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Treating Alzheimer's Disease: A New Era Begins

SPECIAL REPORT

By Dennis J. Selkoe, MD, Professor of Neurology and Neuroscience, Harvard Medical School and Codirector of the Center for Neurological Diseases, Brigham and Women's Hospital, Boston, Mass.

Few consultations in neurology are more dispiriting than conveying a diagnosis of Alzheimer's disease (AD) to patient and family. Providing this diagnosis is accompanied by the knowledge of an impending, inexorable decline in the patient's most human qualities, with little or no hope for meaningful therapeutic intervention. But recent dramatic progress in deciphering the fundamental mechanism of AD has brought us to the verge of testing novel treatments that offer the first real hope of slowing the course of this devastating disorder. Neurologists need to become increasingly aware of these emerging therapeutic opportunities so that they can participate in their evaluation and explain how they work to anxious patients and their families.

At the outset, it is important to emphasize that useful symptomatic treatments for some of the features of AD are presently available. These include psychotropic medications that temporarily ameliorate one or another debilitating symptom of the disease, such as anxiety, agitation, depression, or psychotic behavior. The choice and dosage of psychotropic agents must be considered carefully, and the array of possibilities in this area has recently been reviewed (Mayeux R, Sano M. *N Engl J Med* 2000;341: 1670-1679). A second group of available agents comprises the acetylcholinesterase inhibitors. Beginning with tetrahydroaminoacridine (Cognex), then donepezil (Aricept), and, recently, rivastigmine (Exelon), the pharmaceutical industry has developed inhibitors to enhance the level of acetylcholine in the synaptic cleft and thereby attempt to decrease, at least temporarily, those symptoms of the disease principally related to cholinergic deficiency. To date, these inhibitors have provided modest and temporary benefit at most to the majority of patients in whom they have been tried. Nevertheless, they represent a potentially helpful modality for patients newly diagnosed with AD, and the more

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INSIDE

recent compounds have relatively few side effects.

Cholinesterase inhibitors are not expected to address the underlying mechanism of cholinergic cell loss, which is one of numerous neurotransmitter deficiencies occurring in AD. Indeed, no drugs proven to significantly retard the progression of AD are currently available. But this sense of therapeutic nihilism may soon change. To understand the nature of the new compounds that are now entering clinical trials and will come on line in the next few years, we need to review briefly what is currently understood about the causes and mechanism of AD.

Some have said that studying the senile (amyloid) plaques and neurofibrillary tangles that Alois Alzheimer described would be unlikely to provide important insights into the etiology of AD, since these lesions appeared to represent tombstones of the pathogenic process in the brain. The application of biochemistry and molecular genetics to the problem has shown this concern to be unfounded.

Beginning in the mid-1980s, scientists isolated and analyzed the vascular and plaque amyloid deposits and neurofibrillary tangles purified from postmortem brain tissue. These studies led to the conclusion that the extracellular amyloid deposits in vessels and plaques were composed of the 40- and 42-amino acid amyloid ß-peptides (Aß), whereas the intraneuronal neurofibrillary tangles were composed of highly phosphorylated forms of the microtubule-associated protein, tau. Subsequent studies led to an increasingly detailed understanding of the origins of these protein deposits and the mechanisms of processing of their precursors, particularly the ß-amyloid precursor protein (APP). This elucidation of the molecular pathology was accompanied by great progress in identifying genetic alterations that could predispose individuals to AD. At least four genes have been unequivocally implicated to date: the APP gene itself, presenilins 1 and 2, and the E-4 allele of the apolipoprotein E gene (reviewed in Selkoe DJ. *Nature* 1999;399:A23-A31).

The next step in research proved to be especially important for developing therapies (i.e., establishing the genotype-to-phenotype relationships for each of the implicated genes). This work led to the conclusion that each of the four gene products that can underlie familial forms of the disease increases the cerebral accumulation and deposition of Aß. Because excessive levels of Aß occur in all "sporadic" cases of AD as well, the link of these causative genes to Aß accumulation is believed to be directly relevant to the pathogenesis of all forms of AD. By mechanisms that are largely distinct at the molecular level, the four genetic factors augment the steady-state levels of Aß peptides in the brain, particularly that of the highly amyloidogenic Aß42 species.

