Import Rules Threaten Research on Primates

Many researchers say authorities have overreacted to the discovery of an Ebola-like virus in imported monkeys last year

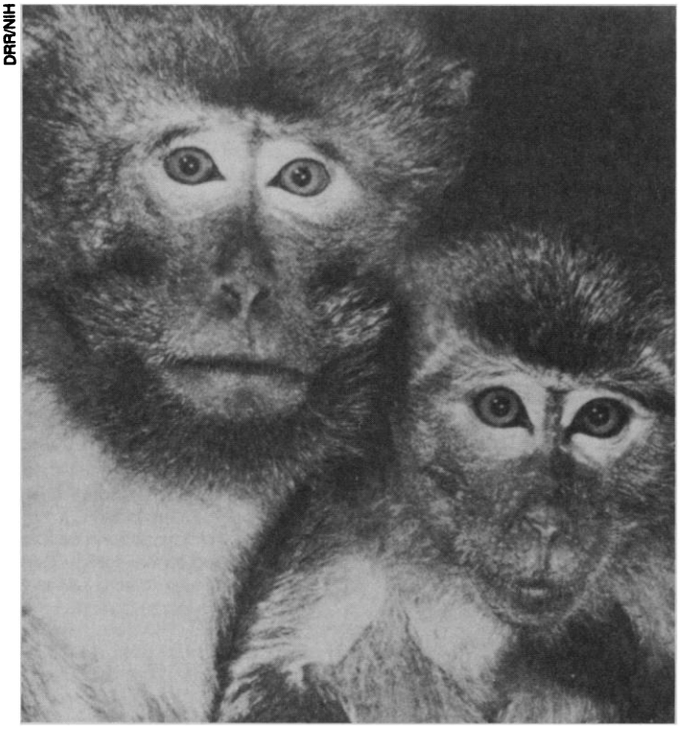
A MYSTERIOUS ILLNESS among monkeys in a quarantine facility in Reston, Virginia, 6 months ago has effectively halted all imports of three species of monkeys that account for most research on primates in the United States. New rules established by the Centers for Disease Control in Atlanta, coupled with import restrictions imposed by New York State and the reluctance of most airlines to handle shipments of monkeys, have cut off imported supplies of cynomolgus, African Green, and rhesus monkeys.

Yet there is a growing conviction among primate researchers that all this represents a gross overreaction that could eventually imperil some types of research. Not surprisingly, animal rights activists are delighted.

The Reston monkeys appeared to have been infected with Ebola virus, a virus deadly to both monkeys and humans. They became sick soon after being imported from the Philippines. But in the past few months, evidence has accumulated that the virus is not the deadly pathogen that was originally feared. Though at least seven people are known to have been infected, nobody has died or gotten sick. Moreover, tests of animals within the United States have indicated that viruses similar to the one found in Reston may be much more widespread than anybody imagined.

"This is a veterinary problem, not a human problem," says Paul Houghton of Primate Products, who has been importing cynomolgus monkeys from Indonesia. But Charles McCance, director of the division of quarantine at CDC, disagrees. "I don't think we know [that]," he says. "Our division is responsible for preventing the introduction of communicable disease into this country. We have to take this virus very seriously, until we know better. If we make an error, we have to err on the side of public health."

Many researchers are arguing, however, that by erring on the side of public health, CDC is threatening research and vaccine production. Although domestic stocks will prevent researchers who use these monkeys from being affected immediately by the import restrictions, pharmaceutical companies, which require large numbers of the monkeys to manufacture and test vaccines, have already begun to scramble to find alternative supplies. And importers warn that if the rules stay in effect, long-term damage will be done to the fragile supply pipeline.



DRR/NIH

Monkey puzzle. *The virus was detected in cynomolgus monkeys imported from the Philippines. But was it really Ebola virus?*

The events that led to the current import moratorium began when scientists at the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) at Fort Detrick, Maryland, isolated an Ebola-like virus from one of the monkeys that died at a quarantine facility in Reston. But was it Ebola?

Ebola is thought to be of African origin, so finding it in monkeys from the Philippines was a surprise. It is one of a group of viruses called filoviruses that also includes the lethal Marburg virus. Ebola is known to be responsible for two deadly outbreaks of disease, one in Zaire in 1976 and another in Sudan in 1979. The Reston virus, as it has now come to be known, looks like Ebola in the electron microscope, but there are genetic differences. "The fact that [the Reston virus] comes from the Philippines and has so far not shown any pathogenicity for man doesn't mean it's not just as much Ebola virus as the Sudan and Zaire strain," says Captain Clarence J. Peters, who headed the USAMRIID investigation. "It may just mean that within what we are calling Ebola virus we ought to make more distinctions."

