

Health Policy Report

PROTECTING RESEARCH SUBJECTS —
THE CRISIS AT JOHNS HOPKINS

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ELLEN Roche, a 24-year-old technician at the Johns Hopkins Asthma and Allergy Center and a healthy volunteer in a study of asthma funded by the National Institutes of Health, died on June 2, 2001. Prompted by Roche's death, the federal Office for Human Research Protections reviewed the system at the Johns Hopkins Medical Institutions for protecting research subjects and found widespread deficiencies.

On July 19, 2001, the office suspended all federally supported research projects at Johns Hopkins and several affiliated institutions — not because of Roche's death but because of the additional problems that had been identified.¹ Johns Hopkins quickly took corrective action, and the suspension was lifted.² Nonetheless, the suspension was “a gigantic shock” to an institution that “has always prided itself on excellence in care and excellence in research,” according to Dr. Edward D. Miller, dean of the Johns Hopkins University School of Medicine.

Along with the 1999 death of 18-year-old Jesse Gelsinger in a gene-transfer trial at the University of Pennsylvania and the suspension of federally supported research at other prominent institutions (Table 1), the shutdown at Johns Hopkins has focused attention on the safety of medical research, particularly when the subjects are healthy volunteers or are employed at the institution where the research takes place. The shutdown has also spurred efforts to improve the effectiveness of the various groups that have a role in protecting research subjects, including investigators, institutional review boards (IRBs), sponsors, and the institutions where the research is conducted. In this report, I examine the crisis at Johns Hopkins and the ongoing response.

BACKGROUND

Federally supported research at an institution is suspended only “when there are systemic problems and when not doing so poses an immediate threat to the potential well-being of the research subject,” according to Dr. Greg Koski, director of the Office for Human Research Protections. In 2001, about 50,000 persons participated as research subjects in studies at Johns Hopkins. At the time of the shutdown, there were about 2500 active protocols. Between fiscal years 1995 and 2000, the total value of the research and training

TABLE 1. SUSPENSIONS OF FEDERALLY SUPPORTED RESEARCH.*

| DATE OF SUSPENSION | INSTITUTION |
|--------------------|---|
| March 1999 | Veterans Affairs—Greater Los Angeles Health Care System, West Los Angeles |
| May 1999 | Duke University Medical Center |
| August 1999 | University of Illinois, Chicago |
| January 2000 | Virginia Commonwealth University |
| June 2001 | University of Oklahoma Health Sciences Center |
| July 2001 | Johns Hopkins Medical Institutions |

*The information is from the Office of Human Research Protections.

grants that the Johns Hopkins University School of Medicine received from the National Institutes of Health increased from \$185 million to \$305 million; the medical school is consistently at or near the top in rankings of institutions according to total federal research support.³

When people are enrolled in a study, there is an inherent trade-off between the potential importance of the information that may be gained and the potential risk to the subject. “At a certain point some patient is going to die in clinical trials,” Miller said. “There is no question about it.” The challenge is to do everything possible to ensure the safety of research subjects and to make the risk as small as possible. The alternative, according to Miller, “is not to do any clinical investigation, the status quo, and still have children on ventilators after polio.”

Research involving healthy people is a particular focus of concern because it often has no direct therapeutic potential. Many argue that such research requires a higher standard for minimizing risks than research involving people who are sick and who may die from their underlying disease. “Research on normal subjects and research on people who are motivated by sickness are very different issues,” said Karen H. Rothenberg, dean of the University of Maryland School of Law.

In large research institutions, employees often participate in studies. The reason for their participation may be an altruistic desire to help the sick, the opportunity to make extra money and get time off from work, or even subtle or explicit coercion. Like other institutions, Johns Hopkins has rules against directly soliciting staff members for research or recruiting employees who report to a researcher or who work in the same group. Many staff members participated in studies at the Asthma and Allergy Center, where Roche worked, and signs were posted soliciting volunteers.⁴ Roche was listed in a registry of normal volunteers and had been in a number of previous studies.

