Tohoku J. Exp. Med., 2005, **205**, 205-214

Invited Review

Medical Treatments and Cares for Geriatric Syndrome: New Strategies Learned from Frail Elderly

HIROSHI KUBO, KATSUTOSHI NAKAYAMA, SATORU EBIHARA and HIDETADA SASAKI

Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine, Sendai, Japan

KUBO, H., NAKAYAMA, K., EBIHARA, S. and SASAKI, H. *Medical Treatments and Cares for Geriatric Syndrome: New Strategies Learned from Frail Elderly.* Tohoku J. Exp. Med., 2005, **205** (3), 205-214 —— In Japan, there are 21 million older people above 65 years, and about 8% of them are frail elderly. Geriatrics is to study the frail elderly as to why they become frail elderly, and to treat patients properly or the remaining 92% older people not to become frail elderly. In order to promote health of the older people, geriatricians have to take deep insights for cares as well as medical treatments. With such a will, we find the way to prevent diseases in the older people. In this review, we describe medical treatments and cares for promoting successful aging. ———— geriatrics; dysphagia; pneumonia; depression; Alzheimer's disease; frail elderly

While a single organ disease may cause various symptoms in young patients, in older patients complicated associations of multiple organ diseases generally cause a single symptom. The frequent problems in the frail elderly are eating problems, aspiration, pneumonia and associated brain disorders. Those geriatric syndromes could be explained with brain disorders. The elderly patients are most ill and most complex, and it is hard to treat the elderly properly. Nevertheless, recent studies make it possible to promote health of the older people.

Dysphagia

Eating generally takes longer in the frail elderly. We find that their reduced appetite may be caused by glucose-intolerance due to age-related impairment of the pre-cingulate gyrus (Hu et al. 2002). Furthermore, some of these patients are unable to swallow food properly. Following insertion of food into their mouths, they only chew it for a short while (He et al. 2004). These subjects might have dysfunction of the pre-insula region (Okamura et al. 2004). The question remains as to how we can treat them to recover their appetite? Aromatherapy with black pepper stimulates the pre-cingulate gyrus and pre-insula regions and improves glucose metabolism that results in the recovery of appetite. This is a method that is effective in some of the elderly to promote meal eating. Acupuncture to stimulate planters, lateral to the knees or medial to the calces is one strategy to promote swallowing, so that the residue in the mouth reduces and aspiration is prevented (Seki et al. 2003). Although it improves their appetite and swallowing function somewhat, these activi-

Received December 9, 2004; revision accepted for publication December 28, 2004.
Present address for reprints: Hidetada Sasaki, M.D., Ph.D., President Akita Nursing and Welfare University, 2-3-4 Shimizu, Oodate, Akita 017-0046, Japan.
e-mail: h-sasaki@well.ac.jp

ties remain problematic for some.

Aspiration occurs when some of food passes into trachea, instead of the esophagus. This does not improve by eating more food, since it is caused by impaired pharyngeal reflexes (swallowing reflex) for adequate swallowing (Nakazawa et al. 1993), and also impaired cough reflex in order to expel aspirated foreign bodies (Sekizawa et al. 1990). To contend with this phenomenon in pulmonary medicine, the Cough Referral Guideline was developed in the US. This guideline discusses the management of persistent or recurrent cough. However, the elderly often have difficulty coughing even when treated with a citrate aerosol that strongly induces coughing. However, the cough guidelines in the US do not relate at all to difficulty of coughing. In fact, difficulty of coughing is more likely to cause aspiration pneumonia that can result in death. The reason why they do not mention it is they do not take the elderly into consideration. The importance of this phenomenon must be considered, when caring for the elderly.

