EMORY UNIVERSITY

Michael M.E. Johns, MD
Executive Vice President for Health Affairs
CEO, Robert W. Woodruff Health Sciences Center
Chairman of the Board, Emory Healthcare

September 29, 2006

Axel V. Wolff, MS, DVM
Division of Compliance Oversight
Office of Laboratory Animal Welfare (OLAW)
National Institutes of Health
RKL1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

Dear Dr. Wolff:

As Institutional Official for Emory University Institutional Animal Care and Use Committee (IACUC), and in accordance with applicable regulatory requirements, I am writing to report on the findings and recommendations from the IACUC's inquiry into the death of a pigtail macaque monkey at the Yerkes National Research Primate Center on June 23, 2006. The IACUC immediately launched an investigation into the death of this animal as soon as it was reported by Yerkes. Yerkes notified the USDA of this event, and the USDA also performed an investigation. Unfortunately, we did not provide OLAW notice coincident with that provided to USDA, as is our custom, and we deeply regret this oversight on our part. Accordingly, this letter contains a description of the circumstances surrounding this event and the results of the IACUC investigation into this matter. A copy of the IACUC committee's full report is attached hereto.

Study:

Protocol Title: Genetics of Neuropathogenic SIV Infection
IACUC Protocol Number: 139-2005Y
Sponsor: NIH
Principal Investigator: Francis Novembre, PhD

Description of Events:

On June 23rd, personnel working on Dr. Novembre's protocol were attempting to perform a time-sensitive MRI procedure on a pigtail macaque monkey (PWc-2). The personnel who normally performed this MRI procedures were on leave, and alternate personnel performed the procedure. During the procedure, the anesthetic apparatus was incorrectly connected to the monkey, resulting in his death. During the investigation, it was also determined that although isoflurane had been used as the anesthetic agent in accordance with veterinary preference, the PI had not filed a modification to his approved protocol for the use of this particular agent.

The Robert W. Woodruff Health Sciences Center
Emory University
1440 Clifton Road NE, Suite 400
Atlanta, Georgia 30322
An equal opportunity, affirmative action university

Tel 404.778.3500
Fax 404.778.3100
mmejohns@emory.edu

Upon being notified of PWc-2's death, the IACUC appointed a subcommittee to conduct an investigation. The subcommittee interviewed all parties involved and review pertinent documentation. The subcommittee's full report, including its findings and recommendations is attached.

Corrective Action:

Yerkes has already implemented the following corrective actions: (1) substitution of color coded tubing for clear tubing running from the oxygen and anesthetic gas cylinders; (2) development and implementation of additional training in anesthetic procedures for veterinary staff responsible for the oversight of scanning procedures; and (3) development of an anesthetic procedure checklist. In addition, the PI on the study in question modified his IACUC protocol to include isoflurane as a recommended anesthetic agent. Further corrective measures suggested by the IACUC are set forth in the attached report, a copy of which has been provided to Yerkes and to the USDA.

We believe that the corrective actions taken thus far, along with Yerkes assurances that it will implement the additional recommendations of the IACUC, will prevent the reoccurrence of this type of incident in the future. Please feel free to contact me or IACUC Chair, Dr. Sam Speck if you would like further information regarding this matter.

Sincerely,

Michael M. E. Johns, M.D.
Institutional Official, Emory University IACUC
Executive V.P. for Health Affairs &
CEO Woodruff Health Sciences Center

Attachment: IACUC Report

cc: David Stephens, PhD
Sam Speck, PhD
Kris West, J.D.
IACUC office

Emory University
Institutional Animal Care and Use Committee
1256 Briarcliff Rd.
Atlanta, GA 30322

MEMORANDUM

August 15, 2006

TO: **IACUC Committee**

FROM: **IACUC Ad Hoc Investigative Committee:**
Michael Huerkamp, DVM
NAME
NAME

SUBJECT: **Inquiry into Apparent Anesthesia-Related Death of Macaque Monkey at Yerkes Primate Center**

Per the request of the IACUC Executive Committee, an *ad hoc* investigative committee (the "Committee") was established to review events surrounding the apparent anesthesia related death of a macaque monkey at the Yerkes National Primate Research Center (Yerkes) on June 23, 2006. This investigation was brought at the request of and with the full cooperation of Yerkes. Members on the Committee are as follows: Michael Huerkamp, DVM, voting-IACUC member; NAME, voting-IACUC member; NAME *ex officio*, non-voting IACUC member. A report of the Committee's activities and findings are set forth herein for presentation to and consideration by the full IACUC Committee.

