, but exposures from needle sticks, cage scratches, and even cultured monkey cells are known. Monkeys "will also urinate or spit on you, throw things, and hurl feces," making exposure through the eyes possible, warns Straus.

Because researchers know so little about B virus, "every case is precious in order to prevent the next case," says Louisa Chapman, a medical epidemiologist at the Centers for Disease Control and Prevention (CDC) in Atlanta, who consulted on Griffin's predicament. The first documented human death from herpes B was a young physician bitten by a rhesus monkey while studying polio in 1932. Two years later, Albert Sabin, whose oral polio vaccine made medical history a quarter of a century later, implicated B virus. Since then only 40 or so cases have been recorded, including outbreaks in Kalamazoo and Pensacola, Fla., in the late 1980s. The latter event provided the only known case of human-to-human transmission, with a woman infected through sores on her hand as she helped her sick husband.

Because of an ongoing investigation by the Occupational Safety and Health Administration (OSHA), Emory University has been tight-lipped about the Griffin case. But an unusual series of events seems to have led to her death.

Griffin followed the rules as she took a monkey to a physical exam that October day. She carried the monkey's cage at arm's length, which Yerkes officials considered a low-risk activity. She wore a lab coat, boots, a mask, and gloves, but she did not cover her eyes because it wasn't called for under the circumstances. And that proved to be her undoing. As she peered into the cage to check the monkey, a still-unidentified fluid hit her eye. Researchers agree that this was the first documented case of mucosal transmission. It was thought such a risk was low to moderate.

Because the eye splash seemed minor, Griffin did not report it for two weeks, when she went to Emory University Hospital with conjunctivitis and a headache. She improved with acyclovir, an antiviral drug, and was released 10 days later. But Griffin returned after a day, her legs weak. Ascending encephalomyelitis paralyzed her, and she died of respiratory failure and infections. The

'NEWSWORTHY': NIAID's Stephen Straus calls the Griffin case "an occupational hazard of current biotechnology and medical research."

Monkeys are challenging research subjects. "We have an image of friendly little guys wearing shorts and running around the jungle with Tarzan. But macaques are extremely vicious," warns Stephen Straus, chief of the laboratory of clinical investigation at the National Institute of Allergy and Infectious Diseases. Macaques' bites, scratches, and sprays can be deadly. However, simple measures can be taken to reduce the risks of working with these animals, including the danger of contracting herpes B.

case was also atypical in that B virus is usually lethal in about four weeks, not six.

Early B virus infection often includes flulike symptoms and herpes blisters at the wound site. Double vision may indicate early neurological damage. Early antiviral treatment can prevent encephalomyelitis (see accompanying story), although Griffin died despite treatment at an early stage.

Herpes B infection is rare, given that CDC receives thousands of reports of monkey bites and scratches, mostly from researchers, each year. "Humans are reasonably refractory to infection," notes David Dreeson, a professor of medical microbiology at the College of Veterinary Medicine at the University of Georgia in Athens. The low incidence is little understood. But once a person is infected, consequences can be catastrophic.

Until recently, infection with herpes B was 70 percent lethal, and survivors suffered severe neurological damage. But the high fatality rate may not reflect true infection levels, researchers say. This is partly because some individuals may develop only flulike symptoms and may not be diagnosed, according to Julia Hilliard, director of the B Virus Resource and Research Laboratory at the Southwest Foundation for Biomedical Research in San Antonio, Texas. Mild cases are important because latent virus may re-emerge. One virologist, identified in the literature only as K.H. to protect his identity, developed an active infection in 1970 at age 61, more than 10 years after he had last worked with monkeys, and was left with severe nerve damage (J. Fierer, *Annals of Internal Medicine*, **79**:225-8, 1973). Newcomer notes that the possibility apparently exists for humans to have had unnoticed B virus infections, although the incidence of these infections is unknown.

But the final verdict is not in. Hilliard and coworkers examined more than 300 monkey handlers and found no evidence of asymptomatic infections (A. Freifeld et al., *32nd Interscience Conference on Antimicrobial Agents and Chemotherapy*, Anaheim, Calif., abstract #1715, page 396, 1992). Fortunately, herpes B has no typhoid Marys.

Perhaps it

Prevention: Only 1 percent to 2 percent of monkeys are shedding virus-releasing it into body fluids-at any given time, but "there is no external way to tell. So as a precaution, it is safest to assume they are shedding," cautions Julia Hilliard, director of the B Virus Resource and Research Laboratory at the Southwest Foundation for Biomedical Research in San Antonio, Texas. Guidelines from the Centers for Disease Control and Prevention (CDC) for preventing herpes B infection include sedating macaques or using restraint devices such as squeeze cages to hold an animal still and loop-ended poles to capture them (W.E. Cole et al., *Morbidity and Mortality Weekly Report*, **36**:680-9, 1987). The guidelines also advise using face shields and goggles; arm-length, reinforced leather gloves; and long-sleeved lab coats. Separate guidelines cover use of cultured monkey cells (D.L. Wells et al., *Diagnosis of Microbiological Infectious Diseases*, **12**:333-6, 1989).

