

Special Article

SHATTUCK LECTURE — NEURODEGENERATIVE DISEASES AND PRIONS

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TWENTY-FIVE years ago, little was known about the causes of neurodegenerative diseases. Now, however, it is clear that they result from abnormalities in the processing of proteins. In each of these diseases, defective processing causes the accumulation of one or more specific neuronal proteins.

Of all the laboratory research on neurodegenerative diseases, the studies that led to the discovery of prions have yielded the most unexpected findings. The idea that a protein can act as an infectious pathogen and cause degeneration of the central nervous system was accepted only after a long and arduous battle.¹ The concept of prions not only has provided an explanation of how a disease can be both infectious and genetic, but has also revealed hitherto unknown kinds of neurologic diseases. This review presents a unifying concept of degenerative brain diseases, based on what we have learned about prions.²

Alzheimer's disease is the most common neurodegenerative disorder (Table 1). In the United States, approximately 4 million people have Alzheimer's disease, and approximately 1 million have Parkinson's disease.³⁻⁵ Much less common are amyotrophic lateral sclerosis, frontotemporal dementia, prion diseases, Huntington's disease, and spinocerebellar ataxias.

With the increase in life expectancy, there has been concern about the incidence of Alzheimer's and Parkinson's diseases. Among persons who are 60 years old, the prevalence of Alzheimer's disease is approximately 1 in 10,000, but among those who are 85 years old, it is greater than 1 in 3.⁶ These data suggest that by 2025, there will be more than 10 million cases of Alzheimer's disease in the United States, and by 2050, the number will approach 20 million.⁴ The annual cost associated with Alzheimer's disease in the United States is estimated at \$200 billion. Age is also the most important risk factor for Parkinson's disease. Nearly 50 percent of persons who are 85 years old also have at least one symptom or sign of parkinsonism.⁷

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TABLE 1. PREVALENCE OF NEURODEGENERATIVE DISEASES IN THE UNITED STATES IN 2000.

DISEASE	NO. OF CASES	NO. PER 100,000 POPULATION*
Prion disease	400	<1
Alzheimer's disease	4,000,000	1450
Parkinson's disease	1,000,000	360
Frontotemporal dementia	40,000	14
Pick's disease	5,000	2
Progressive supranuclear palsy	15,000	5
Amyotrophic lateral sclerosis	20,000	7
Huntington's disease	30,000	11
Spinocerebellar ataxias	12,000	4

*Data are based on a population of approximately 275 million in 2000.

Virtually all neurodegenerative disorders involve abnormal processing of neuronal proteins. The aberrant mechanism can entail a misfolding of proteins, altered post-translational modification of newly synthesized proteins, abnormal proteolytic cleavage, anomalous gene splicing, improper expression, or diminished clearance of degraded protein. Misprocessed proteins often accumulate because the cellular mechanisms for removing them are ineffective. The particular protein that is improperly processed determines the malfunction of distinct sets of neurons and thus the clinical manifestations of the disease.

PRIONS

Prions are infectious proteins. In mammals, prions reproduce by recruiting normal cellular prion protein (PrP^C) and stimulating its conversion to the disease-causing (scrapie) isoform (PrP^{Sc}). A major feature that distinguishes prions from viruses is that PrP^{Sc} is encoded by a chromosomal gene.⁸ Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of approximately 142 amino acids, designated PrP 27–30, which polymerizes into amyloid.⁹

The polypeptide chains of PrP^C and PrP^{Sc} are identical in composition but differ in their three-dimensional, folded structures (conformations). PrP^C is rich in α -helices (spiral-like formations of amino acids) and has little β -sheet (flattened strands of amino ac-

ids), whereas PrP^{Sc} is less rich in α -helices and has much more β -sheet.¹⁰ There is evidence that PrP^C has three α -helices and two short β -strands; in contrast, a plausible model suggests that PrP^{Sc} may have only two α -helices and more β -strands (Fig. 1).^{11,12} This structural transition from α -helices to β -sheet in PrP is the fundamental event underlying prion diseases.

Four new concepts have emerged from studies of prions. First, prions are the only known example of infectious pathogens that are devoid of nucleic acid. All other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. Second, prion diseases may be manifested as infectious, genetic, or sporadic disorders. No other group of illnesses with a single cause has such a wide spectrum of clinical manifestations. Third, prion diseases result from the accumulation of PrP^{Sc}, which has a substantially different conformation from that of its precursor, PrP^C. Fourth, PrP^{Sc} can have a variety of conformations, each of which seems to be associated with a specific disease. How a particular conformation of PrP^{Sc} is imparted to PrP^C during replication in order to produce a nascent PrP^{Sc} with the same conformation is unknown. The factors that determine the site in the central nervous system where a particular PrP^{Sc} is deposited are also not known.

