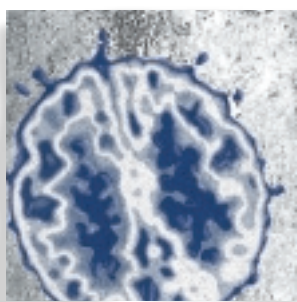# Biochemical aspects of dementias

Christoph Hock, MD

Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, and prion diseases are age-related neurodegenerative disorders associated with a progressive decline of cognitive brain functions. Due to the increase in prevalence rates, and the rising costs associated with clinical and social care, treatments designed to prevent or reverse these diseases are urgently needed. The most common major biochemical characteristic of these neurodegenerative diseases is the deposition of abnormal protein aggregates in brain. The decryption of the mechanisms of aggregation and associated neurotoxicity may reveal new therapeutic targets, which will enable treatment for these devastating conditions.

Dialogues Clin Neurosci. 2003;5:27-33.

Author affiliations: Division of Psychiatry Research, University of Zurich, Zurich, Switzerland

Address for correspondence: Division of Psychiatry Research, Psychiatry University Hospital, University of Zurich, Lenggstrasse 31, PO Box 68, CH-8029 Zurich, Switzerland
(e-mail: chock@bli.unizh.ch)

Over the past 2 decades, the diagnostic classification of dementias has been continuously adapted to the increasing knowledge derived from clinical symptomatology, neuropathology, biochemistry, and clinicopathological comparisons. Before, dementias were attributed primarily to cerebral vascular insufficiency. Later, with the diagnosis of Alzheimer's disease (AD) predominating, further differentiations were categorized: frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), vascular dementia (VD), prion disease, dementia with argyrophilic grains, British dementia, and many more. This development was driven by the results of molecular analyses of the abnormal protein deposits in the brain of the respective diseases in relation to the clinical syndromes. The careful clinical and neurochemical investigation of dementias has led to practical guidelines and improvements in current treatment and care, eg, the use of atypical neuroleptics in patients with DLB due to the high susceptibility to side effects by treatment with typical antipsychotics.

More excitingly, the dissection of the molecular mechanisms and species involved in the aggregation process may allow for the development of specific therapies, which may, in the future, contribute to the prevention and treatment of neurodegenerative diseases.

The following diseases are characterized by the deposition of protein aggregates, termed amyloid, derived from the Greek amylum (starch, sugar); the term was first introduced by Virchow in 1854 on the basis of color after staining with iodine, since he assumed that polysaccharides were the major constituents of amyloid deposits in peripheral tissues.[1] The secondary structure of amyloid deposits both in the brain as well as in peripheral organs shows a strong tendency towards formation of β-pleated sheets; the tertiary structure forms high-order quasi-crystalline complexes that are birefringent under polarized light (eg, when stained with Congo red), and fibrils can be identified by electron microscopy.[1,2] *Table I* lists the neurodegenerative diseases associated with deposition of abnormal proteins in the brain.

Basic research

Alzheimer's disease

AD is the most common form of dementia. It affects about 20 to 30 million people worldwide.[3,4] The prevalence increases exponentially with age between 55 to 64 years (less than 1%) ending up at over 20% in the over-85 age-group.[5] Clinically, AD is characterized by progressive cognitive deficits such as impairment of memory and orientation. With disease progression, noncognitive symptoms such as delusions, agitation, changes in personality, and mood disturbances may also occur. From a genetic point of view, AD may be subdivided into three forms according to the observed mode of inheritance: first, autosomal-dominant familial AD; second, familial AD without clear mendelian inheritance (familial aggregation); and third, sporadic AD without familial aggregation. About 5% to 10% of all AD cases can be fully explained by the presence of genetic factors in terms of autosomal dominant AD. These cases are caused by mutations in the genes encoding amyloid precursor protein (*APP*, located on chromosome 21), presenilin 1 (*PSEN1*, chromosome 14), and presenilin 2 (*PSEN2*, chromosome 1). In other cases, a different familial aggregation can be observed: relatives of AD patients show increased risk of developing dementia compared with relatives of healthy control subjects without clear autosomal-dominant inheritance.[6,7] This type of familial aggregation may be due to shared genetic or environmental risk factors within families. Finally, the major proportion of AD cases is, however, sporadic, which is defined as the absence of evidence for familial aggregation. This group is nevertheless influenced by so-called susceptibility genes that confer a minor genetic risk associated with allelic variations in the form of single nucleotide polymorphisms (SNPs).