Aspiration

One cause of impairment of swallowing (Jin et al. 1994) and the cough reflex (Ujiie et al. 1993) that can cause aspiration is decreased production of substance P in the sensory nuclei of the vagus and glossopharyngeal nerves in the cervical ganglion (Sekizawa et al. 1997). Reduced substance P is caused by decreased production of dopamine in the cerebral basal ganglia that results from cerebrovascular disease in the cerebral deep cortex (Kobayashi et al. 1994; Jia et al. 1998). Therefore, one could say that aspiration caused by brain dysfunction (Yamaya et al. 2001a). Since reduced substance P leads to dysfunction of swallowing and the cough reflex, administration of substance P should resolve this problem (Nakagawa et al. 1995). One exogenous stimulant of substance P release is capsaicin, the key active component of red pepper (Ebihara et al. 1993). Oral administration of capsaicin permits these to be awake and improves swallowing and the cough reflex. Based on these data, we created a capsaicin lozenge with a hole in the center, so as to prevent suffocation in case of aspiration. When the lozenge was administered before meal, swallowing and cough reflex were significantly improved. A combination of black pepper, to stimulate appetite, and the lozenge, may be even more effective.

When assisting the elderly to eat, allowing hot foods to cool down before they eat is not appropriate, because of the impaired swallow reflex. Hot or cool temperatures can accelerate generation of substance P and evokes the swallow and cough reflex (Watando et al. 2004a). This is one strategy to take care of the elderly.

Pneumonia

Patients with pneumonia often exhibit weakness of swallowing or decreased frequency of swallowing (Watando et al. 2004a). Therefore, administration of substance P should improve their dysphagia. Tanatril®, an angiotensin-converting enzyme (ACE) inhibitor, has been shown to suppress degradation of substance P and elicits cough as side effect (Ebihara et al. 1996). We administered Tanatril® to people with impaired swallowing and cough reflex (Nakayama et al. 1998). The results showed that swallow function doubled to within the normal range. We compared between groups treated with and without Tanatril® and found that the group treated with Tanatril® showed improvement of swallowing and the cough reflex, and reduced pneumonia by one-third (Sekizawa et al. 1998). Additionally, since dopamine levels in these people are lower (Kobayashi et al. 1996), we used Symmetrel® to promote production of dopamine (Sekizawa et al. 1999). We compared between a group treated with Symmetrel® for three years and untreated controls. The results indicated that the group treated with Symmetrel® experienced decreased incidence of pneumonia by one-fifth (Nakagawa et al. 1999).

Although antibiotics are used clinically for pneumonia in the elderly, Tanatril® or Symmetrel® are also options as combination therapy with antibiotics or alone as monotherapy. The result of our work suggested that administration of Tanatril® or Symmetrel® reduced the use of antibiotics by half

(Kanda et al. 2004). Furthermore, the incidence of MRSA and death by pneumonia was also reduced. Consequently, the use of Tanatril® or Symmetrel® would likely also increase hospital profits. Although the elderly who have pneumonia are generally treated with antibiotics, if occult aspirations continue, they often lead to deterioration of pneumonia (Kikuchi et al. 1994). Therefore, pneumonia in the elderly has become known as intractable. Care for the prevention of occult aspiration (Nakagawa et al. 1997), as well as treatment with antibiotics reduced medical expenses by two-thirds.

Cerebral infarction

The reports regarding the effects of cholesterol are controversial (White et al. 2000). However, one such report found that elevation of cholesterol improved patients' resistance against infection, and resulted in improving their survival. One additional problem is the progression of arteriosclerosis by homocysteine (Matsui et al. 2001). Homocysteine is known in the pediatric genetic disease, homocysteinuria. In the elderly, elevated homocysteine levels are detected occasionally, and this is a concern as a risk factor for arteriosclerosis (Yamaya et al. 2001b). Vitamin B12 and folic acid are effective at reducing homocysteine levels. Vitamin B12 is found in fish, and folic acid is abundant in vegetables. Ingestion of these prophylactic diets leads to enhanced metabolism, which reduces the level of homocysteine resulting in lower incidence of arteriosclerosis (Sato et al. 2001). Nevertheless some of the elderly do not get sufficient vitamin B12 and folic acid from their diets. We compared between residents in the Onagawa-cho, Miyagi prefecture, i.e., a fishing village, and residents in the mountains area of the Kyusyu prefecture. The people in the fishing village in the Miyagi prefecture eat five times more fish than the people in the mountains. Moreover, the people in a fishing village ingest significantly more folic acid from seaweeds, including *konbu*, which decreases their homocysteine levels, thus preventing cerebral infarction. Therefore, fish and vegetables are indispensable in diets for the elderly.

