

PENINSULA NEUROLOGICAL ASSOCIATES
A MEDICAL GROUP, INC.

January 20,2003

Mary Beth Sweetland

People for the Ethical Treatment of Animals

501 Front Street

Norfolk VA 23510

Re: Neuroprotection/stroke research on baboons at Columbia University

Dear Ms. Sweetland:

I appreciate the opportunity to review this protocol and to offer an opinion on its scientific merits and potential relevance to the care of patients with stroke.

My perspective in reviewing this research is that of a clinician, not a researcher. I received my M.D. from Stanford and served residencies in psychiatry at the University of California, San Francisco and in neurology at Stanford Medical Center. I am board certified in both specialties. For the past sixteen years I have practiced neurology in the San Francisco Bay area. I believe that I am in an excellent position to evaluate the potential clinical importance of research in the neurosciences since as a neurologist I am a prime consumer of this research. Decisions about which research findings are relevant to patient care are part of my job. I have no vested interest in this research project or any other. I should also indicate my bias about animal experimentation: my view is that it is unethical to use animals in research unless this is for a project which is highly likely to yield results which are of practical importance to the prevention or treatment of disease in humans; and then only if it is carried out humanely and in a way that precludes any significant suffering.

The purpose of this research is to test three potential neuroprotective agents in a baboon stroke model. The three therapies to be tested are dehydroascorbic acid, SCR 1sLe, and CD39. They have been shown to decrease infarct size and improve neurological outcome in other animal models. At least 60 baboons will be used. Strokes will be induced by surgically ligating both anterior cerebral arteries and the left internal carotid artery. Half the baboons will receive active treatment, the other half placebo. The benefit will be assessed by measuring infarct volume by MRI. The animals are then euthanized for histologic and immuno-histochemical studies.

The major point I wish to make is that this project is only the latest of a very large number of similar studies of potential neuroprotective agents done over the past twenty years. Over thirty such agents, which were found beneficial in animal models, were then tested in humans. Not a single one showed benefit in the human trials. In 1989 a review of stroke research during the previous decade (1) indicated that of 25 treatments that worked in animals, not one worked in human clinical trials. Updated reviews of this research published recently (2—10) tell the same

story. Over thirty agents have been subjected to human trials at this point, and still none has shown any benefit.

It is interesting to note that the authors of most of these reviews, after summarizing the uniform lack of benefit of neuroprotective agents in human stroke trials, go on to propose that the research should continue. They discuss a variety of methodological problems which, if solved, would permit benefit to be documented. I am not persuaded at all by these arguments.

The chief reason why neuroprotective agents work in animals but not humans is that in animal trials they are given before or immediately after the stroke is induced. In this project the treatments are given after the strokes are induced. In clinical neurological practice, this is obviously impossible due to the inevitable delays in patients presenting to emergency departments and the time necessary for evaluating them. We are currently using thrombolytic therapy (which is different from neuroprotective therapy) in patients with stroke if it can be given within three hours of the onset of the symptoms. Only a tiny percentage of patients (under 3% in my hospitals) qualify. Neuroprotective agents, such as the ones being studied here, require at least this time window, and typically a much shorter one, to demonstrate any benefit. Therefore they would be essentially useless for treatment of humans.

There are a number of other reasons why animal research on these agents translates poorly to humans. One is that less than 25% of human strokes are of the type that is being studied in animal models (11), the latter being induced by tying off one or more large cerebral arteries. This mechanism in fact is not applicable to the vast majority of human strokes. Most are due to emboli (traveling clots), microvascular disease (closure of microscopic arteries), or other mechanisms. Another reason, of course, is that although nonhuman primates are closer than other animals to humans in some respects, their nervous systems are still very different. Many human strokes, for example, involve language dysfunction (aphasia) or impairment of higher cortical functions, i.e. those not present or testable in nonhuman primates.

The fundamental question raised by this situation is: when should you call it quits? The scientists themselves will never do so. It is the people who fund the research who need to address the issue. Does the failure of two decades of research on neuroprotective agents suggest that this is a blind alley and that we should cut our losses and redirect the funding to more promising areas? Or does it mean, as the researchers claim, that it should be continued with various methodological improvements? When is the right time to give up? Now, never, or at some time in between?

If we had unlimited funding for biomedical research, and if this research did not use animals, I suppose “never” would be an acceptable answer. If researchers are willing to spend their careers on this, then why not? But this is not the case. Research funding is finite and in fact shrinking. Accordingly, every dollar devoted to this research is denied to many other areas which in my opinion are far more likely to yield clinically important information. In addition, from an ethical point of view, the use of animals for this research is indefensible, since its clinical promise is practically nil.

In addition to the above points about the scientific merit and clinical relevance of this research, I would also emphasize that the degree of suffering that would be experienced by these baboons is greater than average for laboratory animals. They are kept alive for either three or ten days after experiencing a major stroke and in a condition of profound disability. This is obviously as terrifying for animals as it is for humans unless one believes that animals are incapable of terror and other emotional distress. I should add that the degree of neurological deficit is

underestimated or understated in the protocol. Ligation of a carotid artery and both anterior cerebral arteries produces a complete paralysis on one side, not a “mild spastic limp.” Although the neurosurgery itself is presumably not painful, with general anesthesia, I also note that they are not extubated until the following day, meaning that they are awake, restrained, and with an endotracheal tube. I have experienced this myself and can report that it is extremely distressing and uncomfortable.

In summary, it is now clear that these attempts to demonstrate the benefit of neuroprotective agents in animal stroke models and then to confirm it in clinical trials in humans have been a dismal failure. Even when they have shown some benefit in the animal models, without exception they have not done so in subsequent human trials. The project under consideration here is only the latest in a long series of these experiments, going back at least two decades, and there is nothing about it to suggest that its outcome will be any different. Therefore the use of public funds and animals for this project are without justification. This project should be stopped along with all others in this category, current and future.

Sincerely,

Robert S. Hoffman, M.D.

References

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