PRION DISEASES

Prion diseases have a broad spectrum of clinical manifestations, including dementia, ataxia, insomnia, paraplegia, paresthesias, and deviant behavior.¹³ Neuropathological findings range from an absence of atrophy to widespread atrophy, from minimal to widespread neuronal loss, from sparse to widespread vacuolation or spongiform changes, from mild to severe reactive astrocytic gliosis, and from an absence of PrP amyloid plaques to an abundance of plaques.¹⁴ None of these findings except the presence of PrP amyloid plaques is unequivocally diagnostic of a prion disease.

The sporadic form of Creutzfeldt–Jakob disease, which is typically manifested as dementia and myoclonus, accounts for approximately 85 percent of all cases of prion disease in humans, whereas infectious and inherited prion diseases account for the rest. Familial Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker disease, and fatal familial insomnia are all dominantly inherited prion diseases caused by mutations in the prion protein gene (*PRNP*) (Table 2).^{15–19} Experiments that showed transmission of these diseases by filtrates of brain from familial cases^{20,21} were wrongly attributed to a virus. There is no Creutzfeldt–Jakob disease virus, and familial prion diseases are caused by mutations in *PRNP*.²²

Epidemiologic Features

Prions cause Creutzfeldt–Jakob disease in humans throughout the world. The incidence of sporadic

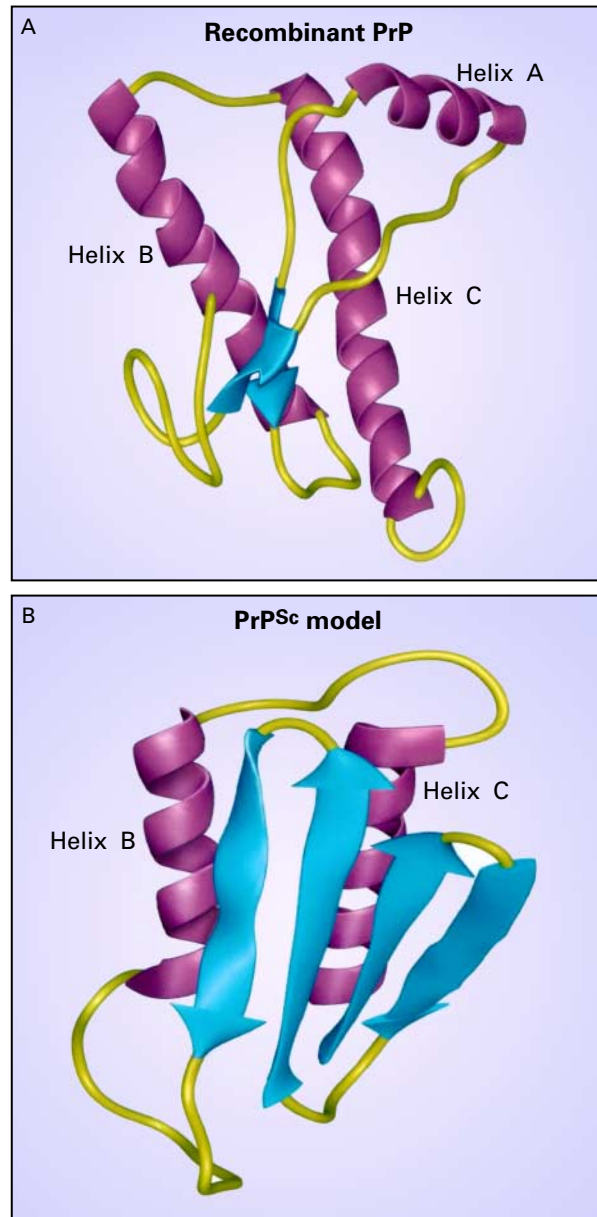


Figure 1. Structures of Prion Protein (PrP) Isoforms.

Panel A shows the α -helical structure of Syrian hamster recombinant PrP 90-231, which presumably resembles that of the cellular isoform (PrP^C). It is viewed from the point at which the scrapie isoform (PrP^{Sc}) is thought to bind to PrP^C. α -Helices A (residues 144 through 157), B (172 through 193), and C (200 through 227) are purple, with loops in yellow; residues 129 through 134, in strand S1, and residues 159 through 165, in strand S2, are blue. Panel B shows a plausible model of the tertiary structure of human PrP^{Sc}. S1 β -strands (residues 108 through 113 and 116 through 122) and S2 β -strands (residues 128 through 135 and 138 through 144) are blue. α -Helices B (residues 178 through 191) and C (residues 202 through 218) are purple, with yellow loops.

TABLE 2. PATHOGENETIC FEATURES OF PRION DISEASES.