Insomnia

Pneumonia develops in the night, because the swallowing reflex decreases in the elderly with cerebrovascular disease in the deep cerebral cortex (Wang et al. 1998), whereas healthy people do not change in their swallowing reflex, even during deep sleep (Pinto et al. 1994). Medical examinations of the brain indicated that one-half of those patients who are more than 65 years old have cerebrovascular diseases, and that they have decreased swallowing reflex, even when they are awake in the daytime (Nakagawa et al. 2000). Regarding the cough reflex as a protective function, patients frequently complain that persistent coughs disturb their sleep. However, this is not true; if people are truly sleeping deeply, they never cough (Zheng et al. 1997). This raises the following question: Does less sleep prevent aspiration pneumonia? We investigated how long elderly people sleep (Manabe et al. 2000). This may sound strange to some people, but to elucidate the universal tendencies of the elderly in their daily life is our guiding principle. Despite their frequent complaints of insomnia, these results showed that they sleep a tremendously long time, 6 hours in the night and 3.5 hours in the daytime, totaling 9.5 hours in a day. We generally prescribe sleeping pills for the elderly patients that constantly complain of insomnia. Although it is safer while they are taking weak hypnotics, if these patients have to switch to stronger ones, due to tolerance induced by chronic treatment, strong hypnotics have been demonstrated to suppress dopamine resulting in a decline of the swallowing reflex (Wada et al. 2001). Although these patients appreciate the effectiveness of the medicine to help their sleep, they are occasionally readmitted to the hospital because of aspiration pneumonia resulting in much more serious conditions. We found that the elderly taking hypnotics exhibit three times greater incidence of aspiration pneumonia.

Oral care

The causes of pneumonia are endogenic for the elderly and exogenic for youths. Since endogenic pneumonias are caused by aspiration of

bacteria from their mouth, cleaning their mouth must be one of the prophylaxes. We recommended bushing of the teeth for five minutes after each meal, which resulted in improvement of their swallowing (Yoshino et al. 2001) and cough reflexes (Watando et al. 2004b). Oral function is associated with 40% of the sensory and motor areas of the brain. This study demonstrated for the first time, that stimulation of their oral cavity led to stimulation of their brain, and consequently enhanced their general function.

We compared between groups with and without oral care and found that the group having oral care had a 40% lower incidence of aspiration pneumonia (Yoneyama et al. 1999). These patients were residents in facilities for the elderly. The elderly living in facilities usually present with more severe pneumonia and 80% of them eventually die (i.e., only 20% can survive). Osler (1898) declared 100 years ago "Pneumonia is friend of the elderly." This statement is true even today; no progress has been made. By contrast, daily oral care decreased the incidence of aspiration pneumonia and resulted in a reduction of mortality by 50% (Yoneyama et al. 2002). Oral care was generally proven to be superior to modern therapeutic antibiotics. The study suggested that elderly patients without teeth also required the same level of oral care as those with teeth.

Aspiration of gastric juice causes pneumonia that is three times greater in severity (Ohrui et al. 1997). How can the elderly prevent aspiration of gastric juice? Simply let them sit up after a meal, so that gravity prevents their aspirations, even when they have gastroesophageal reflux (Matsui et al. 2002). Our work indicated that this method reduced the incidence of aspiration pneumonia to one-third.

Feeding tube

The final decision is whether or not to feed them by mouth (Nakajoh et al. 2000). The elderly with incoherent responses for at least half a year or almost no appetite, are considered towards the end of their life in the US or European countries. In Japan, 10% of them are considered as dying, and 90% of them survive on average one more year by alimentation therapy (Kosaka et al. 2000). When we asked the caregivers about forced alimentation, 60% of people answered that their patients accepted it because they did not have a choice (Kosaka et al. 2003). Meanwhile, 90% of the caregivers responded that they did not wish this to be performed for themselves or their parents. Japanese people are often easily influenced by the opinions of others. When the patients were told, "everybody said they do not want to do it," then forced alimentation therapy reduced by half. To discontinue nutrition immediately after the elderly become bedridden, as in the US, was not appropriate, but prolonging the life for a year or more, was not appropriate either. A compromise between both approaches has become generally accepted in Japan.

