### LETTERS TO THE EDITOR

## FUNCTIONAL DENTAL OCCLUSION MAY PREVENT FALLS IN ELDERLY INDIVIDUALS WITH DEMENTIA

To the Editor: More than one-third of persons aged 65 and older fall each year, and in half, falls are recurrent.<sup>1,2</sup> The prevention of falls in this growing population is a primary concern for maintaining an adequate quality of life. Elderly persons with cognitive impairment and dementia have two times the risk for falls as cognitively normal elderly persons.<sup>3</sup> It has been demonstrated that multifactorial assessment and intervention focused on these risk factors, including impaired gait and balance (postural instability), environmental hazards, drugs, and cardiovascular diagnoses, has been successful in preventing falls in cognitively normal elderly persons but not in the elderly with cognitive impairment and dementia.<sup>4,5</sup> It can be hypothesized that primitive reflexes such as postural stability are more important for demented elderly. When in an upright position, permanent oscillations are generated to maintain balance. Sensorial afferents are provided from proprioceptive, tactile, vestibular, and visual receptors. Proprioception of the mandibular system arises from the masticatory muscular system and dentoalveolar ligaments.<sup>6</sup> Poor or absent dental occlusion may decrease proprioception in this area, interfering with the stability of head posture. In this study, the incidence of falls in individuals with adequate dental occlusion is compared with that of those with inadequate dental occlusion. In addition, in a smaller pilot study, the effect of improved dental occlusion on occurrence of falls was investigated in subjects who had previously fallen re-

Subjects for this study were 146 ambulatory elderly persons who had been admitted to a special geriatric hospital for individuals with behavior disorders who were also suffering from severe dementia. Inclusion criteria limited subjects to those who could walk, with or without a cane, for all of their ambulation. Multifactorial assessments of each patient's function, including the Mini-Mental State Examination (MMSE), and pharmacotherapeutic status were performed, and occupational therapists conducted daily group rehabilitations to maintain physical ability. One dentist (MY) classified each subject's occlusion into one of three categories: Group A—natural dentition with adequate function, Group B—partially or fully edentulous but maintaining functional occlusion with dentures in either or both jaws, and Group C—functionally inadequate occlusion with no dentures. Subjects were also divided into two groups: the high falls group ( $\geq 2$  falls during the previous year), and the low falls group (<1 falls). In a smaller pilot study, denture treatment was provided for a small subgroup of high falls patients who gave informed consent. After denture delivery, the incidence of falls was recorded over 1 year.

During the 1-year investigative period, 41 of 146 patients had recurrent falls. No differences between the high

and low falls groups in proportion of women (75.6% vs 69.5%), mean age (83.1  $\pm$  6.4 vs 81.9  $\pm$  6.9), use of psychoneurotic medications (56.1% vs 61.9%), or mean MMSE score  $(9.6 \pm 6.7 \text{ vs } 11.8 \pm 6.3)$  were found. Dental status was significantly different between the high and low groups (P < .001) (Table 1). In the high falls group, 10 patients (2 men and 8 women, mean age  $\pm$  standard deviation 81.0  $\pm$  8.0, mean MMSE score 12.1  $\pm$  4.0) who gave informed consent received denture treatment. Conventional denture treatments were provided, and all patients used dentures after treatment. During the investigative period after denture delivery, three patients were excluded because they were comatose or dead. All of the seven remaining patients experienced decreased frequency of falls, with five patients experiencing one or no falls during 1 year of follow-up.

Within the limits of this study, it was found that patients with functionally inadequate dental status had significantly more-frequent falls than those with functionally adequate occlusion composed of natural teeth. dentures, or both. Because tooth loss may result in a decrease in proprioception in the masticatory muscles or dentoalveolar ligaments, an associated perturbation of visual stabilization and postural imbalances may be induced.<sup>6</sup> One study<sup>7</sup> indicated that dental occlusal condition is associated with reduced lower extremity dynamic strength, agility, and balance function in elderly people. These findings suggest that functional occlusion of natural or artificial teeth may play an important role in generating an adequate posture reflex through mandibular stability, preventing falls. The current small intervention pilot study, which reconstructed occlusion with dentures, supports these finding.

In conclusion, poor or inadequate dental occlusion may be a predisposing factor for falls in older people, and improving occlusion deserves attention as an approach to prevention of falls in elderly patients. A dental examination is recommended for inclusion in the standard health examination for elderly persons, especially those with symptoms of dementia.

Table 1. Relationship Between Dental Status and Frequency of Falls

Falls Classification	Dentition Status, n		
	Group A*	Group B <sup>†</sup>	Group C‡
High falls	4	10	27
Low falls	23	59	23

<sup>\*</sup>Natural dentition with adequate function.

<sup>†</sup>Partially or fully edentulous but maintaining functional occlusion with dentures in either or both jaws.

<sup>&</sup>lt;sup>‡</sup>Functionally inadequate occlusion with no dentures.

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Author Contributions: Mitsuyoshi Yoshida: study concept and design. Hidehiko Morikawa: acquisition of data. Yayoi Kanehisa: acquisition of subjects and data. Tsuyoshi Taji: oral examination. Kazuhiro Tsuga: data analysis. Yasumasa Akagawa: preparation of manuscript.

