deÞned as the potential stage of AD in which the patient presents as a fully functional individual in cognitive exams such as MMSE, yet the growing pathology within the brain tissue is present, but likely unknown precluding early death from a non-neurodegenerative means (141,144,166). MCI has been described as being the transition stage between normal

genetics, and discoveries from cell biology (13,16,38,169). The increased hydrophobicity of A β42 possibly allows this peptide to integrate within the lipid bilayer initiating the process of cell damage. Schmidt et al. using mass-per-length measurements and electron cryomicroscopy with 3-dimensional reconstruction on an Aβ(1Ð42) amyloid Þbril morphology showed that the Aβ(1Ð42) Þbril morphology has only one protoÞlament, in contrast to Aβ(1Ð40) Þbril forms two protoÞlaments. Further, Aβ(1Ð42) showed pairs of β-sheets at the cores of the two protoÞlaments making up a Þbril (135).

Once Aβ is produced, individual amyloid peptides (A β42 in particular) aggregate to form small assemblies of dimers, trimers, oligomers, protoÞbrils, and large insoluble Þbrils. Studies showed poor correlation between plaque load and cognitive function (113). Recently, the role of Aβ has been amended to suggest that soluble Aβ oligomers are the more toxic species. Further research has indicated that the soluble oligomers and not the plaques correlate well with cognitive decline (44,53,54,117,165,168). Moreover, βA levels and temporal NFT density have been shown to be elevated to a higher degree in LAD when compared with MCI and EAD, which are likewise elevated compared with control (9,11,58,108,159). The relationship between Aβ-containing SPs and NFT formation has been debated, but recently Jin et al. reported that with the addition of soluble A β dimers, tau became hyperphosphorylated before cytoarchitectural disruption was observed, followed by subsequent neuritic degeneration. Interestingly, this process was exacerbated with the overexpression of human tau and prevented with the knockdown of human tau (74). Soluble Aβ has also been shown to modulate the pro-survival PI3K/AKT-GSK3 β pathway, inhibiting various neurotrophin effects including that of α-sAPP (73). These lines of evidence provide insight into the progression of AD and a potential causal relationship between two known pathological hallmarks of this disease.

Genetic Evidences for A β Toxicity

The importance of APP and consequently Aβ in AD pathogenesis has emanated from genetic evidence of patients with familial AD (FAD) and Down syndrome (DS). After the cloning of the

which A $\beta_{1Ð42}$inserts as oligomers into the bilayer and serves as a source of ROS, has been shown to initiate lipid peroxidation (Figs. 4 and 5) (16,17,93,94,101). For a comprehensive review on oxidative/nitrosative stress in the cell, the reader is referred to the following articles (28,29,151).

Oxidative Stress at Different Stages of AD

Oxidative stress and its effects have been found as early as MCI in the progression toward AD. Studies conducted in our laboratory and others have found that oxidative stress markers for protein oxidation/nitration, such as protein carbonyls and 3-nitro-tyrosine, are elevated in brains from subjects with aMCI (6Ð8,25,83). More recently, it has been shown that the phosphorylation proÞlt1.2([(sholtr2([(proteins)-392.8(such)

Increased protein-bound 4-hydroxy-nonenal (HNE) and free HNE, TBARS, and MDA were found, and a higher isoprostane (F_2

mechanism (145). Further, the presence of methionine sulf-

5. Balastik M, Lim J, Pastorino L, and Lu KP. Pin1 in AlzheimerÕs disease: multiple substrates, one regulatory mechanism? Biochim Biophys Acta 1772: 422Ð429, 2007.
6. Barone E, Di Domenico F, Cenini G, Sultana R, Cini C,

