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Volunteer in Asthma Study Dies After Inhaling Drug

By LAWRENCE K. ALTMAN

A healthy volunteer died recently after inhaling a drug in a federally financed asthma study conducted by Johns Hopkins University, officials said yesterday. The volunteer's hospitalization after inhaling the drug led the institution to suspend the research.

Officials at Johns Hopkins declined to identify the volunteer or the date of death, or to release anything more than sketchy information about the study and the circumstances surrounding the fatality. They cited not only confidentiality for the volunteer but also the family's request that they not publicly discuss the study itself.

An autopsy was performed. But in its brief statement, Hopkins said, "The exact cause of death has not been determined."

University officials said that as required, they had notified three federal agencies involved in the research, which was conducted at Johns Hopkins Bayview Medical Center in Baltimore. Officials of those agencies said they would look into the death and the circumstances surrounding it, and referred all questions to Johns Hopkins.

Risk is inherent in research, although experiments on humans vary widely in their danger, and in design.

Clinical trials, for example, are intended to test the safety and effectiveness of an experimental drug that may benefit the volunteers. But the Hopkins study was apparently of a type known as a challenge experiment, testing a theory about how the body responds to various stimuli.

In such studies, a volunteer usually does not stand to benefit directly, though the findings could ultimately contribute to development of a new therapy that the participant might then use. Given the usual lack of direct benefit, ethicists say, these studies require particularly close monitoring, because they can pose a risk to a volunteer's health or life.

In recruiting volunteers for asthma and allergy studies, Hopkins says on its Web site that it will compensate participants for their time.

Before they are started, all federally financed experiments on humans require ethical review by a committee generally known as an institutional review board, maintained by

the researching university. Johns Hopkins said a review board had approved the study in which the volunteer died.

The university described the study at issue as a baseline physiologic test using an inhaled drug, hexamethonium, to determine how the lung protects the airways from narrowing, a development that plays a critical role in asthma.

Ethicists and asthma experts not affiliated with Hopkins expressed hope in interviews last night that the university would quickly make public full details of the study. The experts said that protecting the confidentiality of one affected individual was understandable, but that citing such a reason to withhold other public discussion of a federally financed study was extraordinary.

Providing full disclosure "is what you would expect a leading research institution to do," said Dr. LeRoy Walters, an ethicist at the Kennedy Institute at Georgetown University. He said Johns Hopkins's brief statement "is just the beginning of the disclosure I would hope for."

In response to a request filed by The New York Times under the Freedom of Information Act, the Office for Human Research Protections released three letters it had received from Hopkins. The office is a unit of the Department of Health and Human Services charged with protecting the safety of volunteers in experiments.

The letters sketch a picture of an experiment that went amiss, beginning 24 hours after the volunteer inhaled hexamethonium. On May 7, the volunteer reported dry cough, shortness of breath on exertion, muscular aches and fever. Two days later, the volunteer was admitted to the hospital, and doctors were concerned about a possible reaction to the drug. "This obviously qualifies as a serious adverse event," Dr. Alkis Togias, one of the study researchers, wrote in a letter dated May 9.

In a letter to the federal office dated May 17, Dr. Chi V. Dang, vice dean for research at Hopkins, said that the study had been suspended and that the volunteer remained hospitalized. Dr. Dang noted that before entering the experiment, the volunteer had undergone extensive tests, including those for lung function, and had been found healthy.

In a letter dated June 6, Dr. Dang wrote, "It is with deep regret that I report the death of the subject."

Dr. Dang wrote that Hopkins was asking a laboratory to test the hexamethonium, which, he wrote, the manufacturer had said was 99.6 percent pure. (The letter did not identify the manufacturer.) Dr. Dang also said tests were being conducted on equipment used in the experiment and to determine whether the volunteer had come down with a viral infection.

Researchers say the death of study volunteers, particularly healthy ones, is rare, though official registries of the number of humans involved in experiments are not kept.

The Hopkins death is one of a small number that have come to public attention in recent

years.

Two years ago, Jesse Gelsinger, 18, died in a gene therapy trial at the University of Pennsylvania. Federal officials later cited Penn researchers for numerous violations of safety standards in the experiment.

In research in 1996, Nicole Wan, a healthy college student, died shortly after a bronchoscopy, an examination of the breathing tubes in the lung, at the University of Rochester in New York.

In 1993, 5 of 15 participants died in a drug trial at the National Institutes of Health that was testing a promising drug for hepatitis B.

And in 1999, federal officials temporarily suspended human experimentation at Duke University because of shortcomings in the university's system for protecting volunteers.

Such episodes have led critics to demand that the government strengthen the budgets and roles of review boards to monitor clinical trials, and that academic medical centers police their researchers more strictly.

For the study at Johns Hopkins, the National Heart, Lung and Blood Institute said, it awarded a \$1,553,462 grant to the principal investigator, Dr. Solbert Permutt, to test up to 290 volunteers from Dec. 15, 1998, to Nov. 30, 2002.

The volunteers were asked to inhale hexamethonium as part of deep breathing tests so the researchers could observe the effect on relaxing the airways, officials said. "By offering an in-depth understanding of the way in which airway mechanics lead to the manifestations of asthma, the project should answer many questions behind this disease," Dr. Permutt's team wrote in its request for financing.

The Food and Drug Administration licensed hexamethonium pills in the 1950's to treat high blood pressure and decrease bleeding during surgery. But because the manufacturer withdrew the drug from the market in the 1970's, its use today is considered experimental.

Hexamethonium has been used in several studies involving lung physiology at leading academic medical centers without any unexpected adverse events, Johns Hopkins said.

All three federal agencies notified of the death — the Food and Drug Administration, the Office for Human Research Protections, and the heart, lung and blood institute — said they would investigate the safety of the drug and whether the volunteers had been adequately protected.