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Spotlight on Parkinson's Disease: Report of the Movement Disorder Society's 5th International Congress of Parkinson's Disease and Movement Disorders

CONFERENCE UPDATE

The 5th international congress of parkinson's disease and Movement Disorders was held in New York, N.Y., Oct. 10-14, 1998. Organized by Stanley Fahn, MD, the meeting produced several new and important pieces of information. In the field of genetics, abnormalities of at least four independent gene loci are now known to cause familial Parkinson's disease. M. Polymeropoulos of Washington DC described the discovery of the Contursi kindred, an Italian family afflicted with early-onset autosomal dominant levodopa-responsive Parkinson's disease (*Science* 1997;276:2045-2047). A mutation in alpha-synuclein, a protein encodes on chromosome 4q, is responsible for the family's phenotype. The biology of alpha-synuclein is intriguing. It genetically induces the non-A-beta component of Alzheimer plaques, is preferentially expressed in dopamine neurons, is abundant in Lewy bodies (the pathologic marker of Parkinson's disease), and is even amyloidogenic (Burke R. *Trends Neurosci* 1998;21:249-254). One investigator described his discovery of a gene on chromosome 6q, named "parkin," that is responsible for autosomal recessive juvenile Parkinson's disease (Mizuno Y. *Nature* 1998;392:605-608). This cohort differs from the Contursi kindred: their symptoms began at an earlier age, they developed early dyskinesias and motor fluctuations, and their brains lack Lewy bodies in the substantia nigra.

Two investigators from Boston together amplified their recent publications on the molecular biology of the DYT-1 gene, responsible for early-onset dystonia. The DYT-1 gene, located on chromosome 9q, encodes torsinA, a protein homologous to heat shock proteins (Ozelius L, Penney J. *Nat Genet* 1997;17:40-48). It is expressed in many tissues and abundantly expressed within hippocampus, putamen, cerebellum, and substantia nigra. A deletion of a single amino acid engenders all cases of DYT-1 dystonia. At least six additional loci described by another investigator from New York

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have also been linked to inherited forms of dystonia, most of which begin in adulthood (Bressman S. *Ann Neurol* 1997;42:670-673). Pandolfo, of Montreal, Canada, Klockgether, of Bonn, Germany, Tsuji, of Niigata and Patchek, Salt Lake City, UT, reviewed the enormous strides made in the past decade to map the genes responsible for Friedrich's ataxia, autosomal dominant cerebellar ataxias, DRPLA, and episodic ataxias. These markers for rare diseases—most now commercially available for testing suspected patients—offer unique opportunities to construct transgenic mouse models of disease. Currently, their phenotypes express a spectrum of neurologic presentations that are wider than previously suspected. Commercially available markers (via Athena Neurosciences) include SCA-1, 3, and DRPLA.

New Therapy. In the last 16 months, two new dopamine agonists, Mirapex and Requip, and one catechol-O-methyltransferase (COMT) inhibitor (Tasmar), have been released in the United States. Another COMT inhibitor (Entacapone) may be released next year. Two investigators reviewed the role of the new dopamine agonists and COMT inhibitors in the treatment of Parkinson's disease (Rascol O. *Clin Neuropharmacol* 1998;21:169-175; Nutt J. *Lancet* 1998;351:1221-1221). Mirapex and Requip, both non-ergot dopamine agonists, act at the D2 and D3 receptors, as opposed to Permax and Requip, which also have D1 activity. Despite the assertions of the pharmaceutical companies, no evidence supports the newer agonists superiority to older agonists as add-on therapy to levodopa in fluctuating Parkinson patients. Both new agonists are effective as monotherapy in levodopa-naïve early Parkinson patients. Unfortunately, they also possess the same side effect profile as the ergot agonists (Parlodel, Permax, and Cabergoline), namely hallucinations, orthostasis, and somnolence. Tolcapone, the only currently available COMT inhibitor, decreases the elimination of levodopa and, thus, increases the amount of levodopa that crosses the blood-brain barrier. It is effective in patients with wearing-off phenomena, increasing "on" time. However, the drug is not without side effects. It may occasionally induce diarrhea severe enough to force discontinuation of the drug. More concerning, a small percentage of patients develop abnormalities in liver function. Three patients have died from acute hepatic failure after taking Tasmar. Before starting the drug, physicians must obtain a written informed consent and must check liver function tests on all patients. Liver function tests must then be followed every two weeks for the first year of therapy, every four weeks for the next six months, and then every eight weeks thereafter. Before increasing the dose to 200 mg three times per day, liver function tests should always be checked.