by automated analysis of multicenter FDG PET. Neuroimage 17: 302Ð316, 2002.
67. Hoogland C, Mostaguir K, Sanchez JC, Hochstrasser DF, and Appel RD. SWISS-2DPAGE, ten years later. Proteomics 4: 2352Ð2356, 2004.
68. Hoogland C, Sanchez JC, Tonella L, Binz PA, Bairoch A, Hochstrasser DF, and Appel RD. The 1999 SWISS-2DPAGE database update. Nucleic Acids Res 28: 286Ð288, 2000.
69. Huang X, Atwood CS, Hartshorn MA, Multhaup G, Goldstein LE, Scarpa RC, Cuajungco MP, Gray DN, Lim J, Moir RD, Tanzi RE, and Bush AI. The A beta peptide of AlzheimerÕs disease directly produces hydrogen peroxide through metal ion reduction. Biochemistry 38: 7609Ð7616, 1999.
70. Ida N, Hartmann T, Pantel J, Schroder J, Zerfass R, Forstl H, Sandbrink R, Masters CL, and Beyreuther K. Analysis of heterogeneous A4 peptides in human cerebrospinal ßuid and blood by a newly developed sensitive Western blot assay. J Biol Chem 271: 22908Ð22914, 1996.
71. Jack CR, Jr., Petersen RC, Xu YC, OÕBrien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, and Kokmen E. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 52: 1397Ð1403, 1999.
72. Jarrett JT, Berger EP, and Lansbury PT, Jr. The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of AlzheimerÕs disease. Biochemistry 32: 4693Ð4697, 1993.
73. Jimenez S, Torres M, Vizuete M, Sanchez-Varo R, Sanchez-Mejias E, Trujillo-Estrada L, Carmona-Cuenca I, Caballero C, Ruano D, Gutierrez A, and Vitorica J. Age-dependent accumulation of soluble amyloid beta (Abeta) oligomers reverses the neuroprotective effect of soluble amyloid precursor protein-alpha (sAPP(alpha)) by modulating phosphatidylinositol 3-kinase (PI3K)/Akt-GSK-3beta pathway in Alzheimer mouse model. J Biol Chem 286: 18414Ð18425, 2011.
74. Jin M, Shepardson N, Yang T, Chen G, Walsh D, and Selkoe DJ. Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. Proc Natl Acad Sci U S A 108: 5819Ð5824, 2011.
75. Johansson AS, Bergquist J, Volbracht C, Paivio A, Leist M, Lannfelt L, and Westlind-Danielsson A. Attenuated amyloid-beta aggregation and neurotoxicity owing to methionine oxidation. Neuroreport 18: 559Ð563, 2007.
76. Jomova K, Vondrakova D, Lawson M, and Valko M. Metals, oxidative stress and neurodegenerative disorders. Mol Cell Biochem 345: 91Ð104, 2010.
77. Joshi YB, and Pratico D. Vitamin E in aging, dementia, and AlzheimerÕs disease. Biofactors 38: 90Ð97, 2012.
78. Jovanovic SV, Clements D, and MacLeod K. Biomarkers of oxidative stress are signiÞcantly elevated in Down syndrome. Free Radic Biol Med 25: 1044Ð1048, 1998.
79. Kanski J, Aksenova M, and ButterÞeld DA. The hydrophobic environment of Met35 of AlzheimerÕs Abeta(1Ð42) is important for the neurotoxic and oxidative properties of the peptide. Neurotox Res 4: 219Ð223, 2002.
80. Kanski J, Aksenova M, Schoneich C, and ButterÞeld DA. Substitution of isoleucine-31 by helical-breaking proline abolishes oxidative stress and neurotoxic properties of AlzheimerÕs amyloid beta-peptide. Free Radic Biol Med 32: 1205Ð1211, 2002.
81. Katzman R, and Saitoh T. Advances in AlzheimerÕs disease. FASEB J 5: 278Ð286, 1991.
82. Keeney JT, Swomley AM, Harris JL, Fiorini A, Mitov MI,

