stated that “The model was soon found to be unreliable, perhaps due to failure to document a lack of brain blood flow during the ischemic period and to nonstandardized postischemic supportive care, aspects of peri-ischemic handling that were not appreciated at this time.” In fact, the model itself was never unreliable, as the results in our first report showed.1 Indeed, in developing the model, we were able to ascertain very easily if cerebral perfusion occurred during ischemia by the sustained increase in intracranial pressure (ICP) after tourniquet inflation. The ability to produce complete global brain ischemia using this method was repeatedly verified by gamma camera scanning with technetium-99m and also, as mentioned in our initial report, by intra-arterial injection of xenon-133 with external scintillation detection to verify the lack of cerebral perfusion. Therefore, the reliability of the method of producing complete global brain ischemia was never in question. In fact, I would challenge the authors to give us the figures on the number of failed studies due to continued cerebral perfusion despite adequate control of arterial blood pressure and proper placement of the neck tourniquet. The main reasons for failure of complete ischemia in our experience were usually a ruptured tourniquet bladder or failure to adequately control the hypertensive response to ischemia. For these reasons, it is usually obvious if cerebral perfusion continues during ischemia, and the monitoring of cerebral perfusion during ischemia really does not make it a “better model.”

The precision required in the control of postischemic physiological variables, however, is something that we may not have adequately appreciated prior to 1977. Our primary objective in developing this model was to try to control very precisely all postischemic physiological variables to develop a standardized model of complete global brain ischemia in the primate with standardized postischemic support care. I believe we succeeded in accomplishing this goal. The degree of precision required in the control of physiological variables, however, we appreciated only later. In evaluating the effects of thiopental in ameliorating ischemic brain damage, we failed to control MAP in the first 5 minutes after ischemia equally between thiopental treated and control monkeys such that MAP at 5 minutes was higher in the thiopental-treated monkeys (about 90 mm Hg) compared with the untreated controls (about 80 mm Hg).2 Mean arterial pressure at 15 minutes after ischemia, however, was similar in both thiopental-treated and untreated control groups. Although it was never proven that the difference in MAP explained the beneficial effects of 90 mg/kg thiopental administered at 5 minutes after insult, many have assumed that this was the case. However, the controversial issue on the efficacy of barbiturates in complete global brain ischemia, although of great interest to me, is not the topic of discussion. Suffice it to say that with the recognition of the importance of brain temperature and arterial pressure after insult, we are all much more aware of the importance of precise control of all physiological variables before, during, and after ischemia.

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References

Response
We appreciate the comments of Dr. Nemoto regarding the history and evolution of the primate global brain ischemia model. As an originator of this model, Dr. Nemoto is uniquely qualified to provide an important perspective on the history and science behind the model’s development.1 We agree completely with Dr. Nemoto that incomplete ischemia will not adversely affect the reliability of this model if brain blood flow during ischemia is monitored and those animals that have persistent flow are eliminated from the study. We raised this issue only for emphasis of the importance of this aspect of the model. Dr. Nemoto has thoughtfully reminded us that evidence of incomplete ischemia was always sought when this model was used, and therefore incomplete ischemia is not a likely explanation for why this model demonstrated a highly beneficial effect of early postischemic barbiturate therapy on neurologic outcome, a result not in accordance with the results of later studies using this as well as other models.2–5 Dr. Nemoto agrees with the conventional viewpoint, which we reiterated in our discussion, that the importance of precise control of intraischemic and postischemic physiologic variables may not have been fully appreciated during early development of the model and is now thought to critically influence the model’s reliability.4,5,6 We applaud Dr. Nemoto’s continuing efforts to emphasize this fact and clarify important issues about the evolution and application of this highly relevant animal model of global brain ischemia developed by him and his group.

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References

Oxygen Content, Blood Viscosity, and Cerebral Blood Flow
In their recent article, Korosue and Heros1 convincingly demonstrate that the arterial oxygen content is the predominant determinant of cerebral blood flow (CBF), irrespective of the hematocrit level (see their Figure 2). A reduction in arterial oxygen content from 16 ml to 6 ml/100 ml led to an increase in CBF of around 160% irrespective of whether the hematocrit level was maintained or lowered. The authors reasonably conclude that in normal brain, arterial oxygen content is the major determinant of CBF. The situation in ischemia will of course be different. Here the vessels are maximally dilated, and only perfusion pressure and viscosity can affect CBF.

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Oxygen content, blood viscosity, and cerebral blood flow.

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Stroke. 1993;24:329-330
doi: 10.1161/01.STR.24.2.329

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