Invasive Therapy. The last five years have seen an explosion of interest and renewed experience with neurosurgical interventions for advanced Parkinson's disease (Obeso J, et al. *Mov Disord* 1998;13(1):73-82). Two central questions pervade the use of these approaches: which target should be chosen, and should a lesion be performed or a permanent stimulator implanted? Lesions (thalamotomy or pallidotomy) are less expensive and simpler to perform. However, they are permanent, not titratable, and carry unacceptable risks of neurologic sequelae when performed bilaterally. Stimulators are more expensive (currently only approved in the United States for unilateral V.i.m. stimulation for intractable tremor from Parkinson's disease or Essential Tremor) and carry a risk of infection or hardware failure. Nevertheless, they can be implanted bilaterally, do not damage tissue, and can be titrated to achieve optimal response. Both procedures carry an unavoidable 1-2% risk of operative hemorrhage, stroke, or visual field cut. Pallidotomy remains an effective technique for reducing contralateral levodopa-induced dyskinesias. The anatomy of the pallidum is so complex, however, that many centers are abandoning the pallidum as a site for stimulation. Instead, groups in Grenoble, Paris, and Toronto have implanted bilateral subthalamic nucleus (STN) stimulators. Bilateral STN stimulation is extremely effective in alleviating virtually all of the levodopa-responsive signs of Parkin-

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son's disease, including tremor (*N Engl J Med* 1998;339:1105-1111). Motor scores and videotapes of selected patients with bilateral STN stimulators show remarkable improvement: they can often reduce and sometimes eliminate levodopa altogether. Although these techniques remain experimental and are currently available in the United States only in research protocols or to patients who can afford the operation, the data and clinical opinions suggest a dominant role for bilateral STN stimulation for intractable Parkinson patients in the next decade. **—sf** *(Dr. Steven Frucht is Post-Doctoral Clinical Fellow, Movement Disorders Division, The Neurological Institute, Columbia University, New York, NY.)*

Spotlight on Parkinson's Disease

Source: Lang AE, Lozano AM. Medical progress: Parkinson's disease. Parts 1 and 2. *N Engl J Med* 1998;339:1130-1143;1044-1053.

Supplementing in detail frucht's congress report, Lang and Lozano of Toronto have provided an excellent review article in the *New England Journal of Medicine*. Starting with the announcement that underdiagnosis of Parkinson's disease (PD) may affect as many as 24% of cases, they emphasize the accuracy of careful clinical diagnosis and consider brain imaging as "rarely helpful." The review indicates as many as 45% of PD patients develop a variety of dementia. Pathogenic processes, including mitochondrial dysfunction and oxidative metabolism, are skillfully described to the reader. Excitotoxins, neurotrophic factors, and immune processes receive reasonable attention, as do genetic and other factors in the disorder's development.

Some interesting points are that Asians and African blacks have a lower incidence compared to American blacks and, especially, whites. Remarkably, PD risk declines among those who smoke(d) sometime during their life. A full page deals with the genetic forms of PD and their various biochemical defects that might resemble exogenous factors that may cause the illness. This latter item may particularly indicate that even non-genetic mitocondrial errors may contribute to PD's incidence.