THE ASTHMA STUDY

Asthma is a potentially fatal disease. Its prevalence has increased in recent years, particularly in urban ar-

cas. The purpose of the study for which Roche volunteered, which was entitled "Mechanisms of Deep Inspiration-Induced Airway Relaxation," was to gain a better understanding of the pathophysiology of asthma — specifically, the mechanism of airway hyperresponsiveness.^{5,6} The study was based on the hypothesis that, in normal people, lung inflation protects the airways from obstruction through a neural mechanism and that this protective mechanism may be lacking or impaired in people with asthma.

Under the protocol, healthy subjects were to inhale a ganglionic blocker, hexamethonium. If ganglionic blockade suppressed the protective effects of deep inspiration on the airways, it would suggest that neural mechanisms helped the airways stay open.

Hexamethonium was chosen because it blocks neurotransmission by nonadrenergic, noncholinergic nerves, which were thought to be the nerves that were involved. The substance was once used to treat hypertension but was removed from the U.S. market in 1972 after the Food and Drug Administration (FDA) found that it was ineffective. The hexamethonium bromide used in the study was obtained from a chemical company and was labeled, "For laboratory use only, not for drug, household, or other uses."¹ It was prepared for administration in a laboratory at the Asthma and Allergy Center at Johns Hopkins.

THE DEATH OF ELLEN ROCHE

The events leading to and following Roche's death in June 2001 are summarized in Table 2. If Roche had completed the study, she would have received up to \$365 — \$25 for each of the first-phase visits and \$60 for each of the second-phase visits.⁶

In the consent form, hexamethonium was described as "a medication that has been used during surgery, as a part of anesthesia; this is capable of stopping some nerves in your airways from functioning for a short period."⁷ The section on risks stated that hexamethonium "may reduce your blood pressure and may make you feel dizzy especially when you stand up." Pulmonary or other potential toxic effects were not mentioned. The consent document was later criticized as having "failed to indicate that inhaled hexamethonium was experimental and not approved by the FDA" and because it referred to hexamethonium as a "medication."¹

Roche received hexamethonium on May 4; she was the third subject who received it (Table 2). Mild shortness of breath and a cough had developed in the first subject, resolving over a period of about eight days. The second subject, who received hexamethonium while the first subject still had symptoms, did not report any symptoms.⁶

The day after Roche inhaled about 1 g of hexamethonium, a cough developed. She was hospitalized on May 9 and died on June 2. An autopsy showed dif-

TABLE 2. EVENTS LEADING UP TO AND FOLLOWING THE DEATH OF ELLEN ROCHE.

| DATE | EVENT |
|--------------------|--|
| September 18, 2000 | The institutional review board (IRB) at the Johns Hopkins Bayview Medical Center approves a study, "Mechanisms of Deep Inspiration-Induced Airway Relaxation." The study is a part of the research plan funded by a grant from the National Institutes of Health, entitled "Lung Inflation in Airways Hyper-Responsiveness." |
| April 16, 2001 | Ellen Roche, a 24-year-old healthy volunteer and a technician at the Johns Hopkins Asthma and Allergy Center, provides consent to participate in the study and begins the protocol. |
| April 23, 2001 | Subject 1 [another healthy volunteer] receives about 1 g of hexamethonium by inhalation. The baseline values for forced expiratory volume in one second (FEV ₁) and forced vital capacity (FVC) are 2.68 and 3.23, respectively. |
| April 25, 2001 | Subject 1 reports mild shortness of breath and a nonproductive cough. The values for FEV ₁ and FVC are reduced to 2.33 and 2.74, respectively. |
| May 3, 2001 | Subject 1 reports complete resolution of symptoms. The values for FEV ₁ and FVC are 2.41 and 2.91, respectively — somewhat reduced, as compared with the values on April 23 but similar to those obtained when the subject entered the study. |
| May 4, 2001 | Roche (Subject 3 in the study) receives about 1 g of hexamethonium by inhalation. |
| May 5, 2001 | A dry cough develops in Roche. |
| May 9, 2001 | Roche is hospitalized at Bayview Medical Center with fever, hypoxemia, and abnormalities on a chest film. The IRB is notified of adverse events in Subject 1 and Roche; the study is placed on hold. |
| May 12, 2001 | Progressive dyspnea develops in Roche, and she is transferred to the intensive care unit. |
| June 2, 2001 | Roche dies as a result of progressive hypotension and multiorgan failure. |
| July 16, 2001 | An internal review committee at Johns Hopkins reports that Roche's death "was most likely the result of participation in the hexamethonium phase of the experiment." |
| October 11, 2001 | Johns Hopkins announces a financial settlement with the Roche family. |

fuse alveolar damage but established no specific etiologic diagnosis.⁶ An internal review committee concluded that although the cause will never be certain, "the inhaled hexamethonium phase of the experiment was either solely responsible for [her] illness or played an important contributory role."⁶