Histopathologically, AD is characterized by two hallmarks: the extracellular β-amyloid plaques with amyloid β-peptides (Aβ) as major constituents, and the intracellular neurofibrillary tangles (NFTs), ultrastructurally described as paired helical filaments (PHFs), made up predominantly by tau proteins. Aβ peptides are 38 to 42 amino acids in length and are derived by endoproteolysis of APP by the combined activities of β-secretase (BACE) at the amino terminal and γ-secretase that cleave at the C-terminal, respectively, of the Aβ domain.[8] Alternative amino terminal cleavage by β-secretase (tumor necrosis factor–α convertase [TACE]/A Disintegrin And Metalloproteinase [ADAM10]) within the Aβ domain results in the generation of nonamyloidogenic fragments. Mutations in all three genes causing familial AD—*APP*, *PSEN1*, and *PSEN2*—alter the processing of APP toward the production of more amyloidogenic Aβ species.[9]

Genetic, histopathological, and other experimental findings prompted the hypothesis that Aβ peptides are an essential feature of the pathogenetic cascade causing AD: Aβ deposits into β-amyloid plaques and causes neuronal dysfunction, ultimately leading to neurodegeneration and dementia.[10] $A\beta_{40}$ and, in particular, $A\beta_{42}$ rapidly aggregate to form oligomers, protofibrils, and fibrils[11] that can deposit into β-amyloid plaques, induce cell death,[12] and accelerate formation of NFTs.[13,14] The brain β-amyloid burden increases with age and correlates with the learning capacities in mutated APP-transgenic mice.[15] The functional impact of fibrillar Aβ peptides was demonstrated by Walsh et al[16] in a series of experiments using APP V717F Chinese hamster ovary cells. Intracerebroventricular microinjection of conditioned medium of these cells containing sodium dodecyl sulfate (SDS)–stable Aβ oligomers resulted in marked reduction in long-term potentiation (LTP) in the hippocampus, a measure of synaptic plasticity. Possibly, the formation of a pore-like morphology by Aβ protofibrils resembling cytolytic pore-forming toxins from bacteria plays a role in Aβ-mediated neurotoxicity.[17] These experiments strongly suggest that Aβ aggregation drives the pathology of AD. It remains to be shown which state of the aggregation process is the most toxic: the oligomers, protofibrils, fibrils, or the compact aggregates. Based on the findings mentioned above, oligomers and protofibrils are clearly suspects as central players in the aggregation process. This hypothesis is supported by the recent finding of Nilsberth et al[18]: they discovered a path-

ogenic APP mutation, located within the Aβ sequence, that causes early-onset AD in a Swedish family. Aβ with the Arctic mutation formed protofibrils at a much higher rate and in larger quantities than wild-type Aβ. Thus, rapid Aβ protofibril formation may lead to accelerated buildup of insoluble Aβ intracellularly and/or extracellularly, and thereby cause early-onset AD.

Collectively, AD is caused by formation of fibrils and aggregates of Aβ peptides, a cleavage product from APP, which is a transmembrane type I protein with neurotrophic function. Mutations in genes encoding for APP, presenilin 1, and presenilin 2 result in early onset of AD by increased production of Aβ peptides. Sporadic forms of AD may be caused by impaired clearance of Aβ aggregates from brain.

