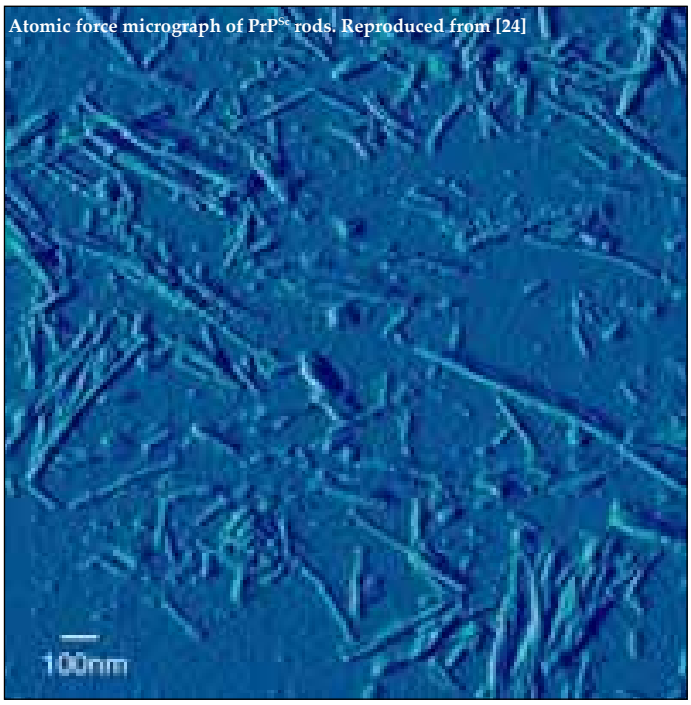
Prions: From Dogma, to Mystery, to Benefit?

David Koren

How do we get sick? Touching an infected door handle, walking through tick-infested areas, and kissing a sick person can spread viruses and bacteria, which use their own DNA or RNA to multiply within the body and cause infectious diseases. However, recent research has revealed a completely different type of disease transmission mechanism. Certain diseases, termed transmissible spongiform encephalopathies (TSEs), spread via a tiny molecular agent that rapidly causes brain tissue wasting and death. This agent is the prion, a protein without nucleic acids that replicates by conferring structural changes onto host tissue [1,2]. Moreover, its unique replication process may provide shocking clues about the nature of the brain and the function of human memory.

In the 1960s, in the wake of the DNA revolution led by Francis Crick—a co-discoverer of DNA's molecular structure—many scientists claimed that the entire phenotype of a living being could be traced to the double helix. Information, they believed, was transcribed from DNA to RNA and translated into proteins, the molecules responsible for the characteristics of living things. Additionally, most scientists believed that the active form of a protein was wholly and exclusively dependent on its primary structure, that is, the precise chain of amino acids formed in translation. As Crick stated regarding the irreversibility of translation, "Nature could not proceed in another way" [1]. This became the "Central Dogma" of biology. Since then, however, much research on TSEs has disproven Crick's conjecture: infectious proteins, too, can be self-replicating [1,2].