Last December, CDC began a widespread search of all imported monkeys to see if filoviruses were turning up in other shipments of imported monkeys. The results were a shock. Ken Herman, a CDC virologist, says when they tested monkey blood from a variety of colonies and species against four different filoviruses—the Reston virus, the two known strains of Ebola, and Marburg—they found that about 10% of the samples reacted to one or more of these viruses. Even more surprising was that some of the monkeys tested were from "closed colonies" that have not had any new animals brought into them for years, including the CDC's own colony in Lawrenceville, Georgia. "This may be a family of viruses that is more common than we previously believed," says Herman. "I get almost a report a week where yet another population is identified to have the antibody," says William Raub, acting director of the National Institutes of Health.

CDC has now identified seven people who have been exposed to the virus, and none has gotten sick. One animal care worker cut his hand while performing a postmortem exam on an infected monkey, and although he developed antibodies within 3 weeks, he is long past the typical incubation period for producing illness without showing any sign of disease.

Nevertheless, CDC issued a new set of rules on 18 April that requires importers to comply with strict quarantine procedures and provide detailed information about how the monkeys will be transported—including how they will decontaminate aircraft that carry the monkeys. New York State, which is the entry point for approximately 80% of imports of these species into the United

States, went even further. A month before CDC issued its regulations, state health officials announced that they would require cynomolgus, African Green, and rhesus monkeys to undergo a 60-day quarantine period both before and after shipment. Moreover, they would have to be tested for antibodies to the virus both before they are imported and after they arrive. "We've got to set the regulations up to maximize the safety of the people of New York," says Leo Grady, a virologist with the state health department. "We can always change things later if it appears that it is not necessary." So far, no one has received CDC's permission to ship monkeys, so no one has even asked for New York State's permission.

For importers, the testing requirement presents a nearly impossible obstacle. Ebola is a class four agent, meaning that to work with it researchers must use the highest level of biological containment. Only two facilities in the country—at CDC and USAMRIID—are capable of testing for filovirus antigens or antibodies, and neither has the capacity to test anything like the 16,000 to 20,000 cynomolgus monkeys that have been coming into this country each year. Both CDC and USAMRIID are trying to interest commercial laboratories in developing an antibody test kit that would not require maximum containment procedures, but that will take some time.

"Animal protection people have been trying for years to stop the monkey trade. Now a little virus has done it for us." —Shirley McGreal

Fulfilling the other CDC requirements will also not be easy. Vance Gordon, vice president for research at the Pharmaceutical Manufacturers Association, says the CDC "placed the burden on the importers of developing a plan that would provide adequate sureties and safeguards, without laying down explicit criteria of what the elements of such a plan would be." Bill Cummins, an importer from Texas, says he's not sure even where to start. "Everyone is trying to comply with current regulations, but how do you totally decontaminate a $50-million aircraft and not damage it?" he asks. "We have not figured that one out yet."

Houghton says importers are well aware of the need for taking health precautions when importing monkeys, but the threat isn't mainly to humans. "We're a hell of a lot more concerned about exposing our monkeys to people than we are exposing people to the monkeys," he says. "The monkeys catch a lot more things from the people and get sick, which is a problem for us, than the other way around." Gordon agrees that experienced handlers know how to avoid risks when dealing with monkeys. "One of the ironies of this situation is we have lived for years with herpes B virus," which is sometimes found in imported monkeys and

IOM Elects New Members

The Institute of Medicine has elected 45 new active members, raising the total active membership to 462. Five persons were elected directly to senior membership, bringing that roll to a total of 397. The foreign associates membership now totals 23 with the election of 10 this year. The new active members are:

Dorothy F. Bainton, University of California, San Francisco; **Samuel H. Barondes**, University of California, San Francisco; **James F. Blumstein**, Vanderbilt University; **Byron Wm. Brown, Jr.**, Stanford University; **Thomas F. Budinger**, University of California, Berkeley; **William T. Butler**, Baylor College of Medicine; **Paul Calabresi**, Brown University; **Joseph A. Califano, Jr.**, Dewey, Ballantine, Bushby, Palmer & Wood, Washington, D.C.; **Michael I. Cohen**, Albert Einstein College of Medicine; **Max D. Cooper**, University of Alabama, Birmingham; **Joseph T. Coyle**, The Johns Hopkins University Medical School, Baltimore; **Joseph W. Eschbach**, University of Washington Medical School, Seattle; **Gerald D. Fischbach**, Washington University, School of Medicine, St. Louis; **Juanita W. Fleming**, University of Kentucky; **M. Judah Folkman**, Harvard Medical School; **Charles K. Francis**, Columbia University.