Sponsor's Role: Dr. Hideo Nakamura, president of Nakamura Geriatric Hospital, allowed data collection in this hospital.

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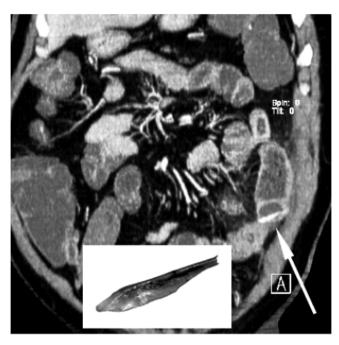
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## BAD DENTITION AND RISK OF JEJUNAL PERFORATION BY FISH BONE

To the Editor: Despite the frequency and variety of foreign bodies ingested, secondary intestinal perforation is a rare occurrence. Preoperative diagnosis using computed tomography (CT) scan is rarely made because of the lack of radiographic contrast of nonmetallic foreign objects. A case of jejunal perforation by a fish bone is reported. Diagnosis was made using abdominal helical CT scan, and surgery was immediately performed. This clinical case allows us to discuss the several fish bone perforation sites and the patient precipitating factors.

Coloenteric perforation by foreign bodies is a rare occurrence and therefore a difficult preoperative diagnosis. A case of jejunal perforation by a fish bone in an old man with



**Figure 1.** Abdominal computed tomography scan (frontal view) showing the fishbone (white arrow) perforating the small bowel and the macroscopic view of the fishbone.

bad dentition is reported. Diagnosis was made using computed tomography (CT) scan before operating.

#### **CASE REPORT**

An 81-year-old male patient suffering from lower left quadrant abdominal tenderness associated with fever (>38.5°C) and elevated white blood cell count (15,000/mm<sup>3</sup>) was admitted to the emergency service. His medical history inseveral laparotomies for cholecystectomy, obstruction of the bowel caused by adhesions, and incisional hernia. Plain abdominal x-ray showed gas shadows in the lower left quadrant without pneumoperitoneum. The CT scan revealed jejunal perforation by a nonmetallic foreign body suggestive of a fish bone (Figure 1). The laparotomy revealed lower left quadrant peritonitis and jejunal perforation by the fish bone, as seen on the CT scan. Removal of the fish bone, suture of the jejunal perforation, debridement, and washing and drainage of the abdominal cavity were performed. The postoperative course was uneventful, and the patient was discharged 12 days after his surgery. The patient was well at his 1-year follow-up. He reported retrospectively that he had eaten fresh fish 2 days before the surgical intervention and did not feel any pain during his lunch.

#### **DISCUSSION**

This case is particularly interesting because the peritonitis was discovered preoperatively using a CT scan. The patient's bad dentition certainly contributed to this complication.

Ingestion of nonmetallic foreign bodies leading to intestinal perforation is a rare occurrence because most foreign bodies pass spontaneously per anus.<sup>1</sup>

Perforation by foreign bodies can occur anywhere in the gastrointestinal tract. Fish bones are more often responsible

for perforation of the esophagus, complicated by mediastinitis.<sup>1</sup> Other parts of the upper digestive tract, such as the stomach or the duodenum, may be perforated.<sup>2</sup> Fish bones may also pass through the gastrointestinal tract and enter other organs of the abdominal cavity such as the liver and the pancreas. One case of a fish bone totally integrated into the hepatic parenchyma has been recently reported.<sup>3</sup> The small bowel<sup>4</sup> or the large bowel<sup>5,6</sup> may be perforated too, and cases of Meckel's diverticulum<sup>7</sup> perforation have been described.

The clinical manifestations of gastrointestinal perforation by foreign bodies are variable. Symptoms may be acute, showing signs of peritonitis associated with pneumoperitoneum visible on plain abdominal x-ray, although the patient may present more-indolent symptoms attributable to carcinoma or chronic disease. One study reported a clinical case of an 80-year-old woman presenting a painless, hard epigastric mass on physical examination 8 days after fish ingestion. She received an antibiotic treatment for abdominal pain secondary to the initially unsuspected perforation of the large bowel by a fish bone. Diagnosis was made at laparotomy. In the case of late diagnosis, a fish bone located inside the duodenum and pancreas was found several months after ingestion.<sup>2</sup>

As with the current patient, elderly persons are more at risk because of the bad quality of their dentition, which is responsible for a lack of mastication.<sup>5,8</sup>

Some cases of intestinal perforation by fish bone discovered using helical CT scan have been previously described.<sup>1,4,6</sup>

Ileal or jejunal perforation by fish bone is a rare occurrence of gastroenteric perforation. Preoperative diagnosis may be made using abdominal helical CT scan in an emergency. It is necessary to carefully remove the bones from fish that elderly persons eat because of the lack of mastication and the bad quality of dentition.

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Sponsor's Role: none.

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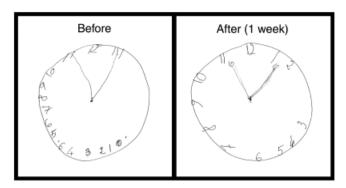
# CHRONIC HYPERCALCEMIA AS A REVERSIBLE CAUSE OF COGNITIVE IMPAIRMENT: IMPROVEMENT AFTER A SINGLE ADMINISTRATION OF PAMIDRONATE

To the Editor: Persistent elevations in serum calcium levels secondary to primary hyperparathyroidism cause neuropsychiatric symptoms, including confusion, alterations in mental status, delirium, and dementia. <sup>1–3</sup> In fact, hypercalcemia has been considered a reversible cause of dementia<sup>2</sup> that can be corrected after parathyroidectomy. <sup>1</sup> Although recent reports support the medical approach toward primary hyperparathyroidism as an alternative to surgery, <sup>4</sup> there are no reports that demonstrate cognitive improvement after medical correction of this disorder.

