CHAPTER V

DISCUSSION AND CONCLUSION

The terms furious and paralysis are used to emphasize that the symptoms and signs are indicative of cerebral involvement in the former and of spinal cord and/or peripheral nerve involvement in the latter. However, deranged mental state, as seen in the case of furious rabies, may be evident in paralytic rabies, but to a much lesser degree. The average survival time is shorter in furious group (5 days vs. 11.5 days in paralytic group).(85) During the last 24 hours when coma supervenes, paralysis is evident in all patients regardless of clinical types. At this stage, it is not possible to determine the exact neuroanatomical basis for weakness.

Analysis of regional distribution of rabies virus antigen in the CNS of human rabies patients of both forms revealed similar pattern.(83) The site of the infecting bites in these patients did not have any influence on the distribution of antigen. Rabies virus antigen preferentially localizes in the spinal cord and brainstem and midline structures of thalamus, basal ganglia if the survival period is less than 7 days. Similar findings were found in MRI study of which spinal cord, brainstem and midline structures were involved predominantly in both forms. Based on above-mentioned evidence, paralysis should be the presenting and major manifestations in all rabies patients. However, this has been proven otherwise suggesting indirect mechanism(s) rather than direct effect of rabies virus infection in dictating clinical outcome.

Recently, it has been shown that limb weakness in paralytic rabies patient is explained by peripheral nerve dysfunction based on serial electrophysiolgic examination prior to coma stage (Mitrabhakdi, et al, in press). In case of non comatose furious rabies patients, anterior horn cell dysfunction in the

spinal cord can be observed. These patients do not exhibit any demonstrable weakness of the arms and legs.

In vivo and *in viro* experiments showed that spinal cord motoneurons resist to cytolysis and apoptosis.(50) Apoptosis of spinal cord motoneurons is influenced by other types of cell or neuron and is not affected by a physiological surface contact between motoneurons and others.

In this study, absence of MOMP evidence in the spinal cord of rabies patients was in accord with studied of Celine G. and Patrice C.(50) and can explain the lack of paralysis due to spinal cord dysfunction in both forms of rabies patients. Although there was more inflammation in the spinal cord in furious rabies(9,85) (Mitrabhakdi, et al, in press) this seems unrelated to weakness and may appear later in the disease course. Cytochrome C is a major inducer of apoptosis by activating caspase cascades 9 and 3 which eventually lead to cellular death. Widespread TUNEL staining in all CNS regions is not surprising since all patients succumbed to death by cardiovascular collapse and hypoxia and might be mediated by other arms of apoptosis pathways. Our study, therefore, may explain why spinal cord in rabies patients is not vulnerable to the deleterious effect of rabies virus infection. Moreover, in some patients who died shortly, brainstem also lacks of MOMP evidence. This may also suggest why rabies encephalitis is unique among all viral brainstem encephalitides of which degeneration of consciousness is the clinical hallmark. The limitation in this study was that spinal cord of non-rabies patients was not studied in parallel. Therefore, it may be premature to suggest what mechanism is responsible for this "resistance" phenomenon. Whether this is due to an intrinsic property of spinal cord / brainstem or relative absence of cytokine-chemokine influence on neuronal dysfunction and intracellular cascades needs to be studied further.

Regarding findings of enhancement in white matter of the brain, areas where virus cannot replicate itself, this study failed to disclose any cytoskeleton or white matter defects. Whether it is other elements of cytoskeleton structures that are perturbed or it is other mechanisms mediated via free radicals and nitric oxide or chemokines remain to be determined. In conclusion, this study underscores that clinical manifestations of human rabies patients are not related to the distribution of virus. Moreover, spinal cord and, probably, brainstem areas where early rabies virus replication can be demonstrated, are MOMP negative regions, thus, explaining the lack of spinal cord weakness and preservation of consciousness in rabies patients. It also points out that neuronal dysfunction and deaths are separate processes not depending on the amount of virus proteins and may be manipulated if precise mechanisms are known. Lack of cytoskeleton and white matter defects raises the importance of *in vivo* study in animals using techniques which can elucidate axonal changes and myelinopathy and inflammatory tracking methodology.