FEDERAL EXPRESS

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William R. Brody, MD
President
The Johns Hopkins University
242 Garland Hall
3400 N. Charles Street
Baltimore, MD 21218-2691

Dear President Brody,

I have enclosed the report of the external review committee charged by you to review the circumstances surrounding the unfortunate death of a healthy volunteer. As you requested, we reviewed the findings of the internal review committee, the communications with the FDA and OHRP as well as interviewing the involved Johns Hopkins personnel. We hope that this report will prove to be of value in your considerations of this unfortunate matter in particular and of clinical research in general at Johns Hopkins.

Sincerely yours,

Samuel Hellman, MD, Chair

cc: Dr. Christine Cassel
Dr. Christine Stock
Dr. Alastair Wood
Dr. Warren Zapol

Report of
Johns Hopkins University External Review Committee

Mandate of the Committee

The Johns Hopkins University President, the Board of Trustees the Dean and CEO of Johns Hopkins Medicine have asked this external review committee to investigate the tragic death of a healthy volunteer in a study of the mechanisms of deep inspiration airway relaxation. In this capacity we have reviewed the internal review committee's report, the Investigational Review Board (IRB) material, other pertinent documents which were supplied to us, and have interviewed those involved in the study and its review. These include the Principal Investigator (PI) Alkis Togias, Internal Review Committee chair Lewis Becker, IRB chair Gary Briefel, Vice Dean for Research Chi Dang, and the administrative director of the IRBs at both Bayview and East Baltimore campuses, as well as Solbert Permutt the Principal Investigator of the overall grant of which this study was a part. Further, we have been asked to help strengthen the policies and procedures involved in clinical research at Johns Hopkins. We also hope that this review will be relevant to improving clinical research at other academic medical centers.

Brief Summary

The facts and chain of events as outlined in the internal committee report are not in dispute. Ms. Roche received inhaled substances in Dr. Togias' laboratory. Within 48 hours, she developed a cough, fever, rhinorea and myalgia. This illness progressed to ARDS and she died of this illness on June 2, 2001. This tragedy provides an opportunity to review the initiation, evaluation, conduct and oversight of clinical research at Hopkins at various levels: the PI, the preparation of pharmaceutical material, scientific internal peer review at the departmental or research center level, and the IRB. The committee has suggestions to strengthen all of these areas. In this committee's opinion, the inadequacies of institutional oversight created an environment that increased the likelihood that this tragic episode would occur.

Discussion

The Principal Investigator: Responsibilities and Action.

The PI of a clinical study should provide a well-designed study of an important hypothesis. S/he should seek input internally and externally to improve the scientific process and ensure safety. The PI should provide information on the scientific value of the proposal and the results of a literature search supporting and ensuring subjects' safety to his/her academic unit and later to the IRB. The PI is responsible for carefully monitoring the study for compliance with the approved protocol, for unexpected events, and to keep abreast of current scientific findings in the field. The PI must inform the IRB

of protocol changes and unexpected or serious events that occur during the course of the study.

Dr. Togias should have been expected to be responsible for understanding and adhering to the standards for research with human subjects. Even if the IRB was lax in their review of the proposal he should have identified certain shortcomings and corrected them. Dr. Togias should have exercised more meticulousness in the preparation of the inhalant to ensure its sterility and purity. While the elaborate process that the investigator put in place suggests sterility, it is in large part an ineffective ritual because the original substance and the instruments that were used to measure it out and determine pH were not themselves sterile. For example, performing the microfilter step under a non-sterile fume hood does not insure lack of contaminants, pyrogens or sterility.

Dr. Togias' review of the literature on inhaled hexamethonium was reasonable and consistent with most institutions' standards. His literature review did not identify hexamethonium pneumotoxicity. Subsequent literature review raised questions about the association of chronic hexamethonium administration with pulmonary toxicity. Even if these papers had been identified in advance, the association of pulmonary toxicity with an acute hexamethonium administration would have appeared weak. In all likelihood, the study would have gone forward, but would have included an informed consent that mentioned pulmonary toxicity as a remote risk. At our committee's meeting a number of those interviewed mentioned a rumor of an unreported previous possible instance of hexamethonium pulmonary toxicity in a volunteer who received it by inhalation. Confirmation of this case has been now reported in the press. Apparently a healthy volunteer in a 1978 asthma study at the University of California in San Francisco developed similar symptoms thought at the time to be an incidental viral pneumonia. Since the present study use of hexamethonium was based in large measure on that study, a description of this untoward reaction would have aborted the use of hexamethonium or changed the study design and informed consent. It surely would have caused the study to be aborted after the first patient developed pulmonary symptoms. Even without that information Dr. Togias should have reported the unexpected pulmonary toxicity observed in the first subject.