101. Mattson MP. Cellular actions of beta-amyloid precursor protein and its soluble and Þbrillogenic derivatives. Physiol

the role of lipid peroxidation in the progression and pathogenesis of AlzheimerÕs disease. Neurobiol Dis 30: 107Ð120, 2008.
130. Reed TT, Pierce WM, Jr., Turner DM, Markesbery WR, and ButterÞeld DA. Proteomic identiÞcation of nitrated brain proteins in early AlzheimerÕs disease inferior parietal lobule. J Cell Mol Med 13: 2019Ð2029, 2009.
131. Reed TT, Pierce WM, Markesbery WR, and ButterÞeld DA. Proteomic identiÞcation of HNE-bound proteins in early Alzheimer disease: insights into the role of lipid peroxidation in the progression of AD. Brain Res 1274: 66Ð76, 2009.
132. Ritchie CW, Bush AI, Mackinnon A, Macfarlane S, Mastwyk M, MacGregor L, Kiers L, Cherny R, Li QX, Tammer A, Carrington D, Mavros C, Volitakis I, Xilinas M, Ames D, Davis S, Beyreuther K, Tanzi RE, and Masters CL. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. Arch Neurol 60: 1685Ð1691, 2003.
133. Robinson RA, Lange MB, Sultana R, Galvan V, Fombonne J, Gorostiza O, Zhang J, Warrier G, Cai J, Pierce WM, Bredesen DE, and ButterÞeld DA. Differential expression and redox proteomics analyses of an Alzheimer disease transgenic mouse model: effects of the amyloid-beta peptide of amyloid precursor protein. Neuroscience 177: 207Ð222, 2011.
134. Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, Bird TD, Hardy J, Hutton M, Kukull W, Larson E, Levy-Lahad E, Viitanen M, Peskind E, Poorkaj P, Schellenberg G, Tanzi R, Wasco W, Lannfelt L, Selkoe D, and Younkin S. Secreted amyloid beta-protein similar to that in the senile plaques of AlzheimerÕs disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial AlzheimerÕs disease. Nat Med 2: 864Ð870, 1996.
135. Schmidt M, Sachse C, Richter W, Xu C, Fandrich

159. Tremblay C, Pilote M, Phivilay A, Emond V, Bennett DA, and Calon F. Biochemical characterization of Abeta and tau pathologies in mild cognitive impairment and AlzheimerÕs disease.J Alzheimers Dis12: 377Ð390, 2007.
160. Varadarajan S, Kanski J, Aksenova M, Lauderback C, and ButterÞeld DA. Different mechanisms of oxidative stress and neurotoxicity for AlzheimerÕs A beta(1Ð42) and A beta(25Ð35)J Am Chem Soc123: 5625Ð5631, 2001.
161. Varadarajan S, Yatin S, Aksenova M, and ButterÞeld DA. Review: AlzheimerÕs amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. J Struct Biol130: 184Ð208, 2000.
162. Varadarajan S, Yatin S, Kanski J, Jahanshahi F, and ButterÞeld DA. Methionine residue 35 is important in amyloid beta-peptide-associated free radical oxidative stress.Brain Res Bull50: 133Ð141, 1999.
163. Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, and Citron M. Beta-secretase cleavage of AlzheimerÕs amyloid precursor protein by the transmembrane aspartic protease BACE.Science286: 735Ð741, 1999.
164. Vigo-Pelfrey C, Lee D, Keim P, Lieberburg I, and Schenk DB. Characterization of beta-amyloid peptide from human cerebrospinal ßuid. J Neurochem61: 1965Ð1968, 1993.
165. Viola KL, Velasco PT, and Klein WL. Why AlzheimerÕs is a disease of memory: the attack on synapses by A beta oligomers (ADDLs). J Nutr Health Aging12: 51SÐ57S, 2008.
166. Vlassenko AG, Benzinger TL, and Morris JC. PET amyloid-beta imaging in preclinical AlzheimerÕs disease.Biochim Biophys Acta1822: 370Ð379, 2012.
167. Waldemar G, Phung KT, Burns A, Georges J, Hansen FR, Iliffe S, Marking C, Rikkert MO, Selmes J, Stoppe G, and Sartorius N. Access to diagnostic evaluation and treatment for dementia in Europe. Int J Geriatr Psychiatry22: 47Ð54, 2007.
168. Walsh DM, Klyubin I, Fadeeva JV, Rowan MJ, and Selkoe DJ. Amyloid-beta oligomers: their production, toxicity and therapeutic inhibition. Biochem Soc Trans30: 552Ð557, 2002.
169. Walsh DM, and Teplow DB. AlzheimerÕs disease and the amyloid beta-protein. Prog Mol Biol Transl Sci