Part two of the review starts with pathophysiology emphasizing that the brain's dopa-deficient state inherently is reciprocated by increased, inhibitory GABA circuits resulting in the disease's cortical motor system. For example, both thalamectomy and pallidotomy are considered to reduce inhibitory outflow and both improve unwanted motor activity in PD. Treatment is fully discussed in three categories: protective-preventive, symptomatic, and restorative-regenerative.

No known agent or behavior protects against PD. Early treatment invites disparity because of a paucity of well-designed and completed controlled studies. Lang and Lozano debunk the concept that levodopa is either toxic or accelerates the course of PD if started at onset of diagnosis. Selegeline and amantidine may provide early, but not late, assistance. Dopamine agonists, such as bromocriptine or pergolide, appear to bring mild, early relief, but levodopa sooner or later becomes necessary to lessen symptoms. Sections on late management along with their associated problems deserve the reader's attention since they are discussed in relatively helpful detail. Surgical treatment comes in four forms: 1) transcellular exogenous implants, including the present selectively successful transplants of human fetal nigral dopaminergic cells into the striatum; 2) potential future possibilities of transplanting autogenous dopaminergic cells from the individual's carotid body dopaminergic cells into selected basal ganglia targets (Espego EF, et al. *Neuron* 1998;20:197-206); 3) intracerebral lesioning of the globus pallidus (pallidotomy) to relieve tremor—a procedure with several potential complications; and 4) bilateral stimulation of the internal segment of the globus pallidus or, even more successful in outcome, the subthalamic nucleus. **—fp**

Subthalamic Nuclei

Source: Limousin P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's Disease. *N Engl J Med* 1998;339:1105-1111.

This collaboration of french-based clinical scientists reports the outcomes of 24 patients with severe PD treated by direct stimulation of both subthalamic nuclei (STN). Twenty patients had at least one year of experience with the procedure.

Paradoxically, the STN normally enhances parkinsonian symptoms in monkeys given 1-methyl-4 phenyl- 1, 2, 3, 6-tetrahydropyridine. Nevertheless, high frequency, direct stimulation of the STN also ameliorated the monkey's signs and did the same in advanced human PD in a preliminary study by Limousin et al (*Lancet* 1995;345:91-95). For this study, only patients with disabling motor flutuations were chosen. Of the 24 patients, one developed a severe hemiparalysis and aphasia from a hematoma, one subsequently died of unrelated causes, one was geographically inaccessible for follow-up, and one had electrodes removed because of secondary infection.

All patients treated had disabling motor fluctuations despite drug treatment. During off periods, these patients were severely handicapped (19 had painful dys-

tonia) but could perform most daily activities during on periods. All received levodopa + inhibitor, 21 took a dopaminergic agonist, and 12 received apomorphine. Post-implantation electrical connections were adjusted at follow-up according to need. Detected dementia excluded possible candidates.

Stimulation generally reduced signs/symptoms of patients off medication by 60%. During medication-timed continued stimulation, 10% produced improved scores for akinesia, rigidity, tremor, ability to rise from chairs, gait, and postural stability all during off periods of medication. Other mobilities also improved, especially disabilities previously severe in off times. Painful off-period dystonia ceased in 12 patients and improved in four. All changes were highly significant and maintained. Medication was reduced in about half.

COMMENTARY

Parkinson patients and their doctors should consider this success of ameliorating severe, late developed disabilities by subthalamic stimulation. Presently, the disease must be crippling and advanced, pharmacologically resistant, and dementia-free before such stimulation is considered. What will be the cost? No one for sure can set a cost, but, compared to other risky ventures of like approaches, $100,000 sounds like a bottom price. **—fp**

Surgical treatment for Parkinson's disease has several options. Which of the following appears presently to have the greatest chance of success?

a. Pallidotomy
b. Thalamotomy
c. Electrode stimulation of the subthalamus
d. Autogenous transplantation of a person's dopaminergic cells from the carotid body into selected basal ganglia targets

Distinguishing Lewy Body from Alzheimer's Dementia

ABSTRACTS & COMMENTARY

Source: Hashimoto M, et al. Medial temporal and whole-brain atrophy in dementia with Lewy bodies. *Neurology* 1998;51:357-362; Boeve BF, et al. REM sleep behavior disorder and degenerative dementia. An association likely reflecting Lewy body disease. *Neurology* 1998;51:363-370.

