COMPARISON OF TRANSMISSIBILITY OF AMYLOID DISEASES

Disease	Amyloid protein	Transmissible by amyloid	Transmissible agent
Alzheimer's disease	β A4	No	None
Multiple myeloma	Ig L chain	No	None
Diabetes (type 2)	Amylin (IAPP)	No	None
Familial amyloidotic polyneuropathy	Transthyretin (TTR)	No	None
Chronic dialysis	β_2 Microglobulin	No	None
Thyroid carcinoma	Calcitonin	No	None
Secondary amyloidosis	SAA and SAP	No	*M. tuberculosis*, *M. leprae*, malaria
TSE	PrP^{res}	?	?

eases has been found to be transmissible by injection or ingestion of the polymers themselves in spite of extensive attempts [see the table above and (*10*)]. Thus, there is no precedent for the transmission of TSE by the abnormal polymeric PrP. Either we are missing some vital and unique factor that distinguishes the polymers of TSE from those of other amyloid diseases, or the agent of transmission may not be the abnormal polymers themselves.

The alternative is that a virus is the transmissible agent. It is certainly conceivable that a virus might induce polymerization of a normal or mutant cell protein, as has been shown for B19 parvovirus and sickle cell hemoglobin (*8*, *11*). Although no direct evidence for a TSE virus has been obtained, searching for unknown viruses is not straightforward. Even with the powerful methods of molecular biology, without a specific probe or unique sequence, new viruses can be extremely difficult to detect. However, this should not deter future search efforts as new viruses (Borna and hepatitis), continue to be discovered.

Support for the protein-only hypothesis also comes from the apparent spontaneous generation of a neurodegenerative disease in transgenic mice that overexpress a mutant form of PrP associated with familial TSE disease in humans (*12*, *13*). These results are inconclusive for several reasons. First, these mice differ from all known TSE models in that no abnormal protease-resistant PrP is detectable in diseased brain tissues by protein immunoblot. Second, brain disease is produced only when the mutant transgene is overexpressed, but not when it is present as a single-copy gene in the normal PrP locus. Third, transmission of this disease occurs only in transgenic mice expressing low levels of the same mutant PrP transgene, and not in normal nontransgenic mice. Thus, "transmission" could be due to transfer of cytokines or other molecules from diseased brain, which up-regulate mutant PrP transgene expression in the recipient mice. Nor have the transmitted materials been shown to have the typical properties of TSE agents, such as unusual resistance to inactivation by heat and harsh chemicals. To explain the lack of transmission to normal mice, it has been proposed that the PrP mutation (Leu^{102}) in the transgene causes a barrier to transmission to normal (Pro^{102}) mice. Although theoretically possible, it is unlikely because effective transmission can occur from humans with Leu^{102} PrP humans to both monkeys and mice with Pro^{102} (*14*, *15*).

Hopefully, open-minded future research will resolve the mysteries regarding the nature of the TSE agent. Additional information on this subject must be obtained to better facilitate development of drugs. Evidence suggests that treatment with drugs that interact with the abnormal PrP can prolong survival in experimental mouse or hamster scrapie, a TSE disease originally derived from sheep. Other approaches—gene therapy with TSE-resistant PrP alleles or elimination of the PrP gene itself—are also possible, particularly for domestic animals. Clearly, we are in the very early stages of exploration of this subject. It would be tragic if the recent Nobel Prize award were to lead to complacency regarding the obstacles still remaining. It is not mere detail, but rather the central core of the problem, that remains to be solved.

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Edited by David Voss

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