John’s Hopkins’ IRB and Consent Violations in the Hexamethonium Study

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(Based on University of Arizona College of Medicine Bioethics Course for GCRC RSA activities)
Overview

- Human Subjects Research
- Historical context, Legislation, Regulations
- Recent violations and further Regulation
- Summary of the case
- Investigator
- Issues with the case
- Outcome
- Solutions
- Discussion/References
Definitions

- **Research**: A systematic investigation including research development, testing and evaluation designed to develop or contribute to generalizable knowledge
  - Quantitative or Qualitative

- **Human Subject**: A living individual about whom and investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information
Historical Context

- 1932 Tuskegee Syphilis Study
  - Miss Evers’ Boys (movie documentation)
- Nazi Medical Experiments
  - [http://www.auschwitz.dk/mengele.htm](http://www.auschwitz.dk/mengele.htm)
- Milgram’s Obedience to Authority Study
  - Study based on Holocaust events
  - “I was just following orders”
- Zimbardo’s Stanford Prison Study
  - [http://www.prisonexp.org/](http://www.prisonexp.org/) (Abu Ghraib?)
Legislation

- Belmont Report (1979)
  - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issues “Ethical Principles and Guidelines for the Protection of Human Subjects”
  - Expansion of the Nuremberg Code
  - Established 3 ethical principles
    - Respect for persons – informed consent
    - Beneficence – assessment of risks and benefits
    - Justice – subject selection
USA Federal Regulations

- 45CFR46 ("Common Rule")
  - Federal Policy for the Protection of Human Subjects
- 21CFR50 (Protection of Human Subjects)
  - FDA-regulated clinical investigations
- 21CFR56 (Institutional Review Boards)
  - Responsibility of IRBs that review FDA-regulated clinical investigations
Notable Violations

- May, 1999: Duke University failed to respond to requests for proper monitoring of human volunteer subjects. Federal regulators temporarily suspended research;
- September, 1999: 18-year-old Jesse Gelsinger died as a result of participating in a gene transfer trial at the University of Pennsylvania;
- These violations provoked further action by the government.
Government Actions

- The National Institutes of Health policy for data and safety monitoring, initially published in 1998\(^1\) and expanded in 2000\(^2\) stipulated that all clinical trials will require ongoing oversight and monitoring to ensure the safety of participants and the validity and integrity of data.

- May 17, 2001: National Center for Research Resources (NCRR) issued recommendations for General Clinical Research Centers (GCRCs) to assist investigators in developing and implementing Data and Safety Monitoring Plans (DSMPs) for research studies.

Overview: Johns-Hopkins Case

- NHLBI funded study: “Mechanisms of Deep Inspiration-Induced Airway Relaxation” (PI: Alkis G. Togias, MD)
- Objective: To study how the lungs of healthy people protect against asthma attacks
- 24-year-old Ellen Roche, 3rd subject, consented 4/16/01
  - Healthy volunteer; worked in the study laboratory
  - Included inhalation of hexamethonium (5/5/01)
  - Developed a cough within 24 hours
  - Hospitalized with fever, hypoxemia (5/9/01)
  - Died at Johns Hopkins Bayview Medical Center 6/2/01
- Office of Human Research Protections (OHRP) suspended 2,600 federally-funded protocols due to widespread safety lapses 7/19/01
Timeline of Events
(Steinbrook R. (2002). NEJM 346:717)

- 9/18/00 JH Bayview MC IRB approves NHLBI study
- 4/16/01 Ellen Roche, 24 y/o JH volunteer consented
- 4/23/01 S1 inhales ~1g hexamethonium
- 4/25/01 S1 reports mild SOB and dry cough
- 5/3/01 S1 has resolution of symptoms
- 5/4/01 S3 (Roche) inhales ~1g hexamethonium
- 5/5/01 Roche reports a dry cough
- 5/9/03 Roche admitted with fever, hypoxemia
  - IRB notified of AEs for Roche and S1; Study placed on hold
- 6/2/01 Roche dies of hypotension/multi-organ failure
- 7/16/01 IRB finds death associated with hexamethonium
- 10/11/01 JH settles with Roche family ($ undisclosed)
Investigator

- Alkis G. Togias, MD
- Associate Professor
  - Senior Laboratory Investigator
- Divisions of Clinical Immunology & Respiratory
  Johns Hopkins University School of Medicine
- Asthma and Allergy Center
- Interests
  - Lung mechanics in asthma
  - Asthma morbidity in inner city
  - Role of sensory nerves in airways hyperresponsiveness
- http://www.hopkins-allergy.org/info/faculty/fac-togias.html
Pre/Post Publication History

- September 2000 - August 2001
  - 10 publications (Medline search)
    - Respiratory, Allergy, Genetics journals, JAMA
    - Predominantly senior author

