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Mini-Review—The Rabies Virus

Pathogenesis of rabies—Editorial

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Although rabies is an ancient disease and we now have the ability to prevent most human cases, many people continue to die of rabies in the developing world and the years of life lost rank rabies seventh among all infectious diseases (Coleman, 2004). Treatment of human rabies has been futile except in a few cases when rabies vaccine was administered prior to the onset of clinical disease (Jackson, 2002). It is certain that improvements in the management of patients with rabies will require a better understanding of the pathogenesis of disease (Jackson *et al*, 2003). In October 2003, a conference was held at The Wistar Institute in Philadelphia, Pennsylvania, in which many of the active rabies pathogenesis researchers from North America, Europe, and Asia participated. Frederick Murphy, who was a pioneer of rabies pathogenesis studies, presented a review of historical developments in the field. Ten additional topics were discussed by the participants. In this issue of the *Journal of NeuroVirology*, five mini-reviews highlight some of the important topics that were discussed at this conference.

Monique Lafon (2005) addresses the role of the three putative rabies virus receptors, including the nicotinic acetylcholine receptor, the neural cell adhesion molecule, and the p75 neurotrophin receptor. Little is known of their role *in vivo*, although Lafon suggests that there may be biological importance of binding of rabies virus to the nicotinic acetylcholine receptor at the postsynaptic membrane of the neuromuscular junction and to the neural cell adhesion molecule at the presynaptic membrane of the neuromuscular junction, whereas the p75 neurotrophin receptor may have a role in facilitating retrograde axonal transport along axons.

In natural rabies, neuronal death is not usually prominent, which has led to the idea that neuronal dysfunction must be responsible for the severe clinical disease. Fu and Jackson (2005) review experimental studies performed to understand the bases of this dysfunction. Neuronal death, usually occurring via an apoptotic mechanism, is also observed under particular experimental circumstances, and the potential significance of this phenomenon is discussed.

Reverse genetics technology has provided tools to make direct genetic manipulation of the rabies virus genome possible. Schnell *et al* (2005) review how this technology can be applied to increase our understanding of rabies pathogenesis and also in the development of novel rabies vaccines.

Hooper (2005) discusses the complex interactions of rabies virus and the immune system, and he shows how immune responses may be either protective or immunopathological under different circumstances. Finally, Hemachudha *et al* (2005) address potential mechanisms for the two clinical forms of rabies: encephalitic (furious) and paralytic (dumb). This is a difficult topic to study, and we are just beginning to have an understanding of the many factors that might be involved in the clinical expression of the disease, which likely involves immune responses and the peripheral nervous system.

Unfortunately, when therapies become available to prevent a disease, attention often shifts to other conditions. The five mini-reviews in this issue of the Journal will confirm that rabies pathogenesis is both complex and interesting. Although research in this area requires much investigation, study in the field continues to move forward and our understanding of this ancient disease broadens.

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