DISEASE	HOST	MECHANISM OF PATHOGENESIS*
Kuru	Fore people in New Guinea	Infection through ritualistic cannibalism
Creutzfeldt–Jakob disease		
Iatrogenic	Humans	Infection from prion-contaminated human growth hormone, dura mater grafts, and so forth
New variant	Humans	Infection from bovine prions?
Familial	Humans	Germ-line mutations in the <i>PrP</i> gene
Sporadic	Humans	Somatic mutation or spontaneous conversion of Pr ^{PC} into Pr ^{PSc} ?
Gerstmann–Sträussler–Scheinker disease	Humans	Germ-line mutations in the <i>PrP</i> gene
Fatal familial insomnia	Humans	Germ-line mutations in the <i>PrP</i> gene (D178N, M129)
Sporadic fatal insomnia	Humans	Somatic mutation or spontaneous conversion of Pr ^{PC} into Pr ^{PSc} ?
Scrapie	Sheep	Infection in genetically susceptible sheep
Bovine spongiform encephalopathy	Cattle	Infection with prion-contaminated meat and bone meal
Transmissible mink encephalopathy	Mink	Infection with prions from sheep or cattle
Chronic wasting disease	Mule deer, elk	Unknown
Feline spongiform encephalopathy	Cats	Infection with prion-contaminated beef
Exotic ungulate encephalopathy	Greater kudu, nyala, oryx	Infection with prion-contaminated meat and bone meal

*A question mark indicates that the mechanism has not been confirmed. PrP denotes prion protein.

Creutzfeldt–Jakob disease is approximately 1 case per 1 million population,²³ but among persons between the ages of 60 and 74 years, the incidence is nearly 5 per 1 million.²⁴ Cases in patients as young as 17 years and as old as 83 have been recorded.^{23,25} Creutzfeldt–Jakob disease is relentlessly progressive and usually causes death within a year after its onset. Each geographic cluster of cases of prion disease was initially thought to be a manifestation of viral communicability,²⁶ but each was later shown to be due to a *PRNP* gene mutation except for new variant Creutzfeldt–Jakob disease.

Neuropathological Features

There are often no recognizable gross abnormalities in the brains of patients with Creutzfeldt–Jakob disease. Patients who survive for several years have variable degrees of cerebral atrophy. The microscopical features of Creutzfeldt–Jakob disease are spongiform degeneration and astrogliosis (Fig. 2A and 2B).²⁷

Amyloid plaques occur in approximately 10 percent of cases of Creutzfeldt–Jakob disease. These plaques are positive for antibodies against Pr^{PSc} on immunohistochemical staining.^{28,29} The amyloid plaques in patients with Gerstmann–Sträussler–Scheinker disease consist of a dense core of amyloid surrounded by smaller globules of amyloid (Fig. 2). A characteristic feature of new variant Creutzfeldt–Jakob disease is

the presence of “florid plaques” composed of a core of Pr^{PSc} amyloid surrounded by vacuoles (Fig. 2E and 2F).

Strains of Prions

The existence of prion strains raises the question of how heritable biologic information can be encrypted in a molecule other than nucleic acid.^{30–32} Strains of prions have been defined by the rapidity with which they cause central nervous system disease and by the distribution of neuronal vacuolation.³⁰ Patterns of Pr^{PSc} deposition have also been used to characterize these strains.^{33,34} There is mounting evidence that the diversity of prions is enciphered in the conformation of the Pr^{PSc} protein.^{35–39} Studies involving the transmission of fatal familial insomnia and familial Creutzfeldt–Jakob disease to mice expressing a chimeric human–mouse PrP transgene have shown that the tertiary and quaternary structure of Pr^{PSc} contains strain-specific information.³⁷ Studies of patients with fatal sporadic insomnia have extended these findings,⁴⁰ making it clear that Pr^{PSc} acts as a template for the conversion of Pr^{PC} into nascent Pr^{PSc}.

Sporadic, Genetic, and Infectious Forms of Prion Disease

Sporadic prion diseases might be initiated by a somatic mutation and in this respect might develop in a manner similar to prion diseases caused by germ-line

