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老人性肺炎予防の新戦略－Evidence Based Medicine 確立のための大規模研究

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「老人性肺炎予防の新戦略—Evidence Based Medicine 確立のための大規模研究」

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**研究要旨** 高齢者における肺炎は、脳血管障害に伴う嚥下機能および咳反射の低下を基盤に発症する誤嚥性肺炎が多く、そのため再発性かつ難治性で致死率も高くその予防法の確立が急務である。本研究では、嚥下機能および咳反射改善作用を有するアンギオテンシン変換酵素 (ACE) 阻害剤の投与が、脳血管障害を有する高血圧患者において肺炎の予防効果を有するか否かについて、前向き、コントロールとの比較試験を実施した。その結果、ACE 阻害剤投与群で、他の降圧剤投与群および非高血圧合併脳血管障害群に比して有意に肺炎の発症が抑制された。以上の結果より、ACE 阻害剤は、高血圧合併脳血管障害患者に対して、肺炎の予防効果を有する事が明らかにされた。また、長期療養型老人福祉施設に入所中の ADL の低下した高齢者を対象として、無作為、ランダム化、前向き研究を行い ADL の低下した高齢者に対する肺炎球菌ワクチンの有用性について明らかにした。その結果、ワクチン投与群では非投与群に比して、発熱日数の有意な減少および肺炎による入院回数の有意な減少を認めた。以上の結果より、寝たきり高齢者における肺炎球菌ワクチンの投与は有効で、今後、これらの方々にワクチン投与を積極的に推奨すべきと考えられた。

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**A. 研究目的**

これまで、私共の一連の研究により、ACE 阻害剤が脳血管障害を有する高齢者において、嚥下機能および咳反射機能を改善する事が明らかにされている (Lancet 1995、1998)。そこで今回、私は、高血圧を有する脳血管障害患者に対して、降圧剤として ACE 阻害剤、カ

ルシウム拮抗剤、利尿剤のいずれかを投与し、一方、高血圧非合併脳血管障害患者をコントロールとして 3 年間にわたる前向き観察研究を施行し、ACE 阻害剤の肺炎予防効果の有無につき明らかにした。また、近年、欧米での大規模臨床研究により、高齢者に対する肺炎球菌ワクチンの有用性が明らかにされつつあるが、わが国における研究成果は皆無に等しい。そこで、今回私は、長期療養型老人福祉施設に入所中の ADL の低下した高齢者を対象とし

て、無作為、ランダム化、前向き研究を行い ADL の低下した高齢者に対する肺炎球菌ワクチンの有用性について明らかにしここに報告する。

## B. 研究方法

対象は、外来通院中の 1,426 名の高血圧合併脳血管障害患者(年齢 68 歳から 89 歳まで、平均 75 歳)である。高血圧合併脳血管障害患者を、本人および家族の同意を得た上で、無作為に (1) ACE 阻害剤投与群、(2) カルシウム拮抗剤投与群、(3) 利尿剤投与群のいずれかに分割し、その後の肺炎の発症の有無につき前向きに 3 年間調査した。コントロールとして、(4) 高血圧非合併脳血管障害患者 (160 名、平均年齢 76 歳) も同時に登録し、各群総計 1,586 名を追跡調査した。途中、重篤な免疫不全状態および悪性腫瘍の発症などが確認された場合、および転院、転居などのために追跡不能の場合は脱落とみなした。肺炎の診断は、発熱、咳、痰などの症状に加え、血液学的所見、胸部レ線像によって総合的に行われた。統計解析は、Log-rank test および Cox proportional hazards model を用いて行われた。ワクチンについては、対象は、高齢者介護施設に入所中の寝たきり高齢者 294 名(平均年齢 81 歳、男性 70 人)で、本人および家族の同意を得た上で、無作為にワクチン投与群および非投与群に分割した。ワクチン投与群には、肺炎球菌ワクチン(ニューモバックス) 0.5mL を皮下注射し、その後、両群間で 1 年間における発熱状況、他病院への入退院の有無、生命予後につき比較検討をした。

(倫理面への配慮) 本研究は、本人および家族の同意を得て実施しており、薬物そのも

のも市販されて久しく医療保険上の問題もない。

## C. 研究結果

3 年間にわたる追跡期間中、ACE 阻害剤投与群の 83 名、カルシウム拮抗剤投与群の 79 名、利尿剤投与群の 74 名が脱落し、最終的に 1,350 名に関して解析が行われた。その結果、ACE 阻害剤投与群で 430 名中 12 名(2.8%)に、カルシウム拮抗剤投与群で 409 名中 36 名(8.8%)に、利尿剤投与群で 351 名中 29 名(8.3%)に、コントロール群で 160 名中 14 名(8.8%)に、追跡期間中の新規の肺炎発症が確認された。即ち、ACE 阻害剤投与群では、コントロールに比して有意に肺炎発症率が抑制された [ハザード比 0.30 (95%信頼区間、0.14-0.66、 $p=0.001$ ) ]。一方、カルシウム拮抗剤投与群 [ハザード比 1.01 (95%信頼区間、0.53-1.92、 $p>0.40$ ) ]および利尿剤投与群 [ハザード比 0.94 (95%信頼区間、0.48-1.83、 $p>0.30$ ) ]では、コントロールに比して肺炎発症率に差は見られなかった。

ワクチン投与群では非投与群に秘して発熱日数の有意な減少(平均±標準誤差:  $3.7 \pm 0.5$  日/人/年 vs  $6.6 \pm 0.8$  日/人/年、 $p=0.002$ )、および肺炎による入院回数の有意な減少( $0.23 \pm 0.04$  回/人/年 vs  $0.46 \pm 0.06$  回/人/年、 $p=0.0006$ )を認めた。しかし、両群間で、肺炎および敗血症による死亡率は有意差を認めなかった。

## D. 考案

高齢者における肺炎は、脳血管障害に伴う嚥下機能および咳反射の低下を基盤に発症する事が多く、そのため再発性かつ難治性で予

後が不良であるといわれてきた。これまで、私共の一連の研究により、ACE 阻害剤が脳血管障害を有する高齢者において、嚥下機能および咳反射機能を改善する事が明らかにされている。本研究では、嚥下機能および咳反射改善作用を有するアンギオテンシン変換酵素 (ACE) 阻害剤投与が、脳血管障害を有する高血圧患者において肺炎の予防効果を有する事が明らかにされた。今後、このような肺炎発症のリスクを有する高齢患者では、有力な選択肢の一つになり得るものと考えられた。

また、これまで、肺炎球菌は市中肺炎のみならず介護施設肺炎の起炎菌として重要であると報告されてきたが、わが国における肺炎球菌ワクチンの効果ことに ADL の低下した方におけるの効果に関する検討は皆無であった。本研究で、私は、高齢者介護施設に入所中の ADL の低下した高齢者でも、肺炎球菌ワクチン投与が発熱日数を有意に減少させ、他の病院への入院率を低下させる効果があることを実証した。

## E. 結論

以上の結果より、ACE 阻害剤は、高血圧合併脳血管障害患者に対して、肺炎の予防効果を有する事が明らかにされた。また、寝たきり高齢者における肺炎球菌ワクチンの投与は有効で、今後、これらの方々にワクチン投与を積極的に推奨すべきと考えられた。

## F. 研究成果の公表状況

### 1. 論文発表

Arai T, Sekizawa K, Ohru T, Fujiwara H, Yoshimi N, Matsuoka H, Sasaki H.

Angiotensin-converting enzyme inhibitors and protection against pneumonia in elderly patients with stroke. (*Neurology* 64:573-574, 2005)

Chiba H, Ohru T, Matsui T, Fukushima T, Sasaki H.

Benefits of pneumococcal vaccination for bedridden patients.

*J Am Geriatr Soc* 52:1410, 2004

## 2. 学会発表

2004年1月 日本老年医学会東北地方会

## G. 知的財産権の出願

特になし。

## 研究成果の刊行に関する一覧表

発表者氏名	論文タイトル	発表雑誌名	巻号	ページ	出版年
Arai T, Sekizawa K, Ohru T, Fujiwara H, Yoshimi N, Matsuoka H, Sasaki H.	Angiotensin-converting enzyme inhibitors and protection against pneumonia in elderly stroke patients.	<b>Neurology</b>	64	573-574	2005
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Arai T, Yoshimi N, Fujiwara H, Sekizawa K.	Serum substance P concentrations and silent aspiration in elderly patients with stroke.	<b>Neurology</b>	61	1625-1626	2003

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## ACE inhibitors and protection against pneumonia in elderly patients with stroke

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Pneumonia is the most common cause of death from nosocomial infection in the elderly. The increased incidence of pneumonia and the high mortality are consequences of a number of age-related factors, including coexisting illnesses, therapeutic interventions, and the aging process itself.<sup>1</sup> Pneumonia has been estimated to occur in about one third of patients with stroke.<sup>2</sup> The most important factor contributing to the risk of pneumonia in patients with stroke is suggested to be dysphagia with aspiration.<sup>1</sup>

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve silent aspiration<sup>3</sup> and prevent pneumonia in elderly patients with stroke.<sup>4</sup> However, little is known about whether ACE inhibitors have a beneficial role in reducing the risk of pneumonia as compared to other classes of antihypertensive drugs in elderly patients with stroke. Thus, we investigated whether ACE inhibitors can reduce the risk of pneumonia as compared to other antihypertensive drugs.