Irving H. Goldberg, Harvard Medical School; **DeWitt S. Goodman**, Columbia University; **Robert Graham**, American Academy of Family Physicians, Kansas City; **Joseph C. Greenfield, Jr.**, Duke University Medical Center; **Gerald N. Grob**, Rutgers University; **Michael Grossman**,The City University of New York; **Thomas S. Inui**, University of Washington, Seattle; **Stephen C. Jacobsen**, University of Utah; **Morris J. Karnovsky**, Harvard Medical School; **David J. Kupfer**, University of Pittsburgh Medical School; **Robert Langridge**, University of California, San Francisco; **Judith R. Lave**, University of Pittsburgh; **Walter F. Leavell**, Drew University of Medicine and Science, Los Angeles; **David M. Livingston**, Harvard Medical School; **Roger O. McClellan**, Chemical Industry Institute of Toxicology, Research Triangle Park, NC.

Ruth McCorkle, University of Pennsylvania; **John D. Michenfelder**, Mayo Clinic; **Mortimer Mishkin**, National Institute of Mental Health, Bethesda; **Herbert L. Needleman**, University of Pittsburgh Medical School; **Robert E. Patricelli**, Value Health Inc., Avon, CT; **William E. Paul**, National Institute of Allergy and Infectious Diseases; **Roy M. Pitkin**, University of California, Los Angeles; **William L. Roper**, Centers for Disease Control, Atlanta; **Murray B. Sachs**, The Johns Hopkins University Medical School; **Charles R. Schuster**, National Institute of Drug Abuse, Rockville; **Howard M. Temin**, University of Wisconsin; **Bailus Walker, Jr.**, State University of New York, Albany; **Peter A. Ward**, University of Michigan Medical School; **Joseph B. Warshaw**, Yale University Medical School.

Elected directly to senior membership are:

Thomas P. Almy, Dartmouth Medical School, Etna, NH; **Jane F. Desforges**, New England Medical Center; **Robert R. Marshak**, University of Pennsylvania, Kennett Square; **Alexander Rich**, Massachusetts Institute of Technology; **James E. Strain**, American Academy of Pediatrics, Elk Grove Village, IL.

Newly elected foreign associates are:

Albert J. Aguayo, McGill University, Montreal; **Jorge E. Allende**, Universidad de Chile, Santiago; **Haile T. Debas** (Canadian citizen), University of California, San Francisco; **Uta Francke** (German citizen), Stanford University Medical Center; **Egon Jonsson**, The Karolinska Institute, Stockholm; **Wataru Mori**, Council for Science and Technology, Tokyo, Japan; **D. Keith Peters**, University of Cambridge School of Clinical Medicine, England; **Ross L. Prentice** (Canadian citizen), University of Washington, Seattle; **Evert Reerink**, State University Limburg, Maastricht, The Netherlands; **Simone Sandier**, Centre de Recherche, d'Etude et de Documentatin en Economie de la Sante, Paris, France.

is "quite as lethal as Ebola," he says.

As for the airlines, Joseph Chan of the International Air Transport Association says it's up to individual carriers whether they will carry the monkeys. Most have refused to ship the three species subject to restrictions, and some have refused to carry any monkeys of any species.

In the meantime, researchers are faced with the prospect of supply shortages that could cripple research. Although most researchers will be able to find domestic sources for their immediate needs, Mortimer Mishkin, a neurobiologist at the National Institute of Mental Health, says that without access to imported monkeys, "research will come grinding to a halt." "To the extent that the permit system turns into a de facto ban for any long term, then it's extremely serious for the medical research community," says Raub.

And even if the moratorium were to disappear overnight, importers warn that there could still be long-term supply disruptions. "The supply side of this primate business is extremely fragile," says Houghton. "It's not like you can stop things and then start them right back up again. We're already looking at a 4- to 6-month downtime even if things were to completely open up again right now."

The import restrictions have been embraced by animal rights activists who have long been fighting what they call the "monkey slave trade." Shirley McGreal of the International Primate Protection League doubts that the present moratorium on imports will halt the trade altogether, but she has hopes that it will force better conditions for the monkeys that are imported. "Animal protection people have been trying for years to stop the monkey trade," she says. "Now a little virus has done it for us."