Hopkins should ensure that all investigators understand the definition of "serious or unexpected adverse events". Conventional study design would dictate that Dr. Togias stop further enrollment of subjects into the study until the first subject's symptoms resolved, and he would report the first subject's experience to the IRB. Even without knowledge of the California experience, the Principal Investigator should have had a very low threshold for reporting any pulmonary symptoms as unexpected adverse events especially when the study involved healthy volunteers. Dr. Togias still has some reservations as to the etiology of the pulmonary disease in the decedent. The conclusion that Ms Roche had a viral infection does not exclude a role of the inhalant as having a causative role. Indeed the symptoms of malaise, fever and muscle aches as well as pulmonary symptoms have been reported with other toxic inhalants and are not necessarily atypical of a toxic lung effect.

The preparation of hexamethonium used has now been found to be 97% pure. This was not known by the investigator before clinical use nor was the nature of the remaining 3%. Despite a letter in 1997 as well as repeated telephone requests the FDA did not respond to the question as to whether the use of a non-therapeutic inhalant required submitting an IND. If the substance had gone through the FDA process, had been procured as a pharmaceutical formulation from another country where it is used as a pharmaceutical or had been processed through a Hopkins investigational drug service, its degree of purity would have been known. Following the development of respiratory symptoms in the first subject the inhalant was changed. It was buffered and the nebulizer changed in order to increase the rate of delivery of hexamethonium. This latter change effectively increased the concentration of the agent presented to the lung and conceivably might have increased the toxicity. These changes should have been reported to the IRB.

Protocol Review: Departmental Review

Each department or research center should internally review every protocol that emanates from its members, including discussion of every protocol proposed for approval. Discussion at this level is important, as the departmental members' discussion of the protocol is likely to enhance the scientific value of the proposed study. The signature of the departmental (or research center's) research committee chair would assure the IRB that the institution's scientific experts in the field had examined the proposed study for scientific worth, valid study design, and safety. With the exception of the oncology division, it appears that most other Hopkins departments and research centers do not conduct formal internal protocol review that requires individual discussion of each proposal.

Protocol Review: IRB

The IRB is responsible for assessing the risk/benefit ratio of every study and to ensure that the subjects are cognizant of the risks of the study and of the scientific goals and values of the study. The IRB should perform this role through active, vigorous discussion by all members of the IRB, in which all constituencies are heard. The IRB is responsible for ensuring that the informed consent accurately reflects the risks and benefits to the subject, and scientific value of the study. The IRB should create written minutes of each meeting in a timely way. These minutes should be used to construct the letters of response to the investigators. OHRP regulations require that the IRB review every new proposal at a convened meeting of the committee with a quorum present. The Johns Hopkins IRB both at Bayview and at the East Baltimore campus conducts review in a different manner. Every member of the IRB is expected to read every application, amounting to approximately 800 new (non-expedited) protocols a year at the East Baltimore campus and 150 at the Bayview campus. Members are asked to fill out printed forms that solicit their comments or concerns, and a subcommittee of the full board then reviews these. At the subcommittee meeting the members present (a quorum is not required) sequentially review these comments and members present put their comments on a single piece of paper divided into eight 3x2 inch boxes each of which is expected to be adequate to contain their full comments. This seems to have ill-served Dr. Togias and

his subject since attendance, as judged by there being only four comments in the boxes, suggests only four members were present although this is unclear as no minutes are kept of these meetings. At the subcommittee meeting on 9/08/00 two of the four reviewers were concerned, one with the safety of the hexamethonium and the other with its sterility. This piece of paper is then used to formulate the letter to the investigator. The investigator's response is then sent to the full IRB, which if they are satisfied approve in a block fashion with a single vote encompassing a large number of protocols. Only if these comment sheets or the original proposal stimulate dialogue does the entire committee discuss the proposals. This occurs with only a few proposals per meeting and sometimes if no proposals are discussed the meeting is used for educational purposes with invited speakers. We are told – the minutes are not available – that there was no general discussion of Dr. Togias' proposal at a regular IRB committee meeting. We also noted that until June 2001 there was only one IRB committee, meeting once every two weeks at the East Baltimore site, responsible for the review of 800 new proposals and the annual reviews resulting from them. We view this as grossly inadequate.