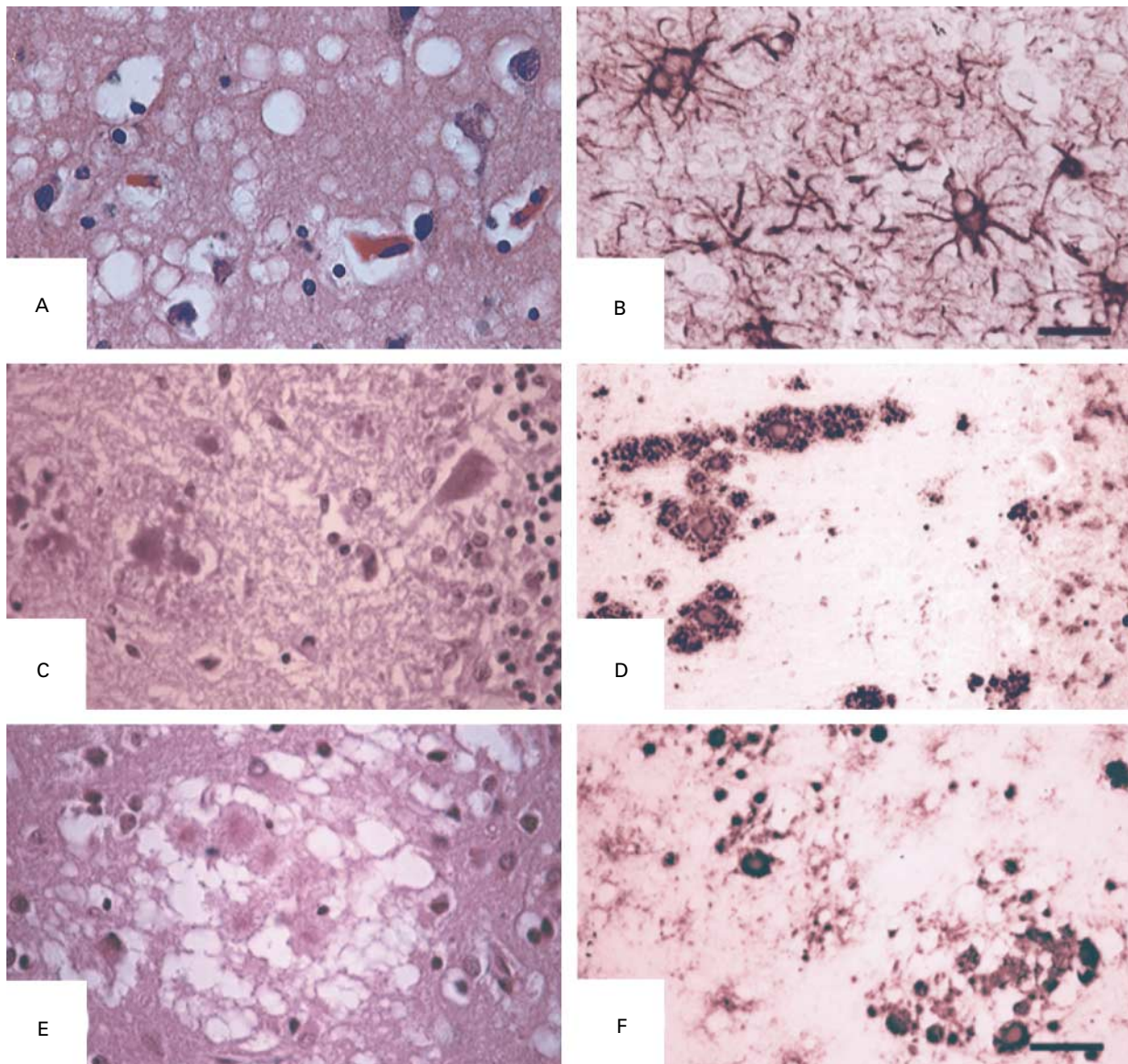


Figure 2. Neuropathological Features of Prion Diseases in Humans.

Sporadic Creutzfeldt–Jakob disease is characterized by vacuolation of the neuropil in the gray matter; by exuberant reactive astrocytic gliosis, the extent of which is proportional to the degree of nerve-cell loss; and in rare cases by the formation of prion protein (PrP) amyloid plaques. The neuropathological features of familial Creutzfeldt–Jakob disease are similar. Gerstmann–Sträussler–Scheinker disease due to a substitution at codon 102 (P102L), as well as other inherited forms of Gerstmann–Sträussler–Scheinker disease, is characterized by numerous deposits of PrP amyloid throughout the central nervous system. New variant Creutzfeldt–Jakob disease is distinguished by the abundance of PrP amyloid plaques, which are often surrounded by a halo of intense vacuolation.

Panel A shows widespread spongiform degeneration in a specimen of cerebral cortex from a patient with sporadic Creutzfeldt–Jakob disease (hematoxylin and eosin, $\times 200$). Panel B shows widespread reactive gliosis in a specimen of cerebral cortex from a patient with sporadic Creutzfeldt–Jakob disease; the specimen is immunostained with antibodies against glial fibrillary acid protein. Panel C shows a specimen of the cerebellum from a patient with Gerstmann–Sträussler–Scheinker disease. Most of the plaques are in the molecular layer, which occupies all but the right-hand portion of the panel; many but not all of the plaques stain positively with periodic acid–Schiff ($\times 200$). Granule cells and a single Purkinje cell are present at the right-hand side of the panel. In Panel D, a specimen of the cerebellum, obtained at the same location as that in Panel C but subjected to hydrolytic autoclaving and immunostaining, reveals more PrP plaques ($\times 100$). In Panel E, a specimen of cerebral cortex obtained from a patient with new variant Creutzfeldt–Jakob disease shows amyloid deposits within vacuoles (hematoxylin and eosin, $\times 200$). These deposits have been referred to as “florid plaques.” In Panel F, a specimen of cerebral cortex obtained from the same location as that in Panel E but subjected to hydrolytic autoclaving and immunostaining for PrP reveals numerous PrP plaques, many of which are in clusters, as well as minute deposits of PrP surrounding many cortical neurons and their proximal processes ($\times 100$). The bar in Panel B represents $50\ \mu\text{m}$ and also applies to Panels A, C, and E. The bar in Panel F represents $100\ \mu\text{m}$ and also applies to Panel D. The specimens from the patients with new variant Creutzfeldt–Jakob disease were provided by James Ironside, Jeanne Bell, and Robert Will.