General Summary of Precipitating Event

Protocol: On June 23, 2006, four pigtailed macaque monkeys assigned to the IACUC protocol entitled *Genetics of Neuropathogenic SIV Infection* (#139-2005Y, Dr. A, PI) were scheduled for experimental procedures that included MRI scans. The procedures were to be done at a specified interval post-infection.

Location of Event: Events took place in Imaging Area at Yerkes. This Imaging Area consists of the following rooms/areas:

(a) I271: Preparation Room located across the hall from the suite in which imaging is actually done. The animal has an i.v. catheter inserted while it is in the Preparation Room and it also is intubated and connected to non-rebreathing circuit and anesthetic vaporizer in this room.
(b) I262: Console Room located across the hall from the Preparation Room and next to the room in which the MRI scanner is located. Computer equipment for MRI scanner is located in Console Room as is a second anesthesia vaporizer unit.
(c) I263: Imaging Room located across the hall from the Preparation Room and immediately adjacent to the Console Room. This room contains the MRI scanner and is the site of anesthesia delivery from the vaporizer located in I262.
(d) Gas Cylinder Area: This area is located immediately outside doorway into Preparation Room and across the hall from the Console Room and Imaging Room. By design, clear plastic tubing ran from oxygen tanks through ceiling into Console Room where they attached to an anesthesia vaporizer unit and then extended from the vaporizer unit through ceiling in the Console Room into the Imaging Room. This arrangement was used because the anesthesia vaporizer unit and gas tanks were ferrous and could not be located in Imaging Room with the MRI scanner. At the time of the event, some of the tanks were re-arranged and disordered including the tank supplying oxygen to the vaporizer in the Console Room and ultimately used to deliver anesthetic gas to subjects in the Imaging Room.

Background Information Regarding Imaging Area: The Imaging Area is part of the Core Imaging Center run by Yerkes to provide MRI and PET scans of research animals to investigators. The Director of the Center is Dr. G, Ph.D. The Imaging Area had been under repair because of a leak in an overhead water line that was reported by Dr. H to Yerkes facility management on June 12, 2006. By design, the ferrous water line appeared to have been inappropriately installed within the magnetic field of the unit and may have been distressed with leaks resulting from the magnetic pull. The room was out of commission until repairs were complete. The MRI magnet was turned off during this time. Re-energizing of magnet occurred from Tuesday, June 20 until late on the evening of Thursday, June 22. The scan of PWc-2 was the first procedure performed in the Imaging Room after the repairs.

Personnel Involved in Event: Scanning procedures were typically performed by Research Specialist Research Specialist A and/or Research Nurse Sr. Research Nurse. Dr. B, DVM had assisted in performing MRI scanning procedures, but largely had been an observer and had never done a procedure without assistance of Research Specialist A or Sr. Research Nurse until the day of the event. On day of the event, Research Specialist A was scheduled for leave and Sr. Research Nurse was assisting with a time-critical research procedure in an operating room in another area of the center. Dr. B, Dr. C, DVM and Research Specialist Research Specialist B were the personnel assigned and

present for preparation of PWc-2 for the scan. Dr. H was the imaging specialist assigned to operate the MRI scanner and was present for the anesthetic procedure in the Imaging Room prior to positioning of PWc-2 for scanning. After PWc-2 was moved from the Preparation Room (I271) to the Imaging Room (I263) and while initiating the anesthetic procedure in the Imaging Room, Dr. B requested the immediate assistance of Sr. Research Nurse. At the time that Dr. B requested assistance from Sr. Research Nurse, Sr. Research Nurse was located in aforementioned operating room. Sr. Research Nurse left the operating room to come to Imaging Area, and she was replaced in operating room by Dr. C, who left the Imaging Area.