Consensus guidelines for the diagnosis of Dementia with Lewy bodies (DLB) (McKeith IG, et al. *Neurology* 1996;47:1113-1124) delineates certain features that are frequently associated with DLB, such as the early occurrence of parkinsonism without tremor, waxing and waning confusion, hallucinosis, and increased neuroleptic sensitivity—all in the context of progressive cognitive decline. Nevertheless, current clinical criteria are said to fail to identify 25% or more of true cases. Three recent studies provide insight into other features that could ultimately prove useful in the differential diagnosis of DLB.

Olichney et al (Olichney JM, et al. *Neurology* 1998;51(2):351-357) analyzed data from the USCD Alzheimer's Disease Research Center and the Consortium to Establish a Registry for AD (CERAD) to determine the rate of decline on the Minimental state examination of patients with autopsy proven Alzheimer's Disease (AD) (u = 148) vs. the Lewy body variant of AD (LBV) (u = 40). LBV as defined by Olichney et al includes patients with dementia who met neuropathologic criteria for AD but also had one or more Lewy bodies present in the brainstem or cerebral cortex. Analysis of change scores on the MMSE over a five-year period showed a faster rate of decline among the LBV patients, who declined an average of 1.6 MMSE points per year more than the AD patients. The survival time of the LBV groups also appeared shorter, with LBV patients dying an average of 1.6 years earlier than AD patients. Although previous case reports and clinical series have shown similar effects, this is reported to be the first autopsy-proven study of LBV to demonstrate faster cognitive decline.

It has been reported that neuronal cell counts in the hippocampus of patients with DLB are closer to normal than in AD patients. Hashimoto and colleagues used MRI volumetry to determine hippocampal volumes in 27 normals, 27 patients with DLB, and 27 age- and gendermatched patients with AD of comparable severity. They found that average hippocampal volumes in DLB were significantly greater than in AD but less than in normals. Hashimoto et al suggest that this is consistent with previous reports of less severe glucose hypometabolism in the medial temporal lobe and less severe declarative memory impairment in DLB patients compared to AD patients.

Boeve and associates studied 37 patients with degenerative dementia and a history of sleep-associated vigorous movements of the arms and legs with vocalization and dream recall, comprising symptoms of a REM sleep behavior disorder. They found that the sleep disorder preceded or began concurrently with the dementia in all but two cases. The mean age of onset on sleep disturbance was 61.5 years, whereas the onset of cognitive disturbances was, on average, age 68.1. Ninety-two percent of the patients met current criteria

for a diagnosis of DLB. Three patients in this series came to autopsy and all had Lewy bodies within the limbic system. Boeve et al expressed the belief that the combination of REM behavioral disturbances and degenerative dementia most likely reflects underlying DLB, although they concede that similar findings may be associated with other disorders.

COMMENTARY

DLB is reportedly the second most common form of neurodegenerative dementia after AD. DLB is important to recognize and distinguish from AD because its management poses distinct challenges to clinicians as well as caregivers. For example, DLB patients can experience fixed delusions and visual hallucinosis early in the course of their illness, and these patients may develop dramatic worsening of their extrapyramidal symptoms when treated with neuroleptics. DLB patients may respond favorably to acetylcholinesterase inhibitors.

