The clinical syndrome of dementia refers to a pattern of cognitive deficits characterized by impairment in memory and at least one other cognitive domain (e.g., language, executive functions, visuospatial abilities) that is sufficiently severe to impact behavior and interfere with social or occupational functioning (American Psychiatric Association, 2000). Dementia may be progressive, static, or remitting, and its onset and course of symptoms are a function of underlying neuropathology from various causes. For example, dementia because of a neurodegenerative process tends to involve an insidious onset with gradual progressive cognitive impairment. In contrast, dementia from vascular or acquired brain injury tends to involve an abrupt onset of clinical symptoms that may remain static or show stepwise cognitive decline that corresponds to episodes of cerebrovascular accidents.

The most common causes of dementia are neuropathologically distinguished on the basis of the presence of beta-amyloid (Aβ) plaques and neurofibrillary tangles (e.g., Alzheimer’s Disease); multiple or strategically placed infarctions, ischemic injury, or hemorrhagic lesions (e.g., vascular dementia); cell loss and the deposition of Lewy bodies in sub-cortical, limbic, and neocortical regions (e.g., dementia with Lewy bodies); and prominent frontal and temporal lobar atrophy (frontotemporal dementia). Dementia can also be found in the context of other neurological, infectious, or metabolic conditions, such as Parkinson’s Disease, Huntington’s Disease, human immunodeficiency virus, or traumatic brain injury.

Despite recent advances in amyloid imaging and cerebral spinal fluid analysis, neuropathological changes are often only accurately assessed at autopsy. This makes definitive diagnosis during an individual’s lifetime difficult. Effectively differentiating between forms of dementia or normal aging requires reliance on the neuropsychological definition of a specific pattern of cognitive deficits.

Epidemiology and Neurobiology of Alzheimer’s Disease

Alzheimer’s Disease is the leading cause of dementia in elders and accounts for 60 percent to 80 percent of all dementia cases. An estimated 5.3 million Americans have Alzheimer’s Disease. Reports indicate the disease is the seventh leading cause of death in the United States, and deaths because of Alzheimer’s Disease are on the rise, with an increase of 46 percent between 2000
and 2006. Given the advancing age of the baby boom generation, by 2050, 14 million older Americans and 81 million adults worldwide are expected to have the disease (Alzheimer's Association, 2010a).

Alzheimer’s Disease is an age-related degenerative brain disorder characterized by the abnormal accumulation of extracellular fibrillar amyloid deposits and intra-neuronal neurofibrillary tangles in the brain. These characteristics lead to neuronal atrophy and synapse loss in medial temporal lobe limbic structures that are critical for episodic memory and extend to the association cortices of the frontal, temporal, and parietal lobes with disease progression (Braak and Braak, 1991). Consistent with these widespread neuropathological changes, the primary clinical manifestation of Alzheimer’s Disease is a progressive global dementia syndrome that usually begins in later life.

It is generally agreed that the pathological cascade of brain changes occurs gradually in Alzheimer’s Disease, beginning with the very early accrual of Aβ plaques in the brain, and is followed by a variable lag time after which neuronal dysfunction and neurodegeneration become the leading pathological process (Jack et al., 2010). Although Aβ neuropathology is thought to be causal, clinical symptoms are more closely related to neurofibrillary tangles than amyloid deposition. The finding that a substantial proportion of cognitively intact older adults also have significant levels of Aβ plaques in their brains further suggests that Aβ may be necessary (in that it appears to trigger subsequent neurodegenerative events) but not sufficient for progression to Alzheimer's dementia.

Despite recent advances for in vivo biomarker measurement, neuropathological changes are often only accurately assessed at autopsy.

While Jack’s model is one prevailing view, the authors acknowledge that it is incomplete and anticipate its evolution to incorporate additional clinical and laboratory studies as they become better validated and their sensitivity and specificity for Alzheimer’s diagnosis is established. This may include alterations in cerebral metabolism, cerebral blood flow, and blood oxygenation level–dependent response during cognitive activity or during rest, using positron emission tomography, arterial spin labeling, and functional magnetic resonance imaging techniques.