mutations. In this situation, the mutant PrP^{Sc} must be capable of recruiting wild-type PrP^C, a process that may occur with some mutations but is unlikely with others.⁴¹ Alternatively, the activation barrier separating wild-type PrP^C from PrP^{Sc} may be crossed on rare occasions in the context of a large population of people.⁴² Twenty mutations in the large human *PRNP* gene have been found to segregate with inherited prion diseases.⁴³ Missense mutations and expansions in the octapeptide-repeat region of the gene cause familial prion diseases.¹⁵⁻¹⁹

Although infectious prion diseases constitute less than 1 percent of all cases of prion disease, the circumstances surrounding the transmission of these infectious illnesses are often dramatic (Table 2). Ritualistic cannibalism has resulted in the transmission of kuru among the Fore people of New Guinea, industrial cannibalism has been responsible for bovine spongiform encephalopathy (BSE), or “mad cow disease,” in Europe, and an increasing number of patients have contracted new variant Creutzfeldt–Jakob disease from prion-tainted beef products.¹³

The restricted geographic and temporal distribution of cases of new variant Creutzfeldt–Jakob disease raises the possibility that BSE prions have been transmitted to humans. Although over 100 cases of new variant Creutzfeldt–Jakob disease have been recorded,^{44,45} no dietary habits distinguish patients with this disease from apparently healthy persons. Moreover, it is unclear why teenagers and young adults seem to be particularly susceptible to the disease. These cases may mark the start of an epidemic of prion disease in Great Britain like those of BSE and kuru, or the number of cases of new variant Creutzfeldt–Jakob disease may remain small, as with iatrogenic Creutzfeldt–Jakob disease caused by cadaveric human growth hormone.⁴⁶

The most compelling evidence that new variant Creutzfeldt–Jakob disease is caused by BSE prions comes from studies of mice expressing the bovine PrP transgene.⁴⁷ The incubation times, neuropathological features, and patterns of PrP^{Sc} deposition in these transgenic mice are the same whether the inoculate originated from the brains of cattle with BSE or from humans with new variant Creutzfeldt–Jakob disease.⁴⁷ The origin of BSE is still obscure, although epidemiologic studies indicate that BSE probably arose from a single point source in the southwest of England in the 1970s.⁴⁸ It probably originated from a rare case of prion disease in either sheep (Scott M, Prusiner SB: unpublished data) or cattle.⁴⁸ Once established, the disease was spread in cattle by ingestion of prion-contaminated meat and bone meal.

The accidental transmission of Creutzfeldt–Jakob disease to humans appears to have occurred with corneal transplantation⁴⁹ and use of contaminated electroencephalographic electrodes.⁵⁰ The same improperly decontaminated electrodes that had caused Creutzfeldt–Jakob disease in two young patients with

intractable epilepsy were found to cause Creutzfeldt–Jakob disease in a chimpanzee 18 months after their implantation in the animal.⁵¹ More than 70 cases of Creutzfeldt–Jakob disease associated with the implantation of dura mater grafts have been recorded.⁵² One case occurred after the repair of a perforated eardrum with a pericardial graft.⁵³ Prion-contaminated human growth hormone preparations derived from human pituitary tissue have caused fatal cerebellar disorders with dementia in more than 120 patients ranging in age from 10 to 41 years.^{13,54,55} Four cases of Creutzfeldt–Jakob disease have occurred in women who received human pituitary gonadotropin.⁵⁶

Polymorphisms influence the susceptibility to sporadic, inherited, and infectious forms of prion disease. Dominant negative alleles in approximately 12 percent of the Japanese population⁵⁷ encode for lysine at position 219 and interfere with the conversion of wild-type PrP^C into PrP^{Sc}.^{58,59} Dominant negative inhibition of prion replication has also been found in sheep, with a substitution of the basic residue arginine at position 171.^{60,61}

OTHER NEURODEGENERATIVE DISEASES

Like cases of the prion diseases, most cases of Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and frontotemporal dementia are sporadic; 10 percent or less are inherited. Although age is the most important risk factor in all these sporadic forms of disease, the factors that initiate neurodegeneration remain unknown. In the prion diseases, the initial formation of PrP^{Sc} leads to an exponential increase in the protein, which can be readily transmitted to another host. In the other neurodegenerative diseases, the events that lead to the production of aberrantly processed proteins, as well as the driving forces that sustain their accumulation, are unknown. It is important to stress that in contrast to the prion diseases, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and frontotemporal dementia are not infectious and have not been transmitted to laboratory animals.