Frontotemporal dementia

FTD designates a clinical syndrome characterized by behavioral changes, including social misconduct, disinhibition, hyperorality, apathy, etc, and also memory deficits.[19-21] Usually, the behavioral symptoms outweigh the cognitive deficits in these patients. Among the neurological features, Parkinsonism can develop with disease progression and may become predominant in some patients.[19] FTD was clinically classified by consensus criteria some years ago[22,23] and was therefore supposed to be underrecognized by the usual dementia screening procedures established in the last decades in dementia clinics. It is estimated that FTD accounts for up to 20% of dementia with early onset.[18] The subclassification list includes such syndromes as frontal dementia, progressive aphasia, and semantic dementia.

The frontal type includes Pick's disease, characterized by circumscribed frontal or temporal atrophy, as one specific and rare subtype. Neuropathological features of FTD are diffuse bilateral atrophy of the frontal and anterior temporal lobes and degeneration of the striatum. Histopathological findings include loss of large cortical nerve cells and spongiform (microvacuolar) degeneration of the superficial neuropil, gliosis, and tau- or ubiquitin-positive inclusion bodies.[19] The microtubule-associated tau proteins are essential for the assembly and stabilization of microtubules.[24] Tau proteins are widely expressed in the central nervous system (CNS), predominantly in axons, and to a much lesser extent in glial cells.[25] During neurodegenerative diseases, tau is redistributed to the somatodendritic compartments. In the human brain, six isoforms of tau ranging from 352 to 441 amino acids are produced from a single gene mapping to 17q21 by alternative mRNA splicing.[25] In the AD brain, PHF tau is abnormally phosphorylated.[26] Consequently, the kinases and phosphatases regulating tau phosphorylation are a focus of therapeutic research.

A portion of FTD syndromes is characterized by prominent filamentous tau inclusions and neurodegeneration in the absence of β-amyloid deposition. This tau form of FTD was therefore grouped together with other neurodegenerative diseases where tau pathology was predominant and termed "tauopathies": sporadic corticobasal degeneration, progressive supranuclear palsy, Pick's disease, as well as hereditary FTD and Parkinsonism linked to chromosome 17 (FTD-17).[25] Clinical manifestations of the tauopathies are not restricted to the brain; they may include other

Disease	Abnormal protein	Deposition	Gene	Chromosome	Other brain diseases with similar abnormal protein deposits
Alzheimer's disease	Aβ	β-Amyloid plaques	*APP* *PSEN1* *PSEN2*	Chromosome 21 Chromosome 14 Chromosome 1	Down syndrome
	Tau	Neurofibrillary tangles	*tau*	Chromosome 17	
Frontotemporal dementia	Tau	Filamentous tau deposits Neurofibrillary tangles	*tau*	Chromosome 17	Corticobasal degeneration Progressive supranuclear palsy Dementia pugilistica Tangle-only dementia Argyrophilic grain dementia
Dementia with Lewy bodies	α-Synuclein	Lewy bodies	*α-SYN*	Chromosome 4	Parkinson's disease
Prion disease	PrP^Sc	PrP^Sc-positive plaques	*PRNP*	Chromosome 20	Scrapie, BSE

Table I. Neurodegenerative diseases are associated with deposition of abnormal proteins in brain. BSE, bovine spongiform encephalopathy.

organ systems, eg, in Hallervorden-Spatz disease, myotonic dystrophy, or Niemann-Pick disease type C.

Tau proteins vary among the different tauopathies in isoform and phosphorylation state. Since several tau mutations were shown to be causative for several tauopathies including FTD, tau abnormalities that may be mechanistically involved in the pathogenesis of neurodegeneration were investigated. It was hypothesized that different tau mutations are pathogenic because they impair tau function, promote tau fibrillization, or perturb tau gene splicing, thereby leading to formation of biochemically and structurally distinct aggregates of tau.[25]

Collectively, tauopathies, including a portion of FTD, are associated with deposition of aggregated, abnormally phosphorylated tau proteins which normally stabilize microtubule function in the cell.