General Summary of Problems that Occurred:

A. Problems Regarding Administration of Anesthetic:

Problems occurred in Imaging Room when PWc-2 was under anesthesia. Initially Dr. B had difficulty in (a) identifying correct tubing for oxygen in Imaging Room, (b) in attaching the anesthesia supply lines from the remote vaporizer into PWc-2's endotracheal tube, (c) and locating the proper oxygen supply tank. Dr. B called Sr. Research Nurse for assistance. After Sr. Research Nurse arrived, Dr. B requested that she locate the correct oxygen tank and turn on the oxygen. Immediately before or at about the time the gas was turned on by Sr. Research Nurse, Dr. B, assisted by Dr. H, had attached the anesthesia gas supply tube directly to the endotracheal tube with use of a connecter that may have been provided by Dr. H. Dr. B, Dr. H, Sr. Research Nurse and Research Specialist B did not initially notice that the tube through which the anesthesia gas was administered to PWc-2 was incorrectly attached. Specifically, the anesthetic supply tube was connected directly to the endotracheal tube in PWc-2, as opposed to being attached via an appropriate non-rebreathing apparatus that would have provided a way for gas pressure to be relieved and regulated. Once the gas was turned on, PWc-2 was noted to have distended air sacs. PWc-2 was quickly disconnected from the anesthesia gas tube, but there was no respiration and resuscitation attempts were not successful. PWc-2 was submitted to the pathology service for necropsy, which showed severe pulmonary emphysema. The death of PWc-2 was reported to the IACUC and to the USDA. USDA inspectors inspected the site on July 11, 2005 and issued an inspection report of the same date.

Scanning of the other three monkeys that were scheduled for that day took place on June 23 without further incident.

B. Problem Regarding Discrepancy between Anesthetic Agent that was Used During the Procedure and Anesthetic Agent Identified in Approved IACUC Protocol:

Isoflurane was used as the anesthetic agent during the scan of PWc-2. Propofol was the anesthetic agent that was specified for use in the original approved IACUC protocol. Although scans at the Imaging Center were originally performed using Propofol, on recommendation of the veterinary staff, the switch was made to Isoflurane. The PI, however, inadvertently did not file a modification to the protocol seeking the addition of

Isoflurane prior to the time that this anesthetic was put in use. Upon being made aware of this error, the PI filed the appropriate modification on July 11, 2006 and it was approved by the IACUC on July 15, 2006. (See *IACUC Chronology of Protocol* below.)

Persons Interviewed:

Name	Title	Role Re. Event	Interview Date
Research Specialist A	Lead Research Specialist	Specialist who was in typically in charge of preparing subjects for MRI imaging. One of two persons experienced in the use of the MRI anesthetic equipment. Out on scheduled leave on day of event.	July 17, 2006
Dr. F	Assoc. Director, Animal Resources	Supervisor over Drs. Dr. B & Dr. I. Out on scheduled leave on day of event.	August 8, 2006
Professor	Assoc. Director, Scientific Programs	Performed internal Yerkes review of event and assisted Committee in coordinating investigation.	July 17, 2006
Dr. K	Research Prof.	Co-PI on protocol in which PWc-2 was a subject.	August 8, 2006
Dr. C	Clinical Veterinarian	Present at time PWc-2 was prepared for MRI scan.	July 19, 2006
Research Specialist B	Research Specialist	Present at time PWc-2 was prepared for MRI scan.	July 19, 2006
Sr. Research Nurse	Sr. Research Nurse	One of two persons experienced in use of the anesthesia equipment in the MRI resource. Came to assist Dr.	July 17, 2006

		Dr. B in locating correct oxygen cylinders and turning on gas for PWc-2.	
Dr. B	Assoc. Veterinarian	Veterinarian in charge of preparing PWc-2 for MRI scan and administering anesthesia.	July 17, 2006
Dr. A	Assoc. Research Prof.	PI on protocol in which PWc-2 was enrolled.	July 19, 2006
Dr. I	Chief/Clinical Medicine, Veterinarian	Dr. Dr. B's supervisor. Came to imaging area while attempts were made to revive PWc-2.	July 17, 2006
Dr. H	Imaging Specialist	Imaging specialist present at time PWc-2 was to undergo MRI scan.	July 19, 2006

IACUC Chronology of Protocol

1. Protocol 139-2005Y (*Genetics of Neuropathogenic SIV Infection*, PI Dr. A, Ph.D.) was submitted to the IACUC as a three-year renewal on June 1, 2005. It was approved on July 6, 2005, and the current expiration date is July 6, 2008.

