

JOHNS HOPKINS UNIVERSITY—ASTHMA CASE STUDY

On June 2, 2001 Ellen Roche, a participant in an asthma study being conducted at Johns Hopkins Asthma and Allergy Center, died of progressive hypotension and multiple organ failure (13). Ellen Roche was a healthy volunteer recruited to participate in a study designed to examine bronchoprotection and bronchodilation (7). The study, entitled “Mechanisms of deep inspiration—induced airway relaxation,” was directed by Dr. Alkis Togias along with his co-investigator Solbert Permutt (7, 13). Their hypothesis was that in people without asthma, lung inflation protects airways from obstruction through some neural messaging mechanism and that this mechanism is somehow disabled in asthmatics (13). The investigators set out to test this hypothesis by administering methacholine, a substance that mimics the symptoms of asthma, to healthy individuals not afflicted with the disease (9). A select group of participants would subsequently be given a dose of hexamethonium, a ganglionic blocker that would prevent the neural signal to dilate the bronchials from returning to the lungs (9, 11). On September 18, 2000 the institutional review board at Johns Hopkins Bayview Medical Center approved the study proposed by Dr. Alkis Togias (13).

Ellen Roche was employed at the Asthma and Allergy Center when she responded to a flier advertising the research study. She volunteered to participate in the investigation and signed a “clinical investigation consent form” outlining the purpose of the project; the procedures and risks involved (11). However, the form did not include any information on the risks involved with inhaling hexamethonium. This substance was once used, in tablet form, to treat hypertension in the 1940s and 1950s, but the FDA withdrew approval because they found it to be an ineffective treatment (10). Knowing that hexamethonium

could cause marked decrease in a person's blood pressure, Dr. Togias assured his volunteers that a physician would be present throughout the period that it was administered (3). This was not the only risk involved with the use of this substance. In the 1950s, research on hexamethonium had found it to be toxic to lungs—another fact that researchers failed to present in their consent form (9).

Ellen Roche was a healthy volunteer who participated in a study that she understood would provide no therapeutic benefits to herself, but may help in the fight against asthma. Whether she was motivated by the altruistic act of helping make advances in the research on asthma, or by the \$365 that would be paid to her at the termination of her participation; she entrusted her health to the judgment of the investigators and health professionals conducting the study (3). Maybe she would have proceeded differently if she had been fully informed about the risks involved with inhaling hexamethonium.

On May 4, 2001 Ellen received 1g of hexamethonium by inhalation, developed a dry cough the next day and by May 9 she was hospitalized at Bayview Medical Center with fever, hypoxemia, and abnormalities on a chest X-ray. Her condition worsened and she was moved to the intensive care unit, where she died on June 2, 2001 of progressive hypotension and multi-organ failure (13).

Ellen Roche had died in her altruistic effort to participate in an asthma study. The professionals in charge of the study had failed to protect her from the risks involved. Her trust had obviously been misplaced. She had trusted that the highly knowledgeable researchers would follow the “Basic Ethical Principles” on which all research on human subjects is based. As outlined in the Belmont Report, the three “basic ethical principles” are the respect of persons, beneficence, and justice (12).

Respect of persons states that all persons should be treated as autonomous and that people lacking autonomy should be protected (12). This implies that people should be given all necessary information to be able to decide for themselves whether or not to give consent to participation in a human research study. The researchers involved in the asthma study failed to fully disclose the risks involved with the use of hexamethonium and that the use of it as an inhalant was not approved by the Food and Drug Administration (2). This violated the principle of respect of persons.

Beneficence is the principle of maximizing benefits while minimizing harm (12). This principle was violated by the failure of the investigators to minimize risks in relation to the expected benefits to society (1). When one volunteer developed unanticipated adverse effects following hexamethonium treatment, the investigators failed to report these adverse effects to the investigational review board as required by FDA regulations (2). This was a gross oversight by the investigators because such a report may have prevented the subsequent administration of hexamethonium treatments and thus prevented the death of Ellen Roche.

The principle of justice states that all individuals should be treated as equals (12). While there was monetary compensation for participation in the study, the modest amount was not sufficient to indicate the coercion of certain groups of people. This principle therefore does not appear to have been violated by the investigators.

Response from the scientific community over the death of the healthy volunteer, Ellen Roche, was immediate. Three agencies gathered to individually investigate the cause of her death including the Food and Drug Administration (FDA), the internal review committee at Johns Hopkins University, and the Office for Human Research Protection (OHRP) (13).

The FDA cited five violations of the federal code during its investigation and outlined them in an FDA form 483 “Inspectional Observations.” David Lepay, a senior advisor for clinical science at the FDA, contended that Dr. Alkis Togias grossly compromised federal guidelines installed to ensure the safety of human research subjects (4). The violations cited by the FDA inspector were failure to submit an Investigational New Drug (IND) application for the use of hexamethonium as an inhalant, failure to report adverse affects of the first subject in the study to the IRB, making changes to the protocol without first getting approval from the IRB for these changes, and failure to advise participants that the use of hexamethonium by inhalation was an experimental procedure (2).

The internal review committee at Johns Hopkins University criticized the investigators and the IRB for failing to initially acquire FDA approval for the use of hexamethonium as an inhalant (13). It also questioned the complacency of the investigators when they ignored the respiratory problems experienced by the first test subject and for not suspending further treatments with hexamethonium (13). This could have helped prevent the untimely death of Ellen Roche.

The OHRP was most harsh in its criticisms of the leaders of the study. On July 19, 2001 the OHRP suspended all research involving the use of human subjects pending compliance by Johns Hopkins University (13). One of the most prestigious medical schools in the nation, Johns Hopkins University at the time was receiving approximately \$301 million dollars in federal funding and was conducting close to 2,400 investigations at the time of the suspension (10). The OHRP found it necessary to suspend all these studies because of the widespread noncompliance to federal guidelines of research involving human subjects. They cited lack of minutes documenting 18 of the last 21 meetings of the IRB as a main point of noncompliance (13). They also criticized the IRBs

failure to properly review new protocols and to provide a “substantive and meaningful” review of current projects (13). Moreover, the OHRP was concerned that the investigators continued to expose additional participants to hexamethonium prior to fully investigating and resolving the adverse affects to the first test subject (5).

The scientific review agencies that investigated the death of Ellen Roche were in agreement that the researchers did not act in the best interest of the participants by failing to fully disclose the potential risks involved with using hexamethonium. While the university adamantly opposed the suspension of all of its studies stating that the suspension was “unwarranted, unnecessary, paralyzing and precipitous,” they did take full responsibility for Ellen Roche’s death and immediately suspended any studies being conducted by Dr. Alkis Toggias (15). The suspension did not last very long and following some changes by the university, the OHRP partially lifted its suspension after only three days while requiring full re-review of some 2,000 investigations (13). The effects of the suspension will be felt for some time, however. The re-review of protocols will take the university months to complete, says Sharon S. Krag, PhD, associate dean for graduate education and research at the University, and will cost the university a great deal of money and jobs to some research staffers (8).

While scientists around the country are still unsure of where to place blame for the unfortunate death of Ellen Roche—on the researcher, the University or on the system responsible for protecting human subjects (9)—on October 11, 2001 the family of Ellen Roche reached an out-of-court settlement with Johns Hopkins University for an undisclosed amount (6).

Reference List

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