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Reply:

We thank Sherif and Plenk for their careful reading of our work and thoughtful comments. They gave us an occasion to read more recent material from their laboratory, which unfortunately could not be included in our review, which was limited to 1961–2008. We are also grateful to have the opportunity to elaborate on our thoughts and opinions, unhampered by the obligation of reserve and objectivity essential to a systematic review.

We do not believe (and never wrote) that "the lack of correlation between angiographic and pathohistologic results is a major limitation to the validity of experimental aneurysm studies" as the writers of this letter suggest. These discrepancies were reported by other authors (some in collaboration with the writers of the letter) working with the venous pouch rabbit aneurysm model, as an insightful discovery of the model; this has nothing to do with and does not question the validity of models in general. As we understand it, those authors were simply stating that angiographic evaluation of results was less reliable than microscopic examination of specimens. Furthermore, the items included in Table 4 were never meant to be "a critique of the rabbit venous-pouch bifurcation model," as the commentators believe, but a selection of key characteristics extracted, as faithfully and objectively as possible, from source articles on the various published models. Similarly, the drawbacks of the rabbit model, such as a lower aneurysm patency rate and higher morbidity, were reported as they appeared in the literature; at the time of our writing, we could not include the progress report of still unpublished work on the rabbit model from the present commentators.

There are many limitations to systematic reviews, 1 being the imperfect selection of articles, presumably relevant to the research question. Our failure to include their 2006 article[1] in the meta-analysis was perhaps a result of the chosen title, which suggested that the topic was a computer-quantification method, not an evaluation of animal models per se. Another limitation of systematic reviews, of course, is the impossibility of accurately summarizing hundreds of heterogeneous articles, each focusing on various topics, in a short article.

It seems possible to gain precision by using computerized quantification, as suggested by Sherif et al,[1] but only to the extent that expectations do not surpass physical constraints, such as the attenuation of platinum not allowing x-rays to penetrate a coil mass. We welcome any improvement in research methods and thank the authors for proposing new, perhaps more precise quantification methods of angiographic results. Time and experience (beyond 8 animals from 1 team) will tell how helpful such methods may prove to be. However, improved precision, no matter how welcome, is not our main concern with animal models. Too often animal models are used as tools specifically designed to meet marketing tactics or to please arbitrary bureaucratic requirements. In the long run, this cannot but undermine the credibility of experimental animal work.

We certainly believe in the importance of animal models to explore hypotheses and to prevent the premature introduction of new intravascular devices for the care of human beings. However, our main concern with animal experiments is not their validity but their interpretation. Attempts to make them say and conclude more than what they are entitled to are all too frequent. The description of certain pathologic features, such as "endothelialization" of devices or "increased fibrosis," are too hastily interpreted as signs of "improved healing," while no one has proved that such "meanings" are reliable indicators of better outcomes for our patients.

We insist that models should reproduce the problem that the research is directed toward solving or preventing, such as aneurysm recurrences, and that the minimal criterion for a useful positive study is the demonstration that the choice of 1 action leads to improved results, compared with an appropriate control. Since Claude Bernard, this classic, yet often overlooked, criterion of experimental evidence is much more important than surrogate pathologic end points, the potential meaning of which remain, in our young field, speculative. Models designed to solve the problem of aneurysm recurrences should compare the number of recurrences found in the experimental and control groups, not surrogate end points such as degree of endothelialization, number of inflammatory cells, and so forth.

In a similar vein, discussions regarding how similar, or different, animal models are compared with humans and human aneurysms, aside from the need to always acknowledge study limitations and the uncertain nature of our results, are usually biased in favor of the author's particular model and, in the end, are fruitless.

Finally, "hemodynamics may be the most important factor leading to recanalization" is a dogmatic statement. We believe this statement may be, at least in one sense, false and, in another sense, empty. Either way, as stated, it remains a purely conceptual statement, but this is not the place to expand on this difficulty. When we admit that mathematic models are used to simulate hemodynamics, when we recognize the diversity and complexity of aneurysmal flows, when we consider how fragmentary and speculative our current understanding is regarding the relationship between aneurysm flows and ruptures (as recent catastrophes with flow diverters have shown) and how uncertain our notions of rupture risks are, we must also admit that statements such as "hemodynamic similarities of true bifurcation aneurysm models to human aneurysms with high rupture risks" are, to say the least, shaky—if meaningful at all. We do believe in the importance of experimental models, but we must exercise restraint in our interpretations because models remain models.[2]

References

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2. Raymond J, Salazkin I, Gevry G, et al. **Interventional neuroradiology: the role of experimental models in scientific progress.** *AJNR Am J Neuroradiol* 2007;28:401–05

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