**Methods.** We recruited patients with stroke who were followed up for more than 6 months after their ictus from eight outpatient clinics. We enrolled 1,190 patients in April 1999, and prospectively followed them for 35 months. The criteria for diagnosis of pneumonia and the patients' inclusion and exclusion criteria were described previously.<sup>5</sup> Eligible patients were those who received antihypertensive therapy, had a history of stroke, but were not bedridden.

We analyzed the incidence of pneumonia in three groups of hypertensive patients with stroke who were classified on the basis of treatment with antihypertensive drugs as follows: patients who received ACE inhibitors, calcium-channel blockers, and diuretics. Our hypertensive patients received only the same class of antihypertensive drugs. The control group consisted of non-hypertensive patients with stroke who did not receive any antihypertensive drugs. Follow-up data were available for all participants.

For the main analyses, we used the log-rank procedure and Cox's proportional hazards model to calculate the CI. Cumulative incidence curves were generated by the Kaplan-Meier method for endpoints in the ACE inhibitors, calcium-channel blockers, diuretics, and control groups. Significance was set at  $p < 0.05$ .

**Results.** There were no significant differences in age, sex, stroke severity as assessed by NIH Stroke Scale,<sup>6</sup> and poststroke duration among the four groups (table). During the follow-up, new

pneumonia was diagnosed in 12 (2.8%) of the 430 patients in the ACE inhibitors group, 36 (8.8%) of the 409 patients in the calcium-channel blockers group, 29 (8.3%) of the 351 patients in the diuretics group, and 14 (8.8%) of the 160 patients in the control group. The patients in the ACE inhibitors group had a lower risk of pneumonia than those in the control group; the hazard ratio was 0.30 (95% CI 0.14 to 0.66,  $p = 0.0013$ ). However, the risk in the calcium-channel blockers group (1.01, 95% CI 0.53 to 1.92,  $p > 0.40$ ) or the diuretics group (0.94, 95% CI 0.48 to 1.83,  $p > 0.30$ ) did not differ from that in the control group.

**Discussion.** We found a significantly reduced risk of pneumonia in patients receiving ACE inhibitors vs control patients. No such decreased risk was noted in users of calcium-channel blockers or diuretics. Silent aspiration reportedly disappears by treatment with ACE inhibitors in association with an increase in the serum substance P levels in hypertensive patients with stroke.<sup>3</sup> ACE inhibitors may increase the serum substance P levels, thereby reducing aspiration pneumonia in elderly patients with stroke.

A recent large-scale randomized trial has demonstrated that treatment with ACE inhibitors significantly reduced the risk of pneumonia among the participants of Asian ethnicity, although the protective effects of ACE inhibitors against pneumonia were not observed in the non-Asian participants.<sup>7</sup> However, this trial<sup>7</sup> included patients with a history of transient ischemic attacks and the mean Barthel index score of the patients was quite high. Since the incidence of pneumonia increased in association with a decrease in the Barthel index score,<sup>8</sup> the effects of ACE inhibitors against pneumonia might be underestimated by a population of patients with a high activity of daily life. Our present study only included patients with well-documented cerebral hemispheric strokes.

The present study supports the hypothesis that treatment with ACE inhibitors may be beneficial in reducing the risk of pneumonia in elderly patients with stroke.

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Table Characteristics and clinical features of the four groups

	ACE inhibitors	Calcium-channel blockers	Diuretics	Control
No.	430	409	351	160
Female/male	224/206	213/196	183/168	78/82
Mean age, y	75 (1)	75 (1)	75 (1)	76 (1)
Stroke severity	6 (1)	6 (1)	6 (1)	6 (2)
Poststroke duration, y	3.1 (1.1)	3.3 (0.9)	3.4 (1.1)	3.3 (1.2)

Values in parentheses are SD.

ACE = angiotensin-converting enzyme.

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## Hyponatremia from a hunger strike as a cause of osmotic myelinolysis

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Too rapid correction of hyponatremia often causes osmotic myelinolysis. A rapid shift from normal to hypernatremia may also be dangerous. We report a hunger striker that developed an extreme serum sodium concentration followed by coma and radiologic abnormalities characteristic of osmotic myelinolysis.

**Case report.** A 19-year-old Algerian asylum seeker started a hunger strike after his residence permit had been rejected. His medical history was unremarkable. He used no medications, including lithium. One month before fasting, he was placed in isolation because of behavioral disturbances. At this time, the weather was hot, and the patient refused sufficient intake of water and food. One day after he stopped eating and drinking, he became confused; after another 5 days, he became somnolent. He was transferred to a penitentiary hospital. On admission, his serum sodium level was 187 mmol/L, creatinine 213  $\mu$ mol/L, and glucose 6.8 mmol/L. Urine osmolality was not measured. A feeding tube rehydration regimen was started with 2 L/day of water. His sodium level was 172 mmol/L the next day. After 2 days, he became comatose and was referred to our intensive care unit. On admission, his blood pressure was 105/55 mm Hg, temperature was 38.5°C, Glasgow Coma Scale score was 6 (E1M4V1), the pupillary light reflex was delayed, and the Achilles tendon reflexes were absent. Sodium level was 152 mmol/L, potassium 2.5 mmol/L, creatinine 91  $\mu$ mol/L, urea 7.3 mmol/L, phosphate 0.41 mmol/L,

magnesium 0.96 mmol/L, and albumin 26 g/L. CT of the brain and CSF analysis were normal. EEG showed diffuse slowing. A chest radiograph showed bilateral infiltrates. The patient was intubated and treated for aspiration pneumonia. Potassium and phosphate were replaced.

Because of the extreme hypernatremia, osmotic myelinolysis was considered. Brain MRI 5 days after admission was consistent with pontine and extrapontine myelinolysis (figure, A and B). MRI also revealed acute hydrocephalus (see the figure, B) and posterior fossa edema (see the figure, C). An external ventricular drain was inserted. The intracranial pressure proved normal. As the patient did not respond to 6 days of drainage, the drain was removed. Over the next days, the pupillary light reflex normalized and the patient regained consciousness. When asked, he was able to open, close, and move his eyes and slightly move his fingers. No other voluntary movements were possible. After 1 month, his neurologic condition gradually improved. After 4 months, he was able to speak and walk short distances. After 7 months, he was fully recovered but needed a cane while walking.

**Discussion.** We present a hunger striker that developed osmotic myelinolysis due to extreme hypernatremia from dehydration. The clinical presentation with confusion and coma several days after onset of the severe electrolyte disturbance followed by spontaneous recovery in the course of months is consistent with osmotic myelinolysis.<sup>1</sup>

Central pontine myelinolysis was first described in 1959, associated with alcoholism and malnutrition.<sup>2</sup> In 1976, it was first linked to hyponatremia.<sup>3</sup> In hypotonic hyponatremia, water initially enters brain cells, resulting in cerebral edema. The brain cells adapt by losing electrolytes and organic osmolytes, thus arresting a further influx of water. If chronic hyponatremia is cor-

