and unsteadiness in walking. Later on, speech is noted to become dysarthric, and eye movement abnormalities develop. Many affected individuals develop lymphoid neoplasms, which are most often T-cell leukemias.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive disorder in which there is loss of upper motor neurons in the cerebral cortex and lower motor neurons in the spinal cord and brainstem. Loss of these neurons results in denervation of muscles, producing weakness that becomes profound as the disease progresses. The disease has an overall incidence of about 2 cases per 100,000 population, affects men slightly more frequently than women, and commonly emerges in the fifth decade or later. Sporadic ALS is more common than familial ALS (FALS), which may account for up to 20% of cases.

Molecular Genetics and Pathogenesis. **Both sporadic and familial ALS are associated with degeneration of upper and lower motor neurons, often in association with evidence of toxic protein accumulation.** Close to two dozen genetic loci have been identified as causing familial ALS, with nearly all being autosomal dominant disorders. One of the earliest discovered hereditary forms of ALS has mutations in the gene encoding copper-zinc superoxide dismutase (*SOD1*) on chromosome 21; this variant accounts for about 20% of familial cases. A wide variety of missense mutations have been identified throughout the gene. The A4V mutation is the most common in the United States; it is associated with a rapid course and rarely involvement of upper motor neurons.

Initially, identification of *SOD1* mutations suggested that neuronal injury in ALS might reflect an impaired capacity to detoxify free radicals, but it is now believed that mutations lead to an adverse gain-of-function phenotype associated with mutant SOD1 protein. It appears that mutated SOD1 protein misfolds and forms aggregates (that can include wild type protein) and result in cellular injury through a variety of mechanisms including disruption of proteasome function and autophagy, direct effects on axonal transport and mitochondrial function or sequestration of other proteins within the aggregates. Accumulation of protein aggregates can eventually trigger the unfolded protein response, with subsequent initiation of apoptosis. Development of aggregated SOD1 has also been observed in ALS without mutations in this gene, suggesting that this path to cellular injury may contribute to sporadic ALS as well. For this reason, methods for clearing misfolded SOD1 are being developed as therapeutic approaches. The overall importance of protein degradation pathways is reinforced by discovery of a range of uncommon mutations in genes implication in protein degradation that are also associated with familial ALS.

The most common mutation that gives rise to ALS and FTLD simultaneously is an expansion of a hexanucleotide repeat in the 5′-untranslated region of a transcript of unknown function, C9orf72. This mutation is estimated to be the basis of up to 40% of familial ALS and a smaller fraction of what appear to be sporadic cases of ALS. Non-AUG-initiated translation (in all three reading frames) can occur from these expanded repeats, and neuronal deposits of the derived proteins have been found in the setting of the mutation. Whether these novel protein aggregates contribute to cellular injury remains obscure.

Other genetic loci that cause ALS and FTLD encode proteins with RNA-binding capacity, such as TDP-43 and FUS. The underlying link between altered RNA-binding proteins and manifestations of motor neuron disease remain unclear. Possibly, nuclear depletion of TDP-43 results in inappropriate processing of some RNAs, while the aggregation of the protein in the cytoplasm activates the unfolded protein response common to many of the proteinopathies.

MORPHOLOGY

The anterior roots of the spinal cord are thin (Fig. 28-43*A*), due to loss of lower motor neuron fibers, and the precentral motor gyrus in the cortex may be atrophic in especially severe cases. There is a reduction in the number of anterior-horn neurons throughout the length of the spinal cord, associated with reactive gliosis. Similar findings are seen in the hypoglossal, ambiguus, and motor trigeminal cranial nerve nuclei. Remaining neurons often contain PAS-positive cytoplasmic inclusions called Bunina bodies, which appear to be remnants of autophagic vacuoles. Skeletal muscles innervat ed by the degenerated lower motor neurons show neurogenic atrophy. Loss of the upper motor neurons leads to degeneration of the corticospinal tracts, resulting in volume loss and absence of myelinated fibers, which may be particularly evident at the lower segmental levels (Fig. 28-43*B*).

Clinical Features. Early symptoms of ALS include asymmetric weakness of the hands, manifested as dropping of objects and difficulty in performing fine motor tasks, and cramping and spasticity of the arms and legs. As the disease progresses, muscle strength and bulk diminish, and involuntary contractions of individual motor units, termed fasciculations, occur. The disease eventually involves the respiratory muscles, leading to recurrent bouts of pulmonary infection. While most affected individuals have a combination of both upper and lower motor neuron involvement as determined by clinical features and pathologic examination, there are other patterns observed. The term *progressive muscular atrophy* applies to those relatively uncommon cases in which lower motor neuron involvement predominates, while *primary lateral sclerosis* refers to those cases with mostly upper motor neuron involvement. In some affected individuals, degeneration of the lower brainstem cranial motor nuclei occurs early and progresses rapidly, a pattern referred to as *progressive bulbar palsy* or *bulbar ALS*. In these individuals, abnormalities of deglutition and phonation dominate, and the clinical course is inexorable during a 1- or 2-year period; when bulbar involvement is less severe, about half of affected individuals are alive 2 years after diagnosis. The motor neurons innervating extra-ocular muscles are among the last to be involved in ALS; with long survival, usually associated with ventilator support, even this form of motor output fails. Familial cases develop symptoms earlier than most sporadic cases, but the clinical course is comparable.

While ALS is considered a disease of the motor system, it is clear that a significant fraction of affected individuals