Dementia with Lewy bodies

DLB accounts for about 20% of the dementias in the elderly.[27] This disorder has clinical and pathological features in common with both AD and Parkinson's disease (PD).[19,27] Dementia is often associated with Parkinsonism, visual hallucinations, orthostatic hypotension, and, typically, fluctuations in cognitive performance and levels of consciousness.[19,27] Lewy bodies contain filamentous aggregates and α-synuclein as major constituents[28] and deposit in paralimbic and cortical brain areas along with neuritic changes.[29,30] Cooccurrence of β-amyloid plaques and vascular disease is frequent, whereas the presence of NFTs is rare.[31] In contrast to FTD and in line with AD, there is a pronounced deficit in cholinergic neurotransmission, which makes this disease a possible indication for treatment with acetylcholinesterase inhibitors.[27]

α-Synuclein is abundantly expressed in presynaptic terminals and probably regulates synaptic neurotransmission.[32] Mutations in the α-synuclein gene located to chromosomal 4q21-23 are linked to autosomal-dominant PD.[33,34] α-Synuclein containing Lewy pathology or α-synuclein fibrils were also shown to be present in Hallervorden-Spatz disease (neurodegeneration with brain iron accumulation type 1) and multisystem atrophy, as well as pure autonomic failure and Lewy body dysphagia.[32,35,36] The term multisystem atrophy summarizes olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome.

α-Synuclein is a naturally unfolded protein with α-helical domains. The synuclein family consists of three members, α-, β-, and γ-synuclein, ranging from 127 to 140 amino acids in length.[37] In the filaments associated with PD and DLB, the amino terminal region of α-synuclein seems to be buried in the body of the filament, while the carboxy terminal region is exposed on the filament surface.[36] The conversion of native α-synuclein to protofibrils and fibrils continues to be a matter of intense research. Factors that promote fibril formation in vitro include high temperature, low pH, high concentration, and oxidative conditions.[32]

Together, diseases associated with Lewy bodies including DLB are associated with abnormal neuronal aggregates of α-synuclein, a protein associated with synaptic function.

Prion diseases

Prion diseases are caused by infectious proteins that convert normal cellular prion protein (PrP^C) into the disease-causing scrapie (PrP^{Sc}) isoform.[38] In contrast to the aforementioned neurodegenerative disorders, prion diseases are transmissible and, in contrast to viruses, PrP^{Sc} is encoded by a chromosomal gene, located on chromosome 20, termed *PRPN*.

The class of prion diseases summarizes such conditions as kuru, Creutzfeldt-Jakob disease (CJD; sporadic, familial, iatrogenic, and new variant), Gerstmann-Sträussler-Scheinker disease, as well as fatal familial and sporadic insomnia in humans.[38,39] In addition, prion diseases are known in species such as sheep, cattle, mink, mule deer, elk, cats, kudu, nyala, and oryx.[38,40] The incidence of sporadic CJD is highest between the ages of 60 and 74, almost 5 cases per million.[37] The increasing incidence of the new variant of CJD is associated with the bovine spongiform encephalopathy (BSE) epidemic in cattle and affects predominantly younger subjects.[41] Familial forms can be caused by mutations in the prion gene. The clinical manifestations are heterogenous and include dementia, myoclonia, visual disturbances, ataxia, insomnia, paraplegia, sensory symptoms, and behavioral disturbances.[42] The characteristic neuropathologial features are spongiform degeneration and astrogliosis.[43] Amyloid plaques positive for PrP^{Sc} have been found, and they occur as "florid" plaques in the new variant CJD form, composed of a dense core PrP^{Sc} amyloid plaque surrounded by vacuoles.[38] The mature PrP^C is a result of two processing steps from the 254 amino acid PrP^C precursor protein, resulting in a 209–amino acid PrP^C.[44] PrP^C and PrP^{Sc} are identical in amino acid sequence and posttranslational modifications, but differ in secondary and tertiary structures,

resulting in partial protease resistance of the latter. In case of prion infection in humans or animals, the point of entry is outside the nervous system. The march of prions into the CNS ("neuroinvasion") may involve the lymphoreticular or autonomic nervous system.[40]

Together, prion diseases are caused by aggregation of prion proteins, most likely initiated by conversion of a physiological conformation (PrP^C) into an infectious form (PrP^{Sc}), which serves as a seed that induces polymerization,[45] formation of fibrils, and deposition.