Immunity

The elderly commonly suffer from infections with unknown origin, such as pneumonia with Mycobacterium mavium-intracellulare complex, because of their immunocompromised status, namely, deficiency of cellular immunity against bacterial infection (Ebihara and Sasaki 2002a). They are not exposed to bacteria every day, which reduces their immunologic competence. Some of the more active elderly people hurt themselves by minor injuries, which increases their immunity. Too much cleanliness decreases their immunity, as infection with a BCG vaccine enhances immunity (Ohrui et al. 2000). A PPD test is the best way to investigate cellular immunity (Nakayama et al. 2000). Elderly Japanese who are more than 65 years old should be positive for PPD, whereas if they are immunocompromised, it changes to negative. BCG vaccinated people who are positive for PPD, have elevated immunity that is prophylactic for pneumonia (Nakayama et al. 2002).

Influenza vaccination is routine for those who need in-home care or are residents in facilities (Fukushima et al. 1999a). Data from our own work contributed to establish this guideline (Fukushima et al. 1999b). Furthermore, Pneumococcus contributes to 30% of community-acquired pneumonia. Pneumovax against Pneumococcus is effective for those who need in-

home care as well. Only 1% of the elderly receive the vaccine in Japan, whereas, 58% of the elderly are given the vaccine in the US and European countries. The US government plans to raise this number to 90%. This plan should be implemented to the same degree in Japan as well.

Pulmonary disorders

Pulmonary functions including vital capacity, which generates energy for living, decrease with advancing age (Nakamura et al. 2002). The vital capacity declines until it becomes difficult to live, in 100 year-old people, even those who are nonsmokers. All organs in their body decrease in function (Ohrui et al. 2004a). The Ministry of Health, Labour and Welfare in Japan has stated that statistically almost all of the 100 year-old people suffer from dementia. Cardiac or kidney functions also decline in these people. These elderly must accept their fate with resignation. Men seem more powerful than women, but yet they generally die seven years earlier than women. Only few men are able to survive longer. By contrast, if women have a long life, their physical performances generally appear lower.

The aforementioned statistics deal with nonsmokers. Smokers have an even shorter life (Suzuki et al. 2001a). They never refrained from smoking. In addition to the damage they do to themselves directly, secondhand smoke is even more environmentally toxic. This is worrisome especially for the children. Thirty percent of children of tobacco smoking parents exhibit a tendency to develop asthma that is common worldwide. However, the results from our study demonstrated that the incidences of asthma are the same in the children of smoking or nonsmoking parents (Ohara et al. 2002). This is likely because 70% of Japanese smoker parents do not smoke at their home, and more than 99% of smoker parents do not smoke when they are with their children. Since they have learned that abstaining from smoking does not harm their children, they should quit smoking when they are with other children or even in public.

Leukotriene receptor antagonists are used as treatment for asthma. Although they are not so efficacious, they work occasionally during sleep (Kanda et al. 2000). This suggests that the allergic reaction and activity of cranial nerves in which allergic reactions take place are important. Both of these are indispensable to the development of an asthmatic attack. One of the conditions resulting in the most significant decrease in function of the cranial nerves is Alzheimer's disease. Asthma never manifests, if the cranial nerves, where the allergic reactions occur, exhibit lower activity, even if airway hypersensitivity or IgE allergy is evident (Ohrui et al. 2002). Thus, asthma does not develop in patients with Alzheimer's disease.