The situation is showing some signs of loosening up. McCance says CDC has now received two applications for import permits, and he expects that some permits will be issued within the month. On 16 May, CDC mailed out specific criteria for releasing from quarantine animals imported before the restrictions were imposed. If they show no evidence of new infection and a veterinarian declares they are healthy, they may be released to users, even if they do have antibodies to filovirus indicating a prior exposure. CDC warns that "data are insufficient to determine whether monkeys that have completed import quarantine are noninfectious," and users are urged to use safe handling procedures.

But getting new supplies into the country would still pose a problem unless New York State eases its requirements and the airlines resume shipments. ■ JOSEPH PALCA

A European Superlaser?

Five European countries are quietly considering a proposal to build the world's most powerful research laser. Next month, senior officials from the central funding organizations of France, West Germany, Italy, Spain, and the United Kingdom will meet to discuss a confidential report that sets out options for a European High Performance Laser Facility. The total cost of such an undertaking is estimated to be $200 to $300 million.

The report, produced by a working group established by the five organizations, calls for a two-stage development process that would result in a machine three to four times as powerful as Lawrence Livermore National Laboratory's NOVA, which is currently the world leader.

The goal is to create a laser capable of delivering 100 kilojoules (kJ) of energy at ultraviolet wavelengths. "That kind of power is very dramatic indeed," notes Michael Key, director of the central laser facility at the Science and Engineering Research Council's Rutherford Appleton Laboratory, who cochaired the working group that produced the report.

The report says that two technologies are capable of delivering the goods. One is the neodymium-glass laser, which is similar to the familiar ruby-rod laser. The big advantage is that its technology is very well understood. "One could build it today, it's only a question of money," says working group member Sigbert Witkowski, director with special responsibility for lasers at the Max Planck Institute for Quantum Optics, outside Munich. But neodymium-glass lasers have some disadvantages, too. They are inefficient, and hence costly, and they take several hours to recycle after each shot.

More promising is the so-called excimer laser, based on a mixture of krypton and fluorine gases. This system is more energy-efficient and is capable of being fired very rapidly. But the technology is still being developed. The largest KrF laser is the Aurora laser at Los Alamos, which delivers 1 kJ. "The step from 1 kJ to 100 kJ in this new technology is too big," says Witkowski.

For that reason, the report recommends an initial phase in which two intermediate power lasers—one neodymium-glass, one KrF—would be built side by side. Researchers would then be able to compare their performance before picking one for the final assault on 100 kJ.

One goal of the European High Performance Laser would be to free European laser scientists from their dependence on high-powered machines in the United States and Japan. Phase one would do that. Phase two—regardless of the chosen technology—would put them well ahead of their U.S. colleagues.

But transatlantic competition is not the only driving force. A superlaser would enable scientists to investigate some fundamental questions of physics, such as the interactions between atoms and electromagnetic fields and the behavior of plasmas. The intense pulse of such a laser would also create conditions even hotter than the core of a burning star. "It's not just red hot," Key explains, "it's x-ray hot." That means the superlaser could become the most powerful source of x-ray pulses on Earth. And that may speed development of x-ray lasers, which could enable scientists to create holographic pictures of single genes and other details of living organisms.

European researchers also have their sights set on inertial confinement fusion. When a powerful laser is trained on a pellet of hydrogen, the intense heat ignites a tiny atomic fusion reaction—a process Key calls "micro-miniaturizing the hydrogen bomb." The rapid-fire capability of KrF lasers holds out the hope of producing several such fusion explosions a second, which would be required for a fusion reactor. Such a reactor would be the fusion equivalent of an internal combustion engine, as distinct from the steady burning of magnetically confined fusion.

The five funding agencies are due to consider the working group's report on 7 July. Preliminary indications are mixed. Professor Edouard Fabre, director of France's high-intensity laser laboratory, and a cochair of the group, says his paymasters may want to "pause" before committing themselves to another expensive project. "It's a question of funding, not of physics," Fabre notes. Witkowski says he has heard, unofficially, that the report enjoyed "a friendly reception" in Germany. Italy, Spain, and the United Kingdom are saying nothing. If the report is accepted, there will be a year of what Key calls "serious engineering design." Phase one would take 3 or 4 years and phase two a further 3 or 4 years. ■ JEREMY CHERFAS