The many subsequent steps in the different evolutions of neuronal/synaptic dysfunction, microgliosis, and astrocytosis in the Alzheimer brain are not fully understood. A growing consensus, however, believes that an imbalance between Aß production and Aß clearance leads gradually to a buildup of Aß in diffusible and, later, particulate (plaque-like) forms. The result has stimulated a strong interest in identifying compounds that chronically lower Aß levels in the brain. The ability to identify such molecules flowed from the discovery that Aß is normally produced by cells throughout life and is a natural metabolic product that circulates in the plasma and cerebrospinal fluid (CSF). As a result, scientists used cultured cells that secrete Aß to screen large libraries of compounds and detect "hits" that lower Aß levels in the cell medium without noticeably injuring the cells. Through a laborious iterative process carried out by several pharmaceutical companies, such compounds have been analyzed and then chemically modified in an attempt to achieve Aß inhibitors with drug-like properties that can be administered to humans. In general, this

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process has gone well, and several companies are apparently at advanced stages of preclinical development. In one case, human trials of an Aß-lowering compound have recently begun.

Most of the compounds currently emerging from pharmaceutical screening appear to act as inhibitors of the enzyme called g-secretase. This protease is one of two (the other is called ß-secretase) that sequentially cleave APP to release the Aß peptides. It is not currently clear why drug screening has yielded few inhibitors of ß-secretase; perhaps these lead to some general cellular toxicity or cannot penetrate cells and therefore do not emerge from these cellular screens. In any event, Aß-lowering drugs that appear to act by inhibiting g-secretase represent one hopeful therapeutic approach that has recently entered phase I clinical trials. The testing of such drugs will now take several years, assuming that there are no major untoward effects in the early safety trials.

A separate and novel approach to lowering Aß levels in the brain has come from the observation that immunizing APP transgenic mice that display the early features of Alzheimer pathology leads to a high anti-Aß antibody titer and a subsequent clearing of Aß deposits from the brain. The exact mechanism of this immunological effect is under study. Nonetheless, the results in the mouse model have been sufficiently robust to lead to initiation of phase I trials of this "Aß vaccination" approach. Again, one will not know whether this will constitute a useful therapy until several years of trials conclude.

While the Aß-lowering strategies described here will require extensive clinical evaluation, they offer the first hope of slowing and perhaps even preventing the progression of AD. The currently planned trials are therapeutic (i.e., they attempt to treat diagnosed patients with mild to moderate cognitive symptoms). Later on, if such trials have some success, there may well be an attempt to prevent the disease in subjects predisposed to AD, genetically or otherwise. One important subgroup of symptomatic patients will be those diagnosed with "minimal cognitive impairment" (MCI), many of whom gradually convert from a subtle, early memory disturbance to frank progressive dementia.

While much hard work in the clinic lies ahead, the rate of progress in elucidating AD and moving toward potentially disease-altering drugs has been impressive. One can only hope that the emerging trials will achieve at least a modicum of success sufficient to allow us to offer our patients a way of slowing this tragic disorder. **—djs**

Treatment-Induced Cortical Reorganization After Stroke in Humans

ABSTRACT & COMMENTARY

Source: Liepert J, et al. Treatment-induced cortical reorganization after stroke in humans. *Stroke* 2000;31:1210-1216.

Neurologists have made great efforts to prevent stroke and to reduce the degree of brain damage associated with acute stroke. They also have largely neglected rehabilitation efforts, although several important advances in that specialty have made important contributions. In any event, neuroscientific guidances have had little to add to present day peripheral physical therapy. Recent neuroscientific findings in both subhuman primates and humans, however, have identified considerable evidence of cerebral plasticity following injury. Much of this work indicates a capacity to restore at least a part of acute functioning losses due to either cerebral or even to peripheral arm-hand injuries. (For a brief review of both primate and human studies, see Liepert J, et al. *Neurosci Lett* 1998;250:5-8.)

One new example of neuroscience-engendered post-stroke rehabilitation consists of constraint-induced (CI) therapy for hemiparetics. The procedure involves constraining the patient's remaining functional arm so as to force her or him to use the paretic member several hours daily, addressing and improving functional ability to perform activities of daily living (ADL). Outcomes have been favorably reported.