> **"Nature could not proceed in another way"... became the "Central Dogma"**

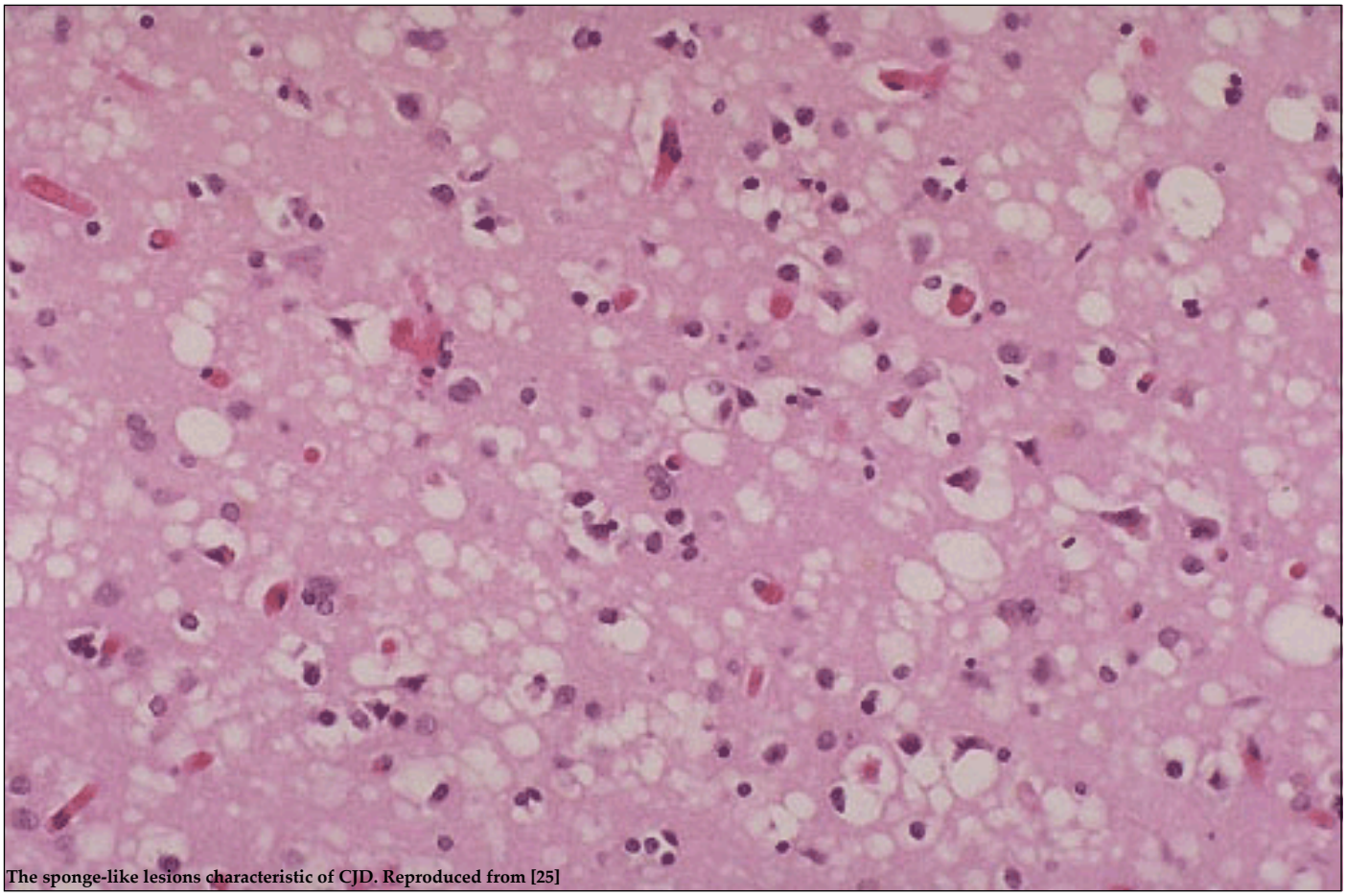


Atomic force micrograph of PrP^{Sc} rods. Reproduced from [24]

By the early 20th century, scrapie, a neurodegenerative disease in sheep marked by the infected animals' devastating habit of wool scraping, threatened to ruin European farmers. This prompted scientific inquiry into the epidemic. Initial hypotheses implicated a diverse range of molecules, from polysaccharides and lipids to virus-like agents. However, as the incubation time of TSEs is frequently measured in years [3], a viral mode of infection was virtually ruled out [1]. But, hindered by their complete faith in the Central Dogma, scientists had difficulty considering the notion of a protein-only pathway. The mathematician J. S. Griffith proposed three potential mechanisms for scrapie in a 1967 paper, adding that "there is no reason to fear that the existence of a protein agent would cause the whole theoretical structure of molecular biology to come tumbling down" [4]. Still, it was not until 1982 that Griffith's ideas were seriously considered; in the interim, proposed mechanisms of replication—viroids, DNA complexes, membranes—were all associated with nucleic acids in one way or another, consistent with Crick's Dogma [1].