Diagnostic Criteria for Alzheimer’s Disease

The prevailing diagnostic standards for Alzheimer’s Disease are based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 2000) and the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA) working group (McKhann et al., 1984). These accepted criteria support a probabilistic diagnosis of Alzheimer’s Disease within a

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disease (Dubois et al., 2007; Pruvlovic and Hampel, 2011; and Dubois et al., 2010).

The National Institute on Aging at the National Institutes of Health (NIH) and the Alzheimer’s Association organized a project beginning in 2009 to revise diagnostic criteria for Alzheimer’s Disease. These recommendations were recently published and propose the inclusion of both clinical and cognitive criteria and biomarker measures, and delineate three phases of the disease including pre-clinical Alzheimer’s Disease (Sperling et al., 2011), mild cognitive impairment (Albert et al., 2011), and the clinical diagnosis of Alzheimer’s Disease (McKhann et al., 1984; Jack et al., 2010).

In contrast to the prior criteria that was specific to Alzheimer’s Disease, the proposed revised criteria separate a clinical diagnosis of Alzheimer’s Disease from an “all-cause” dementia diagnosis, wherein a memory impairment may be apparent but is not required for diagnosis, thereby recognizing an insidious onset of symptoms with primary memory impairments and primary non-memory impairment profiles (McKhann et al., 1984).

Validation and further specification of these revised criteria are needed before they can be fully adopted by the clinical and research communities. Because several of the emerging biomarker assessment techniques are only available for use in research settings, there is limited standardization of biomarker assay methods, and optimal cut-off values have not been identified because of inter-laboratory variability. The distinction between clinical expression and the presence of Alzheimer’s neuropathology may uncouple the Alzheimer’s diagnosis from its dementia syndrome and facilitate earlier treatment during the period in which treatment may be most effective in delaying the onset of cognitive symptoms.

**Neuropsychology of Alzheimer’s Disease**

Despite attempts to integrate physiological biomarker evidence into the Alzheimer’s diagnostic framework, Alzheimer’s Disease remains a clinical syndrome with distinct patterns of cognitive deficits that differentiate it from other neuropathologically different age-associated neurodegenerative disorders. Sensitive neuropsychological assessment techniques will continue to be one of the primary diagnostic approaches for Alzheimer’s Disease. In the usual case, the Alzheimer’s dementia syndrome is characterized by early episodic memory decline (e.g., amnesia), consistent with early neuropathology targeting the medial temporal lobes, with additional deficits in language and semantic knowledge, abstract reasoning, executive functions, attention, and visuospatial abilities that contribute to decline in everyday function (Salmon and Bondi, 2009).

A number of performance characteristics on episodic memory measures help differentiate between mildly demented Alzheimer’s patients and normal older adults. These characteristics include an abnormally high rate of forgetting, whereby patients with early Alzheimer’s Disease are particularly impaired on measures of delayed recall; failure to benefit from recognition testing, in which retrieval demands are reduced, indicating storage loss of memory for recently learned information rather than a retrieval deficit; and an abnormal serial position effect characterized by an attenuation of the primacy effect (i.e., recall of words from the beginning of a list), suggesting ineffective transfer of information from short-term memory to long-term memory. Additional characteristics are less typical improvement in episodic memory performance with semantic encoding, and an enhanced tendency to produce intrusion errors on both verbal and nonverbal memory tests, especially in response to cues and presumably due to increased sensitiv-
ity to interference or decreased inhibitory processes (Salmon and Bondi, 2009).

A number of higher-order cognitive abilities are also affected in Alzheimer’s Disease and are thought to correspond to the spread of neuropathology beyond medial temporal lobe structures to the association cortices of the temporal, frontal, and parietal lobes (Braak and Braak, 1991). Patients with Alzheimer’s Disease develop a semantic memory deficit characterized by a loss of general knowledge and impair-ment of language abilities (i.e., aphasia). Patients with Alzheimer’s Disease are often impaired on tests of confrontation naming, verbal fluency, and semantic categorization.

Deficits in executive functions responsible for concurrent mental manipulation of information and concept formation also occur early in the course of the disease, and Alzheimer’s patients perform worse than non-demented peers on tests requiring set shifting, self-monitoring, or sequencing, but not on tests that require cue-directed attention or verbal problem solving.