The Hopkins IRB believes their system is superior to one requiring full discussion by the IRB of every proposal after primary and secondary reviewers summarize the proposal and their findings since at Hopkins everyone is expected to carefully review every proposal (150 and 800 respectively plus the annual reviews). We believe, to the contrary, the Hopkins system results in never having anyone with the explicit responsibility to conduct a thorough review of a specific proposal and then present it to the full committee. Although some of the important questions such as those related to inhalant preparation, hexamethonium toxicity and the informed consent form did surface, the investigator answered them without discussion by the full committee. While it cannot be determined whether this discussion, had it occurred, would have prevented the unfortunate outcome, we believe that had adherence to such a generally accepted review process occurred it would have increased the likelihood that the study or the informed consent would have been modified. Hopkins uses a mechanism of review that does not achieve the goals of open discussion for every proposal, which individually strengthens each proposal in scientific merit and subject safety. The importance of the diverse skills and experience of a large committee cannot be over emphasized.

The Hopkins system limits, by its design, active discussion by the full committee, and loses the expertise that committee members bring to the review. The absence of active discussion of every protocol from all constituencies runs the risk of missing valuable input from the diverse background of members of the IRB. Ideally there would be an interactive arm of the IRB that would enhance communication between the investigator and pharmacy to allow open discussion concerning protocol changes, or changes in drug preparation. There is no evidence that the investigator, his senior colleague, or the IRB considered the important role of drug tissue concentration on the role of pulmonary toxicity. This lack of discussion was a source of serious concern for our committee. Further, our committee was informed that there are no transcribed minutes from IRB meetings from the past 18 months. Clearly, these minutes can not have formed the basis of the letters sent to the investigator, to ensure that the response to the investigator reflects the discussions and deliberations of the IRB. In spite of the

previous review by OHRP whose conclusions mirrored many of our concerns, Johns Hopkins vigorously defended the current practices during our visit.

The Principal Investigator, who has spent his entire training and career at Hopkins, made several errors in the course of this research protocol. Most importantly, he depended on the judgement of the IRB about the adequacy of the consent form and the review of the entire process of this study. Since the IRB approved the protocol the investigator might be excused for believing that the consent form, protocol and procedures were ethically and scientifically acceptable. Institutional oversight of clinical research should be viewed not as a set of bureaucratic rules and obstructions, but rather we believe, that these processes are of considerable scientific value and should be an integral part of the clinical investigation process. Based on our visit and the response to the OHRP, it appears that Hopkins investigators believe that these processes are barriers and restrictions rather than opportunities to enhance the quality and safety of clinical investigation. It is critical that the culture of the institution change to support the value of these initiation, evaluation and oversight processes.

The Consent Form

The consent form is inadequate. It was not reviewed or available when the proposal was initially sent to IRB members and was apparently not seen at the initial executive committee meeting. Hexamethonium is referred to as a "medication" which "has been used as an anesthetic." However, in fact, it has not been licensed for medical use in the United States since 1972. The suggestion that it has a current therapeutic use would tend to give inappropriate reassurance to both the IRB and volunteers. The consent form contains no mention of potential risk for serious or unknown side effects. Surely if the California experience were known the agent would not have been used or at least the risk presented. Even so, given the limited use of the agent as an inhalant and especially at this dose and concentration, the consent form should have contained warning about the potential for unexpected serious events. The consent form is not meant to reassure the subject, quite the contrary, it is meant to raise every possible concern that might be relevant to the subject's participation. Thus, informed consent is especially required when there is no therapeutic intent when administered to healthy volunteers.

Pharmacological Review

In the current Hopkins system, so much is delegated to the Executive/Subcommittee, that insufficient attention is given to the formulation of the informed consent, preparation of the drug and consideration of the dose rate. In addition there was fundamentally insufficient pharmacologic review. The institution has a special responsibility for pharmacological review of novel substances, administered by novel routes, or with novel preparation. This should be a special responsibility of a pharmacologist on each IRB. Our committee found little evidence of rigorous pharmacological review in this instance. Further, the preparation of materials administrated to Ms Roche was not held to appropriate safety or purity standards. The

quality of the substance and the integrity of its preparation should be ensured by an institutional research pharmacy. This service should be mandatory and without financial barriers to its use. The institution should insist that all substances administered to humans be prepared to acceptable standards. This highlights the lack of a national, uniform and robust system for production and review of agents not officially approved as medications or given in a non-approved manner – specifically those for which there is no pharmaceutical sponsor. The lack of interaction with the FDA points to a national problem. The Hopkins investigators did not submit an IND and, in our opinion, the Hopkins procedure is not unusual among academic medical centers. In this case no answer was given to written and telephone requests by Hopkins to the FDA as to whether an IND was needed in such studies.

