

Clinical Issues in Animal Models of Stroke and Rehabilitation

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Stroke remains the third greatest killer in the United States. Patients surviving a stroke often have significant impairment and disability. During the weeks to months after a stroke, most patients show some improvement in clinical status, but the extent of recovery is often insufficient. As a result, stroke remains the leading cause of adult disability in the United States (Gresham et al. 1995)

Since the 1970s, an increased number of clinical trials have focused on new therapies for acute stroke (Uchino et al. 2001). Although in many cases animal models have shown efficacy in improving outcome, very few human trials have documented clinical benefit, and the benefit has generally been in relation to hyperacute thrombolysis. A number of authors have explored the basis for these outcomes of clinical trials in acute stroke (del Zoppo 1995; Fisher and Ratan 2003; Grotta 1995; RCTEAST 2001), and future trials will likely take advantage of these lessons.

Thus, development of new therapeutic options is still needed for a common and devastating medical condition. This need is compounded by the fact that nationally, more than 98% of patients with acute stroke are not accessing currently approved hyperacute thrombolytic options (Reed et al. 2001). Many of the articles in this issue of *ILAR Journal* describe new approaches for understanding and improving outcome after stroke. In this context, several clinical issues are worth emphasizing.

Patients with acute stroke are heterogeneous. Premorbid neurological function is variable, multiple stroke risk factors and concomitant diseases are often present, the site of the lesions is very variable, and the average age in the United States is approximately 71 yr with high variance. A number of pathophysiological processes can produce an acute stroke, such as low flow, embolism, or hemorrhage. However, many animal studies introduce experimental infarcts into only one location (mostly cortical) into homogeneous, young, healthy animals in an identical way. Increased attention to clinical heterogeneity in preclinical studies may yield results that more consistently extrapolate to the human condition.

In many stroke studies—experimental animal and human—the time period between early intervention (typically hours to days after stroke) and assessment of primary outcome (usually 3 mo after stroke) is a physiological black

box. Additional behavioral measures may be tabulated during this interim, but often little more is measured or even considered. However, the events during this period of restoration may have substantial impact on final outcome. For example, a distinct pharmacology characterizes the events of this clinical period (Gladstone and Black 2000). In experimental animal studies, specific chemical insults introduced during this period worsen neurological status; the limited data available on this topic in humans are concordant but inconclusive (Feeney et al. 1982; Goldstein 1998; Lazar et al. 2002). Further studies are needed to increase our understanding of this phenomenon.

The pharmacology of recovery may also be an avenue for improving outcome after stroke. Several new therapeutic approaches are described herein. Growth factors, cellular therapies, catechol-related compounds, and other small molecules have been found to improve behavioral outcome in experimental animal stroke models, often with a time window measured in days to weeks. Pilot human studies are promising thus far. Human brain mapping studies are beginning to yield data on the physiology of recovery that may soon prove useful for guiding restorative treatment protocols (Cramer et al. 2002; Green et al. 1999; Marshall et al. 2000; Nelles et al. 1999; Traversa et al. 1997). More recently, animal models have been introduced that allow non-invasive brain mapping of the events related to recovery after stroke (Dijkhuizen et al. 2003).

The role of physiotherapy in clinical practice is becoming more firmly established. Studies using animal models have described benefit from increased motor activity after experimental infarct (Jones et al. 1999; Nudo et al. 1996). Evidence in human studies increasingly suggests that high levels of physiotherapy after stroke may be associated with improved clinical outcome (Kwakkel et al. 1999), although it remains unclear whether one school of therapeutic approach is of greater or lesser efficacy than the others.

Increased environmental complexity has been shown in normal animals and in animal models of stroke to affect brain and behavior favorably (Johansson and Belichenko 2002; Kempermann et al. 1997; Kolb and Gibb 1991). However, there has been limited translation of this work into the human experience.

A range of other clinical considerations commonly affect recovery after stroke in human patients but are not commonly addressed in animal models. The clinical course after stroke in humans commonly includes a number of complications. A majority of human patients are diagnosed

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with complications such as deep venous thrombosis, pulmonary embolism, aspiration pneumonia, urinary tract infection, or cardiac ischemia during the course of recovery from stroke (Dromerick and Reding 1994; Kalra et al. 1995). Careful medical therapy during the poststroke rehabilitation phase can reduce the incidence of these events and thereby support behavioral recovery. These clinical accompaniments are not usually incorporated into animal models of stroke and stroke recovery. Cognitive deficits after stroke are common and often devastating. Recent work with animal models has begun to address some of these issues, as described herein. Depression is present in 30 to 40% of stroke patients, and its presence may correlate with poorer outcome (Paolucci et al. 2001). Increased attention in animal models to measures that correspond to depression might increase the generalization of results to stroke recovery in humans. From a broader perspective, the animal behaviors used to assess whether a new treatment improves outcome after experimental infarct sometimes have only an indirect or limited relationship with clinical endpoints of interest to human patients.

Clearly, it will be necessary to address a large number of issues to understand the complex changes that take place in the central nervous system after stroke and to devise means to offer treatments for stroke survivors with permanent disability. The strongest bridges between animal models and the human condition after an acute stroke may be built on consideration of numerous social, physical, psychiatric, pharmacological, and medical morbidity issues. The recent development of additional animal models of stroke and the more recent increased focus on recovery models have resulted in substantial progress toward these ends. The articles contained within this issue are part of a body of research that will pave the way to a new set of tools to promote poststroke recovery.

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