OBJECTIVES: The specific aims of the Neuropathology/Histochemistry core of the program project are: 1) to fully characterize the anatomical pathology of animal lesions produced in projects 1 and 3 by defining the spatial distribution of lesions and the extent of oxidative injury affecting histochemically defined neuronal subsets; 2) to determine the light and ultrastructural changes produced by manipulation of superoxide dismutase (SOD) expression in cell culture systems and 3) to perform detailed postmortem analysis on human brains studied in the center for the confirmation of diagnosis, the detection of specific patterns of oxidative injury in affected neuronal classes and the detection of clinical variants associated with specific genetic abnormalities.

RESEARCH PLAN: Tissue is processed for histopathological examination in a standardized and reproducible manner to minimize variability among cases. Frozen serial sections of the entire brain and cervical, thoracic, and lumbar spinal cord segments are made at 50 μm intervals. Sections are subsequently stained for Nissl substance using cresyl violet and for immunohistochemical localization using a variety of primary antibodies that are markers for specific neuronal classes, gene transcription, identified enzymes and neurochemicals, inflammation, apoptosis, and/or oxidative injury. Tissue analysis is accomplished utilizing video microscopy and the Neurolucida image analysis system to capture and study markers in tissue sections. METHODS: Postmortem specimens and experimental animals are studied to determine the effects of altered SOD expression on brain anatomy and to validate transgenic SOD mice as animal models for neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and aging.

FINDINGS: Ongoing work is focused on the ALS transgenic mouse model including the quantitative effects of therapeutic agents such as Ginko and minocycline on specific neuronal classes, gene transcription, identified enzymes and neurochemicals, inflammation, apoptosis, and oxidative injury.

CLINICAL RELEVANCE: In vivo studies such as the ones we are performing may provide clues to prophylactic or curative therapies for neurodegenerative diseases such as Alzheimer's, ALS, and Parkinson's.