The following tests show excellent sensitivity and specificity for the detection of very mild Alzheimer’s Disease using receiver operating characteristic curve analyses: learning and delayed recall measures from the California Verbal Learning Test (sensitivity: 95%–98%; specificity: 88%–89%); the category fluency test (sensitivity: 96%; specificity: 88%); and Part B of the Trail-Making Test (sensitivity: 85%; specificity: 83%) (Salmon and Bondi, 2009). Deficits in attention and visuospatial abilities develop during the course of Alzheimer’s Disease, but they are usually less salient than other cognitive deficits in the early stages of disease.

Taken together, these results indicate that deficits in episodic memory, semantic knowledge, and certain executive functions are particularly characteristic of early Alzheimer’s Disease. However, because normal aging can detrimentally affect many of the same cognitive abilities affected by the disease, the prominence of specific deficits related to Alzheimer’s Disease may be much less evident in the very old (older than 80) than in the young-old (younger than 70), especially after performance is standardized to that of the age-appropriate normal cohort (Bondi et al., 2003).

The reduced saliency of the deficit profile as a diagnostic marker of Alzheimer’s Disease may be much less evident in the very old highlights the significant risk of false negative diagnostic errors in very elderly Alzheimer’s patients. Accurate detection of Alzheimer’s Disease in the very elderly patient may require a multifaceted approach to diagnosis that integrates neuropsychological assessment, in vivo biomarkers, neuroimaging, and genetic factors. Others also emphasize the need to consider a person’s longitudinal course of cognitive change when making an Alzheimer’s diagnosis.

Risk Factors for Alzheimer’s Disease

Age is the greatest risk factor for Alzheimer’s Disease, with the incidence of disease increasing from approximately 1 percent in adults age 60 years to nearly 45 percent in those age 85 years and older (Barak and Aizenberg, 2010). Susceptibility for Alzheimer’s Disease is also conferred through genetic risk factors.

Early-onset familial Alzheimer’s Disease has been linked to the presence of mutations in one of three genes—amyloid precursor protein (APP) on chromosome 21, presenilin 1 gene on chromosome 14, or presenilin 2 gene on chromosome 1—or duplication of APP as may occur with Down Syndrome, presumably due to these genes’ impact on Aβ.

The apolipoprotein E (APOE) ε4 allele on chromosome 19 is a well-known genetic risk factor for late-onset Alzheimer’s Disease that is found in approximately 20 percent of Caucasians and
may account for as much as 50 percent of the risk for developing Alzheimer’s Disease. The APOE ε4 genotype has been linked with increases in Aβ deposition and cerebrovascular disease. Non-demented APOE ε4 carriers show subtle functional and structural brain differences (Wierenga and Bondi, 2007) and cognitive changes (Bondi et al., 2008) that may reflect a prodromal phase of Alzheimer’s Disease. By contrast, young ε4 carriers have been shown to demonstrate better episodic memory performance and reduced learning- and retrieval-related activity, suggesting that the negative effects of the APOE ε4 allele accelerate with age, whereby the ε4 allele appears to have protective effects in younger adults, but well-known detrimental effects during the post-reproductive years.

Genome-wide association studies are beginning to identify additional gene variants associated with late-onset Alzheimer’s including CR1, CLU, and BIN1, and more recently MS4A, CD2AP, CD33, and EPHA1 (Naj et al., 2011).

Cerebrovascular disease risk factors such as stroke, atherosclerosis, cardiovascular disease, systolic hypertension, elevated pulse pressure, elevated serum cholesterol, current smoking, obesity, and diabetes have been increasingly implicated in the development of Alzheimer’s Disease. These factors also can contribute to an accelerated rate of decline after establishment of an Alzheimer’s diagnosis, with hypertension being most consistently associated with the development of the disease. Although the precise mechanisms linking cerebrovascular disease risk factors and Alzheimer’s are not fully understood, several theories have been proposed.

Vascular pathology may have an additive effect by increasing the overall burden of pathology. Another theory is that Alzheimer’s and vascular diseases may interact to worsen pathologic effects. Finally, Alzheimer’s Disease may be conceptualized as a vascular disorder with amyloid deposition linked to a breakdown in the blood–brain barrier and alterations in brain perfusion.

