The prion protein (PrP) has been strongly implicated as the causative agent of transmissible spongiform encephalopathies (TSEs) . After an extensive series of purification procedures, find that the infectivity of the agent causing scrapie in sheep was associated with a single protein species that was not complexed with detectable nucleic acid. This infectious protein is designated PrPSc (Sc = scrapie). It is highly resistant to proteolytic degradation and tends to form insoluble aggregates of fibrils, similar to the amyloid found in some other diseases of the brain. A noninfectious form of PrPC (C = cellular), encoded by the same gene as the infectious agent, is present in normal mammalian brains on the surface of neurons and glial cells. Thus, PrPC is a host protein. No primary structure differences or alternate posttranslational modifications have been found between the normal and the infectious forms of the protein. The key to becoming infectious apparently lies in changes in the three-dimensional conformation of PrPC. It has been observed that a number of α-helices present in noninfectious PrPC are replaced by □-sheets in the infectious form