The case of a 79-year-old woman with known primary hyperparathyroidism (adjusted serum calcium levels of 2.80–2.87 mmol/L for at least 3 years) who presented with a 6-month history of progressive cognitive impairment, self-isolation, confusion, and generalized functional deterioration, including severe limitations in performing instrumental activities of daily living (IADLs) is reported. Upon admission, the patient was found to be anxious and disoriented as to time and space; no focal neurological deficits were found. Her general physical examination was otherwise normal.

Chronic hypercalcemia was considered to be the likely cause of her clinical findings. The patient was prescribed 60 mg intravenous pamidronate to be administered monthly. No other medications that might have modified her cognitive status were administered. The Mini-Mental State Examination (MMSE) and the Clock-Drawing Test (CDT) (Figure 1) were administered 1 day before and 7 days after the initial pamidronate dose. Furthermore, occupational therapy conducted a global functional assessment using the global Structured Assessment of Independent Living Skills, a standardized assessment of functional motor, cognitive, instrumental, and social performance.<sup>5</sup>

Serum calcium levels declined to within normal limits (2.80 mmol/L at baseline, 2.69 mmol/L immediately after pamidronate administration, 2.46 mmol/L 3 days after pamidronate administration). The only adverse effect of the treatment was paresthesias in the fingers and toes, likely due to the relatively low serum calcium levels after a prolonged period of elevated serum calcium. MMSE score im-



**Figure 1.** Free-drawn clocks before and 7 days after administration of 60 mg of intravenous pamidronate. The clock drawings were assessed using the 10-point score, 5 which was found to be 2 points before and 8 points after treatment.

proved from 15 out of 30 before to 23 out of 30 1 week after pamidronate administration, and CDT was substantially improved, as measured using the 10 o'clock draw analysis<sup>6</sup> (Figure 1). In addition, the patient's functional status (IADL) as determined by her performance on the Structured Assessment of Independent Living Skills, showed improvement from 44 to 125 points (possible score 0–145).

In summary, correction of elevated serum calcium levels with one dose of intravenous pamidronate led to immediate improvement in MMSE, CDT, and functional capacity in a 79-year-old woman with long-standing primary hyperparathyroidism. In some cases, dementia can be reversible, and blood tests could be indicated to detect potential reversible causes. Because primary hyperparathyroidism is not an uncommon disease in older people, calcium levels should be tested in patients with cognitive impairment. In conclusion, this case supports the notion that, in some cases, reversibility of dementia is possible with subsequent gain in the patient's independence and function.

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## RECTOSIGMOID STRICTURE PROBABLY FROM ISCHEMIA PRESENTING AS CONSTIPATION IN AN ELDERLY PATIENT

To the Editor: Constipation in an elderly patient may be a presenting symptom of an underlying etiology. If the symptoms are overlooked and are treated symptomatically, it may lead to potentially life-threatening complications. Nonocclusive ischemic injury of the colon usually involves the watershed areas such as splenic flexure and rectosigmoid junction when associated with atheromatous emboli or low-flow states. The following case is presented to emphasize the importance of antecedent ischemia events causing constipation in elderly patients.

#### **CASE REPORT**

A 76-year-old man recently discharged from a rehabilitation facility presented to the emergency department complaining of constipation of 5 days duration and no passage of flatus for the previous 24 hours. He denied nausea, vomiting, or diarrhea. He had tried stool softeners and sodium phosphate enema without effect. On examination, the abdomen was minimally distended, soft, nontender without rebound or guarding. Bowel sounds were present. Rectal examination found no stool in the vault and was guaiac negative.

His medical history was significant for hypertension, coronary artery disease, abdominal aortic aneurysm (AAA) repair 2 months before the current admission, and diverticulosis (diagnosed on routine colonoscopy 6 months prior). Cardiogenic shock and respiratory failure requiring inotropic support for 4 days and mechanical ventilation for 11 days had complicated the AAA repair. For presumed sepsis, he received ciprofloxacin and piperacillin/sulbactam.



**Figure 1.** Computed tomography scan of the abdomen revealing featureless transverse colon.

He had progressive abdominal distension, and a computed tomography (CT) scan on the 10th postoperative day showed a dilated and featureless colon (Figure 1). On the 12th postoperative day, he underwent colonoscopy and was found to have pseudomembranous colitis. He was started on metronidazole, and the other antibiotics were discontinued. He developed atrial fibrillation that was rate controlled with metoprolol and diltiazem. Anticoagulation with warfarin was initiated. Over the next several days, his diarrhea resolved, and his condition stabilized. He was transferred to a rehabilitation unit, and during his stay there, he underwent elective cardioversion. After 1 month he was discharged.