In 1982, Stanley Prusiner published the first of many papers that would revolutionize the field and later earn him a Nobel Prize [2]. Affirming that scrapie was not caused by a known agent, he named the structure "prion," denoting "proteinacous infectious particle." Nevertheless, Prusiner was not immediately certain whether or not the prion contained a nucleic acid; considering a self-replicating protein, he believed, was "heretical" [1]. Fortunately, for Prusiner, "heretical" did not mean "impossible." Two years later, he published theories of two potential methods of prion replication. The first of his propositions was that the prion protein, PrP, stimulated DNA transcription, causing further PrP production. Prusiner's second idea stipulated that the conformation of infectious PrP served as a template for the formation of new PrP molecules—without any involvement of nucleic acids [5]. Incidentally, these hypotheses mirrored two of the mechanisms that Griffith proposed seventeen years earlier [4].

Much evidence from PrP studies from the 1980s favored the latter of Prusiner's hypotheses. Indeed, PrP-coding mRNA was found to exist in infected mice in equal quantities as in uninfected mice, revealing that PrP was a naturally-found protein in mammals [5]. Furthermore, animals that lacked the normal PrP protein (PrP^{C}) were unaffected by the "infectious" form of the protein, PrP^{Sc} [6,7]. Examining the two forms of the protein revealed no differences in primary structure, suggesting that the only difference was conformational [8]. Together, this evidence formed the basis of the modern hypothesis of the prion. PrP^{Sc}, an insoluble and protease-resistant conformation of the prion protein, replicates by converting naturally occurring PrP^{C} molecules [7]. As such, prions present a major challenge to



The sponge-like lesions characteristic of CJD. Reproduced from [25]

the Central Dogma as it was understood by Crick and his colleagues [2].

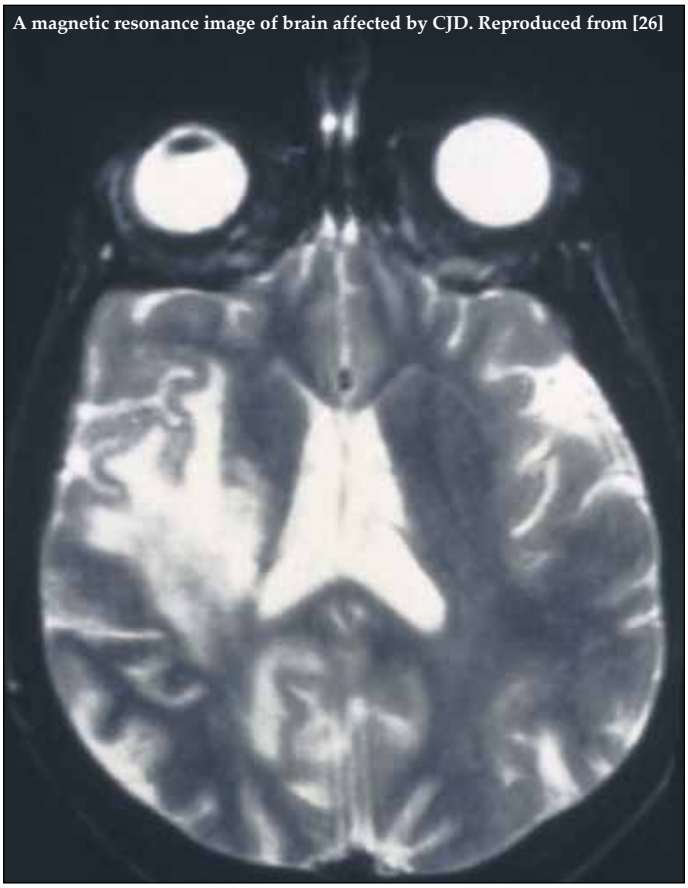
The structure of the prion protein has been conserved throughout evolution, allowing TSEs to occasionally cross between different species [7]. Such was the case when bovine spongiform encephalopathy (BSE) sickened upwards of 150 people in Britain who had consumed prion-infected beef [9]. Cases of the human analogue of BSE, called Creutzfeldt-Jakob disease (CJD), are still reported on a sporadic basis. Due to its long incubation time and the possibility of transmission via blood transfusion, future epidemics of CJD still threaten Western Europe and North America [10].