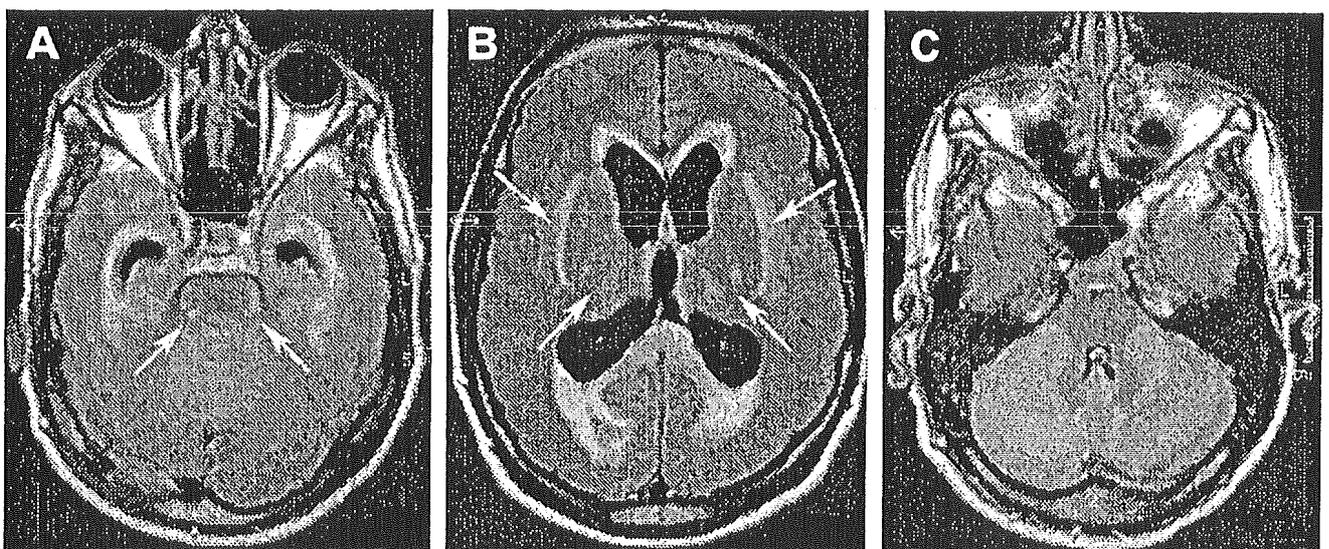


Figure. Axial fluid-attenuated inversion recovery MRI of the brain showing hyperintensities in the dorsolateral regions of the pons (A) and bilaterally in the thalamus, globus pallidus, and capsula extrema (B), consistent with osmotic myelinolysis. Also note the enlargement of the lateral and third ventricles with periventricular hyperintensities (B). This acute triventricular hydrocephalus was presumably caused by posterior fossa edema, yielding impaired CSF circulation (C).

In this case, the diagnosis of insulinoma was made in the examination of recurrent falls, and suspected because the falls always occurred after an overnight fast but in the absence of any other symptom. Also, the patient was alert and did not give the impression of frailty so often seen with recurrent falls. A careful history can identify unusual but treatable causes of recurrent falls.

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## AN ADVERSE EVENT ASSOCIATED WITH HIP PROTECTORS

*To the Editor:* Hip protectors have been demonstrated to reduce fracture rates.<sup>1</sup> There are few descriptions of any adverse events associated with use of hip protectors. Of side effects described, most have been minor (e.g., not being comfortable (too tight/poor fit)).<sup>2</sup>

In January 2004, hip protectors were prescribed in a 74-year-old resident of an assisted living facility. One month later, she began to complain of right gluteal-area pain that radiated down her leg along the distribution of the sciatic nerve. The pain was worse after sitting for prolonged periods. Her history was noteworthy for mild Alzheimer's disease, treated depression, and hypothyroidism controlled with exogenous L-thyroxin. She got some relief of her pain from a Level 3 on the Functional Pain Scale to a Level 2 using acetaminophen and refecoxib.<sup>3</sup> Physical examination showed tenderness over the posterior superior iliac spine and an abnormal gait favoring her right leg. Tenderness was exacerbated in the seated position with external rotation of the leg and knee flexion. Within 6 weeks of discontinuing her hip protectors, the hip pain resolved completely.

Many clinicians have witnessed the delight of a patient who has had "wallet sciatica" resolve after simply discontinuing the practice of carrying a bulky billfold in the hip pocket. Other cases have been described of leg pain resolve after removal of piriformis muscle pressure.<sup>4</sup> This is believed to be the first case associating hip protectors with

piriformis syndrome or sciatica. Tight-fitting elastic or increased pressure from the protector pad over the piriformis muscle adjacent to the sciatic nerve is likely to be the source of compression on the sciatic nerve resulting in sciatic neuropathy and should be considered when similar complaints arise in individuals who have been prescribed hip protectors.

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## HOMICIDES OF DISABLED OLDER PERSONS BY THEIR CAREGIVERS IN JAPAN

*To the Editor:* Following the lead of the Netherlands and Germany, in April 2000 Japan launched a long-term care (LTC) insurance system nationwide in a courageous attempt to comprehensively solve the problems of caring for frail older people.<sup>1,2</sup> This new system was unprecedented in making the government rather than the family responsible for the care of the disabled elderly. Specifically, the goals of the LTC insurance system are to allocate limited resources to impaired elderly in a way that adequately reflects need, support home care, and reduce caregiver burden.<sup>3,4</sup> Under this care, the level of services provided are keyed to the degree of a recipient's impairment. To assess the effectiveness of the new insurance system, we investigated the prevalence of caregivers murdering frail older recipients because of exhaustion from the care burden before and after the inception of the insurance system in Japan. We employed the key words of "kaigo" (care) and "satsujin" (homicide) and collected more than 600 articles associated with caregiver murders between January 1997 and December 2003 using a computerized surveillance system (<http://www.asahi.com/>) provided by a major Japanese newspaper, the *Asahi Shinbun*. Thereafter, we carefully analyzed the eligibility of the articles to this study one by one and summed up the yearly cases accordingly. Eligible recipients were disabled persons who were aged 40 and older living with their caregivers in their own home and were killed by their caregivers because of exhaustion associated with the care burden (confirmed by police records). Cases were excluded if caregivers were drug abusers or had psychological disorders such as depression and schizophrenia.

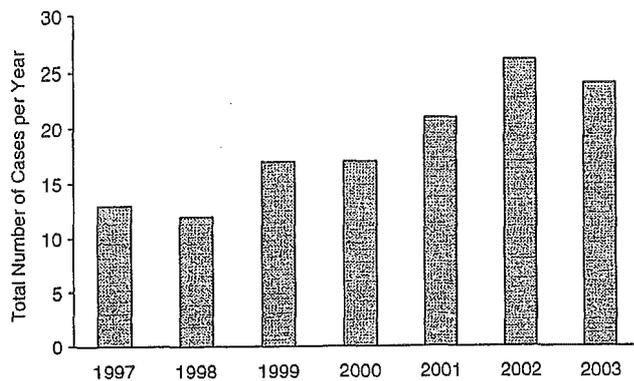


Figure 1. Annual prevalence of caregiver murders.

Finally, we found 130 cases eligible for this study. The mean age  $\pm$  standard deviation of the caregivers was  $66.3 \pm 13.4$  and that of the recipients was  $72.5 \pm 11.9$ . The most frequent cases were murder between sons or daughters and their parents (50%), followed by husbands and wives (47%) and others (3%). As shown in Figure 1, the annual prevalence of caregiver murder seems to be increasing even though the new LTC insurance was implemented in 2000. The recipients' principal physical conditions were dementia (57%), bedridden condition due to stroke with or without dementia (40%), and others (3%). The murders were by strangulation (68%), stabbing (13%), striking (9%), and other (10%). We could find no significant difference in any parameters described above before and after the new insurance system was begun.

We demonstrated that the current prevalence of murder by exhausted caregivers to the frail recipients was increasing rather decreasing after the inception of the new LTC insurance system. Now, 4 years after its inception, it seems necessary to ask whether the program has developed a fair and appropriate way of allocating limited resources to people with different diagnosis. Services are allocated based on the Government-Certified Disability Index.<sup>1,3</sup> Recent reports describe that the needs of demented elderly are often underestimated because of a lack of field-proven items to accurately assess their cognition and behavioral problems under the current insurance system.<sup>3,5</sup> This might be one explanation of the unexpected result of the present study, because most of the killed frail elderly suffered from dementia. The induction of Japan's new LTC system was quite significant in making clear the plight of the aged and their caregivers, but the system should be improved to lighten the caregiver's burden, especially in caring for demented people who require a great amount of assistance from family caregivers to live in the community.

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## TEACHING THE OLDER ADULT

*To the Editor:* Older adults learn in the same way as do all other adults.<sup>1</sup> They must be motivated and be in an environment that is conducive to learning (i.e., it must be quiet, well lit, at a comfortable temperature, and have a relaxed atmosphere).<sup>2</sup> The best motivator for adults is when they have an immediate need or requirement for the information. This is further enhanced when their personal goals and objectives are clarified and addressed before the information is presented. The older adult can benefit from certain adjustments to the teaching methodologies that address the various sensory impairments and cognitive changes common to this age group. (It is important to remember that not all older adults suffer from these.)