In the emergency department, an abdominal obstructive series (Figure 2A) showed a dilated colon, followed by a CT scan that revealed a narrowed sigmoid colon with a rectosigmoid stricture causing large-bowel obstruction

(Figure 2B). After admission, the patient underwent sigmoidoscopy, and a tight stricture in the rectosigmoid with an estimated diameter of less than 5 mm was seen 20 cm from the anal canal. There was intermittent passage of liquid stool and flatus. The patient was started on parenteral nutrition. Over the next 10 days, he had two unsuccessful attempts at dilatation to pass the scope through the tight stricture. Once after an attempt at dilatation, he developed septic shock and required vasopressor and mechanical ventilatory support. His condition improved, and 1 week later he underwent sigmoid resection. Histopathologic examination revealed areas of mucosal ulcerations, and the findings were not inconsistent with ischemia. Wound dehiscence and multiorgan failure complicated his postoperative hospital course, and he eventually died.

#### **DISCUSSION**

Rectosigmoid stricture can be a complication of vascular compromise, malignancy, radiation, inflammation, or infection. In this patient, ischemia from interruption of blood flow was the most likely etiology. Possibilities include hemodynamic compromise that occurred in the postoperative period or atheroembolic disease. In an individual with a history of diverticulosis, complications associated with this entity should be considered.

Ischemic colitis generally involves the watershed areas at the splenic flexure and the rectosigmoid junction, which are at greatest risk for injury because the collateral blood flow is most vulnerable. Elderly patients with atherosclerosis typically present with evidence of ischemic colitis after episodes of hypotension or low-flow states to the colon or during shock. The length of the involved segment of the colon depends on the cause of injury. Atheromatous emboli can cause damage to short segments, whereas nonocclusive injury usually involves much larger portions of the colon. Surgery, including AAA repairs, can result in episodes of colonic ischemia but may involve larger portions of colon. As seen in this patient, with cardiovascular compromise after AAA surgery, he might have had a vascular insult, seen as a featureless colon on CT scan (Figure 1), which might

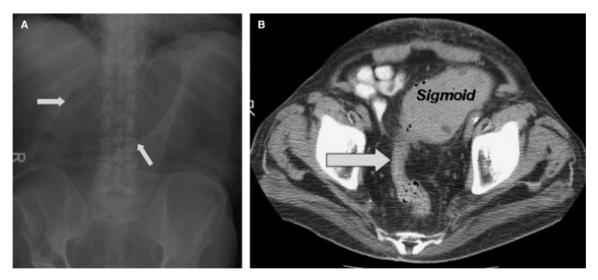


Figure 2. A. Abdominal x-ray revealing dilated colon. B. Computed tomography scan of the abdomen showing rectosigmoid stricture.

have resolved but left residual effect on the watershed rectosigmoid region, causing a stricture. This stricture in turn caused the patient to have constipation, causing him to come to the emergency department.

In conclusion, the clinical presentation of elderly patients with constipation should be clinically correlated with their recent medical and surgical history to minimize the morbidity and mortality associated with this condition.

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## LONGEVITY AND CHRONIC BACK PAIN IN OLDER PEOPLE

To the Editor: Chronic back pain (CBP) is a common complaint of older people. Estimates of prevalence range from 18% to 68% in the population aged 65 and older, reflecting the numerous definitions based on self-reported symptoms. A number of consistent associations with functional disability, increased medical burden, and predictive factors have been described. Although the consequences of chronic pain are a subject of much focus, nonetheless the long-term effect of CBP on mortality in older people is unknown. The single study identified with an age range from 53 to 98 observed no interaction between CBP and mortality over 23 years of follow-up, a finding consistent with mortality data in younger CBP populations, highly from cardiovascular disease.

The Jerusalem Longitudinal Study<sup>8,9</sup> addressed this issue, drawing data from an age-homogenous, representative sample of 458 West Jerusalem residents (209 women and 249 men), comprehensively interviewed and examined at

age 70. Mortality data after 12 years was available from death certificate examination. Patients who reported frequent back pain were defined as suffering from CBP. Significant sex differences were observed, with CBP reported in 54% of women and 31% of men (P < .001). Lower mortality was observed in subjects with CBP at age 70, of whom 75% were alive after 12 years, versus 62% of those free from back pain (P < .003). This effect was sex-dependent (Figure 1), being found in men (P = .01) but not women (P = .80). A proportional hazards model was performed for men and women separately and included the independent variables of back pain, physical activity, self-rated health, hypertension, diabetes mellitus, ischemic heart disease, neoplasm, and smoking at age 70. Back pain was a significant predictor of lower 12-year mortality in men only (P < .001, hazard ratio = 2.43,95% confidence interval = 1.48-4.02).

To analyze the protective nature of CBP, the original proportional hazards model was repeated for all subjects together, this time including a number of factors proposed to increase survival. The suggested protective factors were more visits to the doctor, greater emergency department use, overall medication usage, and the specific use of non-steroidal antiinflammatory drugs. The model included the original model variables and sex, in addition to each suggested protective factor alone or as an interaction with CBP. Only the interaction between doctor visits and CBP showed a trend toward significance (P = .09).