Alzheimer's disease

One of the objective diagnostic methods for Alzheimer's disease is to detect the presence of phosphorylated Tau in cerebrospinal fluid (CSF) that occurs in 85% (Itoh et al. 2001). Following objective diagnosis of Alzheimer's disease, how will it be possible to treat them? Oral care to stimulate their cognition might improve only one of 30 points in MMC score. Aricept is not so effective. One of the Chinese medicines, kamiuntanto®, is effective, but is equivalent to Aricept®. Combinations of these medicines are slightly more effective, but generally last only half a year (Suzuki et al. 2001b). However, the ACE inhibitor, Coversyl®, has been shown to decrease Alzheimer's disease to one-quarter (Ohrui et al. 2004b). Some of the ACE inhibitors penetrate the blood-brain barrier (BBB) and increase substance P that stimulates neutral endopeptidase (NEP), which degrades substance P (Ohrui et al. 2004c). However, this NEP has also been shown to resolve amyloid β-protein. Dr. Saido in Japan described the biochemical pathway by which NEP can catabolize amyloid β-protein in Nature Medicine in 2002 (Iwata et al. 2000). We found a prophylactic treatment for Alzheimer's disease on the basis of their data. We administered Coversyl® to the patients with Alzheimer's disease and decreased only one point in the MMC score after a year, whereas a Ca^{2+}-antagonist decreased it by four points (Ohrui et al. 2004d). Today, the newest treatment for Alzheimer's disease is vaccine therapy against amyloid β-protein.

However, 6% of these patients may develop nonbacterial meningitis (Hock et al. 2003). Therefore, we believe that other treatments, such as Coversyl®, would be more efficacious.

However, Alzheimer's disease does not resolve by simply ceasing the decline in cognitive function. Behavior disorders are also to be noted in these patients, which occasionally manifest as violation or vocal abuse. Consequently, if Gramalil® or a major tranquilizer is prescribed, it can cause reduced dopamine levels that can result in aspiration or inability to walk. When we prescribed the Chinese medicine, Yokukansan®, behavior disorder and activities of daily living (ADL) improved in these patients.

Depressive state

The elderly often suffer from depression, which may be due to social or familial problems (Shinkawa et al. 2002a). The depression causes the elderly to experience a common cold three times more frequently (Shinkawa et al. 2000). Decreased humoral as well as cellular immunity renders them susceptible to common colds or even cancers, as some data have demonstrated. Older patients with limited ADLs are most susceptible to the complications of influenza or common cold, resulting in severe dehydration, heart failure, or secondary bacterial pneumonia. Therefore, it is important to examine the condition of immunity in disabled older people according to their emotional state. We examined the emotional state of disabled older people with the Geriatric Depression Scale (GDS) and immune conditions by antibody responses to influenza vaccination and delayed-type hypersensitivity (DTH) responses to tuberculin, as humoral and cellular immunoreactivities, respectively (Shinkawa et al. 2002b). The rates of positive antibody response and positive tuberculin response of depressed and nondepressed patients were compared. Our results showed that disabled, depressed older people have reduced reactivity in humoral and cellular immunity (Table1). One cause of their depression is their ever-increasing medical expenses. Three children have to take care of one elderly parent. Some of the elderly feel that they do not want to bother their children or are embarrassed that they are living longer. However, to live longer means less medical expenses (Nakajoh et al. 1999). Furthermore, the historical and present-day working populations are almost the same - approximately 50% (Sasaki et al. 1996). We recommend these people to live longer and tell them "It is nothing to worry about."

We investigated the period for living since these elderly patients became bedridden (Kosaka et al. 1998). If they are bedridden after 80 years of age, they will pass away within a year. If this occurs after 90 years of age, they will pass away even sooner. If they are bedridden before 80 years of age, they will likely live for a couple of years. In-home care is most expensive. If you employ in-home caregivers for 12 hours a day, it would cost 10,000 yen. If you also need them during the night, an additional 12 hours will cost a total of 20,000 yen. This would cost 600,000

TABLE 1. *Depressive state and immunoreactivities*

Group	Increased Influenza antibody titers			Positive tuberculin response
	New Caledonia strain	Panama strain	Yamanashi strain	
Non-depressed (n = 18)	66.7%	55.6%	50.0%	88.9%
Depressed (n = 28)	14.3%	21.4%	17.9%	53.6%
Odds ratio	12.0 (95% CI3.1-45.7)	4.6 (95% CI1.3-16.1)	5.2 (95% CI1.4-19.1)	6.9 (95% CI1.5-31.8)

yen in a month. Moreover, if you add medical expenses to these costs, the total would be 1,000,000 yen in a month, and even 10,000,000 yen in a year. Thus, medical care staff and home caregivers should try to not confine these patients to their beds. It would be more prudent to encourage these patients to consult at the clinic and to start treatment at an earlier stage. The elderly pay only 20,000 yen a month on outpatient bills that would be much less expensive than that of in-home care. Avoiding being bedridden is essential in geriatric medicine.

