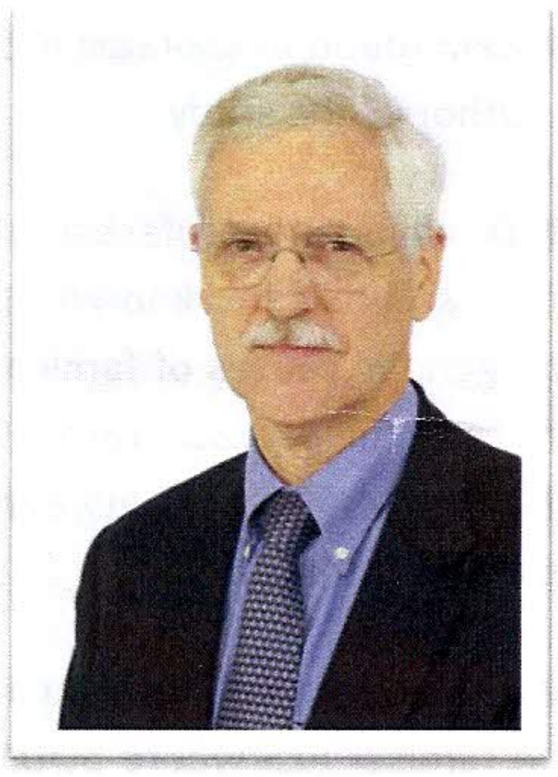
## *ALS Research at the University of Massachusetts Medical School*

The Neurology Department at the University of Massachusetts Medical School has renewed its commitment to expand and invigorate research in neurology throughout central Massachusetts and New England. The recruitment of Dr. Robert H. Brown in 2008 as Chair of Neurology has brought an expansion in faculty and facilities devoted to improving the level of the neurosciences. The University of Massachusetts Medical School's Neurology department is the largest training, research and clinical neurology facility in central New England.

**Robert J. Brown, Jr. DPhil, MD**, is professor and chair of neurology at the University of Massachusetts Medical School and UMass Memorial Medical Center. He is also the Director of the Day Neuromuscular Research Laboratory at the University of Massachusetts Medical School.



Dr. Brown graduated from Harvard Medical School and completed his doctoral training in neurophysiology at Oxford University. Dr. Brown trained in Neurology at the Massachusetts General Hospital. In 1984, The Day Neuromuscular Research Laboratory was founded by Dr. Brown to investigate neuromuscular diseases, including Miyoshi myopathy and ALS.

This is an exciting time in neurology as powerful new technologies in basic neurobiology and the clinical neurosciences have rapidly improved our understanding of neurological illnesses. Prospects have never been better for finding effective new treatments for even the most devastating neurological disorders. The laboratories of our skilled faculty explore the exciting and growing fields of neurology as new technologies accelerate our understanding of the central nervous system and the diseases that plague it.

### Identification of Gene Defects and Neuromuscular Disease

Dr. Brown's laboratory has focused on the identification of gene defects that elucidate the molecular pathogenesis of selected neuromuscular diseases including amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), muscular dystrophy, adrenoleukodystrophy, hereditary neuropathy and hyperkalemic periodic paralysis. Knowledge of these disease genes has facilitated the creation of mouse and cell-based models of these disorders. In turn, these resources have allowed study of therapeutic strategies using conventional small molecule approaches and new modalities such as inhibitory RNAi.

## *Recent Findings:*

## *Gene Connection Extends Possible Treatments to More ALS Patients*

---

Researchers at the UMass Medical School have uncovered new evidence suggesting that a gene, SOD1, which is implicated in 20 percent of inherited cases of amyotrophic lateral sclerosis (ALS), also plays a part in the more common sporadic forms of the disease. Discovery of this connection, described in the Oct. 17 online edition of *Nature Neuroscience*, may mean that current treatments under development could be extended to a much larger population of ALS patients.

While the SOD1 gene has long been understood to play a role in familial ALS, scientists suspected a connection to the more common form of ALS, for which there is no known cause, and sought to establish a shared pathological pathway. Only 10 percent of ALS cases are familial, while roughly 90 percent are sporadic in nature—meaning there is no identifiable familial risk or family history.

"This common ALS pathology between sporadic and familial ALS means that current gene silencing and immunotherapeutic treatments being developed in academic and commercial labs that target the mutant SOD1 gene may be extended to target non-mutant SOD1 protein found in sporadic ALS cases," said Daryl Bosco, PhD, assistant professor of neurology and lead author of the study.

In 1993, a team of researchers led by Robert H. Brown Jr., DPhil, MD, chair and professor of neurology, discovered the first gene linked to familial ALS, a protein anti-oxidant known as superoxide dismutase, or SOD1. When Dr. Brown began researching the genetic causes of familial ALS, he hoped that one day research would provide insight into the more common sporadic form of the disease. "It has been hypothesized that there are common pathogenic pathways between familial and sporadic ALS," said Brown. "Our new findings strongly suggest that is the case."

"This research shows that under certain conditions and absent a mutation in the gene, a normal SOD1 protein can have the same toxic characteristics that are found in familial ALS where SOD1 gene is mutated," said Brown. "What's more, we found the presence of these aberrant proteins in select cases of sporadic ALS."

"Until now, factors linking both forms of ALS have been lacking," said Bosco. "These results demonstrate that this protein plays a role in both forms of the disease."

Bosco cautions that while a modified form of the SOD1 protein may play a part in sporadic cases of ALS, it's still unclear what is causing the modification, how many cases may be as a result of the modification or whether it is the primary cause of the disease. "Despite the presence of the normal gene, we show that modifications to the protein made by the gene makes it behave like the toxic, mutated forms of protein," said Bosco. "Further research is needed to understand properties of this toxic protein and how it's being modified."

This study was supported by funding from the National Institutes of Health, the ALS Therapy Alliance, the ALS Association, the Angel Fund and Project ALS.

---