The interesting observation that CBP serves as a protective factor in elderly men would seem counterintuitive, especially when juxtaposed with the findings that "illness burden" is greater in CBP sufferers,<sup>2,3</sup> that greater disability is observed in women with CBP, and that recovery of mobility in women with CBP is less,<sup>10</sup> all of which introduce domains typically thought to be harbingers of greater morbidity and mortality. Much of the existing literature has focused on women, whereas this finding was limited to men, raising the possibility that CBP may be etiologically different between the sexes. Perhaps it is incorrect to view the common symptomatology as a homogenous entity—for research and, more importantly, for clinical practice.

The interaction between CBP and doctor visits (P = .09) may in part explain the protective aspects of CBP as being a catalyst for increased medical attention and surveillance in this group, but the full explanation of this enigmatic finding remains elusive.

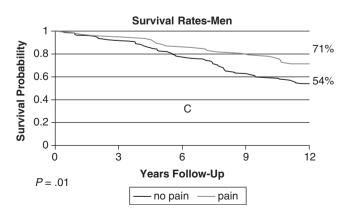


Figure 1. Twelve-year survival data comparing men with and without chronic back pain.

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trying to find surrogates who may predict this skill? If we are truly interested in patients' and the public's safety, we should be advocating for accessible and mandatory professional driving evaluations for all patients with early dementia who wish to continue to drive.

inently measurable skill, why not test it directly instead of

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#### WHO SHOULD DECIDE DRIVING COMPETENCE?

To the Editor: The increasing attention being paid to the evaluation of driving ability in patients with early dementia is well deserved. Being able to predict this ability, as Brown et al. attempt in their recently published study, would be a valuable tool in the care of patients and for the safety of the general public. Their findings suggest that a neurologist who is a dementia expert is a better predictor than the patient or the patient's family, but as the authors state, a professional driving instructor was more than five times better than the neurologist at predicting driving ability. Given that the driving instructor was much more stringent in his evaluation and the excellent interrater reliability of the driving instructors, I would propose a different conclusion from that of the authors.

Rather than calling for more investigation to evaluate other types of doctors to see whether they could do as "well" as the neurologist, those most qualified to perform this evaluation—professional driving instructors—should be encouraged to do so. Because driving ability is an em-

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#### RESPONSE LETTER TO DR. BRAUNER

To the Editor: We appreciate the interest Dr. Brauner has in our paper. He also makes an excellent recommendation: optimally, mandatory driving evaluations conducted by professional driving instructors would assess driving abilities in patients with mild dementia (rather than relying on physician assessments), but there are practical concerns regarding this recommendation. Given the ever-increasing numbers of individuals with dementia, due to our growing aging population and the limited number of driving instructors who are experienced with elderly drivers, it simply is not currently possible to have all demented drivers professionally evaluated. There also are concerns regarding the cost of these evaluations and who should be responsible for them. Moreover, research suggests that many patients and families look to their physicians for advice on this matter and that physician recommendations often play a key role in the decision to stop driving.<sup>1</sup>

We believe that a two-tiered system is necessary; valid screening measures are needed to assess patients on a large-scale basis, followed by subsequent referral for on-road testing by a professional driving instructor for those who the screening measures flag. Our results suggest that the assessment of a physician who is knowledgeable about dementia and driving may be helpful in the process of screening for unsafe driving, although this is an ongoing area of investigation, and neuropsychological tests of executive and visuospatial function or driving simulators may prove to be more valid and reliable at screening individuals than the physician.

Detection of the unsafe demented driver remains a challenge for many communities, and we thank Dr. Brauner for underscoring the need for formal assessments.

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## DROWSINESS AND DISORIENTATION IN A WOMAN WITH DEPRESSION

To the Editor: A 57-year-old woman with a history of manic-depressive psychosis presented to the emergency department with altered mental status of a week's duration. She was a lifelong nonsmoker and consumed alcohol occasionally. Her medications included sodium valproate (VPA) 250 mg twice daily and aspirin 81 mg once daily. On examination, she was afebrile and hemodynamically stable, with oxygen saturation of 100% on room air. There was no pallor, icterus, or stigmata of chronic liver disease. She had a prominent flapping tremor of her upper extremity (asterixis).

She was drowsy but arousable and had a markedly diminished attention span. Her pupils were reactive, motosensory examination was unremarkable, and the plantar response was flexor bilaterally. Her neck was supple, and the rest of the examination was noncontributory.

Laboratory values, including complete blood count, liver function tests, and coagulation profile, were normal, as were her arterial blood gases, serum and urine toxicology screen, electrocardiogram, chest radiograph, and computed tomography (CT) scan of the brain.

The clinical presentation of altered sensorium and reactive pupils, absent focal neurological deficits, suggested global cerebral dysfunction with clinical diagnosis of metabolic or toxic encephalopathy. Asterixis, defined as a lapse in voluntarily sustained posture, commonly occurs in the setting of hyponatremia, uremia, hepatic encephalopathy, and carbon dioxide narcosis, none of which could be invoked as a cause in this patient. The negative CT scan made a structural cause such as a cerebrovascular accident/space-

occupying lesion less likely. The negative toxicological screen excluded a wide variety of drug-induced toxic states.