Visual deficits can be accommodated for by providing larger typeface (12 point or larger) and using a nonserif font with high contrast between type color and background. Auditory deficits are overcome by speaking distinctly and slowly, in a slightly louder voice, and at a deeper pitch than usual, while looking directly toward the person. The use of multiple-sensory input (i.e., written and auditory (also tactile and olfactory, if appropriate)) is helpful. Also, avoiding the necessity of writing or using small dials or buttons to access the information and eliminating background "noise" (auditory and visual) enhances accessibility of the information.<sup>3</sup>

Building upon previously acquired knowledge can accommodate cognitive changes, as can providing new information in shorter, simpler segments (no more than 3-5 points in one session). Use the same terms to refer to the same points each time, allowing the person to problem solve to come to conclusions on his/her own. Focus on problem solving and limit information to that necessary to make learning and retention easier. Frequent repetition of previously learned information (concepts) through different sensory channels and reducing the necessity of abstract thinking are also useful techniques to employ. Allow more time for older adults to absorb new information and permit them to set their own pace. Encouraging active participation and providing ways to reinforce memory can also improve learning and retention (e.g., posted lists/steps).<sup>3</sup>

Most older adults still prefer to learn in familiar ways: one-to-one oral instruction, written material, and classroom instruction—if it is relaxed and if they are treated with respect and dignity. However, the fastest-growing group of people learning to use the Internet is those aged 55 and older. This is likely to become a common method of learning for many older adults in the near future—within the next 10 years. It appeals especially because of its availability for those who may not be as mobile as they had been and because of its instant availability to fit into the increasingly busy lifestyle

mean ages at death of mothers of cases dead at younger than 75 versus those aged 90 and older were 70.4 and 70.9, respectively. No significant differences were found between the mothers' mean ages at death in relation to age at death in cases. The mean ages at death of fathers of cases dead at younger than 75 versus those aged 90 and older were 68.9 and 71.3, respectively. When comparing the extreme groups (cases dead at age 60–64 vs  $\geq 96$ ), a statistically significant association was found between fathers' lifespan and mean age at death of the cases (Table 1). This association remained when maternal and paternal lifespan were combined into one estimate. Thus, a trend for longevity was found in cases with fathers with longer lifespan. No association was found between mothers' and cases' lifespan. As described above, the current series was based on a birth-cohort from the end of the 19th century recruited from two small farming villages in northern Sweden judged to be homogenous with regard to living and working conditions and with limited effect of urban lifestyle. This study is, to our knowledge, the first published report addressing results that indicate different effect of mothers' and fathers' longevity with regard to cases' lifespan. The results in the current series indicate that the magnitude of paternal lifespan might have been stronger if the cohort had encompassed a larger proportion of very old cases ( $\geq 96$  at death), but despite this fact, there was a clear trend showing an association between fathers' and cases' lifespan.

In conclusion, fathers appear to be at least as important as mothers. Individuals reaching very old age (95) had older fathers. The finding that paternal (but not maternal) factors play a variable role upon age at death merits further examination.

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## ACARBOSE ATTENUATES HYPOGLYCEMIA FROM DUMPING SYNDROME IN AN ELDERLY MAN WITH GASTRECTOMY

*To the Editor:* Dumping syndrome, a well-recognized complication of gastric surgery, is thought to result from the

rapid passage of carbohydrates into the small intestine, producing circulatory hypovolemia through an osmotic effect (early dumping) or a sharp rise in plasma glucose with subsequent hypoglycemia caused by an excessive insulin secretion (late dumping).<sup>1</sup> Sympathoadrenal activation, which is believed to act as a self-protective mechanism against an abrupt fall in plasma glucose,<sup>2</sup> is known to occur during late dumping, but no report has described the role of the sympathetic nervous system in the pathophysiology of late dumping syndrome. We present a case of sudden loss of consciousness associated with meals, which was diagnosed as late dumping syndrome and concomitant sympathetic nervous dysfunction and was successfully treated with an alpha-glucosidase inhibitor, acarbose.

A 78-year-old man was referred to our hospital for investigation of unexplained loss of consciousness in January 2004. He had a history of partial gastrectomy due to gastric cancer in 1996. He had been well until December 2003, when he had experienced sudden loss of consciousness without reactive vasomotor symptoms such as palpitation, sweating, or tremor approximately twice a week after a meal. After admission, brain, chest, and abdominal computed tomography scans and cardiovascular, electroencephalographic, hematological, and biochemical examinations were normal except for hyperglycemia (blood glucose  $> 250$  mg/dL) followed by hypoglycemia (blood glucose  $< 30$  mg/dL) after a meal. Late dumping syndrome was suspected, and an oral glucose tolerance test was performed. After glucose administration, the plasma glucose and insulin rose sharply from a basal value of 112 mg/dL and 2  $\mu$ U/mL to a peak level of 317 mg/dL and 215  $\mu$ U/mL at 60 minutes, respectively. At the second hour of the test, he developed a hypoglycemic coma with a blood glucose level of 28 mg/dL, whereas plasma norepinephrine level remained low ( $< 0.2$  ng/mL). He regained full recovery after glucose infusion. Other physical examinations revealed a positive head-up tilt test. Although there was no apparent structural heart disease, clear defects of diffuse myocardial meta-iodobenzylguanidine ((MIBG) an analog of norepinephrine) uptake were observed with iodide-123-MIBG single photon emission computed tomography (SPECT) imaging<sup>3</sup> (Figure 1). In contrast, thallium-201 SPECT distribution was normal.

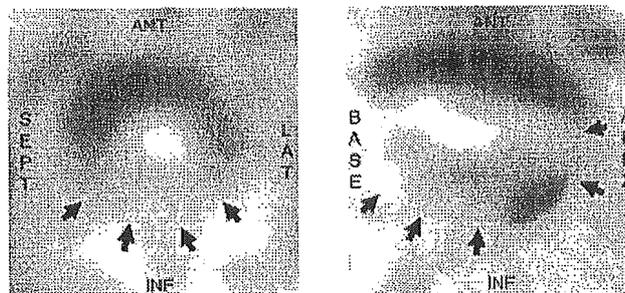


Figure 1. Clear defects of diffuse myocardial meta-iodobenzylguanidine (MIBG) uptake on iodide-123-MIBG single photon emission computed tomography (SPECT) imaging were observed (arrows). The left panel shows an axial view; the right panel shows an apical view of the left ventricle. ANT = anterior; LAT = lateral; INF = inferior; SEPT = septal.

A diagnosis of late dumping syndrome with idiopathic autonomic failure was made,<sup>4</sup> and the patient was referred for acarbose treatment.<sup>5</sup> Acarbose was orally administered at a dose of 100 mg, three times a day before each meal. Thereafter, the rapid changes of plasma glucose level associated with a meal were attenuated (range 100 mg/dL–200 mg/dL), and the patient was free from dumping-related loss of consciousness.

Acarbose attenuates the postprandial increase in plasma glucose levels and is widely used for the treatment of non-insulin dependent diabetes mellitus.<sup>6</sup> A previous report showed that acarbose attenuates postprandial reactive hypoglycemia and improves symptoms in patients with dumping syndrome.<sup>5</sup> The present case suggests that sympathetic nervous activation plays a preventive role against the development of severe late dumping and that acarbose is effective for the treatment of hypoglycemic coma associated with late dumping.

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## OPTIMIZING ANTILIBIDINAL TREATMENT WITH MEDROXYPROGESTERONE ACETATE

To the Editor: Sexual disinhibition in demented patients is not a common problem<sup>1–3</sup> but can be a tremendously disruptive one for all concerned. Medroxyprogesterone acetate (MPA) has been shown to be effective for and well tolerated by such patients, generally in modest doses.<sup>3,4</sup> The mechanism of action seems to be suppression of follicle-stimulating hormone and luteinizing hormone secretion at the pituitary level, leading to decreased testosterone production and decreased libido.<sup>2</sup> Although there is some contrary evidence,<sup>5</sup> reduction in serum testosterone levels seems to correlate with behavioral improvement. We recently cared for a seemingly refractory patient in whom

monitoring of serum testosterone levels ultimately led to successful treatment with a fairly high dose of MPA.

A 76-year-old man with a 15-year history of alcoholic dementia had had ongoing problems with sexually disinhibited behavior for about 10 years. These behaviors included masturbating publicly and verbal and physical sexual advances toward women and had resulted in multiple hospitalizations and discharges from assisted living facilities. Medical history was noncontributory, and there was no evidence of hypersexual or paraphilic behavior or psychiatric illness (other than alcoholism) before the onset of the dementia. Mental status examination was significant for deficits in memory and executive function; there was no evidence of mania or psychosis.

The sexual behavior had failed to respond to various neuroleptics and mood stabilizers in the past but had remitted for 5 years with paroxetine, although ultimately the behavior recurred for unclear reasons and failed to respond significantly to substitution of intramuscular MPA in doses as high as 300 mg per week.

MPA was titrated as high as 600 mg per week, and paroxetine was ultimately reintroduced, but the sexual behavior did not improve significantly. At this point, a serum testosterone level of 72.1 ng/dL was noted. The MPA dosage was increased to 750 mg per week, and repeat testosterone level was 48.4 ng/dL. At that dosage, the sexual behavior improved markedly; there have been no further sexual advances toward women in the past 2 months, and he masturbates only rarely and discreetly in his room.