Other risk factors for Alzheimer’s include head trauma, low education, oxidative injury, depression, never having been married, having low social support, or meeting diagnostic criteria for mild cognitive impairment. The latter is a pre-dementia condition in elders that was originally characterized by both subjective and objective memory impairment occurring in the
face of relatively preserved general cognition and functional abilities. For reasons that are unclear, older African Americans and Hispanics are more likely than older white Americans to have Alzheimer’s or other dementias.

**Protective Factors Against Alzheimer’s Disease**

The prevention of dementia remains a significant challenge for clinicians and researchers. Recent emphasis has focused on identifying potentially modifiable risk factors for dementia, including interventions to promote cognitive engagement, physical activity, and nutrition as well as increasing antihypertensive medication use (Barak and Aizenberg, 2010). Based on review of more than 3,400 articles evaluating risk for dementia, Patterson et al. (2008) concluded the most compelling evidence for effective primary prevention of Alzheimer’s was controlling vascular risk factors, especially hypertension. The commonly used antihypertensive drugs, angiotensin receptor blockers and the ACE inhibitor lisinopril, appear most effective in reducing the incidence and progression of Alzheimer’s Disease, though major clinical trials are needed to validate these primarily observational findings (Barak and Aizenberg, 2010).

Weaker evidence was found for lifestyle factors and medications to protect against Alzheimer’s, though moderate wine consumption, high level of physical activity, and educational attainment have been shown to reduce the relative risk of the disease. Dietary factors such as the Mediterranean diet or intake of antioxidants, polyunsaturated fatty acids, cereals, vegetables, and omega-3 fatty acid have also been shown to reduce the incidence of dementia in population and observational studies.

Despite early excitement, the NIH Consensus and State-of-the-Science Panel issued a formal statement indicating insufficient evidence to support the use of pharmaceutical agents or dietary supplements to prevent cognitive decline or Alzheimer’s Disease (Daviglus et al., 2010). This caution includes the once popular use of vitamin E and hormone replacement therapy.

Participation in activities that are mentally, socially, and physically stimulating may postpone the onset of dementia, and increased frequency of cognitive engagement may not only reduce dementia risk but explain the association between education and Alzheimer’s risk (Daviglus et al., 2010). Further support for exercising the brain is provided by evidence that speaking more than one language serves to protect against pathological cognitive decline as seen by a later onset of dementia in bi- and multilinguals (Craik, Bialystok, and Freedman, 2011).

After careful review of existing randomized clinical trials and observational studies that met high standards of scientific quality, the NIH State-of-the-Science Panel reported that existing data concerning modifiable risk factors associated with Alzheimer’s Disease do not support firm conclusions regarding effective Alzheimer’s prevention. Scientifically rigorous clinical trials are critical to elucidate the interaction of pharmaceutical agents, physical exercise, cognitive engagement, and nutrition on dementia prevention as well as to reveal the histopathological correlates of clinico-epidemiological findings.

**Treatment Approaches**

To date there is no approved disease-modifying drug therapy for Alzheimer’s Disease. Early therapeutic development was led by the “cholinergic hypothesis” that states Alzheimer’s Disease results from a deficiency in the production of acetylcholine. The first-generation cholinesterase inhibitors (ChEIs) (including donepezil, rivastigmine, and galantamine) are now established as a symptomatic treatment for mild-to-moderate Alzheimer’s Disease, but only show modest efficacy for reducing cognitive and behavioral symptoms.
A second-class NMDA receptor antagonist (memantine) has also received U.S. Food and Drug Administration approval to treat Alzheimer’s symptoms. These medications, though sometimes beneficial, have not led to a cure, and no new treatments have been approved since 2003. A large number of other compounds are currently being tested in clinical trials for therapeutic use in Alzheimer’s Disease, including compounds aimed at decreasing Aβ production, increasing Aβ clearing, or stimulating cholinergic cell regeneration (Prvulovic and Hampel, 2011).

Subtleties of Pre-Clinical Alzheimer’s Disease
The pathologic cascade of events in Alzheimer’s Disease suggests that subtle cognitive decline is likely to occur in a patient with Alzheimer’s neuropathology well before the clinical diagnosis can be made. Identification of the cognitive changes that occur during this “pre-clinical” phase of the disease might provide a way to reliably detect Alzheimer’s Disease in its earliest stages.