Neither rate of progression of cognitive decline, hippocampal volume loss, nor an association with REM sleep disturbances are likely to become major new diagnostic criteria for DLB. Nevertheless, eliciting a history of an antecedent REM sleep disturbance, seeing a less than expected degree of hippocampal atrophy, or observing a more rapid than expected rate of cognitive decline might serve to trigger reconsideration of the patient having DLB rather than AD. The current means for distinguishing AD from DLB need to be improved upon and further studies using larger cohorts of demented patients are needed. **—nrr**

All of the following have been associated with Dementia with Lewy bodies *except*:

a. more rapid cognitive decline than in Alzheimer's.
b. REM sleep disturbance before or concurrent with onset of dementia.
c. lesser degree of hippocampal atrophy than in Alzheimer's Disease.
d. lower hippocampal cerebral metabolism than in Alzheimer's.
e. parkinsonism without tremor.

Prophylactic Transfusions Prevent Strokes in Vulnerable Sickle Cell Disease

ABSTRACT & COMMENTARY

Source: Adams RJ, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial doppler ultrasonography. *N Engl J Med* 1998;339:5-11.

Stroke is an infrequent but devastating complication of sickle cell anemia. In a previous study of 315 sickle cell patients (*N Engl J Med* 1992;326:605-610), Adams showed that transcranial Doppler blood flow velocities exceeding 200 cm/sec in the ICA or MCA predicted an increased risk for stroke. The multicenter study, Stroke Prevention Trial in Sickle Cell Anemia (STOP), was undertaken using transcranial Doppler to test whether periodic transfusion would lower stroke risk.

During two years of screening, 3929 transcranial Doppler studies were performed on 1934 children ages 2-16 with sickle cell anemia or sickle thalassemia. To be considered abnormal, mean blood-flow velocity had to be at least 200 cm/sec in either the ICA or MCA. Two hundred six children had two or more abnormal studies and were, therefore, considered eligible for the study. Because of either ineligibility or drop out, only 130 children (60 boys, 70 girls) were enrolled. Sixty-three were randomized to receive transfusions and 67 to standard care. The transfusion goal was a target hemoglobin S concentration of less than 30% total hemoglobin. Once established, children received maintenance transfusions every 3-4 weeks for a median follow-up period of 22.2 months compared to 18.3 months for the standard care group. The end point was cerebral infarction as determined by blinded evaluators based upon MRI and clinical criteria. Eleven children in the standard care group and one child in the treatment group had strokes.

The risk of stroke was 92% lower in the transfusion group ($P < 0.001$). The rate of stroke in the standard care group was 10% per year. In 10 of 11 children, the strokes were large vessel (carotid territory) infarctions. Two patients were left with major disability, five had mild-moderate impairments, and three were discharged without disability. Because of the high rate of stroke in the standard care group, the study was stopped 16 months earlier than planned so that transfusions could be offered to the standard care group.

COMMENTARY

This study of SCA patients found both a high rate of stroke in children with abnormal results on TCD (the higher the blood flow velocities, the higher the risk of stroke) and a beneficial effect of transfusion to reduce Hemoglobin S concentration. Transfusions have been proven effective in preventing recurrent strokes in SCA patients.[2] The present treatment trial has established a role for prophylactic transfusions in children with TCD evidence of intracra-

nial arterial stenosis. The study does not, however, establish how long transfusions must be continued to prevent strokes. In the current trial, the risk of stroke was high, about 10% per annum, without treatment. Whether stroke risk remains at this level indefinitely is unknown. Therefore, if long-term prophylactic transfusion therapy is necessary in all such SCA patients, the benefits of treatment may be limited by the cost and complications of treatment. Nevertheless, Adams et al have made a noteworthy advance in the non-invasive diagnosis and treatment of stroke-prone SCA patients. Further studies, no doubt, will answer the questions this study has raised. **—jjc & jr**

References

1. Ohene-Frempong K, et al. Cerebrovascular accidents in sickle cell disease: Rates and risk factors. *Blood* 1998;91:288-294.
2. Pegelow CH, et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. *J Pediatr* 1995;126:896-899.