Dr. Alkis Togias, who directed the study, did not report the symptoms in the first subject to the IRB until Roche was hospitalized. The same day, he said he learned through an additional literature search that hexamethonium can have pulmonary toxic effects.⁶ Togias told the internal review committee that the adverse event in the first subject "was not an 'unexpected and serious adverse event,' because it was self-limited and required no treatment and therefore did not require immediate reporting." According to the committee's report, he thought the symptoms were related to an upper respiratory tract infection and did

not seriously consider the possibility of hexamethonium toxicity until later.⁶

THE INTERNAL INVESTIGATION

Roche's death led to four separate reviews of clinical research at Johns Hopkins (Table 3). These were conducted by internal and external review committees convened by the university,^{4,6} by the FDA,^{8,9} and by the Office for Human Research Protections.^{1,2} After Roche died, Johns Hopkins temporarily suspended all studies involving healthy volunteers. The internal review committee, which "had full access to all the information" was established "to give us a very frank look at all aspects of the issues involved," said Miller.

The internal review committee found that the "study had solid scientific rationale and was well designed" and that the use of hexamethonium "was scientifically sound."⁶ Nonetheless, it criticized the IRB for approving the study without requiring "more safety evidence for a non-FDA approved drug no longer in clinical use, and administered by a non-standard route." Togias was criticized for not reporting the symptoms in the first subject promptly, not delaying the exposure of the next subject to hexamethonium until the symptoms in the first subject had resolved, and not searching "more comprehensively" for previous reports that hexamethonium has pulmonary toxicity.⁶ "Our internal report was very critical of the fact that when patient number one had a cough, we did not take a variety of other steps that we should have," Miller said. "It was critical that we didn't rethink the protocol and look at every part of it again."

Togias declined to be interviewed. Through his attorney, Daniel A. Kracov of Washington, D.C., he expressed "deep concern and sorrow regarding the death."¹⁰ He stated that he "does not in any way intend to deny or diminish his own role in ensuring the safety of research subjects" but that "the responsibility for protection of patients in research activities is collective and systemic in nature, and investigators need clear and unambiguous guidance."¹⁰

A particularly contentious issue has been whether the IRB, as part of its efforts to obtain additional safety data, should have asked Togias to obtain a written opinion from the FDA on the need for an investigational new drug (IND) application for the use of inhaled hexamethonium. Such an application might have led to a more intensive review of hexamethonium, as well as the discovery of more information about its potential toxicity. The report of the internal review committee stated that the requirements were unclear. The committee acknowledged that the FDA had not responded in a timely fashion to a query from other investigators at Johns Hopkins about another substance. It concluded, however, that the IRB should have asked Togias "to obtain a written opinion from the FDA about the need for an IND [application] for inhaled hexamethonium for safety reasons."⁶

TABLE 3. REVIEW OF CLINICAL RESEARCH AT JOHNS HOPKINS MEDICAL INSTITUTIONS.

| DATE | EVENT |
|-------------------|--|
| June 28, 2001 | The Food and Drug Administration identifies problems in the implementation of the protocol for the study in which Ellen Roche died. |
| July 16, 2001 | An internal review committee at Johns Hopkins reports on Roche's death. |
| July 16-18, 2001 | The Office for Human Research Protections (OHRP) conducts an on-site evaluation of Roche's death and the system for protection of research subjects at Johns Hopkins. |
| July 19, 2001 | OHRP suspends all federally supported research projects at Johns Hopkins, as well as the federal agreement under which this research is conducted, known as a Multiple Project Assurance. The institutions affected include the Johns Hopkins University School of Medicine, the Johns Hopkins Hospital, and the Johns Hopkins Bayview Medical Center, but not the Johns Hopkins School of Public Health, which has a separate Multiple Project Assurance. |
| July 21, 2001 | Johns Hopkins submits a corrective plan. |
| July 22, 2001 | OHRP accepts the plan, lifts the suspension, and reinstates the Multiple Project Assurance, subject to major restrictions and conditions. |
| August 8, 2001 | An external review committee reports on Roche's death. |
| October 3, 2001 | OHRP responds to the first progress report submitted by Johns Hopkins and cites additional concerns. |
| December 12, 2001 | Johns Hopkins responds to OHRP's additional concerns. |
| January 2002 | The IRBs at Johns Hopkins complete a re-review of about 2600 clinical research protocols. |