This patient responded to a much higher dose of MPA than other demented patients reported in the literature; Cooper<sup>3</sup> used a fixed dose of 300 mg weekly, and Weiner et al.<sup>4</sup> used doses of 100 mg to 200 mg every other week. We found that monitoring testosterone levels helped to explain the patient's apparent refractoriness and to guide successful treatment. This experience was similar to that of others; Cooper<sup>5</sup> reported a mean 90% reduction in serum testosterone levels in his successfully treated patients (we unfortunately did not check a pretreatment testosterone level in our patient), and Cordoba and Chapel<sup>6</sup> reported testosterone levels reduced "nearly to female values" (25ng/dL–90 ng/dL,<sup>7</sup>) in their younger, nondemented patient. Serious sexual disinhibition is a potentially devastating problem in demented individuals, leading to hospitalization, restrictive placements, and potential legal liability; MPA can be effective in such patients, and monitoring of serum testosterone levels may be a useful strategy for optimizing treatment.

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of two units of blood performed. Physical examination was normal. Ultrasonogram of the abdomen and kidneys were normal. Plasma erythropoietin was suppressed to an undetectable level. A diagnosis of hormone-induced polycythemia was made. He was reassured but advised to stop the medication. Two months after cessation of treatment, his blood counts had returned to normal (Hb = 15.4 g/dL, WBC =  $6.6 \times 10^9/L$ , and plt =  $182 \times 10^9/L$ ). Plasma erythropoietin level had risen to 5.9 mU/mL (reference range = 2.9–24.5). His latest blood counts and erythropoietin levels have remained normal, nearly 1 year afterward.

None of the hormones used in this case has been reported to give rise to polycythemia when administered at the dose described. Therefore, the development of polycythemia was likely due to the synergistic interactions of the three hormonal supplements. Neither the benefits nor the long-term safety of hormonal supplementation are known. In elderly subjects, concerns have been raised about the possibility of increased cancer risks with GH administration.<sup>2</sup> This case showed that even physicians might find it difficult to determine the risk and benefits from the existing literature. The medical profession and the lay public should wait for future clinical and laboratory research to determine the role of hormonal supplementation in the elderly population.

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## DEPRESSED INVOLUNTARY SWALLOWING AND RISK OF PNEUMONIA

*To the Editor:* Swallowing disorders are common and cause significant morbidity and mortality due to aspiration pneumonia in the elderly.<sup>1–4</sup> Because it is reported that prolonged swallowing reflex is an important risk for pneumonia,<sup>3–4</sup> involuntary swallowing, which can regulate the quality and quantity of oropharyngeal secretions in the pharynx,<sup>1</sup> may also be a predictor for risk of pneumonia. However, involuntary swallowing has not been studied in elderly patients at high risk for aspiration. We therefore examined the frequency of involuntary swallowing in elderly patients with aspiration pneumonia and compared the results with those in age-matched healthy controls. Furthermore, we administered angiotensin-converting enzyme (ACE) inhibitors<sup>5</sup> and compared the pretreatment

data with those after treatment in patients with aspiration pneumonia.

Twenty-two institutionalized patients (13 men) were eligible for this study, with a mean age  $\pm$  standard deviation of  $77.2 \pm 9.4$ . They had had at least two episodes of aspiration with chest radiographic evidence of inflammation in the lower pulmonary segments but were not bedridden. Computed tomographic scans revealed various degrees of cerebral atrophy and lacunar infarction. The 18 controls, mean age  $78.4 \pm 4.5$ , were healthy volunteers. All subjects had been free from pneumonia for more than 2 months before this study. To eliminate diurnal variation, studies were performed at mid-interval between breakfast and lunch. Each subject refrained from taking food and water for at least 1 hour before the study. The swallowing action was identified using visual observation of the characteristic laryngeal movement and an electromyogram attached to the chin.<sup>4</sup> Frequency of swallowing was counted while awake but at rest in a supine position over an hour. After baseline data were obtained, imidapril, an ACE inhibitor, was orally administered at 5 mg/d<sup>5</sup> to six randomly selected patients of the 22 patients with pneumonia, and the study was repeated after 2 weeks of treatment.

Mean swallowing frequency was significantly lower in patients with recurrent pneumonia than in controls ( $5.3 \pm 2.8$  vs  $18.3 \pm 9.8$  times/h, respectively,  $P < .001$ ) (Figure 1). Imidapril significantly increased the frequency of involuntary swallowing in all six subjects compared with pretreatment data (pretreatment  $6.2 \pm 1.7$  vs posttreatment  $13.7 \pm 4.3$  times/h;  $P < .02$ ).

The present study demonstrated that frequency of involuntary swallowing was lower in elderly patients with aspiration pneumonia and that this might be an independent marker for an increased risk for pneumonia. Use of ACE inhibitors increases swallowing frequency and consequently augments clearance of oropharyngeal secretions, which might add an alternative beneficial mechanism for ACE inhibitor-induced reduction of aspiration pneumonia in institutionalized elderly subjects.<sup>1,5,6</sup> The simple visual measurement of swallowing might be useful for evaluating

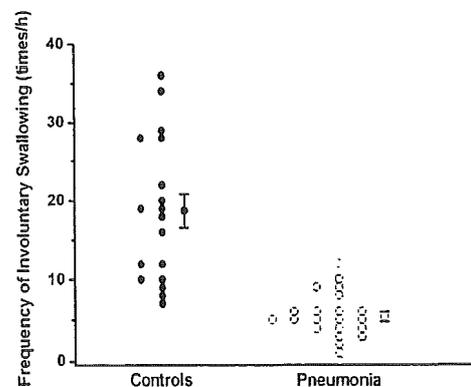


Figure 1. Frequency of involuntary swallowing in controls (closed circles) and patients with aspiration pneumonia (open circles). Vertical bars indicate standard errors of the mean values.

swallowing functions and provide us with a chance to develop an appropriate preventive strategy for elderly aspiration pneumonia.

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## SYRINGOMYELIA: AN UNCOMMON CAUSE OF MYELOPATHY IN THE GERIATRIC POPULATION

*To the Editor:* Myelopathy is a relatively common finding in the geriatric population, resulting from many different causes. The most common (and to some extent treatable) causes for myelopathy include structural abnormalities such as cervical spondylosis, trauma, and tumor.<sup>1</sup> We report on one unusual cause of myelopathy, syringomyelia, secondary to the Arnold-Chiari I (ACM-I) malformation, its presentation and manifestation in an elderly patient. The presentation of syringomyelia and ACM-I in elderly patients is rare—a literature search revealed only one other case report.<sup>2</sup>

## CASE REPORT

The patient is an 80-year-old African-American woman who presented with complaints of gait difficulty and anesthetic, dysesthetic, and paraesthetic sensory abnormalities—especially in the hands, which she stated, “feel like sandpaper.” Her complaints had begun approximately 5 years previously with cervical pain and numbness in a cape-like distribution. She had been diagnosed 2 years previously with extensive syringomyelia extending from vertebral levels C2 to T4. A suboccipital craniectomy and a C1-C2 laminectomy with duraplasty was recommended, but the patient refused intervention.

Her current complaints included progression of her symptoms, extending to her right pinna, difficulty with walking, and frequent burns of her fingers while cooking. She also reported compulsive nail biting, resulting in mutilation of several digits. Her social and medical histories were noncontributory. She reported no other symptoms of

visual, breathing, swallowing, or bowel and bladder dysfunction.

The general examination was significant for extensive healed and open ulcers of the fingertips bilaterally. A complete neurological examination revealed anesthesia to temperature involving the right scalp, face, and pinna. Motor function was 4 out of 5 on the right side and 5 out of 5 on the left side, with normal bulk and tone bilaterally. Sensory examination demonstrated anesthesia for pinprick and temperature in the entire upper extremities bilaterally. Coordination was intact, but gait was unsteady. Reflexes were absent, with the exception of symmetric dorsiflexion of the great toes bilaterally.

The differential diagnosis included progressive syringomyelia with syringobulbia. A magnetic resonance image and laboratory studies were obtained (Figure 1). The patient was re-referred to a neurologist, neurosurgeon, and physiatrist. She was unsuccessfully treated with ibuprofen, gabapentin, nortriptyline, and sertraline. During a trial of gabapentin, the patient significantly reduced her self-mutilating behavior of compulsive nail biting.