In this report, Leipert and colleagues describe a special protocol to evaluate two functional changes using vigorous CI therapy. The program was as follows: one aspect measured the physical recovery of manual activity following a stringent CI therapy period of 12 days. The other part mapped the size of the functional hand area in the damaged cerebrum using transcranial magnetic stimulation (TMS) applied to the scalp over the identified hand area. (The point of the latter technique was to map the size of the frontal motor hand area of the damaged cerebrum by evoking muscular responses from the impaired ipsilateral hand before and after a fixed, vigorous CI treatment protocol.) Using a motor activity log (MAL), physical recovery was quantified by testing improvements in 20 important ADL functions before and after the 12-day CI therapy.

Complete studies included 10 appropriate patients possessing approximately 20° of wrist and 10° of finger

movements in the hemiparetic arm. Time after the acute stroke averaged 4.9 ± 5-7 years. Following baseline, pre-treatment clinical evaluations, and TMS motor studies, each patient underwent 12 days of CI therapy consisting of 12 ADL tasks plus 10 incorporated days of added, vigorous six-hour therapy related to a variety of rigorous tasks called "shaping." Patients wore immobilizing splint-slings on their nonparalyzed arm 90% of all 12 wakeful days. Results after treatment were evaluated as follows (parentheses indicate number of subjects): day 1 (1), week 4 (9), and 4 and 6 months (7). MAL improvement affected all patients proportionately to baseline levels that preceded the onset of the protocol. All patients physically improved. Four who had almost no hand use at the start gained only slight improvement but the remainder achieved half to three-fourths improvement over their baseline functions.

TMS brain mapping prior to the onset of testing indicated that the cerebral forearm-hand area contralateral to the paralysis was 60% less than its healthy, transverse counterpart. On the first post-testing day, the abnormal cerebral motor area reversed to +137% and six months later was approximately even to the other side. TMS motor-response threshold over the injured hemisphere was consistently elevated by about 50% above the normal hemisphere throughout.

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The pragmatic result of this important report is: CI therapy, vigorously applied over a two-week period, can greatly improve movement in paralytic hands and forearms of poststroke hemiparetic patients when applied several years after onset. Using Leipert et al's protocol, the beneficial response remained for at least six months and possibly much longer. The experimentally induced enlargement of the damaged cerebral motor hand area after the 12 successful CI treatment days must have reflected new afferent proprioceptive stimuli emanating from the previously immobile, now-moving hand. Such a rapid conclusion cancels the possibility that the enlargement could reflect either axonal regrowth or synaptic degeneration. Leipert et al propose that either a loss of activity from local cortical inhibitory neurons may simply "unmask" pre-existing connections or, conversely, synaptic strength increases in pre-existing connections. Several years ago, efforts somewhat like these were tried immediately after acute strokes without apparent effects and became largely abandoned. We cannot yet be sure that this delayed protocol will materially improve recovery of function when applied immediately following acute stroke. If the results can be promptly reproduced, however, neurologists should urge physical therapists to apply similar protocols as general health returns. **—fp**

Diffusion-Weighted Imaging Part I: Does a Positive DWI Guarantee Permanent Damage?

ABSTRACTS & COMMENTARY

Sources: Li F, et al. Transient and permanent resolution of ischemic lesions on diffusion-weighted imaging after brief periods of focal ischemia in rats: Correlation with histopathology. *Stroke* 2000;31:946-954; Kidwell CS, et al. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol* 2000;47:462-469.

Data from animal experiments and observations in humans suggest that diffusion-weighted imaging (DWI) positivity is synonymous with irreversible neuronal energy failure. According to this view, a DWI lesion would inevitably go on to manifest as stroke in all cases. The important work by Li and colleagues and Kidwell and associates suggests that this may not be the case. As these studies suggest, further understanding of pathology at the tissue level is provided by perfusion-weighted imaging (PWI). Using bolus gadolinium enhancement, PWI measures the total volume of tissue being starved of blood flow and therefore at risk for infarction. Mismatch between the DWI and PWI allows measurement of the "tissue at stake," identifying tissue potentially salvageable with thrombolytic therapy. It is possible that in well-selected patients with such a mismatch there may be therapeutic benefit from aggressive treatment long after the conventional time frame for IV or intra-arterial thrombolysis. The ticking of the "tissue clock" may be more important than the "time clock," as clinicians make often-hurried decisions about these potentially risky therapies.