THE FDA REVIEW

On June 28, about a month after Roche died, the FDA criticized Togias for failing "to submit an IND [application] prior to conducting [the] clinical investigation" with hexamethonium and for failing to inform potential subjects that "inhalation administration of hexamethonium was an experimental use of the drug."⁸ In an interview, Dr. David Lepay, senior adviser for clinical science at the FDA, said, "They did not specifically ask [the] FDA about this study or this compound." Lepay acknowledged, however, that the FDA had to do a better job of responding to queries and providing investigators with clear information about when IND applications are required. We need a "very tight and coordinated system to answer [these sorts of] queries properly and consistently," he said.

THE SUSPENSION OF FEDERALLY SUPPORTED RESEARCH

On July 16, five staff members from the Office for Human Research Protections, three outside consultants, and a representative from the FDA began an intensive on-site evaluation of the death of Ellen Roche and the system of protection for research subjects at

Johns Hopkins. On July 19, in a letter that was hand-delivered to Miller, the office detailed its conclusion that there was widespread lack of compliance with federal regulations and announced the suspension of "all Federally supported research projects at the covered institutions"¹ (Table 3).

The strongest criticism was the office's conclusion that the medical school's two IRBs failed to review new protocols properly and to provide a "substantive and meaningful" review of ongoing projects. "The minutes and audiotapes of IRB meetings, and our discussions with IRB members and administrators, indicate that no review takes place at convened meetings for most protocols undergoing initial review. Most protocols are neither individually presented nor discussed at a convened meeting of any IRB."¹

The office criticized the minutes of the IRBs for often failing "to document the basis for requiring changes in research" or discussion of "unresolved concerns following review by the IRB subcommittee." It noted that minutes "do not yet exist for 18 of the last 21 meetings dating back to October 2000."¹ In a subsequent letter, the office said that "not preparing minutes for nearly all meetings . . . for over 9 months is generally considered an unacceptable practice."²

On July 21, Johns Hopkins submitted a corrective plan.¹¹ The Office for Human Research Protections accepted it on July 22 — subject to restrictions, conditions, and ongoing monitoring — and the suspension was lifted.² University officials agreed to make many changes, including re-reviewing about 2600 protocols using procedures consistent with federal regulations. The net effect was that whereas some studies could continue, others remained suspended pending a re-review and approval.

The Office for Human Research Protections was particularly concerned that protocols had been extensively reviewed by subcommittees of the IRBs, but not by the full committees,^{1,2} a procedure that university officials defended.¹¹ An IRB should have members with a broad range of expertise, including members whose primary interests are in nonscientific areas; thus, federal officials viewed the larger group as the key review body. The office noted that "the site visit team did not find the use of executive subcommittees to be objectionable in and of itself" but "unanimously found that the executive subcommittee review process, which does not represent substantive and meaningful IRB review, was used to preempt review by the IRB at convened meetings for most research projects."²

THE EXTERNAL INVESTIGATION

Johns Hopkins also asked a five-member external review committee, chaired by Dr. Samuel Hellman of the University of Chicago, to report on Roche's death.⁴ The external review committee was more critical than the internal review committee. Togias, the principal

investigator, was criticized in its report for using an "inadequate" consent form that was "misleading in that it suggests more assurance of safety with hexamethonium than was known and it suggests that the agent is a medicine in use in anesthesia."⁴ He was also criticized because the "inhalant preparation was not sterile. It was not analyzed. It was not prepared in a fashion appropriate for medical use." The Asthma and Allergy Center was criticized for a "culture of possible coercion" with regard to the solicitation and recruitment of volunteers for its studies.

