

Hopkins Researcher Faulted in Death

Internal Probe Also Cites Review Panel; Trial Standards to Be Tightened

By Susan Levine
Washington Post Staff Writer
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An internal investigation by a Johns Hopkins University committee into the death of a healthy young woman involved in an asthma study faults the principal researcher and the institution's review board for inadequately scrutinizing the risks of the chemical used in the trial and not sufficiently warning volunteers about them.

Results of the month-long inquiry were discussed yesterday during a news conference in Baltimore, with a trio of university medical officials repeatedly stressing that Hopkins takes full responsibility for what happened.

Ellen Roche suffered "a tragic and untimely death," said Edward D. Miller, chief executive officer of the Hopkins medical system and dean of its medical faculty. "We all have profound respect for her life and her contribution."

The exact cause of the 24-year-old woman's death might remain a mystery, but the committee decided that it clearly was tied to the hexamethonium she inhaled in early May while participating in a clinical trial conducted by Alkis Togias. The asthma specialist, described yesterday as a "stellar scientist" conducting important research, was looking at the neural mechanisms that help the airways of healthy lungs remain open even when exposed to irritants or allergens. Hexamethonium was administered in this case to provoke airway constriction.

The internal investigation concluded that Togias should have been required to give more details about the chemical's safety or toxicity in humans to the institutional review board that approved his study. Hexamethonium was prescribed for hypertension until it was supplanted by other drugs and taken off the market in 1972. Its use as an inhalant is considered experimental.

In his application, Togias cited four published studies involving hexamethonium from the 1980s but "did not explicitly point out that the information on safety and efficacy was derived from only 20 research subjects," according to the committee's 32-page report.

And while the review board followed standard procedures before giving him the go-ahead last fall, a majority of the internal investigation committee felt that "an adequate evidence base did not exist for [the review board] to be confident that inhaled hexamethonium was safe" for Roche or the eight other healthy volunteers who signed up for the physiological "challenge" study.

In addition, the nine participants were not provided enough information about the risks they were taking, and the consent form they signed should not have been sanctioned by the review board, the report says. The form should have specified that hexamethonium was not authorized for medical use by the Food and Drug Administration, that its inhaled use was unproved and that there was the "possibility of a serious adverse event or death" existed.

"It is a lot easier to judge things in retrospect, in hindsight," said cardiologist Lewis Becker, who led the seven-member review panel. At the request of Hopkins, another review will soon be conducted by an advisory group of physicians from medical schools elsewhere in the country. Inquiries by the FDA and the federal Office for Human Research Protections also are in progress.

The Hopkins committee was unanimous in numerous conclusions but disagreed on two key points:

- It was divided on whether Togias did an adequate search for case reports involving the potential toxicity of hexamethonium. He located the work from the 1980s on a medical Web site and in standard pharmacology and pulmonary medicine textbooks. But he failed to find articles from the 1950s that would have alerted him to acute pulmonary reactions to extended oral and intravenous use of the chemical.
- It also split on whether the Hopkins review board should have asked Togias to submit what is called an "investigational new drug" application to the FDA. Even though Togias was not proposing to use hexamethonium for therapeutic reasons, the committee said it was unclear whether the substance would have been exempt from agency regulation.

In a preliminary finding two weeks ago, the FDA indicated that Togias should have filed that application. Hopkins officials say they have tried for several years to get an agency clarification for when an application is required.

Chi Van Dang, vice dean for research at Johns Hopkins, said it was premature to discuss possible disciplinary action by Hopkins against Togias. He had more than 10 research studies in progress when Roche died, and the university has put all on hold pending a review. It also has suspended 16 other studies involving substances for which FDA opinions were not sought.

The university will increase scrutiny of all research procedures and increase the number of random checks of ongoing trials, Dang said. It will also develop standards for physicians and scientists conducting searches of past studies and establish a research training curriculum.

The committee did not learn why Roche participated in Togias's study, and no one knows whether she would have done so even if the risks had been spelled out more clearly. Roche, of Reisterstown, Md., had worked as a laboratory technician at the Johns Hopkins Asthma and Allergy Center since January 1999. She had previously volunteered for two clinical trials.

She signed the consent form for the study April 16, received a 1 gram dose of hexamethonium May 4, was hospitalized with respiratory problems within five days and died June 2. Extensive tests revealed no separate bacterial or viral infections that would have caused her death.

Miller said university officials have met with her family "and are working with a family representative." Asked whether Hopkins would pay compensation for her death, he responded that "nothing concrete" has been decided.

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