In a prospective observational study, the use of estrogen replacement therapy appeared to protect—by about 50%—against development of AD in women. This study seemed to confirm the results of two earlier case-controlled studies. Sadly, a prospective placebo-controlled study of a combined estrogen-progesterone therapy for asymptomatic postmenopausal women increased, rather than decreased, the prevalence of dementia. This study markedly dampened enthusiasm for hormonal treatments to prevent dementia. Additionally, no benefit has been found in the treatment of AD with estrogen alone.

A controlled trial of an extract of *Ginkgo biloba* found modest improvement in cognitive function in subjects with AD and vascular dementia. Unfortunately, a comprehensive 6-year multicenter prevention study using ginkgo found no slowing of progression to dementia in the treated group.

Vaccination against $A\beta_{42}$ has proved highly efficacious in mouse models of AD, helping clear brain amyloid and preventing further amyloid accumulation. In human trials, this approach led to life-threatening complications, including meningoencephalitis, in a minority of patients. Another experimental approach to AD treatment has been the use of β and γ secretase inhibitors that diminish the production of $A\beta_{42}$, but the first two placebo-controlled trials of γ secretase inhibitors, tarenflurbil and semagacestat, were negative, and semagacestat may have accelerated cognitive decline compared to placebo. Passive immunization with monoclonal antibodies against $A\beta_{42}$ has been tried in mild to moderate AD. These studies were negative, leading some to suggest that the patients treated were too advanced to respond to amyloid-lowering therapies. Therefore, new trials have started in asymptomatic individuals with mild AD, in asymptomatic autosomal dominant forms of AD, and in cognitively normal elderly who are amyloid positive with PET. Medications that modify tau phosphorylation and aggregation, including tau antibodies, are beginning to be studied as possible treatments for both AD and non-AD tau-related disorders including FTD and progressive supranuclear palsy.

Several retrospective studies suggest that nonsteroidal anti-inflammatory agents and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) may have a protective effect on dementia if used prior to the onset of disease but do not influence clinically symptomatic AD. Finally, there is now a strong interest in the relationship between diabetes and AD, and insulin-regulating studies are being conducted.

Mild to moderate depression is common in the early stages of AD and may respond to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are commonly used due to their low anticholinergic side effects (for example, escitalopram, target dose 5–10 mg daily). Seizures can be treated with levetiracetam unless the patient had a different regimen that was effective prior to the onset of AD. Agitation, insomnia, hallucinations, and belligerence are especially troublesome characteristics of some AD patients, and these behaviors can lead to nursing home placement. The newer generation of atypical antipsychotics, such as risperidone, quetiapine, and olanzapine, are being used in low doses to treat these neuropsychiatric symptoms. The few controlled studies comparing drugs against behavioral intervention in the treatment of agitation suggest mild efficacy with significant side effects related to sleep, gait, and cardiovascular complications, including an increased risk of death. All antipsychotics carry a black box FDA warning and should be used with caution in the demented elderly; however, careful, daily, nonpharmacologic behavior management is often not available, rendering medications necessary for some patients. Finally, medications with strong anticholinergic effects should be vigilantly avoided, including prescription and over-the-counter sleep aids (e.g., diphenhydramine) or incontinence therapies (e.g., oxybutynin).

VASCULAR DEMENTIA

Dementia associated with cerebrovascular disease can be divided into two general categories: multi-infarct dementia and diffuse white matter disease (also called *leukoaraiosis, subcortical arteriosclerotic leukoencephalopathy,* or *Binswanger's disease*). Cerebrovascular disease appears to be a more common cause of dementia in Asia than in Europe and North America, perhaps due to the increased prevalence of intracranial atherosclerosis. Individuals who have had strokes may develop chronic cognitive deficits, commonly called *multi-infarct dementia*. The strokes may be large or small (sometimes lacunar) and usually involve several different brain regions. The occurrence of dementia depends partly on the total volume of damaged cortex. Patients typically report previous discrete episodes of sudden neurologic deterioration. Many patients with multi-infarct dementia have a history of hypertension, diabetes, coronary artery disease, or other manifestations of widespread atherosclerosis. Physical examination may show focal neurologic deficits such as hemiparesis, a unilateral Babinski sign, a visual field defect, or pseudobulbar palsy. Recurrent strokes result in a stepwise disease progression. Neuroimaging reveals multiple areas of infarction. Thus, the history and neuroimaging findings differentiate this condition from AD; however, both AD and multiple infarctions are common and sometimes co-occur. With normal aging, there is also an accumulation of amyloid in cerebral blood vessels, leading to a condition called *cerebral amyloid angiopathy* (without dementia), which predisposes older persons to lobar hemorrhage and brain microhemorrhages. AD patients appear to be at increased risk for amyloid angiopathy, and this association may explain some of the observed links between AD and stroke.

Some individuals with dementia are discovered on MRI to have bilateral T2 signal hyperintensities in the subcortical white matter, termed *diffuse white matter disease*, often occurring in association with lacunar infarctions (see Fig. 35-2). The dementia may be insidious in onset and progress slowly, features that distinguish it from multi-infarct dementia, but other patients show a stepwise deterioration more typical of multi-infarct dementia. Early symptoms include mild confusion, apathy, anxiety, psychosis, and memory, spatial, or executive deficits. Marked difficulties in judgment and orientation and dependence on others for daily activities develop later. Euphoria, elation, depression, or aggressive behaviors are common as the disease progresses. Pyramidal and cerebellar signs may be present, and a gait disorder is seen in at least half of these patients. With advanced disease, urinary incontinence and dysarthria with or without other pseudobulbar features (e.g., dysphagia, emotional lability) are frequent. Seizures and myoclonic jerks appear in a minority of patients. Often, this disorder results from chronic ischemia due to occlusive disease of small, penetrating cerebral arteries and arterioles (microangiopathy). Any disease-causing stenosis of small cerebral vessels may be the critical underlying factor, although hypertension is the major cause. The term *Binswanger's disease* should be used with caution, because it does not clearly identify a single entity.

Other rare causes of white matter disease also present with dementia, such as adult metachromatic leukodystrophy (arylsulfatase A deficiency) and progressive multifocal leukoencephalopathy (Chap. 164). A dominantly inherited form of white matter disease is known as *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL), discussed later in "Other Causes of Dementia."

Mitochondrial disorders can present with stroke-like episodes and can selectively injure basal ganglia or cortex. Many such patients show other findings suggestive of a neurologic or systemic disorder such as ophthalmoplegia, retinal degeneration, deafness, myopathy, neuropathy, or diabetes. Diagnosis is difficult, but serum or (especially) CSF levels of lactate and pyruvate may be abnormal, and biopsy of affected tissue, preferably muscle, may be diagnostic.

Treatment of vascular dementia must be focused on preventing new ischemic injury by stabilizing or removing the underlying causes, such as hypertension, diabetes, smoking, or lack of exercise. Recovery of lost cognitive function is not likely, although fluctuations with periods of improvement are common.

FRONTOTEMPORAL LOBAR DEGENERATION SPECTRUM

Frontotemporal dementia (FTD) refers to a group of clinical syndromes united by underlying frontotemporal lobar degeneration (FTLD) pathology. FTD most often begins in the fifth to seventh decades and