The external review committee's strongest criticisms, however, like those of the Office for Human Research Protections, were directed at the review of research protocols. In its report, the committee stated, "The protocol review process is grossly inadequate and it does not conform to current standards."⁴ The committee concluded that "the inadequacies of institutional oversight created an environment that increased the likelihood that this tragic episode would occur." It noted that "until June 2001 there had been only one IRB committee, meeting once every two weeks at [Bayview Medical Center], responsible for the review of 800 new proposals and the annual reviews resulting from them. We view this as grossly inadequate." The committee also stated, "Our interviews suggest that many people at Hopkins believe that oversight and regulatory processes are a barrier to research and are to be reduced to the minimum rather than their serving as an important safeguard."⁴

JOHNS HOPKINS'S RESPONSE

Johns Hopkins initially took a combative stance toward the Office for Human Research Protections and vigorously defended its practices. "We find it difficult to understand why a relatively new agency would take these draconian measures in an institution that has cared for thousands of people in clinical trials," Miller said in a statement that was broadcast on public television in July. "We have done clinical trials for over a hundred years here at Hopkins. We have had one death in all of these years in a human, healthy volunteer."¹²

Within weeks, however, officials at the medical center were emphasizing collaboration, not confrontation,¹³ and were talking about the need for a "real culture change" within the institution, according to Miller. This change is required to reject the view that "compliance inhibits creativity" and that regulations to protect research subjects "are just rules that get in our way." The specific changes included more resources; new procedures; more training for investigators and for IRB members, chairs, and staff; and the appointment of a vice dean for clinical investigation to oversee the process.

Spending on IRB personnel and activities has increased from about \$1 million to about \$2 million per

year, according to Miller. The number of review boards has increased to six: two at Bayview and four at the medical center's main campus. An independent board, the Western Institutional Review Board of Olympia, Washington, has also been retained to review selected new protocols, particularly multicenter studies of pharmaceuticals. The university is strengthening and standardizing its procedures for literature reviews and for the reporting of adverse events to the review boards. It now requires that investigators obtain a written response from the FDA with regard to the use of an unapproved substance in clinical research. The research pharmacy at Johns Hopkins has greater involvement in preparing such substances for clinical use and in quality control. In an addendum to its report, the external review committee said it was "very pleased and gratified" by these initiatives.¹⁴

An unsettled issue is the use of employees and students as healthy volunteers in research. Although he acknowledged the criticisms of the external review committee, Miller pointed out, "People work at these institutions oftentimes not just as a job, but because they really want to be involved and they want to contribute [to research]." The university has established a committee chaired by Ruth Faden, executive director of the Johns Hopkins Bioethics Institute, to make recommendations.

THE ONGOING REVIEW

In October, the Office for Human Research Protections said that Johns Hopkins had started to "implement substantive corrective actions," and acknowledged that "this is a major undertaking which has required extraordinary effort."¹⁵ The office also cited ongoing problems. For example, it noted that at a July 23 meeting, one of the IRBs had "reviewed and approved oncology clinical trials without a member with oncology experience and background being present. Indeed, the Chair at one point stated, 'I wish we had an oncologist here,' and another member stated, 'I think we need an oncologist.'"¹⁵

In response, Johns Hopkins said it had adopted procedures to avoid this problem and many others.¹⁶ "I am not saying we have solved every problem and addressed every issue," Miller said. "We are trying to make sure that the solution we have picked is not a Band-Aid solution and that it will stand the test of time."

THE FUTURE

The protection of research subjects is a shared responsibility of many individual people and groups. The safety of subjects is particularly dependent on the investigators who conduct the study and on their prompt recognition of potential adverse events. Investigators, however, conduct clinical research as part of a broader framework. Johns Hopkins has now committed itself

"to do the best job we can and to be responsive," said Dr. Michael J. Klag, the new vice dean for clinical investigation.

Johns Hopkins continues to be monitored by the Office for Human Research Protections. "They indicated they have work to do," said Koski, the director of the office. "They seem to be making a very concerted and diligent effort. They have stated their goal — they want to be a leader and model in the area [of protecting research subjects]. I think that is exactly where they should be."

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