In children with sickle cell anemia, which of the following best predicts stroke risk?

a. Brain MRI abnormalities
b. Results of Transcranial Doppler Ultrasonography
c. Hemoglobin value
d. Hematocrit value
e. Age

Chiropractic Benefit Challenged

ABSTRACT & COMMENTARY

Source: Cherkin DC, et al. A comparison of physical therapy, chiropractic manipulation, and provision of an educational booklet for treatment of patients with low back pain. *N Engl J Med* 1998;339:1021-1029.

In this study from the university of washington, 321 patients aged 20-64 years presented to their primary care physician with non-specific back pain of more than seven days duration. They were randomly assigned to either the McKenzie method of physical therapy, chiropractic manipulation, or minimal intervention by providing an educational pamphlet on the causes and prevention of low back pain. Patients with sciatica were excluded. Physical therapy and chiropractic sessions were limited to nine over a one-month period, with follow-up over a total of two years. The degree of back pain was measured on an 11-point scale and the level of dysfunction assessed on the 24-point Roland Disability Scale.

No significant difference emerged between the chiropractic and physical therapy group at one month, although the chiropractic group appeared to have slightly less severe symptoms than the booklet group (P = 0.02). Differences in the degree of dysfunction among the three groups were small and approached significance only at one year, with slightly greater dysfunction in the booklet group (P = 0.05). No significant differences appeared in the number of days of reduced activity, work, or in recurrent back pain. About 75% of patients in the physical therapy and chiropractic groups were satisfied with their care, compared with about 30% in the booklet group. The mean costs of care over a two-year period were $437 for the physical therapy group, $429 for the chiropractic group, and $153 for the booklet group. Cherkin and associates conclude that patients with low back discomfort had similar benefits and costs from physical therapy and chiropractic manipulation, and they were only marginally better than those patients receiving the minimal intervention of an educational booklet at a fraction of the cost.

COMMENTARY

Back pain is a significant health issue in primary practice and neurology because of its high prevalence and associated healthcare costs. Many patients self-refer to chiropractors for complaints of back pain, as well as other health issues, as "family chiropractic care centers" emerge, claiming to treat back disorders plus a variety of other conditions. An accompanying study concludes that chiropractic manipulation is worthless against childhood asthma (Balon J, et al. *N Engl J Med* 1998;339:1013-1020). Most physicians shudder when presented with chiropractic theory of general ill health created by spinal malalignments treatable by spinal adjustments. Neurologists have also encountered the catastrophic complications of carotid or vertebral artery dissection and devastating strokes following cervical spine manipulation.

Cherkin et al demonstrate that chiropractic manipulation is no more effective than a popular form of physical therapy in patients with low back pain. Indeed, providing an educational booklet about low back pain provided almost as much relief. The main difference between the groups was that patients receiving any form of hands-on therapy had a much higher satisfaction rate with their care. Whether these treatments are worth the additional costs is open to future debate. **—ba**

Alcoholic Acute

Axonal Neuropathy

ABSTRACT & COMMENTARY

Source: Wohrle JC, et al. Alcohol-related acute axonal polyneuropathy: A differential diagnosis of Guillain-Barré syndrome. *Arch Neurol* 1998;55:1329-1334.

Over a three-year period, five chronic alcoholic patients, without a history of diarrheal prodrome or previous symptoms or signs of polyneuropathy, presented with rapidly ascending, flaccid, tetraparesis (n = 4) or paraparesis (n = 1), absent or depressed deep tendon reflexes, glove-stocking loss of multimodal sensation, painful paresthesiae (n = 4) or myalgia (n = 3), and dysautonomia consisting of tachycardia and hyperhydrosis, the latter possibly representing alcohol withdrawal. No patient demonstrated central nervous system signs, sphincteric incontinence, or cranial nerve abnormality, and none required ventilatory support.

