DECONTAMINATION OF CJD PRIONS

Prions are extremely resistant to common inactivation procedures, and there is some disagreement about the optimal conditions for sterilization. Some investigators recommend treating CJD-contaminated materials once with 1 *N* NaOH at room temperature, but we believe this procedure may be inadequate for sterilization. Autoclaving at 134°C for 5 h or treatment with 2 *N* NaOH for several hours is recommended for sterilization of prions. The term *sterilization* implies complete destruction of prions; any residual infectivity can be hazardous. Recent studies show that sCJD prions bound to stainless steel surfaces are resistant to inactivation by autoclaving at 134°C for 2 h; exposure of bound prions to an acidic detergent solution prior to autoclaving rendered prions susceptible to inactivation.

PREVENTION AND THERAPEUTICS

There is no known effective therapy for preventing or treating CJD. The finding that phenothiazines and acridines inhibit PrP^{Sc} formation in cultured cells led to clinical studies of quinacrine in CJD patients. Unfortunately, quinacrine failed to slow the rate of cognitive decline in CJD, possibly because therapeutic concentrations in the brain were not achieved. Although inhibition of the P-glycoprotein (Pgp) transport system resulted in substantially increased quinacrine levels in the brains of mice, the prion incubation times were not extended by treatment with the drug. Whether such an approach can be used to treat CJD remains to be established.

Like the acridines, anti-PrP antibodies have been shown to eliminate PrP^{Sc} from cultured cells. Additionally, such antibodies in mice, either administered by injection or produced from a transgene, have been shown to prevent prion disease when prions are introduced by a peripheral route, such as intraperitoneal inoculation. Unfortunately, the antibodies were ineffective in mice inoculated intracerebrally with prions. Several drugs, including pentosan polysulfate as well as porphyrin and phenylhydrazine derivatives, delay the onset of disease in animals inoculated intracerebrally with prions if the drugs are given intracerebrally beginning soon after inoculation.

DIFFERENT PRIONS CAUSING OTHER NEURODEGENERATIVE DISEASES

There is a rapidly expanding body of literature demonstrating that in addition to PrP, other proteins including amyloid beta (Aβ), tau, α-synuclein, and huntingtin can all becomes prions **(Chap. 444e)**. Experimental studies have shown that transgenic mice expressing mutant amyloid precursor protein (APP) develop amyloid plaques containing fibrils composed of the Aβ peptide approximately a year after inoculation with synthetic Aβ peptides polymerized into amyloid fibrils or extracts prepared from the brains of patients with AD. Mutant tau aggregates in transgenic mice and cultured cells can trigger the aggregation of tau into fibrils that resemble those found in neurofibrillary tangles and Pick bodies. Such tangles have been found in AD, FTDs, Pick's disease, and some cases of posttraumatic brain injury, all of which are likely to be caused by the prion isoforms of Aβ and/or tau.

In patients with advanced PD who received grafts of fetal substantia nigral neurons, Lewy bodies containing β-sheet–rich α-synuclein were identified in grafted cells approximately 10 years after transplantation, arguing for the axonal transport of misfolded α-synuclein crossing into grafted neurons, where it initiated aggregation of nascent α-synuclein into fibrils that coalesced into Lewy bodies. These findings combined with studies of multiple system atrophy (MSA) argue that the synucleinopathies are caused by prions. Brain homogenates from MSA patients injected into transgenic mice transmitted lethal neurodegeneration in approximately 3 months; moreover, recombinant synuclein injected into wild-type mice initiated the deposition of synuclein fibrils.

In summary, a wealth of evidence continues to accumulate arguing that proteins causing AD, PD, FTDs, ALS, and even HD acquire alternative conformations that become self-propagating. Each of these neurodegenerative diseases is caused by a different protein that undergoes a conformational transformation to become a prion. Prions explain many of the features that the neurodegenerative diseases have in common: (1) incidence increases with age, (2) steady progression over years, (3) spread from one region of the CNS to another, (4) protein deposits consisting of amyloid fibrils, and (5) late onset of inherited forms of the neurodegenerative diseases. Notably, amyloid plaques containing PrP^{Sc} are a nonobligatory feature of PrP prion disease in humans and animals. Furthermore, amyloid plaques in AD do not correlate with the level of dementia; however, the level of soluble (oligomeric) Aβ peptide does correlate with memory loss and other intellectual deficits.