Animal Stroke Models
They Are Relevant to Human Disease
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In a recent editorial in Stroke,1 Wiebers, Adams, and Whisnant expressed their doubt about the relevance of drug studies in animal stroke models for development of therapy for the human disorder. They were particularly disturbed by the possibility that the use of animal models "may impede rather than advance scientific progress in the treatment of this disease." We want to debate this issue from our own perspective as physicians involved simultaneously in clinical trials and animal model studies. We believe that both types of studies are vitally important.

Most animal model studies are intended to investigate the disease process and not to evaluate methods of stroke management. We do not think it necessary to document the value of the use of animal models here, but such basic studies are fundamental to much of modern scientific medicine. The key question raised by Wiebers et al1 is whether pharmacologic studies in animal models have any relevance to treatment of the human condition.

We agree that the results of drug studies in animal models have not yet translated into effective therapy in humans, but we disagree with Dr. Wiebers' analysis of the value of such studies. First, drugs such as glutamate antagonists and tissue plasminogen activator, which have recently proven particularly effective in animal models, are only now beginning trial at the bedside. Animal studies of these drugs are providing valuable information about how best to use them and to manage their possible toxicity.2-7 Calcium channel blockers met with mixed success in animal models, and similar results are emerging from recent clinical trials. In some studies,6-13 dihydropyridines were found to increase cerebral blood flow and reduce infarct size if started prior to or very early after focal ischemia. Based on these results, nimodipine has been proven effective and approved for use for cerebral vasospasm after subarachnoid hemorrhage. Furthermore, it is premature to say that calcium channel blockers are ineffective for global ischemia after cardiac arrest or completed infarct if given very early.

Animal studies can be irrelevant to the clinical problems faced by physicians caring for stroke patients. There is clearly a need for investigators to increase the quality of both the design and conduct of animal studies, to adopt models that more closely approximate the clinical situation, and to test the reproducibility of their results. Wiebers and associates correctly point out that no stroke model exactly reproduces clinical stroke in humans. However, since there is no one representative type of human stroke and since the etiology of approximately one fourth of human strokes remains a mystery,14 it is inappropriate to discount all animal studies on this basis. In fact, this may be an argument for more rather than less animal experimentation. Most animal studies use young, healthy subjects, whereas stroke patients are usually elderly and have multiple problems. To compensate for the inherent weakness of simulations, it is best to prove that a form of therapy is effective in several different types of models and, if possible, to understand the mechanism of drug action. Drawing conclusions from animal studies is at best a complex task, and it will continue to be difficult to determine the usefulness of individual animal models for predicting success of treatments in stroke victims until at least one form of therapy is proven effective. Also, it is unethical to subject humans to risky experiments when relevant answers can be gained from animal studies.

Wiebers et al1 point out that claims of therapeutic efficacy have been made for numerous compounds based on studies conducted in animal models, but that "Among those compounds subjected to clinical trials, none has proven efficacious, nor have any of these agents come into general clinical use." The problem here lies with both basic and clinical investigators. Some animal studies have been inadequate, and conclusions have been based on inappropriate extrapolation from the results. Many of the best animal studies have shown that treatment will be ineffective if delayed for more than a few hours after the onset of ischemia. Yet only the NIH-sponsored Phase I study of tissue plasminogen activator for acute ischemic stroke,15 in which all patients were treated within 90 minutes of onset of symptoms, has...
really conformed to these limitations. This study proves that such "hyper-acute" care is possible for stroke victims.\textsuperscript{16} We are all well aware of the difficulties of attempting to treat strokes as acute emergencies, but cardiologists once faced and overcame similar obstacles in the care of cardiac arrest and myocardial infarction. All other clinical stroke trials to date have included patients treated many hours to days after the onset of ischemia. It appears that some of those responsible for designing clinical investigations are unfamiliar with the nuances of results in animals, or are motivated by considerations related to drug marketing or completing a study as rapidly as possible in the largest possible number of subjects. How else can one defend the design of clinical studies that enter patients up to 2 days after stroke onset\textsuperscript{17} when no credible animal study has indicated that any drug has neuronal protective properties at that time? It is not surprising, then, that the results of clinical trials have been disappointing. We suspect that much more time and money are wasted on premature or poorly designed clinical inquiries than on animal experiments.

Wiebers et al.\textsuperscript{1} "assert that the discrepancies between animal research observations and those in humans will not disappear by developing ways of improving clinical research." They conclude by stating that the "questions regarding the underlying pathophysiology and treatment of stroke" lie in advanced technology applied to humans. We think that these statements are partially true, but also incomplete. Our experience with positron emission tomography (PET) in acute stroke patients is that the technique is extremely cumbersome and expensive. Despite years of development, PET studies have been carried out in relatively few acute stroke patients in a very limited number of centers. This deficiency is unlikely to change appreciably soon. Magnetic resonance spectroscopy may be more accessible, but currently its spatial resolution is inadequate for detailed biochemical investigations in patients. Development of stroke care cannot be allowed to wait for further refinement of these techniques.

Imaging techniques suffer from an additional serious impediment for the study of cerebrovascular disease. Strokes in patients are highly variable in size and distribution. The consequent neurologic deficits are profound and only weakly correlated with the volume of the lesion.\textsuperscript{18} Even if a form of therapy is moderately effective, power analysis requires large numbers of subjects to prove the point by image analysis. We currently have no generally accepted specific treatments for stroke. Therefore, it would be a serious error to miss finding a moderately effective but useful drug because our therapeutic trials have insufficient statistical power. We can hope that a form of treatment will be discovered that is so beneficial that efficacy can be proven with more reasonable numbers of subjects. Yet, any therapy that good will be obvious at the bedside and expensive image analysis will not be required.

There is also considerable room for improvement of clinical assessment of patients. Neurologic examinations routinely used by most clinicians are quite useful for diagnosis but may be less accurate for the types of multicenter trials requiring assurances of unbiased and reproducible evaluations. Numerous rating scales for assessment of stroke patients have been devised, but all have limitations and very few have been tested for validity and reliability.\textsuperscript{19–21} Most scales are based on the clinical neurologic exam rather than on functional outcome, which may help with diagnosis or prognosis but does not test whether the drug treatment is effective. The new field of clinimetrics\textsuperscript{22} is making progress in establishing the validity and usefulness of rating methods, but much is left to do.

Finally, communication among researchers is also a problem. Investigators who have experience with both clinical and laboratory investigations of stroke are quite uncommon. In fact, only a few institutions do both types of research. Clinicians and basic scientists generally do not attend the same national and international meetings but even when they do, they usually have separate sessions. A forum that regularly brings together clinical and basic scientists to discuss their mutual problems with an eye to helping one another would be highly useful. At present, however, it is as difficult for many basic scientists to appreciate the practical problems faced by clinical investigators as it is for clinicians to understand the technical challenges confronting basic scientists.

Clearly, the clinical investigator plays the pivotal role in development of stroke therapy, and his task is becoming increasingly complex. The clinical investigator must reconcile laboratory results with clinical reality, make an unbiased assessment of a drug's applicability to human stroke patients, and design and conduct a trial that is likely to evaluate the treatment with validity. Because of this absolute need for laboratory and clinical interaction, we are concerned that the value of animal studies is now being questioned. We believe this is especially inappropriate at a time when clinical trials can finally be scientifically conceived on the basis of relevant laboratory studies. Animal investigators and clinical investigators are working toward a common goal. Both groups must rely on each other in planning and analyzing their work.

References

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/21/7/981.citation