Liver function tests were abnormal in all with macrocytic anemia in four, one with deficient B6, and one with decreased folate. Serum glucose, B1, B12, thyroid function, protein and immunoelectrophoresis, and anti-GM1 antibodies were normal or negative. Cerebrospinal fluid protein was slightly elevated in one (0.63 g/L, normal < 0.50), with normal cell count and negative oligoclonal banding in all. Nerve conduction studies demonstrated low or absent compound muscle action potential amplitudes (n = 5) with proportionately slowed motor conduction velocities, normal or mildly prolonged distal motor latencies, and F-wave responses that were mildly prolonged (n = 2) or absent (n = 2) only in the presence of severely reduced motor amplitudes. Sensory nerve conduction studies were abnormal with decreased or absent action potential amplitudes, and slowed conduction velocities, but not to the demyelinating range. Needle electromyography showed positive waves in four patients by three to four weeks and, in all patients, by six weeks. Sural nerve biopsy performed in only one patient showed large and small fiber axonal dropout without signs of demyelination or inflammation.

All patients regained mobility within months while abstinent from alcohol and partaking of a balanced diet, vitamin supplementation and physical therapy, although two received immunotherapy before the extent of the alcohol abuse was appreciated (one course of plasma exchange and immunoglobulin in one patient each). Acute alcoholic axonal neuropathy is a rare complication of chronic alcoholism, which may be differentiated from Guillain-Barré syndrome by a history of significant alcohol abuse (> 250 g/d for > 3 years in these patients), severe objective sensory loss (uncommon in GBS), sparing of cranial nerve and respiratory muscle function in the presence of profound limb weakness, electrodiagnostic studies showing axonal neuropathy, and an unremarkable CSF formula.

COMMENTARY

Half of the adult U.S. population regularly consumes alcohol, the most frequently abused drug in the world. About 15-20 million Americans are alcoholic, 100,000 people die annually from its effects, and, among the elderly, it results in hospitalization as often as myocardial infarction. All this at a bargain: $100 billion annually (Angell M, Kassirer JP. *N Engl J Med* 1994;331:537-539; Adams WL, et al. *JAMA* 1993;270:1222-1225; Erratum. *JAMA* 1993;270:2055).

The cause of alcoholism remains obscure but improved understanding of its pathophysiology has recently emerged. Most of ethanol's toxic and metabolic effects can be explained by its oxidation, through alcohol dehydrogenase, to acetaldehyde, and then to acetate. NADH is generated by both these conversions and, in excess, results in widespread metabolic abnormalities, including hyperlipidemia, hypoproteinemia, hypoglycemia, hyperlactacidemia, hyperuricemia, and increased collagen synthesis (Lieber CS. *N Engl J Med* 1995;333:1058-1065). Acetaldehyde has equally wideranging toxicity, including lipid peroxidation (which promotes cell death), microtubular binding (blocks protein secretion), pyridoxine (vitamin B6) depletion, inhibition of DNA repair, and impairment of the mitochondrial electron-transport chain (ibid). Induction of the microsomal ethanol-oxidizing system (MEOS, a P450-dependent pathway for ethanol oxidation in hepatic microsomes) also follows chronic ethanol ingestion, with significant (5- to 10-fold) elevation of cytochrome P-4502E1 (an ethanol-inducible isozyme of P450). Cytochrome P-4502E1, which catalyzes the bulk of MEOS activity, is remarkable for its ability to generate toxic metabolites, carcinogens, hepatotoxins, and free radicals from a wide range of foreign precursors, including anesthetics (enflurane), solvents (bromobenzene), and legitimate and illicit medications (isoniazid, acetaminophen, cocaine). Cytochrome P-4502E1 is also present in rat brain in the basal ganglia and cerebellar cortices. Following ethanol treatment, it increases in the basal ganglia and cerebellar cortices and is induced in the substantia nigra and hippocampus, supporting the notion that the brain metabolizes ethanol by P4502E1 and that it may be involved in the neurotoxic effects of alcohol (Sohda T, et al. *Alcohol Alcohol Suppl* 1993;1B:69-75). The

neurology of alcohol is yet to be fully elucidated but more is surely yet to come. **—mr**

Mortality in Myotonic Dystrophy

ABSTRACT & COMMENTARY

Source: Die-Smulders CEM, et al. Age and causes of death in adult onset myotonic dystrophy. *Brain* 1998;121: 1557-1563.