Alzheimer’s Disease

A β -amyloid plaques and neurofibrillary tangles are found in both sporadic and inherited forms of Alzheimer’s disease (Table 3). Like familial prion diseases, familial Alzheimer’s disease has an autosomal dominant pattern of inheritance. Familial Alzheimer’s disease can be caused by a mutation in the gene for amyloid precursor protein (APP), presenilin 1, or presenilin 2 (Table 4).⁶² Cleavage of amyloid precursor protein at residue 671 by β -secretase and at either residue 711 or residue 713 by γ -secretase produces A β (1–40) and A β (1–42), respectively. A β (1–42) forms amyloid fibrils readily and is thought to cause central nervous system dysfunction before it is deposited in plaques.⁶³⁻⁶⁵ Presenilin 1 and presenilin 2 may form

TABLE 3. PROTEIN DEPOSITION IN NEURODEGENERATIVE DISEASES.*

DISEASE	PROTEIN	PATHOLOGICAL FINDING
Prion diseases	PrP ^{Sc}	PrP amyloid plaques
Alzheimer's disease	A β Tau	A β amyloid plaques Paired helical filaments in neurofibrillary tangles
Parkinson's disease	α -Synuclein	Lewy bodies
Frontotemporal dementia	Tau	Straight filaments and paired helical filaments
Pick's disease	Tau	Pick bodies
Progressive supranuclear palsy	Tau	Straight filaments in neurofibrillary tangles
Amyotrophic lateral sclerosis	Neurofilament	Neuronal aggregates
Huntington's disease	Huntingtin	Nuclear inclusions
Spinocerebellar ataxia		
Type 1	Ataxin 1	Nuclear inclusions
Type 2	Ataxin 2	Cytoplasmic inclusions
Machado–Joseph disease	Ataxin 3	Nuclear inclusions

*PrP denotes prion protein, and PrP^{Sc} the scrapie isoform of PrP.

complexes with at least one other protein, nicastrin, a transmembrane neuronal glycoprotein, and these complexes may contribute to the production of A β (1–42).⁶⁶

The age of onset of both sporadic and familial forms of Alzheimer's disease is modulated by allelic variants of apolipoprotein E.⁶⁷ Three alternative allelic products of apolipoprotein E, denoted ϵ 2, ϵ 3, and ϵ 4, differ at amino acid residues 112 and 158. In many persons with two ϵ 4 alleles, Alzheimer's disease develops at least a decade before it does in those with two copies of ϵ 2, and ϵ 3 is associated with an onset of disease at an intermediate age.⁶⁸

Frontotemporal Dementia and Pick's Disease

Mutations in the *tau* gene, which codes for tau, a protein associated with microtubules, cause inherited forms of frontotemporal dementia and Pick's disease.^{69–71} As with Alzheimer's disease, about 90 percent of cases of frontotemporal dementia are sporadic, and the rest are familial. Straight filaments composed of hyperphosphorylated mutant tau have been found in the brains of patients with familial frontotemporal dementia (Table 3).⁷² In some cases, neurofibrillary tangles composed of paired helical filaments have been found; the formation of these filaments seems to depend on the specific mutation and on the specific isoform of the protein (Table 4).⁷³ In sporadic cases of frontotemporal dementia, aggregates of tau are uncommon. Approximately 15 percent of patients with frontotemporal dementia have Pick bodies,⁷⁴ which are intracellular collections of partially degraded (ubiquitinated) tau fibrils in the brain.⁷⁵ As with frontotemporal dementia, most cases of Pick's disease are sporadic. Other disorders caused by the misprocessing of tau include progressive supranuclear palsy, progressive subcortical gliosis, and corticobasal degeneration.^{73,75–77}

TABLE 4. MUTANT GENES IN FAMILIAL NEURODEGENERATIVE DISEASES.

DISEASE	GENE	MUTATION
Prion diseases	<i>PRNP</i>	Point mutations and octapeptide repeats
Alzheimer's disease	<i>APP</i> <i>PS1</i> <i>PS2</i>	Point mutations Point mutations Point mutations
Parkinson's disease	<i>SNCA</i> <i>parkin</i>	Point mutations Point mutations
Frontotemporal dementia	<i>tau</i>	Point mutations, deletions
Pick's disease	<i>tau</i>	Point mutations
Amyotrophic lateral sclerosis	<i>SOD1</i>	Point mutations
Huntington's disease	<i>HD</i>	Polyglutamine expansions
Spinocerebellar ataxia		
Type 1	<i>SCA1</i>	Polyglutamine expansions
Type 2	<i>SCA2</i>	Polyglutamine expansions
Machado–Joseph disease	<i>SCA3</i>	Polyglutamine expansions

Parkinson's Disease

Most cases of Parkinson's disease are sporadic,^{78,79} but both sporadic and familial forms of the disease are characterized by protein deposits in the central nervous system. Mutations in the gene for α -synuclein have been found in patients with familial Parkinson's disease.⁸⁰ In both sporadic and familial cases, antibodies to α -synuclein, a presynaptic intracellular protein, stain Lewy bodies in neurons of the substantia nigra.⁸¹ Whereas the inheritance of Parkinson's disease due to mutations in the α -synuclein gene is autosomal dominant, a childhood form of the disease due to mutations in the gene for ubiquitin–protein ligase (*parkin*) is a recessive disorder (Table 4).⁸² *Parkin* seems to promote the degradation of certain neu-

ronal proteins, and selective nitration of α -synuclein has been observed in Lewy bodies.⁸³