2. An initial modification to the protocol was submitted to the IACUC on December 20, 2005 and was sent out for designated review. This modification added a behavioral test to the cognitive battery that was initially proposed. The reviewers approved the modification and sent an approval letter to the PI on December 21, 2005.

3. A second modification to the protocol was submitted to the IACUC on May 24, 2006 and was sent out for review on June 7, 2006. This modification proposed the premedication of animals undergoing MRIs using Glycopyrrolate (0.004 to 0.008 mg/kg IM) primarily or Atropine (0.05 – 0.1 mg/kg/IM) as a back-up in case Glycopyrrolate is unavailable. This modification was only for animals that would be scanned for MRI studies and would be given only the day of the scan. The reviewers approved this modification and an approval letter was sent to the PI on June 26, 2006.

4. A third modification was submitted to the IACUC on July 11, 2006. This modification was a request to add Isoflurane as an anesthetic in macaques when they were undergoing MRI scanning. Isoflurane would be used at 1.0-2.0% continuous flow,

by inhalation (air flow through vaporizer). Research Specialist A was also added as a tech on this protocol. [NOTE: Research Specialist A was already included as approved staff within the Imaging Center Core facility.] This modification was reviewed and an approval letter was sent to the PI on July 15, 2006.

Documents Received and Reviewed and Attached Hereto

1. July 6, 2005 IACUC Application for Renewal of and Modification to Protocol 139-2005Y (ATTACHMENT 1)
2. July 6, 2005 Letter from IACUC to PI Dr. A Approving Renewal and Modification of Protocol 139-2005Y (ATTACHMENT 2)
3. March 6, 2006 Memo from Dr. E to Veterinary Department, Yerkes Re. Case Report on Death of 05QTX4, Feline (ATTACHMENT 3)
4. March 10, 2006 Memo from Research Specialist A to Veterinary Department, Yerkes Re. Case Report on Death of 05QTX4, Feline (ATTACHMENT 4)
5. March 16, 2006 Memo from Dr. L, DVM to Dr. F, DVM Assessing Anesthetic Related Death of 05QTX4, Feline (ATTACHMENT 5)
6. March 30, 2006 Email String Among Dr. F, DVM, Dr. G, Ph.D. and Dr. L, DVM Regarding Training Provided by Dr. L to MRI Center Staff Addressing Items Noted by Dr. L in her Assessment of Feline Anesthetic-Related Death (ATTACHMENT 6)
7. March 30, 2006 Training Log for Laboratory Animal Care and Use Training Provided by Yerkes Dept. of Veterinary Medicine for Department of Magnetic Resonance Research (Research Specialist A, Sr. Research Nurse and Dr. H noted as attendees) (ATTACHMENT 7)
8. April 18, 2006 Email from Dr. I, DVM to Dr. G (Director of Yerkes Imaging Center) Suspending Additional Imaging Using Felines Pending Evaluation of Anesthetic Problems and Related Anesthesia Record (ATTACHMENT 8)
9. April 20, 2006 Yerkes Necropsy Report on 05QQI3, Feline (ATTACHMENT 9)
10. May 24, 2006 Request to Modify a Previously Approved IACUC Protocol (ATTACHMENT 10)
11. May 26, 2006 Assessment Report for Dr. B from Anesthesiology Consultant Dr. N (ATTACHMENT 11)
12. June 23, 2006 Necropsy Report on PWc-2 from Yerkes Pathology Department (ATTACHMENT 12)
13. July 11, 2006 USDA Inspection Report from Inspection Conducted with regard to Events of June 23, 2006 (ATTACHMENT 13)
14. July 11, 2006 Request to Modify a Previously Approved IACUC Protocol (ATTACHMENT 14)
15. July 14 2006 Memorandum from Manager to Professor Entitled "Chronology of Events Related to Ceiling Leak of 3T Magnet Room" (ATTACHMENT 15)
16. July 14, 2006 Memo from E. Dr. I to Sr. Research Nurse, Dr. M, Dr. O, Dr. B, Dr. L and Dr. C re. Training for Anesthetic Support in Imaging Suite and Attached Training Checklist Entitled "Training: Anesthesia for Imaging Nonhuman Primate (MRI or PET) (ATTACHMENT 16)