Li et al subjected 16 rats to 10 or 30 minutes of focal cerebral ischemia followed by reperfusion. The animals were imaged with DWI/PWI at regular intervals over the next 72 hours. Histopathological study followed. During occlusion, both groups showed abnormal DWI and PWI in the territory at risk. Following occlusion, during reperfusion, DWI and PWI normalized in both groups. However, at 12-hour follow-up, while the 10-minute group remained normal, new secondary abnormalities on DWI (as well at T2-weighted images) reappeared in the 30-minute group. Histopathological damage was demonstrated in both groups. This damage included the 10-minute ischemia group despite these animals being

fully normal by imaging. Though less in degree, this damage suggests that reversibility of DWI lesions does not necessarily indicate a normal histological outcome.

Kidwell et al report similar observations in human cases of acute ischemic stroke. They demonstrate that with successful thrombolysis and recanalization of the occluded artery, DWI abnormalities may be reversed (mean DWI lesion volume at baseline was 23 cc and decreased to 10 cc after thrombolysis). However, in three of six patients at day 7, a secondary increase in DWI lesion volume was observed. PWI was performed in four patients, all showing complete resolution of the perfusion deficit with thrombolysis. **—azs & ayeesha kamal, md** (*Dr. Kamal is Chief Resident of Neurology at New York Presbyterian Hospital.*)

Another Effective Treatment for Acute Ischemic Stroke

ABSTRACTS & COMMENTARY

Sources: Sherman DG, et al. Intravenous ancrod for treatment of acute ischemic stroke: The STAT study: A randomized controlled trial. *JAMA* 2000;283:2395-2403; Mayberg MR, Furlan A. Ancrod—Is snake venom an antidote for stroke? *JAMA* 2000;283:2440-2442.

Sherman and colleagues tested the efficacy of ancrod in reducing functional disability after acute ischemic stroke. Ancrod, a protease derived from Malaysian pit viper venom, induces rapid defibrinogenation. Defibrinogenation produces anticoagulation, decreased blood viscosity, and stimulates endogenous thrombolysis.

A three-day infusion of ancrod or placebo was administered to 500 patients within three hours after the onset of stroke and was followed by subsequent one-hour infusions at four and five days. A favorable outcome was defined as survival to 90 days with a Barthel Index greater than 95.

Ancrod produced a 7.8% absolute and 22.7% relative improvement in functional status (42.2% in the ancrod group vs 34.4% in the placebo group; P = 0.04). The benefit observed with ancrod was consistent in all patient subgroups defined by age, stroke severity, sex, prestroke disability, and time to treatment. There was a trend toward more symptomatic intracranial hemorrhages in the ancrod group vs. the placebo group (5.2% vs 2.0%; P = 0.06) as well as a significant increase in asymptomatic intracranial hemorrhages (19.0% vs 10.7%; P = 0.01). Mortality at 90 days was not different between the treatment groups.

COMMENTARY

Although the 8% absolute benefit in full neurological recovery with ancrod is less than the 12% benefit reported in the NINDS intravenous tissue plasminogen activator (tPA) trial (National Institute of Neurological Disorders and Stroke rt-PA Stroke Group Study Group. *N Engl J Med* 1995;333:1581-1587), the importance of the STAT results is that they confirm the validity of the concept that successful treatment of acute ischemic stroke is possible. Along with the NINDS trial (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995;333:1581-1587) and the PROAC II study of intra-arterial prourokinase (Furlan A, et al. *JAMA* 1999;282:2003-2011), STAT reinforces the role of early reperfusion strategies in acute stroke therapy. A further clinical implication of STAT is that ancrod provides another means, in addition to thrombolytic drugs, for improving outcome after acute stroke. As pointed out by Mayberg and Furlan in their editorial, the challenge for clinical research now becomes how to safely combine thrombolytics, microcirculatory reperfusion, antiplatelet, antithrombolic, and, eventually, cytoprotective agents to optimize neurologic outcome. The future of acute treatment for stroke looks both challenging and exciting. **—jjc**

Incidence of Dyskinesia in Patients with Early Parkinson's Disease Treated with Ropinirole or Levodopa

ABSTRACT & COMMENTARY

Source: Rascol O, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med* 2000; 342:1484-1491.

