

ABSTRACT

**Biochemical Studies of Brain and Liver Mitochondria and Cytochrome c
Oxidase Isolated from Normal and Swayback Diseased Sheep: The
Development of Swayback Animal Models**

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A number of important discoveries mostly related to swayback disease (SD) but a few related to Alzheimer's disease (AD) are presented in this thesis. Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) showed that purified cytochrome c oxidase (COX) isolated from the brain of SD sheep is deficient in subunits II, III and IV. Also, the protein composition of brain and liver mitochondria from SD sheep was found to be different to that of normal sheep. These findings were consistent with difference spectral analysis which showed that other electron transport proteins were either deficient or partly inactive.

Kinetic studies using the oxygen electrode showed that brain mitochondria and purified COX from SD sheep exhibited uncharacteristic Eadie-Hofstee plots. In

addition, brain and liver COX from SD sheep displayed low activity. The brain but not the liver COX also showed uncharacteristic Eadie-Hofstee plots.

Two successful animal models based on the administration of ammonium tetrathiomolybdate (ATM) were developed in the second phase of the study. The ATM treatment produced wide variations in the serum copper levels of treated ewes: More importantly it produced clinical, pathological, and biochemical changes associated with SD in lambs of the treated ewes. Similar pathological lesions were also seen in the offspring of ATM treated rabbits. The metabolic deficiency produced by the ATM also had a profound effect on the health status of the injected ewes. There were a number of abortions and a heavy worm burden found among the pregnant ewes.

Studies with the Klatzo model for Alzheimer's disease (AD) did not detect low activity or altered protein composition for brain mitochondria or brain COX as seen in SD. However, brainstem auditory evoked potential (BAEP) analysis revealed significant changes in peak four of the rabbits injected with the aluminum salt; a finding that could possibly have diagnostic value for AD.