Neurotoxicity of protein aggregates

AD, FTD, DLB, and prion diseases share the deposition of abnormally folded proteins as a common denominator. All of these diseases occur predominantly sporadically with a minor portion caused by mutations associated with familial forms of the disease. The formation of aggregates may be a desperate attempt to eliminate the toxicity of misfolded proteins and their oligomeric or fibrillar states. The pathogenetic mechanisms entail abnormal proteolytic cleavage, posttranslational processing, misfolding, and reduced clearance of protein aggregates. The dissection of the kinetics of folding and deposition, the folding intermediates, and promoting factors will be crucial for the discovery of new therapeutic targets.

The variety of protein species that are capable of forming β-pleated sheets, deposit into amyloid, and induce neurodegeneration suggests an inherent neurotoxicity of protein aggregates. Interestingly, a range of proteins not associated with amyloid diseases are also able to aggregate in vitro into fibrils barely distinguishable from those found in pathological conditions.[46-48] Thus, aggregation may be viewed as a general property of polypeptide chains that occurs in a specific environment. Whether this process ends up in neurodegeneration may depend on the selective vulnerability determined by age-related cellular alterations, genetic background, and capacity of removal and repair mechanisms.

The neuronal cell possesses a defense machinery, eg, chaperones, which protects against protein misfolding, a process that occurs, like DNA replication errors, permanently during protein synthesis and transport.[49] Imperfectly produced proteins are degraded by a sort of clearance pathway, such as the ubiquitin-proteasome system.[50] Dysfunction of both the protein folding defense system and the degrading system of defective proteins may also contribute to the development of neurodegenerative diseases.

Several conclusions can be made from the dissection of abnormal protein deposits in dementias: first, prevention of the deposition of a specific protein, eg, β-amyloid in AD, may be a cure for AD only, and not for the related conditions FTD, DLB, VD, etc, since these are caused by or associated with other protein aggregates; second, there is cooccurrence of dementing conditions in a considerable portion of patients, such as AD combined with VD, or AD combined with DLB, which may require combination of specific therapies; third, there may be an inherent toxicity of protein aggregates that is independent of the specific peptide deposited. The latter may offer the search for treatment targets that are common to a variety of neurodegenerative conditions associated with protein misfolding, aggregation, and deposition.

The future therapy of neurodegenerative disorders may aim to prevent the formation and deposition of abnormal proteins prior to clinical manifestation of the disease. The major prerequisite for such therapeutic strategies is the availability of accurate and reliable preclinical diagnostic markers, a major challenge that is as yet unresolved. Clearance of deposited abnormal proteins from brain may be another therapeutic approach in patients who already display the neurodegenerative disease. It remains to be shown whether such interventions would be capable of relieving the brain of the toxic burden, stimulate recovery of neuronal damage, and, ultimately, result in the restoration of normal function. ❏

REFERENCES

1. Sipe JD, Cohen AS. History of the amyloid fibril. *J Struct Biol*. 2000;130: 88–98.
2. Aguzzi A, Glatzel M, Montrasio F, Prinz M, Heppner FL. Interventional strategies against prion diseases. *Nature*. 2001;2:745-749.
3. Alzheimer's Disease and Related Disorders Association. Statistics About Alzheimer's Disease. 2001. Available at: www.alz.org/AboutAD/Statistics.htm. Accessed 5 March 2003.
4. Alzheimer's Disease International Factsheet. The prevalence of dementia. 1997. Available at: http://www.alzheimers.org.uk/society/p_demography. html#world5. London, UK: Alzheimer's Disease International. Accessed 11 March 2003.