Ropinirole, a d2 and d3 receptor nonergot agonist, reached the U.S. market in the fall of 1998. It has been found effective in ameliorating the motor manifestations of early and advanced Parkinson's disease (PD) in several large clinical trials. In this double-blind, industry-sponsored study, PD patients were treated with ropinirole or levodopa and were followed for more than five years in order to determine the incidence of the development of dyskinesias. Two hundred sixty-eight patients with PD (Hoehn and Yahr stage 1-3) were enrolled. They were eligible for enrollment only if they required treatment with a dopaminergic agent, if they were not demented, if they had

no history of psychosis, and if they had not received prior treatment for more than six weeks with either levodopa or any dopamine agonist.

The 268 patients were enrolled at 30 centers throughout Europe, Israel, and Canada. Two patients were assigned to the ropinirole group for each patient assigned to the levodopa arm. The study was performed in a double-blind, double-dummy fashion. After an initial dose-escalation period, patients were maintained at a stable dose of study drug. For patients whose symptoms were not adequately controlled by study drug alone, supplementary levodopa could be given in open-label fashion. The incidence and severity of dyskinesias were measured by the Unified Parkinson's Disease Rating Scale, which asks patients to assess the severity and daily duration of dyskinesias.

Of the 268 patients who enrolled in the trial, 179 were assigned to the ropinirole arm and 89 to levodopa. The average daily dose of ropinirole during the study was 16.5 mg, and the average dose of levodopa was 753 mg. Dyskinesias developed in 20% of patients in the ropinirole group and 45% of patients in the levodopa group. Eight percent of the patients in the ropinirole group had "disabling" dyskinesias, compared to 23% of the patients given levodopa. The hazard ratio for remaining free of dyskinesias for the ropinirole group compared to the levodopa group was 2.82.

Unfortunately, the decrease in dyskinesias was not achieved without a price. Patients who received levodopa had a statistically significant improvement from baseline in motor performance as measured on section II of the Unified Parkinson's Disease Rating Scale. This was not true for patients who received ropinirole: 32% of patients receiving ropinirole experienced freezing of gait, compared to 25% receiving levodopa. The incidence of nausea, insomnia, and postural hypotension was similar between the two groups. However, patients who received ropinirole had increased incidences of somnolence (27.4% vs 19.1%), hallucinations (17.3% vs 5.6%), and leg edema (14% vs 5.6%).

The premature withdrawal rate from the study was high—53% in the ropinirole group and 49% in the levodopa group. Of 179 patients initially assigned to receive ropinirole, 92 (51%) required supplementation with levodopa during the course of the trial. Only 29 patients were able to remain on ropinirole as monotherapy for the full five years.

COMMENTARY

Over the last decade, a shift in practice has occurred among movement disorder neurologists in how they treat patients with early PD. Most neurologists try to manage these patients with dopamine agonists first, instead of using levodopa. This reflects the commonly held belief that early treatment with levodopa accelerates the onset of motor fluctuations, including the wearing-off phenomenon and the development of dyskinesias. There are also theoretical reasons to support treatment with agonists. In vitro studies have shown that dopamine agonists may be neuroprotective, whereas levodopa has been shown to contribute to oxidative injury in cell culture models.

The present study confirmed the prediction of movement disorder neurologists, that treatment with dopamine agonists produces fewer dyskinesias than treatment with levodopa. The results of the study were heavily publicized when they were first announced in the summer of 1999. However, careful review of the design and analysis of the trial reveals several problems.

The study was designed to examine the effect of agonist monotherapy on "early" PD. To most clinicians, patients with "early" Parkinson's have only limited functional disability. One-third of the patients enrolled in this trial, however, started with a Hoehn and Yahr stage of 2.5 (mild to moderate balance impairment) or 3.0 (no recovery on pull test). Most movement disorder neurologists would not consider a patient with any degree of balance impairment to be "early." At our center, balance impairment is a clear indication for starting levodopa.

The primary outcome measure of the ropinirole study was the development of dyskinesias. Rating dyskinesias is notoriously difficult and the validity of self-rated dyskinesias is unknown. Nevertheless, a dyskinesia rating of 1+ on item 32 of the Unified Parkinson's Disease Rating Scale denotes dyskinesias of less than 25% of the waking day. A self-rating of 1+ on item 33 denotes dyskinesias that are only mildly disabling. Clinical experience suggests that involuntary movements of only 1+ severity are not troublesome. In fact, patients are much more bothered by slowness or stiffness than by occasional involuntary movements. Thus, the primary outcome measure of this study, the development of dyskinesias of 1+ severity on items 32 and 33 of the Unified Parkinson's Disease Rating Scale, may not reflect patients' perception of their disability.