The committee recognizes the considerable importance that has come to mankind from the use of such compounds in humans. Because of that importance and the lack of clear FDA direction, we recommend the development of a system that involves all of the stakeholders, including academic medicine, FDA, NIH, OHRP, and others that ensures appropriate review of the use, preparation, and safety of such compounds. We recognize that such a system will not, nor should it be, identical to that review of drugs being developed for marketing as medications.

Culture of Possible Coercion

There appears to be an informal culture within the Asthma and Allergy Center that raises questions of subtle coercive pressures as well as a more casual approach to safety in research using normal volunteers. It was often the practice of the staff of the Center to participate in Center studies. The investigators carefully followed the restriction forbidding direct staff solicitation but signs were posted soliciting volunteers throughout the center and many staff members participated. In fact, a registry of former participants in trials was maintained as a source for recruitment to new studies. We were told that the majority of the registrants were Asthma Center staff. Ellen Roche herself had participated in a number of previous studies. As far as we can tell, not only were the volunteers compensated, but they also were given time off during the working day to participate. We believe that Hopkins should consider the possibility that these factors might be coercive and prohibit the participation of research subjects from the unit (broadly interpreted) in which he/she is employed.

Conclusion

This unfortunate incident highlights some defects that seem to be particular to Hopkins. While the tragic outcome may have been unavoidable the policies, practices and institutional culture made its occurrence more likely. The oversight of clinical research at Johns Hopkins may be different than at other academic medical centers, however, some of the issues that we identified apply to all. These issues include: special consideration for the protection of normal volunteers, preparation and administration of agents, responsibilities of individual investigators and an interactive oversight process that serves the best interest of the subject, investigation, institution, and the public.

Findings

Principal Investigator

Did not report an adverse event in the first patient.

Did an adequate but not outstanding toxicology literature review.

The Informed Consent 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. It does not mention its limited use as an inhalant.

Changed the protocol without notifying the IRB.

Inhalant preparation was not sterile. It was not analyzed. It was not prepared in a fashion appropriate for medical use.

Department/Research Center

There was no identifiable expert internal peer review or discussion at the level of the whole Asthma and Allergy Center.

Internal Review Board

The protocol review process is grossly inadequate and it does not conform to current standards. Most importantly, there is no required discussion by the whole IRB of each proposal. Indeed, there was no such discussion of Dr Togias' proposal. The minutes were not transcribed in a timely fashion so as to permit their use in preparing the letter to the PI. At the time of the writing of this report they are still not available.

Johns Hopkins University

There appears to be possible subtle coercion in the solicitation and recruitment of volunteers to the Asthma Center Studies. We did not investigate whether this is the case in other units of Johns Hopkins Medicine.

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.

Regulatory Agencies

There is an adversarial relationship with OHRP.

The FDA refused to answer whether an IND was required for a non-therapeutic inhalant.

Recommendations

Oversight of clinical research at Johns Hopkins must be significantly strengthened.

There should be an institutional requirement that expert internal review and discussion of every protocol occur at the department or research center level before a proposal is forwarded to the IRB.

The IRB must be reorganized and expanded as necessary so that each proposal has a full discussion at a meeting of the whole committee.

Special care must be taken to ensure the safety of volunteers in studies, which have no therapeutic potential.

There must be greater sensitivity to possible subtle coercion of volunteers. Participation by staff in studies within academic units (interpreted broadly) should be prohibited. Time spent in any study should be separated from regular working hours.

The quality of the substance and the integrity of the preparation should be ensured by an institutional research pharmacy or its equivalent.

Johns Hopkins University should encourage the Institute of Medicine, or other appropriate body, to convene representatives of academic medicine, the National Institutes of Health and the various regulatory and oversight agencies to collegially develop appropriate standards for non-pharmaceutical substances to be administered to humans.

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