17. July 17, 2006 Memorandum from Professor to Committee outlining events related to death of PWc-2 (ATTACHMENT 17)
18. August 14, 2006 Memo from David Knight to Kris West Re. IACUC Chronology of Protocol 139-2005Y (ATTACHMENT 18)

Committee Findings Based on Aforementioned Interviews and Documentation

Executive Summary: As a result of its investigation, the Committee believes that the death of PWc-2 under anesthesia in room I263 was the result of the convergence of inexperienced personnel using non-standard equipment without sufficient preparation and after unavailability of the scanning resource for an extended period of time, up to and including the time immediately before the start of PWc-2's scan. The scanner's downtime resulted in the delay of scans called for under the protocol in which PWc-2 was enrolled, and this delay contributed to a perception on the part of a few, but not all personnel involved, that there was urgency in proceeding with scan without further postponement. Distilled to its essence, the most qualified person to prepare the room for anesthesia and certify its readiness, Research Specialist A, was on leave and the person empowered to cancel the procedure on account of animal welfare concerns, Dr. B, did not.

In addition to the foregoing procedure errors, in reviewing the IACUC chronology of the protocol, the Committee noted the PI's failure to modify the protocol to include the use of Isoflurane, as well as the lengthy period of time it sometimes took for the IACUC to approve a protocol modification. The Committee believes that the PI's failure to file the modification was an inadvertent mistake, and that the use of Isoflurane as an anesthetic agent was the preference of the veterinary staff.

The Committee is cognizant of administrative delays at the IACUC, and is hopeful that the upcoming addition of an electronic protocol management system and new administrative staff will help to prevent such delays in the future.

Specific Findings

1. Facilities, Equipment and Anesthesia Set-Up

(a) The anesthesia gas tube was inappropriately connected to the endotracheal tube in PWc-2 in that no non-rebreathing apparatus was used. This inappropriate connection caused PWc-2's death due to high pressure over-inflation of the lungs.

(b) The Imaging Room had been out of operation for many days prior to the events of June 23, 2006 as a consequence of plumbing leaks possibly related to inadequate facility design. There was no complete re-check of all of the equipment that was to be used in the procedure involving PWc-2 before the procedure due in part to personnel inexperience, lack of access to the Imaging Room and perception on the part of some personnel involved that research requirements demanded that the scan take place on June 23.

(c) The set-up of the anesthesia system that is used in the Yerkes Imaging Area is inherently confusing because the vaporizer unit is located in a room that is separate from the MRI and the clear plastic tubes that run from the unit into the Imaging Room, one of which supplied anesthetic gas, were not clearly labeled. The oxygen, vaporizer and patient are located in three different areas, and make it difficult to monitor the connectivity of the apparatus. This set-up is used because the vaporizer is unit is not a non-ferrous unit, and cannot be located in the room with the MRI scanner.

(d) The anesthesia set-up in place at the Yerkes Imaging Center was developed in consultation with researchers who came to Yerkes from the University of Texas and the University of Massachusetts and who were expert in the research scanning of animals. The set-up of the anesthesia equipment was similar to that which they used in their research work at their prior institutions, but it was a non-standard arrangement for veterinary general anesthesia.

(e) Some anesthesia-related problems had occurred at the Imaging Center prior to the events of June 23, 2006. Specifically, there were two previous cat deaths associated with imaging, which were reported to IACUC. In response to these deaths, Yerkes suspended anesthesia procedures involving cats and hired a veterinary anesthesiologist as a consultant to provide a review and recommendations. The consultant provided a number of suggestions for improvement, as set forth in the report attached hereto.

2. Personnel

(a) Neither of the key personnel who typically perform the MRI scans was available to perform the scan on June 23, 2006. Sr. Research Nurse and Research Specialist A were the only persons thoroughly trained to perform the procedure and neither was available.

(b) Dr. B had been in training to provide veterinary support to the Imaging Center and she had participated as an observer in other procedures prior to the events of June 23. Nevertheless, Dr. B was the least experienced person in providing anesthesia service in support of the scans, and she had never done this procedure by herself prior to June 23. Dr. B's inhalant anesthesia experience was limited to the use of conventional anesthesia machines.