Frail elderly

It is necessary to learn from the 8% who need in-home care, as to why they become confined to the bed, and to use this knowledge to treat a patient properly, to not become bedridden. This is a key principal in geriatric medicine and care. These data suggest that those persons who are devoted to other people have less serious disease occurrence. Those persons living longer could be called selected people (Katsumata et al. 1995; Kobayashi et al. 1997). The Japanese have the longest life span in the world that indicates having integrated an outstanding culture. In order to increase the average life span by one year, it takes five years (Sasaki et al. 1997). In the US, the life span is five years shorter than that in Japan, indicating that they are behind us by 5 times 5 or 25 years.

There are one million people who are confined to the bed in Japan, meanwhile there are no data representing people who are confined to the bed in the US. However, when we have been to the US to inspect, we have seen several people who are confined to the bed. The individuals requiring in-home care in the US are twice that in Japan, despite a lower number of the elderly in the US (Ebihara et al. 2002b). The Japanese society is affectionate to the elderly, while the American and European society would be cold to the elderly. If we develop a society which has a cold attitude to the elderly as in the US and European countries, the expenditures of elderly care insurance would double, requiring an additional 5.5 trillion yen. It is impossible to cover all these costs. To cut down these expenditures for the elderly, they need to be given adequate status in the society (Ohrui et al. 2004e).

References

Ebihara, T., Sekizawa, K., Nakazawa, H. & Sasaki, H. (1993) Capsaicin and swallowing reflex. *Lancet*, **314**, 1993.

Ebihara, T., Sekizawa, K., Ohrui, T., Nakazawa, H. & Sasaki, H. (1996) Angiotensin-converting enzyme inhibitor and danazol increase sensitivity of cough reflex in female guinea pigs. *Am. J. Respir. Crit. Care Med.*, **153**, 812-819.

Ebihara, T. & Sasaki, H. (2002a) Bronchiectasis with mycobacterium avium complex infection. *N. Engl. J. Med.*, **346**, 1372.

Ebihara, T., Yamaya, M., Ohrui, T., Arai, H. & Sasaki, H. (2002b) Comparison of disabled older people in the U.S.A and Japan. *Geriatr. Gerontol. Internat.*, **2**, 53-56.

Fukushima, T., Nakayama, K., Monma, M., Sekizawa, K. & Sasaki, H. (1999a) Influenza vaccination in bedridden patients. *Arch. Intern. Med.*, **159**, 316-317.

Fukushima, T., Nakayama, K., Monma, M., Sekizawa, K. & Sasaki, H. (1999b) Benefits of influenza vaccination for bedridden patients. *Arch. Intern. Med.*, **159**, 1258.

He, M., Ohrui, T., Azumi, M., Ida, S. & Sasaki, H. (2004) Depressed involuntary swallowing and risk of pneumonia. *J. Am. Geriatr. Soc.*, **52**, 132-1033.

Hock, C., Konietzko, U., Streffer, J.R., Tracy, J., Signorell, A., Miller-Tillmanns, B., Lembe, U., Henke, K., Moritze, E., Garcia, E., Wollmer, M.A., Umbricht, D., De Quervain, D.J.F., Hofmann, M., Maddalena, A., Papassotiropoulos, A. & Nitsch, R.M. (2003) Antibodies against β-amyloid slow cognitive decline in Alzheimer's disease. *Neuron*, **38**, 547-554.

Hu, X.S., Okamura, N., Arai, H., Higuchi, M., Maruyama, M., Itoh, M., Yamaguchi, K. & Sasaki, H. (2002) Neuroanatomical correlates of low body weight in Alzheimer's disease: a PET study. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, **26**, 1285-1289.