In patients undergoing chronic VPA therapy and without hepatic dysfunction, hyperammonemia should be recognized as an important reversible cause of altered mental status. Hence, plasma ammonia levels were measured in this case. (A nonhemolyzed, heparinized venous sample is preferred.)<sup>1</sup> The plasma ammonia level was significantly elevated at 198 µmol/L (normal range 6–47 µmol/L). Although most patients with valproate-associated hyperammonemia (VAH) have plasma ammonia levels in excess of 150 µmol/L, the correlation between ammonia levels and the degree of encephalopathy is poor. CT and magnetic resonance imaging may show cerebral edema in some cases, and electroencephalography may show diffuse slow-wave changes and epileptiform activity. Cerebrospinal fluid glutamine levels may be elevated in VAH.<sup>1</sup>

#### DISCUSSION

Since its approved use as a mood stabilizer in 1995, geriatricians and geriatric psychiatrists have increasingly used VPA in nursing homes and in behavioral institutions. The neurological adverse effects of this drug are postural tremor (seen in about 6%), headache, nystagmus, dizziness, diplopia, incoordination, and a reversible dementia-like syndrome.<sup>2</sup> Hyperammonemia, defined as plasma ammonia greater than 47 µmol/L (80 µg/dL), has been reported in as many as 20% to 50% of patients.<sup>2,3</sup> Hyperammonemia in clinical practice more commonly occurs in the setting of liver disease, although many conditions, including VAH, produce the syndrome of nonhepatic hyperammonemia:<sup>1</sup>

- Inherited urea cycle enzyme deficiency/transport defect disorders
- Primary carnitine deficiency and abnormalities of fatty acid oxidation
- Organic acidurias
- Portosystemic shunts with normal liver function
- Urinary diversion-ureterosigmoidostomy and ileal conduit
- Subureteric injection for vesicoureteric reflux and urinary infection with urease splitting organisms
- Multiple myeloma and myeloid leukemia
- Reye's syndrome—excluding inborn errors of metabolism such as medium chain acyl coenzyme A deficiency
- Drugs such as halothane, enflurane, 5-fluorouracil, asparaginase, and sodium valproate
- Metabolic-hyperinsulinemic hypoglycemia, distal renal tubular acidosis

VPA is a branched-chain carboxylic acid, whose bioavailability after oral ingestion is excellent. It is more than 90% protein bound and undergoes extensive metabolism in the liver via glucoronidation, mitochondrial  $\beta$ -oxidation, and to a lesser extent, cytosolic  $\omega/\omega_1$ -oxidation.<sup>2,3</sup> In VAH, the increased ammonia level is predominantly hepatic in origin, from impaired urea cycle function and subsequent inability to metabolize nitrogen loads. The renal cortex plays a minor part through enhanced glutamine uptake and increased glutaminase activity.<sup>3</sup> L-carnitine deficiency has also been shown to be associated with VAH. VPA is esterified with carnitine to form a valprolyl-carnitine ester that helps in

translocating the drug across the mitochondrial membrane. This complex then diffuses into the cytosol and is eventually excreted, producing a relative carnitine deficiency. This results in impaired  $\beta$ -oxidation of long-chain fatty acid and products of valproate  $\omega$ -oxidation accumulate in the blood, producing hyperammonemia.<sup>3</sup> Also, VPA metabolites reduce levels of acetyl-CoA and glutamate, which results in impaired urea synthesis and increased ammoniagenesis.<sup>3</sup>

VAH often improves with drug discontinuation. Short-term dietary protein restriction, use of nonabsorbable disaccharides such as lactulose and lactilol, and use of a high oral carbohydrate diet or intravenous 10% or 20% dextrose with insulin may reduce nitrogen load. L-carnitine supplementation (100 mg/kg) as intravenous infusion over an hour is currently recommended for valproate-induced liver damage and possibly VAH. For patients with ornithine transcarbamylase deficiency, sodium benzoate and sodium phenylacetate therapy in a specialist-care setting may be appropriate. In resistant cases, hemodialysis will correct the biochemical disorder.

Because VPA levels correlate poorly with VAH, a high index of clinical suspicion is required to make the diagnosis of VAH and is potentially curable.

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### TUNING INTO SILENCE BUT WHISTLING: AN OLD MAN WITH APHASIA

To the Editor: A 76-year-old right-handed man was admitted to our center for a poststroke rehabilitation program. His medical history included gait and speech problems since 1997. He also suffered from recurrent ischemic attacks between 1997 and 2001 without any significant functional sequelae. In 2001, a magnetic resonance angiography was performed that showed atheromatous plaques bilaterally in internal and common carotid arteries with severe luminal occlusions. He has been followed conservatively till 2004, and in the interim, he has also encountered a few more ischemic attacks with mild impairment in cognition and speech and weakness of the extremities. However, he could speak and walk independently with a cane. An endovascular stent was implanted into the left vertebral and right common carotid arteries in August 2004. Two weeks later, he had a right temporoparietal hemorrhagic infarct and was hospitalized with the complaints of severe gait and speech disturbances. After he had been followed in the neurosurgery unit for acute care, he was transferred to our center for rehabilitation.

The physical examination was consistent with aphasia without any cooperation and generalized decrease in muscle strength without overt spasticity. He could be wheeled in a wheelchair or could walk with the aid of two people. During the examination, it was observed that he continuously whistled or attempted to whistle. His whistle was not melodic but was rather in truncated sounds—more or less of the same tone. His relatives declared that he had been whistling the same way for a year and with a higher pitch before the recent episode. They added that, when they had asked him the reason for his whistling, he explained that he whistled to impose authority on the people nearby. They also described the premorbid character of the patient as authoritarian.