(c) Dr. B was the only person available on June 23, 2006 for the procedure. In discussing who would provide staffing for the performance of the scan prior to the procedure, Dr. B had indicated to her supervisor that she felt comfortable in performing the procedure.

(d) Dr. B indicated that she had tried to gain access to the Imaging Room prior to the procedure in order to check the equipment, but Imaging Area personnel were not available to provide access due to continuing repair work. It is possible that the re-arrangement of gas tanks may have occurred as a consequence of repair activity and actions of service personnel.

3. Policies and Procedures

(a) At the time of the event, there was no definitive SOP available describing how the anesthesia was to be provided.

(b) The wrong checklist for the anesthetic procedure was posted in the Preparation Room, and the veterinarian did not know where the correct one was located.

4. Perceptions of Personnel Involved as to Whether a Time-Critical Research Need Existed to Perform the Scan on June 23

(a) There were conflicting viewpoints and impressions among the personnel interviewed by the Committee as to whether or not it was critical to the research to perform the scan procedure that day. Some of the personnel involved in the procedure, including Dr. B, believed that its performance was on that day was critical to the study. Other personnel stated that they believed the procedure could have been postponed, including co-PI Dr. K, who stated that the researchers had considered abandoning the scan because of the repair problems with the MRI. Dr. K acknowledged, however, that this thought was never directly conveyed to Dr. B. The Committee found that the conflicting perceptions among the staff involved as to the timing of the scan's necessity for the success of the research project likely contributed to the decision to perform the procedure even though Research Specialist A, the person who normally led this procedure, was unavailable and the Imaging Room was unavailable for a pre-procedure check by a qualified person.

(b) The scan timing issue was compounded by the fact that a second unrelated time-sensitive procedure requiring specialized support from Sr. Research Nurse was occurring at the same time as the scanning procedure. The sequence of research events (anesthesia, CSF tap, blood collection) culminating in the MRI of PWc-2 may have been started prior to clearance of the Imaging Room for use further possibly increasing the sense of urgency regarding the completion of the scan and the associated stress.

(c) At the time that the event occurred, Dr. B was involved in management and performance issues that were completely unrelated to the event. When viewed through the lens of these unrelated matters, Dr. B may have perceived additional pressure to perform the procedure.

5. IACUC Issues

The investigator did not file a modification requesting to add Isoflurane as an anesthetic agent until after the agent had already been put into use. This was an oversight on the part of the investigator, and the veterinary staff preferred the use of Isoflurane.

6. Corrective Action Already taken by Yerkes

(a) After the feline anesthetic related deaths in the Imaging Center, Yerkes reported the event to the IACUC; performed an internal investigation into possible causes of the death and reported on this to the IACUC; retained an independent anesthesiology consultant to review the situation and make recommendations; suspended feline MRIs until the consultant's review was complete; and instituted additional training for Imaging Center staff.

(b) After the macaque anesthetic related death, Yerkes reported the event to the IACUC; performed an internal investigation into the event; substituted color coded tubing for some of the clear tubing that ran from gas cylinders; developed and provided additional training in anesthetic procedures for veterinary staff responsible for the oversight of scanning procedures; and developed an anesthetic procedure checklist for posting in the Preparation Room.

Committee Recommendations for Additional Corrective Action

1. Obtain a commercially available MRI-compatible non-ferrous anesthesia machine for use in MRI scans.
2. Permanently install oxygen ports in the wall of the scanner room such that oxygen hosing can be directly attached from the non-ferrous machine to a gas source in the wall.
3. Implement and post SOPs for anesthesia induction and maintenance.
4. Continue training and documentation of training of all personnel involved with scanning procedures.
5. The researchers conservatively placed the value of the deceased subject animal at approximately $14,000, based on an estimate of purchase cost, accumulated per diem and training investment. Given the high stakes of untoward anesthetic events associated with the lost value of animals and research, sanctions from regulatory authorities, and adverse public relations, Yerkes administrators and the veterinary staff should conduct a risk-to-benefit assessment of the use of non-standard anesthesia equipment in other areas of the center and in particular for "Act" species.