## DISCUSSION

Syringomyelia represents an abnormal fluid cavity within the spinal cord (syrinx). It is an uncommon problem with prevalence of less than 1 in 10,000,<sup>3,4</sup> but it is more common (60-70%) in individuals with congenital herniation through the foramen magnum of the cerebellar tonsils (ACM-I).<sup>5</sup> Most individuals with this abnormality are diagnosed well before age 65.<sup>6</sup>

The manifestations of syringomyelia are protean. Symptoms referable to dysfunction of the brainstem and high cervical spinal cord include headache, neck pain,

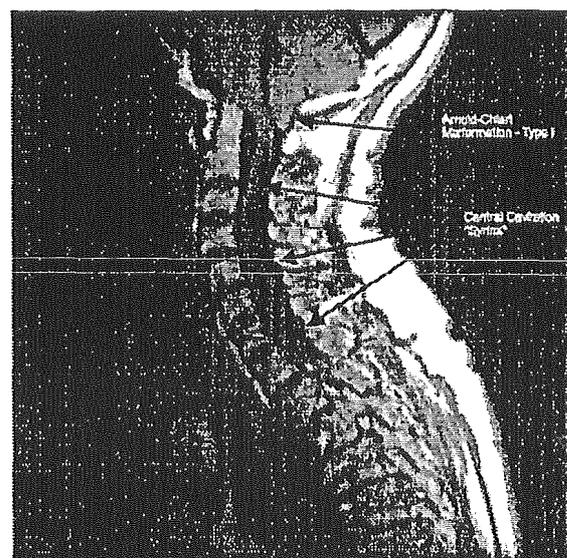


Figure 1. T1 weighted magnetic resonance imaging of the cervical and upper thoracic spine. The cerebellar tonsils descend below the foramen magnum—indicative of the Arnold-Chiari I malformation. A central cavitation is evident from the hypointense signal within the central portion of the cervical spinal cord.

A 75-year-old Hispanic male presented to his internist complaining of daily fevers up to 102° and sore throat for 6 weeks. He was given two courses of azithromycin and then trimethoprim/sulfamethoxazole without benefit. The patient subsequently developed a confluent erythematous rash on the arms and torso that was intermittent and associated with his fever. He was admitted for fever of unknown origin with a worsening pruritic rash. During this hospitalization, he developed bilateral wrist, metacarpophalangeal, and proximal interphalangeal joint pain. He denied recent travel or unusual exposure. Laboratory evaluation revealed a hematocrit of 29.9, white blood cell count of 17,500, blood urea nitrogen of 35, and creatinine of 2.6, and purified protein derivative skin test and controls were anergic. Bone marrow biopsy revealed markedly hypercellular marrow suggestive of possible myeloproliferative disorder. The patient was placed on multiple antibiotics and antifungals without a decrease in the fevers.

He was transferred to a university hospital for further management. Physical examination revealed a thin man with an erythematous rash on face, torso, and extremities without lymphadenopathy. The remainder of the examination revealed lung crackles at the bases and muscle weakness. Magnetic resonance imaging of both thighs and electromyograph were suggestive of myositis, but muscle biopsy and nerve conduction studies were unremarkable. Serum creatine phosphokinase (CPK) was normal, and serum aldolase was elevated. Serum ferritin was as high as 18,000 µg/L.

The patient was diagnosed with adult Still's disease with myositis. He was given methylprednisolone at 1 mg/kg and intravenous immunoglobulin 400 mg/kg for 5 days with prompt resolution of fevers, arthritis, and rash. Serum ferritin, aldolase, CPK, and complement levels all returned to normal values. Corticosteroids were tapered, and 1 year later, the patient had another flare of Still's disease with high fevers, rash, and increased ferritin of 3,000 µg/L. Corticosteroids were increased, and methotrexate was added. The patient is now in clinical remission on methotrexate 20 mg per week and has been tapered off prednisone. All tests have normalized, including ferritin to 150 µg/L.

Adult Still's disease is rare and of unknown etiology, usually affecting people aged 16 to 35.<sup>1</sup> Although it is a disease of young adults, there are two case reports in the Japanese literature of adult Still's disease in the elderly.<sup>2,3</sup> Therefore, adult Still's disease should not be overlooked in the elderly patient.

Clinical manifestations of adult Still's disease are significant for arthralgia (100%), arthritis (94%), fever of 39°C or higher (97%), sore throat (92%), rash (88%), myalgia (84%), weight loss greater than 10% (76%), lymphadenopathy (63%), splenomegaly (52%), and abdominal pain (48%).<sup>4</sup> Laboratory tests that are abnormal include an elevated erythrocyte sedimentation rate, leukocytosis, anemia, and markedly elevated ferritin levels.<sup>5</sup>

One-fifth of people with Still's disease experience long-term remission within 1 year.<sup>6</sup> One-third of patients have a complete remission followed by one or more relapses. Relapses tend to be less severe and of shorter duration. The remaining patients have a chronic disease course.<sup>7</sup>

Approximately one-fourth of patients respond to non-steroidal antiinflammatory drugs. Other patients may re-

quire systemic corticosteroids and disease-modifying agents such as methotrexate and biological agents that target tumor necrosis factor.

Although adult Still's disease affects primarily young adults, it is a disease that can affect all ages. We have described an elderly man who was diagnosed with Still's disease after an exhaustive search for infections, malignancy, and other autoimmune diseases. Adult Still's disease tends to be overlooked in the differential diagnosis when an individual is advanced in age. It should be considered seriously at any age while examining fever of unknown origin. A patient with high, daily spiking fevers, severe myalgia, arthralgia, rash, and leukocytosis is unlikely to have anything other than adult Still's disease. Physicians should consider this diagnosis in elderly individuals with fever of unknown origin.

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## RELATION BETWEEN RETIREMENT AND SUBSEQUENT HEALTH STATUS IN HIGHLY EDUCATED OLDER MEN

*To the Editor:* Retirement from work brings a great change in mental, physical, and social activities in life. Although it has often been conjectured that sedentary life styles after retirement may adversely affect physical and mental health and accelerate aging,<sup>1-3</sup> the relation between retirement age and subsequent health status remains uncertain. The aim of this study was to examine the relationship between retirement age and susceptibility to subsequent medical illnesses or death in elderly male subjects with higher levels of education in Japan.

The survey was conducted between April 2003 and June 2003 using a structured 13-item questionnaire composed of detailed questions about retirement age (or working status if still employed), health status, cognitive function,<sup>3</sup> daily physical activities,<sup>4</sup> spousal health status, and participation in planned exercises such as walking, jogging, bicycling, sports, social activities such as

housework, gardening, hobbies, and social volunteer activities more than twice per week. The questionnaire was mailed to male subjects aged 65 and older who were randomly selected from a graduation list of the School of Engineering, Tohoku University. Subjects were excluded for analysis if they had any significant history of medical, surgical, or psychiatric illness or had any symptoms or signs of cerebrovascular or neurological disease or psychiatric illness at the age of 60 when retirement usually becomes an option or the main reason for their retirement was serious health problems such as cardiac disease, respiratory disease, cerebrovascular disease, or cancers. If a subject had died before this survey, his spouse was asked to answer the questions. Written informed consent was obtained, and the

local institutional review board approved the study protocol. Chi-square test or one-way analysis of variance was used to detect statistical significance between groups. Cox proportional hazards regression analysis was used to evaluate the risk of morbidity or mortality according to retirement age. All multivariate models reported include the covariates in the questionnaire.

Of 936 selected subjects, 642 (68.6%) responded, and 31 were excluded due to the exclusion criteria, leaving 611 (492 retirees and 119 nonretirees) for analysis. The current age of all participants ranged between 72 and 88, with a mean  $\pm$  standard deviation of  $79.5 \pm 6.3$ . The study cohort was divided into four groups according to retirement age (those who retired from work at aged 50–59

**Table 1. Characteristics and Risk of Morbidity and Mortality in Retired and Nonretired Older Men**

Characteristic	Retirement Age				P-value <sup>†</sup>
	50–59 (Group A; n = 56)	60–69 (Group B; n = 294)	70–79 (Group C; n = 142)	Nonretirees (Group D; n = 119)	
Age, mean $\pm$ SD	79.2 $\pm$ 2.6	79.4 $\pm$ 2.4	79.8 $\pm$ 2.1	79.6 $\pm$ 2.2	.24
Follow-up period after retirement, years, mean $\pm$ SD	19.6 $\pm$ 2.7	12.7 $\pm$ 3.6	5.1 $\pm$ 2.8	0	
Cognitive function, n (%)					
With dementia	5 (8.9)	21 (7.1)	10 (7.0)	1 (0.8)	.06
Without dementia	51 (91.1)	273 (92.9)	132 (93.0)	118 (99.2)	
P-value*		.58	.77	.01	
Activities of daily living, n (%)					
Dependent	8 (14.3)	33 (11.2)	21 (14.8)	2 (1.7)	.003
Independent	48 (85.7)	261 (88.8)	121 (85.2)	117 (98.3)	
P-value*		.20	1.00	.01	
Exercises, n (%)					
Participant	17 (30.4)	148 (50.3)	64 (45.1)	48 (40.3)	.04
Non-participant	39 (69.6)	146 (49.7)	78 (54.9)	71 (59.7)	
P-value*		.01	.08	.24	
Social activities, n (%)					
Present	14 (25.0)	69 (23.5)	30 (21.1)	22 (18.5)	.67
Absent	42 (75.0)	225 (76.5)	112 (78.9)	97 (81.5)	
P-value*		.86	.57	.32	
Volunteer activities, n (%)					
Participant	9 (16.1)	50 (17.0)	17 (12.0)	17 (14.3)	.57
Non-participant	47 (83.9)	244 (83.0)	125 (88.0)	102 (85.7)	
P-value*		1.00	.49	.82	
Spousal health status, n (%)					
Absent	7 (12.5)	38 (12.9)	11 (7.7)	15 (12.6)	.81
Healthy	46 (82.1)	241 (82.0)	125 (88.1)	98 (82.4)	
Disability	3 (5.4)	15 (5.1)	6 (4.2)	6 (5.0)	
P-value*		.99	.53	1.00	
Health status, n (%)					
Healthy	30 (53.5)	162 (55.1)	89 (62.7)	99 (83.2)	<.001
Medical illnesses	16 (28.6)	102 (34.7)	43 (30.3)	20 (16.8)	
Death	10 (17.9)	30 (10.2)	10 (7.0)	0 (0.0)	
P-value*		.23	.07	<.001	
Adjusted hazard ratio of medical illnesses or death (95% confidence interval)	1.00	0.75 (0.47–1.19)	0.50 (0.29–0.84)	0.26 (0.13–0.52)	
P-value*		.22	.009	<.001	

\*P-values of individual characteristics were calculated based upon a comparison with retired men aged 50 to 59.