Parkinson's disease in older persons is associated with a high incidence of dementia.⁸⁴ At autopsy, the brains of such patients often have the neuropathological hallmarks of both Alzheimer's disease and Parkinson's disease. Immunohistochemical studies showing the presence of α -synuclein in cortical Lewy bodies have helped resolve the conundrum of how a patient could have insufficient numbers of plaques and neurofibrillary tangles for the diagnosis of Alzheimer's disease but still have dementia. The presence of these α -synuclein deposits, alone or in combination with changes that are characteristic of Alzheimer's disease, may be the second most common form of neurodegeneration, accounting for 20 to 30 percent of cases of dementia among persons over the age of 60 years.^{85,86} A small number of younger persons with Parkinson's disease also have dementia due to diffuse Lewy body disease.⁸⁷

Amyotrophic Lateral Sclerosis

Although most cases of amyotrophic lateral sclerosis are sporadic, familial cases have been identified.⁸⁸⁻⁹⁰ In approximately 20 percent of familial cases of amyotrophic lateral sclerosis, there are mutations in the gene for cytoplasmic superoxide dismutase type 1 (SOD1) (Table 4).⁹¹ Moreover, deposits of SOD1 in the central nervous system have been found in both sporadic and familial cases of amyotrophic lateral sclerosis.⁹² Although in some cases abnormal collections of neurofilaments have been seen in degenerating motor neurons, no familial cases have been shown to be due to mutations in neurofilament genes.⁹²

Huntington's Disease and Spinocerebellar Ataxias

Unlike Alzheimer's disease, frontotemporal dementia, Parkinson's disease, amyotrophic lateral sclerosis, and the prion diseases, which in most cases are sporadic, all cases of Huntington's disease and of spinocerebellar ataxia are caused by expanded polyglutamine repeats (Table 4).⁹³⁻⁹⁵ But these diseases are similar to the inherited forms of Alzheimer's disease, frontotemporal dementia, Parkinson's disease, amyotrophic lateral sclerosis, and the prion diseases in that they are usually manifested as neurologic deficits in adulthood, even though the expression of the mutant gene products in the central nervous system begins early in life. Childhood forms of Huntington's disease and spinocerebellar ataxia are known to be due to large expansions of the causative triplet repeats.^{94,96,97}

Transgenic Mouse Models

Although virtually every facet of the human and animal prion diseases has been reproduced in transgenic mice, attempts to develop transgenic models for the other neurodegenerative diseases have proved more difficult. Despite the lack of perfect transgenic

models for Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementias, Huntington's disease, and the spinocerebellar ataxias, many aspects of these human disorders have been reproduced. Mice expressing transgenes carrying mutations found in the inherited forms of these neurodegenerative diseases develop disorders with many of the neuropathological features that characterize the corresponding human illnesses (Tables 3 and 4).

DIAGNOSTIC TESTS

There is an urgent need for a rapid, antemortem test for prions in humans and livestock. A highly sensitive quantitative immunoassay has been developed on the basis of antigens that are exposed in PrP^C but buried in PrP^{Sc}. Unlike earlier immunoassays for PrP^{Sc}, this conformation-dependent immunoassay does not require limited proteolysis to hydrolyze PrP^C before the protease-resistant core of PrP^{Sc} (PrP 27-30) is measured.³⁸ This assay has been used to identify a new form of PrP^{Sc}, which is protease-sensitive (sPrP^{Sc}).

A diagnostic test would be valuable for distinguishing between early Alzheimer's disease and depression in older persons, since both disorders are so common. In Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and the prion diseases, computed tomography or magnetic resonance imaging may show normal findings or cortical atrophy. In patients with Alzheimer's disease, widespread atrophy with enlarged ventricles is often seen, especially late in the disease, but this finding is not diagnostic. Many elderly persons with normal cognition have similar radiographic findings.^{98,99} Although many patients with Creutzfeldt-Jakob disease have elevated levels of protein 14-3-3 in cerebrospinal fluid, this finding is not specific for the diagnosis.^{100,101} Attempts to measure $A\beta(1-40)$ in blood and urine as diagnostic tests have been unrewarding,¹⁰² but the use of fluorescence correlation spectroscopy to measure $A\beta(1-40)$ in cerebrospinal fluid may provide a reliable diagnostic test for Alzheimer's disease.¹⁰³

Whereas electroencephalographic studies are not useful for the diagnosis of Alzheimer's disease, frontotemporal dementia, or Parkinson's disease, they are often useful for the diagnosis of Creutzfeldt-Jakob disease. Repetitive, high-voltage, triphasic and polyphasic sharp discharges are seen in most advanced cases of Creutzfeldt-Jakob disease, but their presence is often transient.^{25,101,104,105} As the disease progresses, normal background rhythms become fragmentary and slower.

Hashimoto's thyroiditis should always be considered in the differential diagnosis of Creutzfeldt-Jakob disease,¹⁰⁶ since the former disorder is a treatable autoimmune disease whereas Creutzfeldt-Jakob disease is not. The clinical and neuropathological findings in these two disorders can be quite similar, raising the possibility that protein misprocessing underlies both degenerative and autoimmune diseases.