A number of prospective longitudinal studies of cognitive performance in non-demented older adults have revealed a subtle decline in episodic memory often occurs prior to the emergence of the obvious cognitive and behavioral changes required for a clinical diagnosis of Alzheimer’s (Twamley, Ropacki, and Bondi, 2006). These findings led to the development of formal criteria for mild cognitive impairment.

Over time, diagnostic criteria for mild cognitive impairment have evolved into specific clinical sub-types classifying individuals with primary memory impairments or primary non-memory impairments involving single or multiple cognitive domains that may indicate different neuropathologic etiologies (Petersen and Morris, 2005). Although mild cognitive impairment is well-established as a risk factor for Alzheimer’s, the lack of a universal operational definition among clinical and research practices (Dubois et al., 2007; Winblad et al., 2004) results in widely varying prevalence rates and progression rates (Jak et al., 2009). This is complicated by the finding that not all individuals with mild cognitive impairment continue to decline and develop dementia.

Although the search for cognitive changes in pre-clinical Alzheimer’s has largely focused on episodic memory, several recent reviews and meta-analyses suggest that largely nonspecific cognitive decline occurs in the two to three years preceding a dementia diagnosis (Twamley, Ropacki, and Bondi, 2006). These studies consistently find a decline in episodic memory, but they also often reveal additional deficits in executive functions, perceptual speed, verbal ability, visuospatial skill, and attention during the pre-clinical phase of the disease (Albert et al., 2001; Small et al., 2003).

Several lines of evidence suggest that semantic and language abilities may show the earliest cognitive changes. For example, measures of semantic knowledge (i.e., vocabulary, naming, category fluency) demonstrate greater impairment than either episodic memory or executive function measures two years prior to the diagnosis of Alzheimer’s Disease, and the combination of semantic memory and visuospatial learning deficits accurately detect cognitive dysfunction characteristic of pre-clinical Alzheimer’s Disease.

Performance on language tasks predicts pathologic Alzheimer’s Disease six years later in non-demented individuals. Cognitively intact carriers of the E2801 presenilin-1 gene mutation perform worse on naming famous faces than non-carriers, and famous face naming distinguishes between
adults with mild cognitive impairment who progress to dementia and those who do not. In addition, asymmetry in cognitive performance as reflected in the absolute difference between verbal and visuospatial ability can be a marker of pre-clinical Alzheimer's Disease (Jacobson et al., 2002).

Lateralized cognitive deficits (e.g., greater verbal than visuospatial deficits, or vice versa) are well documented in sub-groups of mildly demented Alzheimer’s patients. Compared to cognitively intact adults, a greater proportion of adults who were diagnosed with Alzheimer’s Disease one year later had asymmetric cognitive changes in either the verbal or visuospatial direction that were obscured when cognitive scores are averaged over the entire group.

Taken together, neuropsychological evidence suggests the consideration of both cognitive asymmetry and subtle declines in memory, language, and executive function may improve the ability to detect Alzheimer’s Disease in its earliest, pre-clinical stages. Ultimately, elucidating the link between the pathophysiological process of Alzheimer’s Disease and the emergence of clinical symptoms will enable providers to take advantage of the critical opportunity for potential intervention with disease-modifying therapy during the long pre-clinical phase of the disease.

**Summary**

Alzheimer’s is a progressive neurodegenerative dementia syndrome characterized by cognitive and functional decline due to the abnormal accumulation of Aβ plaques and neurofibrillary tangles in the brain. Recent proposals to revise Alzheimer’s diagnostic criteria integrate advances in the neuropsychological characterization of Alzheimer’s Disease with neuropathological biomarker evidence to more accurately identify the earliest manifestations of the disease.

Less progress has been made in Alzheimer’s prevention and treatment, with some evidence to suggest that diet, cognitive and physical exercise, and cerebrovascular health may slow disease onset and progression. Emphasis has shifted to identifying individuals in the pre-clinical stage so that treatment strategies, as they are developed, can be implemented during the earliest period in which they are most effective.

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