EDITORIAL

NEUROPROTECTION

This initial issue of *NeuroRx*[®] is devoted to the topic of neuroprotection, a concept based upon observations that biochemically induced neural cell death appears to play an essential role in virtually all forms of acute and chronic neurodegeneration. Initially proposed at the end of the 19th century, the concept of secondary or delayed tissue damage received strong experimental support in the 1960s and 1970s from animal studies of spinal cord injury and cerebral ischemia. Many of the early studies focused on the potential pathophysiological roles of released free radicals, inflammatory factors, or neurotransmitters/neuromodulators, and neuroprotective effects were reported using inhibitors of the factors. Although beneficial actions were not uniformly replicated across laboratories or models, several treatments in experimental spinal cord injury were duplicated across leading laboratories and led to clinical trials. In NASCIS II, both methylprednisolone and naloxone were reported to show significant, albeit modest, neuroprotective effects in patients with incomplete spinal cord injury, providing the first clinical proof-of-principle support for the concept of secondary injury and neuroprotection. Subsequently, early treatment with tissue plasminogen activator was shown to improve outcome in ischemic stroke patients.

During the past 6 years there have been major advances in our understanding of cell death. Apoptosis has been demonstrated in acute and chronic neurodegenerative disorders, both in animals and humans. Moreover, key molecular mechanisms of apoptotic cell death have been delineated, thereby expanding the opportunities for developing effective neuroprotective treatments. Yet, despite these promising developments and the clear demonstration of neuroprotection in animal models, clinical studies of neuroprotection have largely failed to show clear benefit. The present issue of *NeuroRx*[®] reviews current concepts of neural cell death and neuroprotection, while providing comprehensive analyses of recent clinical trials in acute and chronic neurodegenerative disorders. Authors also provide critiques of clinical trial failures and propose modifications to improve the likelihood of successful future trials.

The first three papers in this issue deal with molecular mechanisms of cell death and endogenous neuroprotection. Yakovlev and Faden review the complexity of cell death phenotypes and the molecular mechanisms involved; they describe such newly emerging concepts as aponecrosis, paraptosis, programmed necrotic cell death,

and caspase-independent apoptosis, and suggest how such observations may lead to novel treatment approaches. Sugawara et al. review cell death and survival pathways at the molecular level and their implications for neuroprotection in ischemia. Sharp et al. examine certain molecular mechanisms underlying neuroprotection afforded by ischemic pre-conditioning and the implications for treatment.

The next four papers focus on neuroprotection in acute neurodegeneration including stroke, head injury, and spinal cord injury. Chang and colleagues review the successes and failures of neuroprotective treatments in ischemic stroke, emphasizing the methodological problems and lessons learned. Labiche and Grotta review all major clinical trials examining cytoprotection in stroke, which also serves to provide a comprehensive examination of the status of clinical neuroprotection treatment approaches more broadly. Tolias and Bullock summarize basic approaches to neuroprotection in head injury and provide a critical analysis of clinical trials completed to date; emphasis is on lessons learned from failed trials and implications for future trial design. Hall and Springer review pre-clinical and clinical studies of neuroprotection in spinal cord injury; they discuss some of the major controversies and suggest new treatment approaches based upon emerging concepts of secondary injury and cell death.

The following two papers deal with newer treatment approaches. Lipton reviews the concept of open-channel blockers of the NMDA receptor and summarizes recent clinical experience using Memantine in the treatment of dementia. Mattson et al. critically assess neuroprotective treatments involving dietary restriction or behavioral manipulations, based upon the emerging literature on endogenous neuroprotective stress responses.

Papers by Longo and Massa, Kim and Cha, and Fahn and Sulzer critically review the rapidly evolving literature on neuroprotection in chronic neurodegenerative disorders. Citing experimental and clinical studies, they review both clinical trials and future potential neurotherapeutic approaches. Koretsky describes recent and newly developing strategies for the use of MRI to study nervous system injury and the potential application of such techniques to evaluate neuroprotective treatments. Finally, Gallen critically assesses strategies for the development of neuroprotective agents and proposes new

approaches to more efficiently and effectively produce and evaluate such drugs.

Together, these 14 papers are intended to present a state-of-the-art review of the field of neuroprotection and its potential application for the treatment of acute and chronic neurodegenerative disorders. It is hoped that this

issue may serve as a useful reference source for both scientists and practitioners interested in the treatment of disorders of the nervous system.

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Guest Editor