> **"Prions have also been linked to Alzheimer's Disease."**

Still, fewer than two percent of all CJD cases are acquired. The vast majority, eighty-five to ninety percent, of CJD cases are spontaneous (sCJD). These are often accompanied by a homozygous valine or methionine codon on chromosome 20 [11]. Symptoms of TSEs vary depending on the specific PrP strain of the organism [7]. Likewise, each subtype of PrPSc carries slight differences in symptoms or timeframe of disease, although most result in rapidly progressing dementia and death within months of onset. One extremely rare form of CJD, called VV1 (valine-valine), is distinguished by the gradual onset of dementia and atypical brain scan presentations [11]. Additionally, vCJD (variant CJD, the type associated with BSE transmission) has been shown to uniquely induce abnormal excitation in the hippocampus [12]. These examples illustrate that even within a single animal species, variations in prion structure can account for clinically dissimilar cases.

Prions have also been linked to Alzheimer's disease. In both Alzheimer's and CJD, insoluble amyloid aggregates gradually destroy brain tissue. Although some correlation between the development of Alzheimer's and CJD may be attributed to age [13], studies have shown a link between the prion polymorphism (homozygosity for methionine) and Alzheimer's [14]. Experiments have shown that levels of PrP^{C} tend to be inversely correlated with those of amyloid peptides, and that PrP-null mice exhibit deficits in spatial learning and a generally decreased resistance to stress [15]. PrP^{Sc} infection in mice also dramatically increases amyloid formation [16]. Consequently, Baier et al. hypothesize that CJD causes an increase in amyloid plaques due to a loss of function of the prion protein, suggesting that the cellular prion protein may reduce amyloid buildup and combat Alzheimer's [6]. However, a more recent study surprisingly indicated just the opposite, showing that PrP^{C} binds to an amyloid intermediate and thus obstructs synapse strengthening andmemory formation. In mice lacking PrP^{C}, as well as

> **"Prions are sometimes beneficial and sometimes detrimental."**



A magnetic resonance image of brain affected by CJD. Reproduced from [26]

those given an anti-PrP^C antibody, these interactions do not occur [17,18]. Such contradictory findings about the role of the prion protein form the crux of the current debate. According to a leading researcher, "The fact that prions are sometimes beneficial and sometimes detrimental…is at the heart of their biology – … they present a sort of bet-hedging strategy, where in some circumstances it's good to be in the prion state and in some cases it's not" [19]. Thus, although the link between PrPC and Alzheimer's is uncertain, prions present a significant potential for understanding, and eventually treating, Alzheimer's and other neurological disorders [18].

Following evidence that prions can be beneficial in the struggle against Alzheimer's, some research has shifted away from examining TSEs and towards understanding the normal function of PrP^C. Curiously, PrP in the mammalian brain is concentrated at synapses and plays a role in the homeostasis of copper [20]. Since anomalous copper concentrations have been associated with Alzheimer's and Parkinson's, and appear to block synaptic strengthening in the rat hippocampus [21], a memory-related function is clearly suggested. PrP^C appears to moderate activity of the NMDA receptor, which allows Ca^{2+} entry into neurons and is thought to play a role in memory [15,22]. Evidence that memory mechanisms make use of prions came with structural studies of CPEB, a protein that influences long-term memory by inducing mRNA transcription and synaptic strengthening. One of the conformations of this protein is structurally similar to PrP, in addition to exhibiting an environment-dependent form of replication identical to that in prions (as opposed to Mendelian heritability) [6]. Because of this evidence, some have suggested that prion conformational flips may be the "switch" governing memory formation [23], a very intriguing conjecture.

In biology, a practical way to study the function of a structure—a gene, an ion channel, an organ—is to deactivate it. In this case, it appears that nature's random mutations provided scientists with just this type of experiment. Not three decades have passed since Prusiner named this mysterious infectious particle, yet in this short time span, the prion has acquired the potential to revolutionize molecular biology. In 1982, prions were considered just infectious particles in isolated populations; today, they are not only key molecules in mental illnesses but also candidates for significant and surprising roles in the function of the human brain and the mechanisms of memory. ■

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