

KAISER PERMANENTE

Southern California Permanente

Medical Group

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Mary Beth Sweetland

Director, Research & Investigations Department

People for the Ethical Treatment of Animals

501 Front Street

Norfolk, VA 23510

Re: Stroke study on Baboons at Columbia University Dear Ms. Sweetland:

Thank you for the opportunity to review and critique the protocol of a study of neuroprotective agents and stroke in baboons conducted by E. Sander Connolly Jr., M.D. at Columbia University.

I am a clinical neurologist on staff at Kaiser Permanente in Riverside, California, as well as on the Clinical Teaching Staff at the University of Southern California Medical School. My undergraduate degree is from Brown University, my M.D. is from the University of Wisconsin, I completed a residency in Neurology at USC, and fellowship in Neuromuscular disease at the USC Neuromuscular Center. I am board certified in neurology and psychiatry, and have been practicing neurology for many years. Consequently I see many stroke patients, since stroke is an exceedingly common cause of morbidity and mortality.

There are three major areas of concern with this study. The first is inhumane treatment of the baboons. The protocol explicitly states that following surgical induction of ischemia animals will:

- a) remain intubated, sedated, and monitored for at least 18 hours
  - b) be maintained in the ICU with a minimum of three visits per day by a member of the neurosurgical team, to include assessment of function (Spetzler scale) and distress
  - c) Remain intubated until they can “self—care” (eat, maintain body posture, interact) or until euthanasia at 72 hours
  - d) Be observed by a neurosurgical team member at all times until extubated or euthanized
  - e) Animals will be maintained to 10 post-op days if they are self ventilatory, able to sit up, eat, be aware, and be in no distress (“animals cannot be in distress”).
- 1) “At any point animals in distress will be sacrificed”.

Post-Op records show a number of violations of these conditions.

- 1) Baboon B777 could not sit up or eat on post-op day 2, and still could not eat or move and was vomiting two days later. Since this animal was “slouched over”, could not move, could not eat, and was vomiting, he should have been kept intubated until able to self-care and / or euthanized because clearly in distress.
- 2) Baboon B754 was noted not to be moving “at all” on post-op day 2 or 3 (records unclear), and was found dead on post-op day 3. Here is another animal that was not at all self-caring who should have been under constant observation.
- 3) Baboon B739 was found dead, with no entries as to prior assessment.
- 4) Baboon B816 was found slumped over with its cheeks full of saliva on post—op day 2, found dead the following morning. Again, an animal unable to self-care not properly monitored.
- 5) Baboon B819 was unable to sit up, hold up its head, or swallow post-op day 2. He was left in cage unmonitored and found dead the next morning.
- 6) Baboon B778 exhibited progressively worse arm and head swelling, oozing from a forearm wound, skin sloughing and eventual splitting, and pressure necrosis of the paralyzed hand over a period of 7 days until finally he was euthanized.
- 7) Baboon B781 was reintubated for respiratory depression and unresponsiveness, but there are no further records after post-op day 2.

At least 6 of the 33 subjects, or 18%, clearly were not treated humanely with the monitoring promised in the protocol description .A number of these animals exhibited signs that clearly fall within the description of “distress” and yet were not euthanized. It is a judgement call as to whether all of these “stroked” animals were not in distress, given the hemiparesis, which precludes use of one side of the body. The authors quite cavalierly suggest these animals do fine after a stroke although they limp, cannot climb, cannot use the hemiparetic hand, and may be less interactive. This suggests to me a complete lack of sensitivity to the suffering caused by such a dramatic loss of function. Perhaps the authors of this study have never cared for stroke patients.

The second major concern is the repetitive nature of this study. There have been at least thirty different putative neuroprotective agents studied over the last twenty-five years, and none has proven to be of benefit in humans. There is still nothing of this nature that we can give to patients. Prevention is still of the essence, because there is no cure. The one agent that is useful is thrombolytic (tissue plasminogen activator), and that must be given within three hours after the onset of stroke symptoms. Herein lies part of the problem. Only a very small percentage of patients present to an emergency room within that time frame, so even if there were a neuroprotective agent, it will be of use only in a tiny minority of patients.

This leads to the third major concern, which is the lack of carry-over from animal studies to humans. For starters, the agents studied here and in other studies are given to the animals immediately after the vessels are occluded, hence at the very beginning of the ischemic damage. Unless patients have IV equipment in their homes, this can never be duplicated in a human population. Over 95% of stroke victims do not get to a hospital within 3 hours after the appearance of neurologic deficits, let alone immediately after a vessel is occluded. Secondly there are an immense number of substances which have demonstrated benefit for one cause or

another in animal studies , but have been completely useless in humans at best, or harmful at worst — in some cases disastrously so (witness thalidomide).

There are limited funds for research and this study is in my judgment unwarranted because of its repetitive nature. There is very little probability that this study or others like it will produce results that will help in the prevention or treatment of stroke in humans. Moreover, the inadequacy of animal supervision and care, and sloppy record-keeping exhibited by the experimental team under Dr.Connolly's supervision is an alarming example of failure to maintain minimal humane standards which I fear plagues much animal research.

Sincerely,

Ct / L/

Carol J. Van Petten, M.D.