- September 2001 - Present
  - 9 publications (Medline search)
    - 1 AJRCCM
    - 1 Human Genetics
    - 3 Journal of Allergy and Clinical Immunology
    - 2 Clinical Experimental Allergy
    - 2 Ann Allergy Asthma Immunology
  - Author listings: 1 first; 3 senior
  - EM Roche (2nd author) 9/01
Hexamethonium

- Hexamethonium licensed in pill form by FDA for treatment of hypertension in 1950’s
  - Withdrawn in 1970’s after new laws required safety and effectiveness standards, not just safety standard
  - Medline search indicates study use in animals

- Hexamethonium & methacholine used in JH study to induce airway constriction (asthma) to study drugs’ effects during shallow & deep breathing

- Not intended as therapy for asthma, or benefit to healthy volunteers

FDA Preliminary Observations

- FDA inspectors’ report for comments from Dr. Togias
  - 1. Failure by the sponsor/clinical investigator to submit an IND to the FDA prior to conducting this clinical investigation, which involved the administration of hexamethonium bromide by inhalation to 3 human subjects
  - 2. Failure to report an unanticipated adverse event to the IRB (a persistent cough in the first subject, from 4/25-5/3)
  - 3. and 4. Failure to follow protocol and to report changes to the protocol, specifically by adding sodium bicarbonate to the hexamethonium to be administered by inhalation to the second and third subjects, thus altering the saline solution listed in the protocol
  - 5. Failure to obtain effective informed consents from subjects by failing to disclose that inhalation administration of hexamethonium was an experimental use of the drug
Human Subject Issues

- Vulnerability (Belmont: Respect)
  - Employee of JH Asthma/Allergy Center

- Subject recruitment (Belmont: Respect/? Justice)
  - Center flyer; employed by Dr. Togias

- Payment/reimbursement (Belmont: Respect)
  - $25 for phase 1; $60/visit for phase 2 ($365 total)

- Informed consent (Belmont: Beneficence)
  - Consent Deception: “Undisclosed Risks” (next slide)

- Risk/Benefit analysis (Belmont: Beneficence)
  - Young, healthy volunteer (induced asthma study)
  - Physical, psychological, social, economic implications
Consent: Deception

- Risks not disclosed in the consent (FDA 3/03):
  - “Inhalation of hexamethonium bromide was an experimental use of the drug.” Instead, the consent form referred to hexamethonium as “a medication”
  - The chemical grade used was labeled “for laboratory use only and not for drug use”
  - Risk of lung toxicity and death
  - Inhaled hexamethonium bromide “could result in a wide range of adverse events resulting from ganglionic blockade”
  - Unexpected AEs experienced by previous subjects

Review Committees

- Food and Drug Administration (FDA)
- Internal review committee convened by Johns Hopkins
- External review committee convened by Johns Hopkins
- Office for Human Research Protections (OHRP)
IRB: FDA Review

- June 28, 2001: FDA criticized Dr. Togias
  - failed to submit an IND prior to the investigation
  - failed to inform subjects that inhaled hexamethonium was an experimental use of the drug
- FDA acknowledged they had to do a better job of responding to IND queries, and providing investigators with information regarding need for IND

IRB: Internal Review Findings

- Study scientifically sound, but IRB criticized for approving drug no longer used clinically, and given via a non-standard route
- Togias criticized
  - not reporting 1st subject’s AE promptly
  - not delaying 2nd subject’s exposure until 1st resolved
  - not performing extensive search of pulmonary toxicity
- Contentious issue was written opinion from FDA about need for an IND for safety reasons
- Death attributed to inhalation phase of study
IRB: External Review Findings

- Chair: Dr. Samuel Hellman, University of Chicago
- 5-member committee
- More critical than Internal Review Committee
- PI criticized for inadequate consent
  - Suggested more assurance of safety than was known
  - Suggested drug is a medicine used in anesthesia
  - Inhalant preparation not sterile, analyzed, or prepared appropriately for medical use
- Asthma/Allergy Center criticized for coercion
  - Solicitation and recruitment of employee volunteers
**IRB: External Review & OHRP**

- **Strongest criticisms directed at protocol reviews**
  - “…process is grossly inadequate and it does not conform to current standards”
  - Inadequacies of oversight created environment that increased likelihood that tragic episode would occur
- **Until June 2001, only one IRB committee**
  - Met once every two weeks (at Bayview Medical Center)
  - Responsible for review of 800 new proposals and annual reviews resulting from them
- **Pervasive negative attitude re: oversight and regulations**
  - Barriers to research
  - Reduced to minimum rather than serve as safeguards
Suspension of Research

