Preclinical Biomarkers of Parkinson Disease

Wu and colleagues (page 22) point out that the search for markers of preclinical Parkinson disease is becoming increasingly important as pathogenesis-targeted neuroprotective strategies are being developed for future use in at-risk populations, even before clinical onset of disease. Advances in clinical recognition of early symptoms and signs, development of new neuroimaging probes and technologies, identification of new neuropathologic markers of Parkinson disease, and breakthroughs in genetics and basic neuroscience are gradually translating into better understanding of predisposing and preclinical factors that lead to progressive neurodegeneration.

Spreading Depolarization: A New Culprit in the Delayed Cerebral Ischemia of Subarachnoid Hemorrhage?

Leng et al (page 31) emphasize that it is becoming increasingly clear that the pathophysiology underlying delayed cerebral ischemia is multifactorial. Cortical spreading depression is rising as a likely player in this complex web of pathologic changes after subarachnoid hemorrhage. Understanding its role after subarachnoid hemorrhage and its relationship to the other pathologic processes such as vasospasm, microcirculatory dysfunction, and microemboli will be vital to the development of new therapeutic approaches to reduce delayed cerebral ischemia and improve the clinical outcome of the disease.

An Open-Label Trial of Recombinant Human Insulin-like Growth Factor in Myotonic Dystrophy Type 1

Heatwole and colleagues (page 37) evaluated the safety and tolerability of recombinant human insulin-like growth factor (IGF) 1 complexed with IGF binding protein 3 (rhIGF-1/rhIGFBP-3) in patients with myotonic dystrophy type 1. Treatment with rhIGF-1/rhIGFBP-3 was generally well tolerated in patients with myotonic dystrophy type 1. Also, rhIGF-1/rhIGFBP-3 was associated with increased lean body mass and improvements in metabolism but not with increased muscle strength or function. Larger randomized controlled trials will be needed to further evaluate the efficacy and safety of this medication in patients with neuromuscular disease.

Pioglitazone in Treatment of Patients With Alzheimer Disease

Geldmacher et al (page 45) studied the safety of the peroxisome proliferator–activated receptor gamma (PPARγ) agonist pioglitazone in nondiabetic patients with Alzheimer disease (AD) and explored treatment effect sizes on clinical outcomes. Pioglitazone was generally well tolerated in this pilot study. There were no serious or unanticipated adverse events or clinical laboratory changes attributable to pioglitazone during long-term exposure in nondiabetic patients with AD. Pioglitazone’s tolerability in this population and PPARγ effects in laboratory models of AD support further study of this drug class in earlier disease stages.

Insulin Resistance and Alzheimer-like Reductions in Regional Cerebral Glucose Metabolism for Cognitively Normal Adults With Prediabetes or Early Type 2 Diabetes

Baker and colleagues (page 51) examined whether greater insulin resistance, as indexed by the homeostasis model assessment, would be associated with reduced resting cerebral glucose metabolic rate (CMRglu) in areas known to be vulnerable in Alzheimer disease in a sample of cognitively normal adults with newly diagnosed prediabetes or type 2 diabetes. They also determined whether adults with prediabetes or type 2 diabetes have abnormal patterns of CMRglu during a memory encoding task. Their results suggest that insulin resistance may be a marker of Alzheimer disease risk that is associated with reduced CMRglu and subtle cognitive impairments at the earliest stage of disease, even before the onset of mild cognitive impairment.

Cholinesterase Inhibitors and Memantine Use by Patients in the Alzheimer Disease Neuroimaging Initiative

Schneider et al (page 58) indicate that cholinesterase inhibitors and memantine are prescribed to many patients with mild cognitive impairment and mild Alzheimer disease (AD) who are enrolled in the National Institutes of Health AD Neuroimaging Initiative and other studies. However, their effects on the clinical course of study participants are not known, and the efficacy of...
cholinesterase inhibitors for mild cognitive and memantine for mild AD has not been demonstrated. They conclude that academic physicians frequently prescribe cholinesterase inhibitors and memantine earlier than indicated in the Food and Drug Administration–approved labeling to patients who are progressing relatively more severely or rapidly. Their use is associated with clinical decline and may affect the interpretation of clinical trials outcomes.

### Defective Mitochondrial Adenosine Triphosphate Production in Skeletal Muscle From Patients With Dominant Optic Atrophy Due to OPA1 Mutations

Odi and colleagues (page 67) assess whether impaired energy metabolism in skeletal muscle is a hallmark feature of patients with dominant optic atrophy (DOA) due to several mutations in the OPA1 gene. They report that defective oxidative phosphorylation in skeletal muscle is a subclinical feature of patients with OPA1-related dominant optic atrophy, indicating a systemic expression of the OPA1 defect, similar to that previously reported for Leber hereditary optic neuropathy due to complex I dysfunction. However, this defect of oxidative phosphorylation does not appear to depend on the low amounts of mitochondrial DNA multiple deletions detected in muscle biopsies.

### Deficits in Functional Connectivity of Hippocampal and Frontal Lobe Circuits After Traumatic Axonal Injury

Marquez de la Plata et al (page 74) examine the functional connectivity of hippocampal and selected frontal lobe circuits among patients with traumatic axonal injury (TAI). Their findings suggest that TAI affects interhemispheric neural activity, as patients with TAI show disrupted interhemispheric functional connectivity. These results suggest more careful investigation of interhemispheric connectivity is warranted, as it demonstrated a modest association with outcome in chronic traumatic brain injury.

### Perfusion Computed Tomographic Imaging in Transient Ischemic Attack

Rabhakaran and colleagues (page 85) examine the frequency of perfusion computed tomographic abnormalities in the anterior circulation of patients with transient ischemic attack. On acutely per-

### Familial Aggregation of Dementia With Lewy Bodies

Nervi et al (page 90) determine the risk of familial aggregation of dementia with Lewy bodies (DLB) and core symptoms of DLB. They report that DLB and core features of DLB aggregate in families. Compared with siblings of probands with clinically diagnosed Alzheimer disease, siblings of probands with clinically diagnosed DLB have an increased risk of DLB and visual hallucinations. These findings are an important step in elucidating the genetic risk factors underlying DLB and delineating DLB from other neurodegenerative diseases such as Alzheimer disease.

### Deep Brain Stimulation of the Pallidum for Myoclonus-Dystonia

Azoulay-Zyss and colleagues (page 94) determined the efficacy of internal pallidum deep brain stimulation (DBS) in patients with myoclonus-dystonia due to genetically proven ε-sarcoglycan (SGCE–M-D) deficiency. They find that bilateral DBS of the internal pallidum was safe and highly effective in this homogeneous population of patients with SGCE–M-D. They conclude that this therapeutic option should therefore be considered for patients with severe drug-resistant forms of the disorder.

### Meta-analysis of the Association Between Variants in SORL1 and Alzheimer Disease

Reitz et al (page 99) performed a comprehensive, unbiased meta-analysis of single-nucleotide polymorphisms in SORL1 previously described by Rogaeva et al to be associated with Alzheimer disease (single-nucleotide polymorphisms 4 [rs661057], 5 [rs11218304], 8 [rs668387], 9 [rs689021], 10 [rs641120], 12 [rs12285364], 19 [rs2070045], 22 [rs1699102], 23 [rs3824968], 24 [rs2282649], and 25 [rs1010159]) using PLINK. Their comprehensive meta-analysis provides confirmatory evidence that multiple SORL1 variants in distinct linkage disequilibrium blocks are associated with Alzheimer disease.