†P-values were calculated using one-way analysis of variance or chi-square test between four groups and variables.

(Group A,  $n = 56$ ), 60–69 (Group B,  $n = 294$ ), and 70–79 (Group C,  $n = 142$ ) and those who continued to work (Group D,  $n = 119$ ), and the risk of medical illnesses or death according to these groups was determined. No significant differences were found at the age of 60 between the four groups in vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia and cigarette smoking, medications prescribed, or dietary treatment.

Table 1 summarizes demographic characteristics of the four groups, including age, and possible confounding factors for medical illnesses. Group D was significantly more independent in activities of daily living than the other groups ( $P = .003$ ). Over a median follow-up period of 9.1 years (range 0–27 years) after retirement, medical illnesses without death (171 cases) or those with death (60 cases) occurred in 231 cases (26, 132, 53, and 20 cases in group A, B, C, and D, respectively). Group C and Group D had significantly lower risk of medical illnesses or death than Group A after adjustment for other confounding factors (hazard ratio (HR) = 0.50, 95% confidence interval (CI) = 0.29–0.84,  $P = .009$ ; HR = 0.26, 95% CI = 0.13–0.52,  $P > .001$ , respectively) (Table 1). Of the principal medical illnesses reported in all participants, cardiac disease was the most common (63), followed by cancer (32), cerebrovascular disease (29), respiratory disease (21), orthopedic disease (15), and other (71), which is in accordance with the normal elderly population.

This retrospective study demonstrates a significant negative association between retirement age and less medical illness or death in elderly subjects with higher levels of education. Because many types of employment require considerable physical activity, retirees who follow a sedentary life for a longer time may place themselves at increased risk of cardiovascular and cerebrovascular disease and cancer. Work-associated physical activity generally decreases after retirement, which is seldom compensated by planned participation in physical activities after retirement.<sup>1–3</sup> These results indicate that, even after reaching retirement age, elderly subjects who are willing to work should continue to work as long as possible to sustain better overall health status.

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## COGNITIVE SCREENING RAISES FEARS OF IDENTITY THEFT

*To the Editor:* The Short Portable Mental Status Questionnaire,<sup>1</sup> which has been in use since 1975, continues to be used in research with geriatric subjects to scan for gross cognitive impairment.<sup>2–5</sup> We have used this screening test in our own research because it is quick and easy to administer and has been validated for telephone administration.<sup>6</sup>

Much in the world has changed since 1975. We are writing this letter to share a concern we recently had during eligibility testing of a potential research study participant. Shortly after administration of the instrument, the subject became wary of our motives for asking these questions. Two of the 10 questions in the instrument bothered her: one that asks the participant to name his/her date of birth and another that asks the participant to give his/her mother's maiden name. To make matters worse, she explained that she had just read a piece in her local newspaper on identify theft.<sup>7</sup> Reviewing this piece, we found that it specifically urged people not to divulge personal information over the phone to people they don't know. The article went on to explain how identity thieves can use this information to access bank accounts, lease cars, and apply for credit cards. Although this participant had received an introductory letter about the study from a clinician she trusted, she had not met any of the investigators in person.

We believe that this individual expressed a valid concern and are debating whether to switch or modify our screening instrument halfway through subject recruitment for an on-going study. Other instruments also contain questions that might raise fears of identify theft. The Telephone Interview for Cognitive Status, for instance, has a question about subject address.<sup>8</sup>

Luckily, this story has a happy ending. The concerned participant decided to speak to the clinician whom she trusts, who reassured her that we were interested in what she had to say about our research topic, not in stealing any of her money. Unless these instruments are modified not to include questions that ask about personal information, investigators using them may run the risk of scaring away potential research participants.

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## BENEFITS OF PNEUMOCOCCAL VACCINATION FOR BEDRIDDEN PATIENTS

*To the Editor:* Pneumonia, often caused by *Streptococcus pneumoniae*, is a major cause of morbidity and mortality in elderly people, especially in those with chronic medical conditions such as chronic heart and lung diseases.<sup>1,2</sup> Although functional disability in the elderly is believed to increase the risk of pneumonia-related mortality through malnutrition and subsequent decreased host defenses,<sup>3</sup> to our knowledge, the effectiveness of pneumococcal vaccination has not been fully elucidated in elderly patients in a bedridden condition. We therefore prospectively examined the effect of pneumococcal vaccination on the rate of hospitalization for and complications of pneumonia, all respiratory tract conditions, and mortality in elderly bedridden patients in Japan.

With use of the activity of daily living index,<sup>4</sup> 301 patients aged 65 and older from three long-term care facilities were assessed and put into categories of total disability or dependence. The cause of disability was multiple cerebral infarctions. We excluded patients if they were immunocompromised (e.g., those who had active malignant disease, renal dialysis, corticosteroid treatment, or human immunodeficiency virus-1 infection). Finally, we recruited 294 patients and assigned them randomly using a randomization table to a vaccinated group or an unvaccinated group. There were no significant differences in sex ratio, mean age, mean activity of daily living scores, or underlying medical conditions between the two groups. The Tohoku University ethical committee approved this study, and informed consent was obtained from each subject before the study.

Of the 294 bedridden patients, 147 (34 men) with a mean age  $\pm$  standard error of  $82 \pm 1$  were immunized with a 23-valent, pneumococcal polysaccharide vaccine (Pneumovax, Banyu Pharmaceutical Co, Ltd, Tokyo, Japan) in April 2002. The remaining 147 patients (36 men), with a mean age of  $81 \pm 1$ , did not receive pneumococcal vaccination. All participants had received influenza vaccinations every year, but none had ever received pneumococcal vaccination before 2002. We recorded the medical conditions of all participants between April 2002 and April 2003. For analyses, we matched the vaccination data with discharge diagnoses according to the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM). The primary endpoints of our 1-year prospective study were comparisons of the vaccinated group with the control group for overall febrile days (body temperature  $\geq 37.8$  C), total hospital admissions for pneumonia overall (ICD-10-CM J12-J18, J69.0, A48.1), acute respiratory tract infections (ICD-10-CM J20.2, J20.9), and mortality related to pneumonia or invasive pneumococcal disease (ICD-10-CM A40.3, G00.1). Chi-square and Student *t* tests were used for statistical analysis.

During follow-up, pneumococcal vaccination significantly shortened the overall febrile days ( $6.6 \pm 0.8$  days/person/year in controls vs  $3.7 \pm 0.5$  d/person/y in vaccine recipients,  $P = .002$ ) and those of acute respiratory tract infections ( $3.2 \pm 0.4$  d/person/y in controls vs  $1.4 \pm 0.3$  d/person/y in vaccine recipients,  $P = .021$ ). Furthermore, pneumococcal vaccination significantly reduced the rate of hospitalization for pneumonia ( $0.46 \pm 0.06$  times/per-

son/y in controls vs  $0.23 \pm 0.04$  times/person/y in vaccinated group,  $P = .0006$ ), but pneumococcal vaccination did not alter the pneumonia-or invasive pneumococcal disease-related mortality between the two groups (19 deaths/147 persons in controls vs 15 deaths/147 persons in vaccinated group, odds ratio = 0.77, 95% confidence interval = 0.37–1.57;  $P = .47$ ).