- July 16, 2001: 5 OHRP staff, 3 outside consultants, FDA representative did on-site evaluation into the death of Ellen Roche, and human subjects protection system
  - found widespread lack of compliance with regulations
- July 19, 2001: federally supported projects suspended
- Medical school’s 2 IRBs
  - failed to review new protocols properly
  - failed to provide adequate review of ongoing projects
- No review took place at convened meetings
  - from 10/00 on, no prepared minutes for nearly all meetings for over 9 months: unacceptable practice

Johns Hopkin’s Response

- Combative initially
  - Considered measures by OHRP, a new agency, draconian
  - 100 year history of trials, only 1 death
- Within weeks, emphasized collaboration
- Cited need for culture change
  - Rejected view that creativity inhibited by compliance
  - Regulations required to protect subjects, not rules that get in the way of research

Solutions

- Johns Hopkins spending on IRB personnel and activities increased from $1 million to $2 million/year
- Johns Hopkins increased number of review boards
  - 2 at Bayview; 4 at the medical center’s main campus
- Western IRB, WA retained, particularly for multicenter studies of pharmaceuticals ($1,500)
- Literature reviews strengthened & standardized
- Standards implemented for reporting AEs to review board
- Johns Hopkins research pharmacy involved in preparing substances for clinical use, and in QC
- Established committee on use of healthy volunteers

Review of Investigation
(Steinbrook R. (2002). NEJM 346:718)

- **6/28/01**  FDA finds protocol violations related to death
- **7/16/01**  Internal review reports on Roche’s death
- **7/16-18/01**  OHRP does on-site evaluation
- **7/19/01**  OHRP suspends federally-funded research, and federal agreement by which research is conducted (known as Multiple Project Assurance) (IRBs at JHSPH exempted)
- **7/21/01**  JH submits corrective plan
- **7/22/01**  OHRP accepts plan, lifts suspension, reinstates MPA, but with major restrictions and conditions
- **8/8/01**  External review reports on Roche’s death
- **10/3/01**  OHRP responds to 1st progress report, cites more concerns
- **12/12/01**  JH responds to OHRP’s additional concerns
- **1/02**  JH IRBs complete re-review of ~2,600 clinical protocols
FDA Warning Letter (3/31/03)

- A FDA Warning Letter sent to Dr. Togias listing the following specific federal safety violations:
  - “failure to submit an IND” (21 CFR 312.3)
  - “failure to provide adequate animal toxicity data”
  - “failure to provide a summary of previous human studies with hexamethonium”
  - “failure to provide dosing rationale”
  - “failure to describe procedures for identifying, collecting, and reporting adverse events”
  - “failure to notify and obtain IRB approval for changes in protocol, such as dosing conditions, formulation, and delivery system”
  - “failure to promptly report unanticipated problems, such as persistent cough and shortness of breath”

Current Status

- Johns Hopkins no longer allows employees to participate in research
- Johns Hopkins current IRB distribution
  - 8 Medical;
  - 4 Public Health;
  - 4 Arts, Sciences & Engineering;
  - Western in Washington State
- IRB staff has doubled and meets every two weeks
  - Lawyer on every IRB
  - Lay people, often clergy
  - More picky about use of normal volunteers
    - Cannot do BAL on healthy subjects
    - More difficult to do healthy pediatric subjects
RETRACTION

The Editors are retracting the Following Paper and Abstract:


The Dean for Faculty and Research Integrity at Harvard Medical School notified the Editor of SLEEP on February 10, 2009, that they completed a review of both publications and reached the conclusion that Robert B. Fogel, M.D., former Harvard Medical School Assistant Professor of Medicine at the Brigham and Women’s Hospital, falsified and fabricated data that were reported in the paper and the abstract. All other authors on the paper and on the abstract were found to be innocent of misconduct. Having been retracted based on falsified data, the paper and abstract should not be cited.
RETRACTION

At the Request of the Corresponding (First) Author, the Editors of SLEEP are Retracting the Following Paper and Erratum:


Dr. Guilleminault notified the Editor of SLEEP on October 5, 2009, requesting a retraction of both the publication above and the erratum to the publication due to the paper remaining incomplete and inaccurate in regard to its description of methodology. The article states that the patients in the study were enrolled in an Institutional Review Board-approved study protocol. However, the Stanford IRB neither reviewed nor approved the protocol. Dr. Guilleminault indicated that all the patients were covered by an Italian protocol that had approval from an Italian institution. The article and erratum also imply that the patients were referred to the Stanford Sleep Disorders Clinic, when in fact, patients were not treated at Stanford, but they were treated in Italy and France. The first author indicated that the co-authors agree with the retraction. Officials at Stanford University confirmed there was no formal charge or investigation of scientific misconduct. Having been retracted by the authors based on inaccurate and incomplete description of the methodology, the paper and erratum should not be cited.
Discussion:

Internal DSMB for high risk studies?

References