He was followed on a rehabilitation protocol of strengthening exercises and mobilization. Significant improvement was not achieved after 2 months because of his fluctuating, uncooperative mood. Occasionally, he would begin to say individual words or sentences, especially when he read them on signs or when his mood was favorable, and his whistling decreased. A control cranial magnetic resonance imaging revealed a (small) resolving infarct, severe cerebral atrophy, small-vessel ischemic disease, and chronic infarcts in the right frontal and occipital lobes. The psychiatry department provided a consultation, and his whistling was attributed to a regressive behavior that could be seen in patients with cerebral damage due to cerebrovascular accidents and his explanation for it to be a defense mechanism. Vascular dementia was also noted to have contributed to his general psychiatric mood.

In our clinical experience, we have not seen such a patient since, and we could find only one similar report in the pertinent literature mentioning a musically naive patient with dominant frontotemporal and anterior parietal infarct who had developed spontaneous compulsive whistling in addition to hypermusia and musicophilia. The problem of finding correspondence between a particular neuronal organization and a specific function of the human brain remains a central question of neuroscience. Despite the idea that language and music are two sides of the same intellectual coin, research on brain-damaged patients has shown that loss of musical ability does not necessarily accompany loss of verbal function. Further scientific data are awaited to shed light on the possible correlations between language, music, syntax, and brain dysfunction.

In closing, far from elucidating the intricate underlying mechanism in our patient, what we intended to underscore in this report was to orient physicians toward a rare challenge in clinical practice. We also advocate an initial conservative approach, especially in elderly patients, in whom suppressive medications might hamper recovery from brain damage.

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## EVIDENCE OF ACETYLCHOLINESTERASE INHIBITORS IN TREATING ALZHEIMER'S DISEASE IN VERY OLD PATIENTS IS UNCERTAIN

To the Editor: In his editorial, Dr. Royall discussed several important issues in assessing the evidence of acetylcholinesterase inhibitors (AChEIs) in treating Alzheimer's disease (AD) but not the generalizability of AChEI trials. It was reported that dementia research including therapeutic trials was systemically biased toward younger patients. For example, the mean age was 72 in one meta-analysis of done-pezil trials in treating AD. Because the response to AChEIs,

neuropathology, and apolipoprotein E genotype in patients with AD and the incidence and prevalence of dementia were all age dependent,<sup>2</sup> applying the results of the current positive AChEI trials to adults aged 75 and older should not be considered as evidence based but an extrapolation-based approach. AD 2000 was the largest study of donepezil in person-years of placebo-controlled treatment.<sup>4,5</sup> The mean age of the participants was 76. It had a lower attrition rate and fewer missing data than any previous study. It has been the only non-industry-funded study. It is the only reported negative trial.<sup>4,5</sup> This should further increase the current skepticism of medical professionals and the public as to using AChEIs. One ideal solution would be to recruit more participants who are similar to our general population with AD in a future AChEIs trial.

In the face of such a difficult situation, our choice of using AChEIs, just like other medical decisions, should be based on the following five distinct areas: 6 empirical evidence (clinical research including systemic reviews, randomized, controlled trials, other controlled trials, and cohort studies), experiential evidence (personal or expert clinical experience), physiological rationale (an understanding of physiological principles), values of patient, family, and professionals, and system features (economic, logic, legal, and cultural facilitators or barriers to the provision of medical care). The relative weight given to each of these areas is dependent on individual cases. 6

In contrast to Dr. Royall's literature review, I found three head-to-head randomized, controlled trials comparing two AChEIs.<sup>7</sup> Unfortunately, the several serious limitations of these three head-to-head trials based on the Consolidation of the Standards of Reporting Trials criteria make the initial drug choice of AChEIs for patients with AD uncertain.<sup>7</sup>

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#### ANGST IN SHANGRI-LA: JAPANESE FEAR OF **GROWING OLD**

To the Editor: The proportion of Japanese people aged 65 and older reached 19.0% of the total population in 2003.<sup>1</sup> This is due to the longest life expectancy for men (78.4) and women (85.3), but also the longest healthy life expectancy in the world—72.3 for men and 77.7 for women.<sup>2</sup> Japan also has the lowest fertility rate in the world (1.32) next to Italy. This fast-graving nation will soon face an unprecedented situation in which one in four will be an elderly person.<sup>3</sup> Japan's long-term care insurance system was established in 2000 precisely to manage this fast-graying population.<sup>3</sup> How does it feel personally to be among people promised the longest healthy life in the world?

To find out how Japanese people in general feel about aging, a survey was conducted in September 2004, asking the following three subjective questions.

- 1. Would you like to live long?
- 2. Do you worry about getting old?
- 3. What in particular makes you worry about growing old?

Survey participants were selected from a panel organized by the Social Survey Research Information Co. Ltd. in Japan. The panel consisted of 52,478 persons among the general population aged 20 and older. Some 2,224 people were selected using a quota sampling method.<sup>4</sup> The sample consisted of 444 adults aged 20 to 39, 546 adults aged 40 to 54, 563 adults aged 55 to 64, 532 adults aged 65 to 74, and 139 adults aged 75 and older. Each subject received a self-administered questionnaire; 2,031 returned the questionnaire, and the data from 2,025 participants were analyzed.