Among 328 patients with myotonic dystrophy (MD) collected from 1950 onward and followed by two generations of neurologists in Southern Limburg, Netherlands, 180 were characterized as adult onset, between the ages of 10-50 years, of which 83 (47 men and 36 women) died by January 1997. Survival was calculated using the Kaplan-Meier method and was compared to survival tables for the Dutch population. Causes of death, known for 70, were divided into disease and non disease-related categories, and they were compared to expected frequencies for the general Dutch population.

Most patients (63%) died between the ages of 50-65 years, at a mean age of 54 years, 52 years for men, and 56 years for women (difference not statistically significant), with a median (50%) survival of 59 and 60 years for men and women, respectively. Survival to 45 years was slightly, but significantly, lower in the MD group than would be expected for the normal population, and survival to 65 years was a strikingly low 18% compared with an expected survival of 78%. Pneumonia (31%), arrhythmias (29%), fractures (7%), and postoperative complications (6%) were responsible for 73% of deaths (disease-related), whereas 27% died of non-disease related causes (malignancy in 10%, and other causes, including motor vehicle accidents, myocardial infarctions, stroke, and tuberculosis in 17%). Curiously, the frequency of malignancy among the MD patients was lower (10%) than in the general population (37%). Among 13 patients who underwent molecular analysis for the expanded CTG repeat on the long arm of chromosome 19, a weakly positive correlation was found between repeat length and younger age of death (P = 0.08).

COMMENTARY

The myotonic dystrophy (MD) CTG repeat expansion on chromosome 19q13.3 is sandwiched between two genes, one encoding myotonic dystrophy protein kinase (DMPK), and the other myotonic dystrophy associated homeodomain protein (DMAHP). Although CTG repeat length appears to explain disease severity (Kinoshita M, et al. *Muscle Nerve* 1998;Suppl 7:S187), as well as the phenomena of anticipation and variable expressivity, it does not explain the preferential involvement of distal more than proximal muscles. Analysis of CTG repeat length revealed no differences between proximal (vastus lateralis) vs. more severely affected distal (tibialis anterior) muscles among four affected patients (Ansved T, et al. *Muscle Nerve* 1998;Suppl 7:S186). Preliminary evidence suggests that DMAHP, however, may play a significant role in MD pathogenesis (Winchester C, et al. ibid:S45).

Also presently unexplained is the alveolar hypoventilation seen in DM. Among eight MD patients diagnosed on clinical, electrodiagnostic, and muscle biopsy studies, as well as by molecular analysis of family members in five, quantitative immunohistochemical analysis of the autonomic respiratory center in the medullary reticular formation was performed post-mortem. Significant loss of tyrosine hydroxylase immunoreactive neurons was evident in the dorsal central, ventral central, and subtrigeminal medullary nuclei of three MD patients with a history of alveolar hypoventilation, but not in the five MD cases without such history, nor in 10 age-matched controls, both latter groups showing comparable neuronal density (Ono S, et al. *Neurology* 1998;51:1121-1124). Catecholaminergic neuronal dropout may play a central role in the respiratory insufficiency of DM patients.

Therapy for MD remains symptomatic but recent trials suggest that potential treatment may soon be available. Reviewing 19 studies, including 17 published reports, one paper in press involving an open trial using DHEA (an anabolic steroid), and one submitted-for-publication report, anabolic agents including insulin growth factor 1 (IGF-1), DHEA, and troglitazone, a drug used to overcome insulin resistance, appear to increase muscle mass and strength (Moxley RT, et al. ibid:S45). Full reports of these results should be forthcoming in the near future. **—mr**

In Future Issues:

Quantitative MRI and Patients With Idiopathic Generalized Epilepsy