PREVENTION AND TREATMENT

With the exception of levodopa, which ameliorates the symptoms of Parkinson's disease but does not halt the underlying degeneration, there are no effective therapies for neurodegenerative diseases. The history of successful attempts to prevent or reverse protein misprocessing is extremely limited.¹⁰⁷ Developing new drugs directed to specific regions of the central nervous system will be challenging.

Preventing Abnormal Processing of Proteins and Enhancing Their Clearance

Structure-based drug design based on dominant negative inhibition of prion formation has resulted in the development of several compounds.¹⁰⁸ However, the task of exchanging polypeptide scaffolds for small heterocyclic structures without the loss of biologic activity remains difficult. Whether this approach to preventing the aberrant processing of proteins will lead to the development of new treatments for Alzheimer's and Parkinson's diseases, as well as other neurodegenerative disorders, remains to be established.

Several compounds can eliminate prions from cultured cells. A class of compounds known as "dendrimers" seems particularly effective in this regard.¹⁰⁹ Some drugs delay the onset of disease in animals that have been inoculated with prions if the drugs are given around the time of the inoculation.¹¹⁰ A novel approach to treating Alzheimer's disease has been developed in transgenic mice that overexpress a mutant *APP* gene. Immunization of these mice with the A β peptide or injection of antibodies to A β reduces plaque formation.¹¹¹ Whether this approach will prove fruitful in patients is unknown.

Replacement Therapy

Because the neurodegeneration in Parkinson's disease is confined largely to the substantia nigra, especially early in the disease process, replacement therapy with levodopa has proved useful; in many patients, however, the disease eventually becomes refractory to levodopa.¹¹² Similar approaches to the treatment of Alzheimer's disease have been disappointing, primarily because the disease process is so widespread. Similarly, the widespread neuropathological changes in amyotrophic lateral sclerosis, frontotemporal dementia, and prion diseases make it unlikely that replacement therapy will be successful.

SPECULATION ON THE SPECTRUM OF DEGENERATIVE DISEASES

It is tempting to speculate that abnormal processing of neuronal proteins also occurs in other diseases of the central nervous system, such as schizophrenia, bipolar disorders, autism, and narcolepsy.¹¹³ Most cases of these diseases are sporadic, but a substantial minority appear to be familial. The absence of neuropathological changes in these conditions has impeded

phenotypic analysis. In a group of patients with inherited frontotemporal dementia who have a mutation in the *tau* gene, alcoholism and Parkinson's disease are prominent features.¹¹⁴

Whether multiple sclerosis is also the result of defective processing of brain proteins is unknown.¹¹⁵ The immune system features prominently in the pathogenesis of multiple sclerosis, and it is often argued that this disease is a T-cell-mediated, autoimmune disorder. Antibody-mediated demyelination has been found in some cases of multiple sclerosis,¹¹⁶ and in others, degeneration of oligodendrocytes has been observed, with little or no evidence of immune-mediated damage.¹¹⁷ Perhaps ulcerative colitis, Crohn's disease, rheumatoid arthritis, type 1 diabetes mellitus, and systemic lupus erythematosus ought to be considered disorders of protein processing in which misfolded proteins evoke an autoimmune response.

The systemic amyloidoses share important features with the neurodegenerative diseases. In primary amyloidosis, immunoglobulin light chains form amyloid deposits that can cause cardiomyopathy, renal failure, and polyneuropathy.¹¹⁸ In response to chronic inflammatory diseases, the serum amyloid A protein is cleaved and forms the amyloid A protein, which is deposited as fibrils in the kidney, liver, and spleen. The most common form of systemic hereditary amyloidosis is caused by the deposition of mutant transthyretin. Also noteworthy are amylin deposits in the β -islet cells of patients with type 2 diabetes mellitus. These deposits contain amyloid fibrils that are composed of the amylin protein.

THE FUTURE

As life expectancy continues to increase, the burden of degenerative diseases is growing. Developing effective means of preventing these disorders and of treating them when they do occur is a paramount challenge. The problems caused by Alzheimer's disease and Parkinson's disease are already so great that if the prevalence of these maladies continues to increase in accordance with the changing demographic characteristics of the world population, they will bankrupt both developed and developing countries over the next 50 years. It is remarkable to think that by the year 2025, more than 65 percent of persons over the age of 65 years will be living in countries that are now designated as developing countries.¹¹⁹ Unless effective methods of prevention and treatment are developed, this enormous population of people will be subjected to the same risks of Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders as are older persons currently living in the most affluent countries.

Over the past two decades, remarkable progress has been made in elucidating the causes of neurodegenerative diseases, and the time has come to intensify the search for drug targets and for compounds

that interrupt the disease processes. Drugs that block the mishandling of a particular protein may be most effective for certain disorders; for others, drugs that enhance the clearance of an aberrant protein or fragment may prove most useful. Regardless of the therapeutic approach, accurate, early detection of neurodegeneration will be extremely important so that drugs can be given before substantial damage to the central nervous system has occurred. However, the enormity of these tasks — developing useful diagnostic tests and discovering effective therapies — should not be underestimated.

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