Compared to levodopa, patients who received ropinirole failed to experience an equivalent symptomatic benefit. They enjoyed less improvement in their motor scores and had an earlier onset of gait freezing, a potentially serious symptom due to the increased risk of falling. Further, only 29 of 179 patients initially assigned to receive ropinirole were able to continue taking it as monotherapy after five years. This implies that ropinirole does not provide adequate, long-term symptomatic treatment for the majority of Parkinson's patients who

require dopaminergic therapy.

The incidence of adverse events in this trial was not significantly different between its two arms. There was, however, a clear trend toward increased somnolence, hallucinations, and lower extremity edema in the ropinirole group. Hallucinations were particularly troubling, occurring in 17.3% of the ropinirole population and only 5.6% of the levodopa group. Rascol and colleagues also state that there were no reports of falling asleep suddenly in either group. It is not known whether patients were specifically queried on this issue. Recent analyses have shown that patients under-report these events, and that they are often not captured by the standard adverse event questionnaires used in clinical trials.

How should neurologists interpret this study, and what effect will it have on their treatment of patients with PD? This trial showed that some patients can be effectively managed with ropinirole monotherapy for up to five years. However, most patients require supplemental levodopa to prevent unacceptable functional disability. At our center, we hesitate to use dopamine agonists in Parkinson's patients older than the age of 70, as the incidence of adverse events (namely, somnolence and hallucinations) increases with age. Ropinirole monotherapy is a reasonable option in younger patients, particularly those without balance impairment and those who are in the early stages of the illness. Neurologists should keep in mind the recent reports of sudden sleep episodes associated with the newer dopamine agonists, and counsel appropriate patients with respect to safe driving. **—steven frucht, md**

Treatment of Isolated Systolic Hypertension is Beneficial

ABSTRACT & COMMENTARY

Source: Staessen JA, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: Meta-analysis of outcome trials. *Lancet* 2000;355:865-872.

In order to evaluate the risks associated with isolated systolic hypertension in older patients, Staessen and colleagues performed a meta-analysis of eight published trials. Patients were 60 years old or older, systolic blood pressure (BP) was 160 mmHg or greater, and diastolic BP was less than 95 mmHg. More than 15,000 patients with isolated systolic hypertension were followed for a median time of 3.8 years. Untreated systolic BP was a more accurate predictor of mortality and cardiovascular complications than diastolic BP. A 10 mmHg increase in systolic BP was significantly and independently correlated with increases of nearly 10% for total mortality (Relative Hazard Rate [RHR] 1.3; P = 0.0001) and stroke (RHR 1.2; P = 0.02), but not for coronary events (RHR 1.1; P = 0.37). Diastolic BP, in contrast, was inversely correlated with total and cardiovascular mortality. At any given level of systolic BP, the risk of death rose with lower diastolic BP and therefore also with greater pulse pressure.

Active treatment of hypertension reduced total mortality by 13%, stroke by 30%, and coronary events by 23%. The number of patients to treat for five years to prevent one major cardiovascular event was lower in men (18 vs 38), at age 70 or older (17 vs 39), and in patients with previous cardiovascular complications (16 vs 37).

COMMENTARY

Isolated systolic hypertension refers to a rise in systolic BP with increasing age due to decreased elasticity of the large arteries and is not necessarily accompanied by a rise in mean arterial BP or in peripheral resistance. The prevalence of isolated systolic hypertension averages 8% in individuals between 60 and 70 years of age and exceeds 25% in those aged 80 years or older (Staessen J, et al. *J Hypertens* 1990;8:393-405). Nevertheless, systolic hypertension is not a benign aging change. Rather, it is one of the stroke risk factors that is reversible with treatment.

Staessen et al found treatment of systolic hypertension had a greater absolute benefit in men, older patients, those with previous cardiovascular complications, or those with a higher pulse pressure. Why antihypertensive treatment apparently provided less protection against coronary complications than against stroke is unclear. As Staessen et al state, it may be among other reasons that the association between systolic BP and coronary artery disease weakens with increasing age. In summary, the evidence justifies drug treatment of isolated systolic hypertension in the elderly. **—jjc**

Creatine for Muscular Dystrophy

ABSTRACT & COMMENTARY

Source: Walter MC, et al. Creatine monohydrate in muscular dystrophies: A double-blind, placebo-controlled clinical study. *Neurology* 2000;54:1848-1850.