Although pneumococcal vaccination is now recommended for people aged 65 and older who are at high risk of pneumococcal disease,<sup>5,6</sup> pneumococcal vaccine has been little used in many countries, which may partly be a result of the uncertain benefits of vaccination in elderly high-risk patients. The present study provides further evidence that pneumococcal vaccination is of benefit and recommended for elderly disabled patients at high-risk for pneumonia.<sup>1</sup>

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## COBALAMIN REDUCES HOMOCYSTEINE IN OLDER ADULTS ON FOLIC ACID-FORTIFIED DIET: A PILOT, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

*To the Editor:* Total homocysteine (tHcy) levels increase the risk of cerebrovascular disease, cognitive decline, and Alzheimer's type dementia.<sup>1–3</sup> Serum levels of tHcy in the upper part of the normal range are associated with lower cognitive test scores, and modest increases of tHcy over a short period of time are related to decline in an executive function test.<sup>4</sup> Serum levels of tHcy are dependent on folic acid, cobalamin (Cbl), vitamin B<sub>6</sub>,<sup>5</sup> and renal function<sup>6</sup> and are known to increase with age.<sup>7</sup> Folic acid fortification of grain products in Canada since 1998 has resulted in an increase of red blood cell folate (RBC folate) and likely a decrease in tHcy in the population at large, but 7% of our older persons still have elevated levels of tHcy, and 24%

## ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND INCIDENCE OF ALZHEIMER'S DISEASE IN JAPAN

*To the Editor:* According to the Japanese Health and Welfare Ministry, the incidence rate of dementia in Japanese aged 65 and older was 6.3%. The potential reduction of the incidence of dementia using antihypertensive drug treatment<sup>1</sup> may have important public-health implications in view of the increasing longevity of populations worldwide. One possible mechanism for this effect might be an improvement in microvascular pathology of the brain by antihypertensive drugs,<sup>1,2</sup> but others remain unknown.

There is some evidence that certain components of the renin-angiotensin system (RAS) may have a crucial role in learning and memory processes.<sup>3,4</sup> Previous studies have reported elevated levels of angiotensin-converting enzyme (ACE) in the hippocampus, parahippocampal gyrus, frontal cortex, and caudate nucleus of patients with Alzheimer's disease (AD), the most common form of dementia.<sup>3,4</sup> The increased ACE activity may be directly responsible for cognitive impairment in AD because the enhanced formation of angiotensin II would result in an increased inhibitory effect of angiotensin II on acetylcholine release.<sup>3</sup>

Marked differences were observed between certain ACE inhibitors with respect to penetration into the brain, where they could directly affect the activity of RAS.<sup>5</sup> In the present study, we attempted to test the hypothesis that some ACE inhibitors, which can cross the blood-brain barrier (BBB) and significantly inhibit the brain ACE,<sup>5</sup> may have a protective role against the development of AD. Therefore, we investigated the incidence of AD from January 1993 to March 2003 in elderly hypertensive patients treated continuously with ACE inhibitors or other antihypertensive drugs based upon computerized information on patients in our university hospital.

Eligible patients had no previous history of dementia; were aged 65 and older; had a stable systolic blood pressure of less than 150 mmHg and diastolic blood pressure of 90 mmHg or less; and were receiving BBB-crossing ACE inhibitors (captopril 37.5 mg/d or perindopril 2 mg/d),<sup>5</sup> BBB-nocrossing ACE inhibitors (imidapril 5 mg/d or enalapril 5 mg/d), calcium-channel blockers (nifedipine 20 mg/d or nilvadipine 4 mg/d), beta-blockers (atenolol 50 mg/d or metoprolol 60 mg/d), or diuretics (trichlor-methiazide 2 mg/d or furosemide 40 mg/d). We recruited 4,124 patients with a mean age of 69 (range 65–72) at study entry; 46% were women. Mean duration  $\pm$  standard error of follow-up with antihypertensive drugs was  $8 \pm 1$  years. One hundred five (2.5%) of the 4,124 patients were diagnosed with dementia, including vascular and degenerative. In those demented patients, we could identify 90 patients with AD according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association diagnostic criteria.<sup>6</sup> In the analysis of individual groups of antihypertensive drugs, the incidence of AD was similar in subjects assigned to total ACE inhibitors (2.1%), calcium-channel blockers (2.1%), beta-blockers (2.6%), and diuretics (2.6%), but in the subgroup analysis of ACE inhibitors, the use of ACE inhibitors that can inhibit brain ACE was associated with a significantly lower incidence of AD than the use of those that cannot inhibit brain ACE (odds ratio = 0.25, 95% confidence interval = 0.08–0.75;  $P = .014$ ) or the other types of drugs (Table 1). Use of lipid-lowering agents was comparable across different treatment groups.

Long-term use of some specific ACE inhibitors may have a protective role against the development of AD, probably through their direct effects on RAS in the brain. Physicians should consider specific tissue distribution of ACE inhibitors with the hope of correlating these with actions *in vivo* that might be of clinical significance.

**Table 1. Clinical Features and Relative Risk of Alzheimer's Disease (AD) in Five Treatment Groups of Elderly Hypertensive Subjects**

Characteristic	Treatment Group				
	ACE Inhibitors		Calcium-Channel Blockers n = 2,152	Beta-Blockers n = 155	Diuretics n = 383
	Brain Penetrating n = 437	No Brain-Penetrating n = 997			
Age at study entry, mean $\pm$ SE	69.2 $\pm$ 0.6	68.4 $\pm$ 0.4	69.8 $\pm$ 0.2	68.4 $\pm$ 0.8	67.7 $\pm$ 0.7
Female, %	44	45	44	46	45
Follow-up period, years, mean $\pm$ SE	8.2 $\pm$ 0.3	8.1 $\pm$ 0.2	7.8 $\pm$ 0.1	8.0 $\pm$ 0.7	7.9 $\pm$ 0.6
Systolic blood pressure, mmHg, mean $\pm$ SE	138 $\pm$ 2	140 $\pm$ 3	138 $\pm$ 2	140 $\pm$ 1	138 $\pm$ 3
Use of statins, %	22	24	24	26	23
Number of patients with AD (female)	3 (2)	27 (18)	46 (31)	4 (3)	10 (7)
Incidence rate of AD, %	0.7	2.7	2.1	2.6	2.6
Relative risk	0.25	1.00*	0.78	0.95	0.96
95% confidence interval	0.08–0.75	—	0.48–1.27	0.33–2.76	0.46–2.01
P-value	.014	—	.32	.93	.92

\*Patients treated with angiotensin-converting enzyme (ACE) inhibitors, which cannot inhibit brain ACE, served as the reference group. SE = standard error.

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## POSTERIOR SUBCAPSULAR CATARACT AND HIP FRACTURE

*To the Editor:* We read with interest the article "Visual risk factors for hip fracture in older people" by Ivers et al.<sup>1</sup> We would like to congratulate the authors for the detailed analysis in addressing these two common and important health problems of older adults. The authors describe association between posterior subcapsular cataract (PSC) and hip fracture. Because the bone mineral density of the subjects in the study is not known, it would be difficult to determine the role of osteoporosis in this association, but the authors mention, "there is no evidence to suggest that bone mineral density is associated with visual impairment."

Nevertheless, we would like to draw attention to the relationship between use of corticosteroids, PSC, and hip fracture. PSC has been described as a complication of the use of corticosteroids.<sup>2-4</sup> Decreased bone mineral density and hip fracture have also been reported as complications

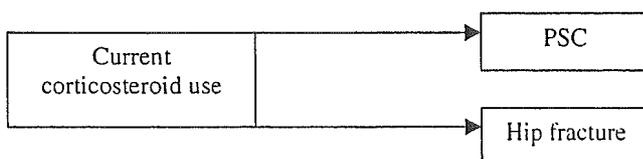


Figure 1. Relationship between corticosteroid use, posterior subcapsular cataract (PSC), and hip fracture.

of the use of corticosteroids.<sup>5</sup> This implies that decreased bone mineral density and PSC (with possible visual impairment) may be seen as complications of the use of corticosteroids.

Investigating the association between systemic corticosteroid use and hip fracture in more detail, one study reported that "fracture risks reverted towards baseline levels irrespective of prior cumulative dose level after cessation of oral corticosteroid treatment."<sup>5</sup> This implies that history of current use of corticosteroids is important in evaluating the relationship between corticosteroid use and hip fracture. In the article by Ivers et al.,<sup>1</sup> the status of the subjects in terms of "current use of corticosteroids" was not presented. In the absence of this information, it may be difficult to estimate the relationship between use of corticosteroids, hip fracture, and PSC. It is possible that the use of corticosteroids at the time of the study may have resulted in PSC and hip fracture in the article reported by Ivers et al.<sup>1</sup>

We feel that this possibility was not addressed in the article (see Figure 1).

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## RESPONSE LETTER TO DR. ENDESHAW

*To the Editor:* We understand your concern about the role of current use of corticosteroids in our recent paper. We collapsed current and past use of corticosteroids into one category (ever use of inhaled corticosteroids, ever use of oral corticosteroids), as we did for other medication types. Of those included in the analysis, 153 study participants were currently using inhaled corticosteroids at baseline, and 191 recorded past use at baseline. Fifty-one participants recorded current use of oral corticosteroids at baseline, and 223 recorded past use.