Basic research

Aspectos bioquímicos de las demencias

La Enfermedad de Alzheimer, la demencia fronto-temporal, la demencia con cuerpos de Lewy y las enfermedades por priones son trastornos neuro-degenerativos relacionados con la edad, asociados con una declinación progresiva de las funciones cerebrales cognitivas. Debido al aumento en las frecuencias de prevalencia y al incremento de los costos asociados a los cuidados clínicos y sociales, se necesita en forma urgente de tratamientos diseñados para prevenir o revertir estas enfermedades. La característica bioquímica principal más común de estas enfermedades neurodegenerativas es el depósito de agregados de proteínas en el cerebro. La descripción de los mecanismos de agregación y neurotoxicidad asociados puede revelar nuevos objetivos terapéuticos que posibilitarían tratamientos para estas devastadoras enfermedades.

Aspects biochimiques des démences

La maladie d'Alzheimer, la démence frontotemporale, la démence avec corps de Lewy et les maladies à prions sont des troubles neurodégénératifs liés à l'âge associés avec un déclin progressif des fonctions cérébrales cognitives. Étant donné l'augmentation des taux de prévalence et des coûts associés aux prises en charge cliniques et sociales, il est urgent de disposer de traitements conçus pour prévenir ou lutter contre ces maladies. La caractéristique biochimique majeure la plus courante de ces maladies neurodégénératives est le dépôt d'agrégats de protéines anormales dans le cerveau. Le décryptage des mécanismes d'agrégation et de la neurotoxicité associée peuvent révéler de nouvelles cibles thérapeutiques qui permettront aux traitements d'agir sur ces troubles dévastateurs.

5. Ott A, Breteler MM, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *BMJ*. 1995;310:970-973.

6. Farrer LA, O'Sullivan DM, Cupples LA, Growdon JH, Myers RH. Assessment of genetic risk for Alzheimer's disease among first-degree relatives. *Ann Neurol*. 1989;25:485-493.

7. Silverman JM, Li G, Zaccario ML, et al. Patterns of risk in first-degree relatives of patients with Alzheimer's disease. *Arch Gen Psychiatry*. 1994;51:577-586.

8. Shoji M, Golde TE, Ghiso J. Production of the Alzheimer amyloid beta protein by normal proteolytic processing. *Science*. 1992;258:126-129.

9. Scheuner D, Eckman C, Jensen M, et al. Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat Med*. 1996;2:864-870.

10. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev*. 2001;81:74-66.

11. Lansbury PT Jr. Evolution of amyloid: What normal protein folding may tell us about fibrillogenesis and disease. *Proc Natl Acad Sci U S A*. 1999;96:3342-3344.

12. Lorenzo A, Yankner BA. Beta-amyloid neurotoxicity requires fibril formation and is inhibited by congo red. *Proc Natl Acad Sci U S A*. 1994;91:12243-12247.

13. Götz J, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P301L tau transgenic mice induced by Aβ42 fibrils. *Science*. 2001;293:1491-1495.

14. Lewis J, Dickson DW, Lin WL, et al. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. *Science*. 2001;293:1446-1447.

15. Chen GQ, Chen KS, Knox J, et al. A learning deficit related to age and β-amyloid plaques in a mouse model of Alzheimer's disease. *Nature*. 2000;408:975-979.

16. Walsh DM, Klyubin I, Fadeeva JV, Rowan MJ, Selkoe DJ. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature*. 2002;416:535-539.

17. Lashuel HA, Hartley D, Petre BM, Walz T, Lansbury PT Jr. Neurodegenerative disease: amyloid pores from pathogenic mutations. *Nature*. 2002;418:291.

18. Nilsberth C, Westlind-Danielsson A, Eckman CB, et al. The ¨Arctic¨ APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation. *Nat Neurosci*. 2001;4:887-893.

19. Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. *Br J Psychiatry*. 2002;180:140-143.

20. Galasko D, Marder K. Picking away at frontotemporal dementia. *Neurology*. 2002;58:1585-1586.

21. Kaye JA. Diagnostic challenges in dementia. *Neurology*. 1998;51(suppl 1):45-52.

22. The Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 1994;57:416-418.

23. Neary D, Snowden JS, Gustafson L et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51:1546-1554.

24. Goedert M. The significance of tau and α-synuclein inclusions in neurodegenerative diseases. *Curr Opin Genet Dev*. 2001;11:343-351.

