Prions’ Travels—Feces and Transmission of Prion Diseases

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(See the article by Safar et al., on pages 81–9.)

“Because men are never so serious, thoughtful, and intent, as when they are at stool...”—Lemuel Gulliver [1]

The epidemiological profile of prion disease varies strikingly among different mammalian species. The overwhelming majority (>90%) of prion diseases in humans are sporadic, with most of the remaining cases due to inherited mutations in the gene (PRNP) encoding the prion protein. Lateral transmission of disease between humans is extraordinarily rare. Most documented cases have been due to direct inoculation of infected material, as is exemplified (1) by transplantation of dural grafts or injection of either human growth hormone or gonadotropins derived from pools of cadaveric pituitary glands, or (2) as in the case of variant Creutzfeldt-Jakob disease (vCJD), by dural grafts or injection of either human growth hormone or gonadotropins derived from pools of cadaveric pituitary glands. Similarly, bovine spongiform encephalopathy (BSE) is almost always acquired through consumption of prion-infected food supplements, and lateral transmission within cattle herds appears to be rare or nonexistent. In contrast to human prion diseases and BSE, both chronic wasting disease (CWD) in cervids and scrapie in sheep are laterally transmitted with high efficiency. In wild populations of deer, >15% of animals may be infected, and, in captive herds, rates of infection can approach 100% [2]. Neither how prion disease spreads easily through herds of sheep or deer nor, conversely, why prion disease fails to spread through herds of cattle or human populations is known.

One explanation for variations in the epidemiological profile of disease may be the differences in how prions spread within infected hosts and are subsequently shed into the environment. Hamsters infected by intracerebral inoculation will accumulate the disease-causing isoform of the prion protein (PrPSc) in taste and olfactory receptors [3]. These cells are shed and can contaminate saliva or mucus. White-tailed deer with oral exposure to the saliva of CWD-infected deer develop CWD [4]. Transfusion of blood from infected donors transmits BSE and scrapie to sheep, CWD to deer, and vCJD to humans [4–6]. Initial reports indicating that urine contained levels of PrPSc that were detectable by immunoblotting have not been reproducibly confirmed, but infectious prions have been found, at least transiently, in the urine of infected animals [7–9].

In this issue of the Journal, Safar et al. [10] report investigations of prions in the feces of Syrian hamsters (SHas) experimentally infected with a hamster-adapted Sc237 prion strain. Prion levels were determined both by bioassay and by a highly sensitive immunobassay. A careful historical analysis of representative animals was performed, and excretion of prions in feces was studied in hamsters infected orally, intraperitoneally, or intracerebrally. For oral inoculations, animals were fed “one-half of the brain from a Sc237-infected SHa in a petri dish.” This is an extremely high oral inoculum of ~10 log10 ID50 per hamster. High titers of infectious prions (6.6 log10 ID50/g) were detected in the feces of orally challenged hamsters in the first week, and then titers decreased to low levels (<2.3 log10 ID50/g; incubation time, 165–314 days), which persisted to 106 days after inoculation.

The capacity of these animals to transmit disease to un inoculated cage mates showed an interesting triphasic pattern. Uninfected cage mates that cohabited with an infected index animal within hours of inoculation of the index animal developed disease rapidly (after ~150 days), reflecting exposure to relatively high doses of PrPSc. Animals that cohabited 24–48 h after oral feeding of the index hamster developed disease more slowly (after 192–254 days), reflecting exposure to lower PrPSc doses. However, animals exposed to the index hamster at 7–14 days after its oral challenge again had relatively short disease incubation times (140–165 days). These results could be explained if the initial short incubation times reflected exposure to the initial challenge inoculum that had been rapidly excreted, with later rates reflecting exposure to PrPSc that had replicated in and was being shed endogenously from the intestinal tract of the index animal. Low levels of prions, detectable by
an incubation time of 221 to >300 days in bioassays, were also detectable in feces but only at late times after intraperitoneal or intracerebral inoculation. This finding suggests that the route of prion entry into the host has important implications regarding the route, dose, and kinetics by which the agent is spread, as well as the resulting risk of exposure for uninfected animals.

Safar and colleagues [10] clearly demonstrate that prions can be found in the feces of infected hamsters and that cohabitation of hamsters allowed lateral transfer of infection. However, one must be careful before concluding that fecal contamination of the environment is the mode by which lateral transfer of prions occurs under natural conditions in deer and sheep herds. As noted earlier, the oral prion challenge received by the hamsters was enormous, and the high titers of prions found in the stool of these animals, at least early after infection, likely represents direct excretion of this inoculum. It is not likely that deer or sheep receive such large oral exposures in the wild. The PrPSc levels detected late after oral, intracerebral, or intraperitoneal exposure (titers of <2.3 \( \log_{10} \) ID50/g and corresponding incubation times that can exceed 300 days) seem more likely to represent what might naturally occur in association with scrapie or CWD. It would have been interesting to see both the frequency of disease transmission and the associated incubation time in infected animals if cohabitation had started after 14 days (the latest time reported).

Extrapolation of these results is also difficult, because the distribution of prions in the host is influenced by both the prions themselves and the species of the infected host. Distinct prion “strains” are characterized by differing clinical, histological, biochemical, and physical properties, even when they are propagated in genetically identical hosts [11]. Two well-studied strains of hamster-adapted prions are called “hyper” and “drowsy” prions. Hyper prions accumulate in both the nervous system and the lymphoreticular system, but drowsy prions seem incapable of replicating in the hamster lymphoreticular system [12]. The prion strains responsible for scrapie, BSE, CWD, and even human prion disease may have dramatically differing tissue distributions as well. With regard to prion strains, it is fascinating that mice intracerebrally inoculated with irradiated feces obtained from mice orally infected with Sc237 showed differences in the distribution of their neuropathological findings, compared with mice intracerebrally inoculated with the same prion strain that had not been passed and excreted through the gut. Such differences in brain distribution, which are characteristic of prion strains, raise the intriguing possibility that the route of prion shedding from the infected host may alter the nature and pathogenic properties of the infectious agent.

The distribution of prions within tissues and organs may differ among host species, even when the host species are infected with the same strain. For example, after oral challenge of cattle with the BSE agent, infectious prions are almost entirely restricted to nervous system tissue, with trace infectivity in tonsils and in the Peyer patches of the distal ileum. In contrast, when sheep are orally exposed to the BSE agent, high levels of prions accumulate throughout the lymphoreticular system, including the spleen and liver [13]. It is likely that the distribution and shedding of CWD prions in deer and other cervids and those of scrapie prions in sheep differ from those seen for Sc237 in hamsters; however, until species and prion strain variables are better understood, extrapolation of findings on experimental pathogenesis in laboratory-inoculated hamsters to natural infection in herds of wild animals remains problematic.

Given the differences in the way prions are distributed in the host, depending on both the host species and the prion strain, the careful investigations of Safar et al. [10] do not prove that feces is the vector responsible for lateral transmission in sheep and deer but, rather, merely suggest that such transmission is plausible. These studies provide a road map for further investigations that should be performed in cattle, deer, and sheep infected with “naturally” occurring prion strains. First, all excreta should be carefully examined for infectious prions by use of sensitive assays such as those used by Safar et al. [10]. Second, the prion strains that are involved should be determined (lines of transgenic mice carrying prion protein transgenes matching those of the natural host might be the best tool for strain typing). Third, the environment in which the animals live should be assayed for infectious prions, again using the sensitive assays now available. Fourth, the results of these assays should be correlated with the behavior of the animals in their usual environment.

References