Thirty-six muscular dystrophy (md) patients, including facioscapulohumeral (n = 12), Becker (n =

10), Duchenne (n = 8), and sarcoglycan-deficient (n = 6) MD, were enrolled in an eight-week, double-blind, placebo-controlled, crossover study of creatine monohydrate (CREAPURE; Cr), followed by a three-week washout period, to determine safety and efficacy of 5 g/d or 10 g/d, for children and adults, respectively. Medical Research Council (MRC) scale, Neuromuscular Symptoms Score ([NSS] Soueidan SA, Dalakas MC. *Neurology* 1993;43:876-879), vital capacity (VC), and patient self-rating were primary end points, and standard statistical analyses, including Wilcoxon's and Fisher's exact tests, were used to assess results.

Muscle strength significantly improved by 3%, and NSS by 10%, on Cr, compared to a declining trend on placebo, with improvement seen in all forms of MD, in both mildly and severely affected muscles, more so in children than adults. Twenty-one of the 36 patients self-reported improvement by Cr vs. no improvement by placebo. VC did not change, serum creatine kinase levels did not rise, and side effects were absent in all patients. Oral Cr is safe, well tolerated, and mildly efficacious. Further larger scale studies are warranted to determine its efficacy in specific MDs as well as in other neuromuscular conditions.

COMMENTARY

Cr may also be beneficial for neurogenic neuromuscular disorders, acting through several potential mechanisms. First, calcium is cytotoxic in certain clinical situations (e.g., cerebral ischemia) and creatine kinase deficiency results in impaired calcium buffering. Cr regenerates adenosine triphosphate (ATP), which is then used by calcium adenosine triphosphatase (ATPase) for calcium buffering, thus inhibiting its cytotoxic effect. Second, in animal models of Huntington's disease, Cr supplementation protects against striatal damage produced by 3-nitroproprionic acid (3-NPA) by attenuating lactate increases, as well as ATP and phosphocreatine decreases, induced by 3-NPA (Matthews RT, et al. *J Neurosci* 1998;18:156-163). Lastly, Cr blocks the mitochondrial transition pore, an opening in the inner mitochondrial membrane that occurs as a result of various stimuli, including excess calcium, and which is linked to excitotoxic and apoptotic cell death (White RJ, Reynolds IJ; Schinder AF, et al. *J Neurosci* 1996;16:5688-5697; 6125-6133). Cr inhibits mitochondrial pore opening by stabilizing mitochondrial creatine kinase. Cr supplementation appears to show promise for the treatment of neuromuscular disease and also is being evaluated in a multicenter trial for amyotrophic lateral sclerosis. We await the results with interest. **—mr**

Correction

The article, "West Nile Virus: Preparing for the Sequel," in the June 2000 issue of *Neurology Alert* contained an error. Paragraph two, sentence one reads: "All three of the eight fatalities were elderly, with ages older than 75 years." The sentence should read: "All three fatalities among the eight initial patients were elderly, with ages older than 75 years." We regret any confusion this may have caused. ❖

News Bulletin

As *Neurology Alert* goes to press (June 20, 2000), identification of West Nile virus has been made in two dead birds and two dead fowl in the Flushing area of Queens, New York City. Disinfection of risk areas has been initiated, but neurologists should be attentive to symptoms. ❖

CME Questions

1. **At least four genes have been shown to predispose individuals to Alzheimer's disease. These include:**
   a. the APP gene.
   b. presenilin 1.
   c. presenilin 2.
   d. E-4 allele of the apolipoprotein E gene.
   e. All of the above

2. **As a result of defibrogenation, ancrod produces all of the following effects *except*:**
   a. anticoagulation.
   b. increased blood viscosity.
   c. improved microcirculation.
   d. stimulation of endogenous plasminogen activators.

3. **Creatine:**
   a. is toxic.
   b. may be beneficial for the treatment of primary muscle and nerve disease.
   c. acts by inhibiting the Na/K pump.
   d. enhances calcium release at the neuromuscular junction.
   e. has no role in the treatment of muscle or nerve disease.

In Future Issues: Phantom Sensations from Congenitally Absent Limbs