B-virus-free monkey colonies are a goal but may be impossible, explains Christian Newcomer, director of the division of laboratory animal medicine at the University of North Carolina in Chapel Hill. "Rambunctiousness is part of the socialization of the macaque. They have intimate contact-fighting and biting-through which they readily transmit infection."

First Aid: CDC guidelines advise immediately soaking or scrubbing a wound or splash site with soap or detergent for at least 15 minutes and rinsing eyes or mucous membranes with sterile saline or water (G.P. Holmes et al., C*linical Infectious Diseases*, **20**:421-39, 1995). Primate facilities typically have first-aid kits, specimen collection kits, and "bite-and-scratch" logs to document injuries. All researchers who work with macaques should know what to do if they are potentially exposed to B virus, advises David Davenport, an associate professor of medicine and infectious diseases at Michigan State University in Kalamazoo.

Diagnosis: Researchers who handle monkeys should note unexplained flulike symptoms, even if they cannot recall a specific encounter. These symptoms may begin from three days to four weeks after exposure, or even later. "People with high-risk activity that have undiagnosed flulike illness with fever for more than 48 hours should seek expert medical attention," says Davenport.

A polymerase chain reaction (PCR)-based diagnostic test has largely replaced serology. "PCR is much more sensitive and faster, and it can work

'TIME BOMB': Chicago's Bernard Roizman warns against having a macaque as a pet.

was the Yuletide timing or the breaking story of the avian flu, but media coverage of Griffin's death was fleeting. "The case was newsworthy, though, because it was dramatic, an occupational hazard of current biotechnology and medical research, and because it is more avoidable than most infections," says Straus. And the event did alarm people in close contact with monkeys-researchers and pet owners. "Any person who has a macaque as a pet is sitting on a time bomb. The combination of a reactivated virus and an irritated monkey can be deadly," cautions Bernard Roizman, a professor of virology at the University of Chicago.

In the biomedical research community, reaction to Griffin's death was swift. At Yerkes, interim guidelines were immediately instituted requiring protective eye wear in all animal areas. Changes also are in the works at the national level, with CDC, the National Institute for Occupational Safety and Health (NIOSH), and OSHA considering collaborating to revise guidelines on handling monkeys and evaluating and treating injuries and exposures. The guidelines may reclassify mucosal transmission as high-risk, according to Davenport.

Griffin's death has heightened awareness among those who work with monkeys. For example, on Christmas eve, Diane McClure, an assistant professor of veterinary preventive medicine at Ohio State University in Columbus, was cleaning instruments she had just used to dissect a macaque when contaminated water splashed behind her face shield. As she felt a drop enter her eye, she thought of Griffin and reacted quickly, lying down and repeatedly irrigating her eye.

As viruses go, herpes B isn't the worst. Unlike Ebola, treatment exists. Unlike influenza, herpes B doesn't mutate easily and is not highly transmissible. And unlike HIV, infection is uncommon.

Still, the tragedy has caused researchers to contemplate the benefits and risks of working with monkeys. Wrote Yerkes director Thomas R. Insel in a letter to employees on the day Griffin died, "The risks can be minimized, but this experience reminds us of the possibly dire consequences of even low-risk situations. Ultimately, the risks can never be completely eliminated, they can only be

with dead or degraded virus," explains Franco Scinicariello, a researcher at Yerkes Regional Primate Center in Lawrenceville, Ga., who developed the assay while in Hilliard's lab (F. Scinicariello, *Journal of Infectious Diseases*, **168**:747-50, 1993). For exposed individuals who do not have symptoms, serology-based tests suffice. Magnetic resonance imaging may be used to confirm central nervous system (CNS) involvement but cannot specifically identify herpes B infection.

Treatment: Prompt use of antiviral drugs such as acyclovir and ganciclovir can lower the risk of fatal encephalomyelitis. "When the virus is already in the CNS, susceptibility to these drugs plummets," says Bernard Roizman, a professor of virology at the University of Chicago. Whether to begin therapy before diagnosis is controversial. By preventing viral replication, drugs suppress the immune response and may thereby complicate diagnosis based on antibody detection.

Antiviral use in confirmed cases should continue throughout life to prevent recurrence, advises Davenport. One of his recovered patients developed new neurological problems after voluntarily discontinuing acyclovir (D. Davenport et al., *Clinical Infections Diseases*, **19**:33-41, 1994). More sensitive diagnostic tests and increasing use of antiviral drugs have cut down on the fatality of B virus infection. Scinicariello adds that work is progressing on improved serological tests, as well as a vaccine for monkeys. With these efforts, a rare but deadly infection may become even more rare.

-B.A.P. and R.L.

balanced against the importance of what we do for both human and nonhuman primates." Adds McClure: "If you work with monkeys, you're going to have exposures."

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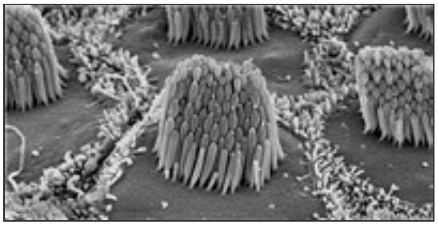

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