25. Lee VMY, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. *Annu Rev Neurosci*. 2001;24:1121-1159.

26. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the micortubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc Natl Acad Sci U S A*. 1986;83:4913-4917.

27. McKeith IG. Dementia with Lewy bodies. *Br J Psychiatry*. 2002;180:144-147.

28. Spillantini MG, Goedert M, Crowther RA, Murrell JR, Farlow MR, Ghetti B. Familial multiple system tauopathy with presenile dementia: a disease with abundant neuronal and glial tau filaments. *Proc Natl Acad Sci U S A*. 1997;94:4113-4118.

29. Kosaka K. Dementia and neuropathology in Lewy body disease. *Adv Neurol*. 1993;60:456-463.

30. Duda JE, Lee VM, Trojanowski JQ. Neuropathology of synuclein aggregates. *J Neurosci Res*. 2000;15:61121-61127.

31. Weiner MF. Dementia associated with Lewy bodies: dilemmas and directions. *Arch Neurol*. 1999;56:1441-1442.

32. Kahle PJ, Haass C, Kretschmar HA, Neumann M. Structure/function of α-synuclein in health and disease: rational development of animal models for Parkinson's and related diseases. *J Neurochem*. 2002;82:449-457.

33. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science*. 1997;276:2045-2047.

34. Kruger R, Kuhn W, Muller T, et al. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat Genet* 1998;18:106-108.

35. Mezey E, Dehejia A, Harta G, Papp MI, Polymeropoulos MH, Brownstein MJ. Alpha synuclein in neurodegenerative disorders: murderer or accomplice? *Nat Med*. 1998;4:755-757.

36. Goedert M. Alpha-Synuclein and neurodegenerative diseases. *Nature*. 2001;2:492-501.

37. Lavedan C, Leroy E, Torres R et al. Genomic organization and expression of the human beta-synuclein gene (SNCB). *Genomics*. 1998;54;173-175.

38. Prusiner S. Shattuck Lecture—Neurodegenerative diseases and prions. *N Engl J Med*. 2001;344:1516-1526.

39. Weissmann C, Aguzzi A. Bovine spongiform encephalopathy and early onset variant Creutzfeldt-Jakob disease. *Curr Opin Neurobiol*. 1997;7:695-700.

40. Aguzzi A, Montrasio F, Kaeser PS. Prions: health scare and biological challenge. *Nature*. 2001;2:118-126.

41. Glatzel M, Rogivue C, Ghani A, Streffer JR, Amsler L, Aguzzi A. Incidence of Creutzfeldt-Jakob disease in Switzerland. *Lancet*. 2002;360:139-41.

42. Brandel JP. Clinical aspects of human spongiform encephalopathies, with the exception of iatrogenic forms. *Biomed Pharmacother*. 1999;53:14-18.

43. Kretzschmar HA. Neuropathology of human prion diseases (spongiform encephalopathies). *Dev Biol Stand*. 1993;80:71-90.

44. Aguzzi A, Heppner FL. Pathogenesis of prion diseases: a progress report. *Cell Death Differ*. 2000;7:889-902.

45. Jarrett JT, Lansbury PT Jr. Seeing ¨one-dimensional crystallization¨ of amyloid: a pathogenic mechanism in Alzheimer's disease and scrapie? *Cell*. 1993;73:1055-1058.

46. Chiti F, Webster P, Taddei N, et al. Designing conditions for in vitro formation of amyloid protofilaments and fibrils. *Proc Natl Acad Sci U S A*. 1999;96:3590-3594.

47. Fandrich M, Fletcher MA, Dobson CM. Amyloid fibrils from muscle myoglobin. *Nature*. 2001;410:165-166.

48. Bucciantini M, Giannoni E, Chiti F, et al. Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases. *Nature*. 2002;416:507-511.

49. Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease. *Science*. 2002;296:1991-1995.

50. Hershko A, Ciechanover A. The ubiquitin system. *Annu Rev Biochem*. 1998;67:425-479.