The survey revealed that 59% of the general public in Japan hoped to live long. Of those who answered that they did not wish to live long, neither age nor sex was associated with a "wish not to live long" (chi-square  $(\chi^2)$  = 6.822, degrees of freedom (df) = 4, P = .15) (Figure 1). Eighty-three percent of the sample answered that they worry about getting old. Again, neither their age nor sex was associated with their apprehensions in this regard  $(\chi^2 = 4.236, df = 4, P = .38)$  (Figure 1). The 1,680 "worried" subjects were then asked about what in particular made them worry about growing old. Specifically, they were asked whether any of the following eight issues caused them concern: becoming ill, becoming bedridden or demented, losing steady income apart from a pension, becoming widowed, spouse or partner becoming ill or bedridden, deteriorating relationship(s) with family members or becoming less close, having to change their way of living, and deteriorating relationship(s) with friends or becoming less close.

Examination of the reasons revealed three key concerns about becoming old. Seventy-eight percent answered that becoming bedridden or demented frightened them about growing old, 72% that becoming ill made them worry about growing old, and 68% that being left without a steady income other than a pension was a basis of their concern about growing old.

The present survey has revealed seemingly paradoxical results obtained from the general public in a country

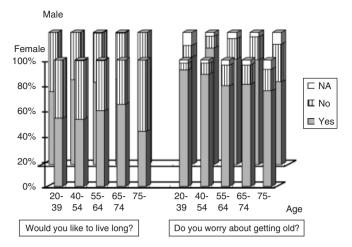


Figure 1. Two main concerns regarding growing old in questionnaire survey.

boasting the longest healthy life expectancy in the world. In fact, the Japanese surveyed in this study showed considerable apprehension about growing old that appeared out of proportion to the long and healthy lives that most can anticipate. These overly pessimistic attitudes may limit the possibilities for successful aging and need to be addressed. First, there needs to be dissemination among the general population of more factual information about aging, stressing that the Japanese are the world's healthiest and longestliving people in the world. The media has only heightened the fear of becoming "impaired." Only a small proportion of the population, not more than 16% of the elderly Japanese aged 65 and older, need care at all.

Second, although the general public must be given a far more realistic view of growing old as Japanese, the existing social system should also be improved so that people will be reassured that a safety net is in place when they become ill, impaired, or short of money in later life.

Third, there needs to be attention paid to the possibilities for successful aging. The survey results may reflect the Alzheimerization of aging; all the publicity given to dementia has raised worries among the entire population. These worries must be balanced with views of successful aging and with prevention programs that could ensure good mental and physical health and perhaps even forestall the development of dementia.5

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## ECONOMIC IMPLICATIONS OF DISCHARGE OF ELDERLY FROM THE EMERGENCY DEPARTMENT TRIAL RESULTS

To the Editor: We enjoyed reading the article by Caplan et al. detailing the results of the Discharge of Elderly from the Emergency Department (DEED II) randomized controlled trial. The trial highlights the many benefits of comprehensive geriatric assessment (CGA)—multidisciplinary care for older adults sent home from the emergency department (ED). We wish to highlight important economic implications of this well-conducted trial. Economic evaluation of healthcare interventions can help to set priorities for scarce healthcare resources. Economic evaluation also influences the policymakers who make funding decisions that can allow the implementation of innovative programs such as the one described in the DEED II trial. Below, a simple cost-benefit analysis based on data from this trial is provided.

In the DEED II trial, patients randomized to receive CGA, multidisciplinary team support, had a lower rate of hospital admission in the first month after the initial ED visit than those who did not. The absolute risk reduction was 5.7% (22.2% – 16.5%). Thus, the number needed to treat to prevent one hospital admission was 17.54 (1/ 0.057).4 In other words, if 17.54 older adults are managed with CGA for up to 28 days, one hospital admission will be prevented. If it is assumed that this intervention costs \$500 per patient, then the cost to prevent one hospitalization is  $\$8,770 (17.54 \times \$500)$ . This cost must be weighed against the cost of the avoided hospitalization. If it is assumed that the cost to hospitalize one frail older adult is \$1,500 per day and that the average length of stay for such a patient is 7 days, then the average cost per hospitalization is \$10,500 ( $\$1,500 \times 7$ ). Thus, implementation of CGA offsets approximately \$1,730 in hospital costs for the average frail older adult (\$10,500 – \$8,770). These simple calculations do not account for the savings in terms of potential downstream costs, consequences of hospitalizing frail older adults (e.g., pressure ulcers, delirium, functional decline).<sup>5</sup> These calculations also ignore the benefits seen in the trial in terms of fewer ED visits.<sup>1</sup> Thus, the potential savings may be substantial.

The costs listed above are purely hypothetical but are likely to be reasonable reflections of the relative costs of the various options regardless of the healthcare setting (e.g., Australia, United States, Canada). Straightforward substitutions of costs could be made in the above model to perform sensitivity analyses of the financial merits of linking CGA to ED care. Investigators should consider collecting cost data alongside clinical outcomes when conducting future trials that evaluate innovative models of geriatric care.<sup>2</sup>

In addition to the impressive clinical benefits seen in the DEED II trial (reductions in ED visits and hospital admissions), healthcare funders may be especially interested to see the cost benefits of implementing CGA alongside usual ED care for frail older adults.

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