Itoh, N., Arai, H., Urakami, K., Ishiguro, K., Ohno, H., Hampel, H., Buerger, K., Wiltfang, J., Otto, M., Kretzschmar, H., Moeller, H.J., Imagawa, M., Kohno, H., Nakashima, K., Kuzuhara, S., Sasaki, H. & Imahori, K. (2001) Large-Scale, Multicenter study of cerebrospinal fluid tau protein phosphorylated at serine 199 for the an-

temortem diagnosis of Alzheimer's disease. *Ann. Neurol.*, **50**, 150-156.

Iwata, N., Tsubuki, S., Takai, Y., Watanabe, K., Sekiguchi, M., Hosoki, E., Kawashima-Morishima, K., Lee, H.J., Hama, E., Sekine-Aizawa, Y. & Saido, T.C. (2000) Identification of the major Aβ1-42 degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. *Nat. Med.*, **6**, 143-150.

Jia, Y.X., Sekizawa, K., Ohrui, T., Nakayama, K. & Sasaki, H. (1998) Dopamine D_1 receptor antagosist inhibits swallowing reflex in guinea pigs. *Am. J. Physiol.*, **274**, R76-R80.

Jin, Y., Sekizawa, K., Fukushima, T., Morikawa, M., Nakazawa, H. & Sasaki, H. (1994) Capsaicin desensitization inhibits swallowing reflex in guinea pigs. *Am. J. Respir. Crit. Care Med.*, **149**, 261-263.

Kanda, A., Yanai, M., Suzuki, T., Ohrui, T. & Sasaki, H. (2000) Nocturnal wheeze in asthmatic patients. *Chest*, **118**, 278.

Kanda, A., Ebihara, S., Yasuda, H., Ohrui, T., Sasaki, T. & Sasaki, H. (2004) A combinatorial therapy for pneumonia in elderly people. *J. Am. Geriatr. Soc.*, **52**, 846-847.

Katsumata, U., Sekizawa, K., Ebihara, T. & Sasaki, H. (1995) Aging effects of cough reflex. *Chest*, **107**, 290-291.

Kikuchi, R., Watanabe, N., Konno, T., Mishina, N., Sekizawa, K. & Sasaki, H. (1994) High incidence of silent aspiration in elderly patients with community-acquired pneumonia. *Am. J. Respir. Crit. Care Med.*, **150**, 251-253.

Kobayashi, H., Hoshino, M., Okayama, K., Sekizawa, K. & Sasaki, H. (1994) Swallowing and cough reflexes after onset of stroke. *Chest*, **105**, 1623.

Kobayashi, H., Nakagawa, T., Sekizawa, K., Arai, H. & Sasaki, H. (1996) Levodopa and swallowing reflex. *Lancet*, **348**, 1320-1321.

Kobayashi, H., Sekizawa, K. & Sasaki, H. (1997) Aging effects on swallowing refle. *Chest*, **111**, 1466.

Kosaka, Y., Nakagawa, T., Matsui, T., Arai, H. & Sasaki, H. (1998) Survival of bed-ridden older patients. *J. Am. Geriatr. Soc.*, **46**, 394.

Kosaka, Y., Satoh-Nakagawa, T., Ohrui, T., Yamaya, M., Arai, H. & Sasaki, H. (2003) Tube feeding in terminal elderly care. *Geriatr. Gelontol. Internat.*, **3**, 172-174.

Kosaka, Y., Yamaya, M., Nakajoh, K., Matsui, T., Yanai, M. & Sasaki, H. (2000) Prognosis of elderly patients with dysphagia in Japan. *Gerontology*, **46**, 111-112.

Manabe, K., Matsui, T., Yamaya, M., Sato-Nakagawa, T., Okamura, N., Arai, H. & Sasaki, H. (2000) Sleep petterns and mortality among elderly patients in a geriatric hospital. *Gerontology*, **46**, 318-322.

Matsui, T., Arai, H., Yuzuriha, T., Yao, H., Miura, M., Hashimoto, S., Higuchi, S., Matsushita, S., Morikawa, M., Kato, A. & Sasaki, H. (2001) Elevated plasma homocysteine levels and risk of silent brain infarction in elderly people. *Stroke*, **32**, 1116-1119.

Matsui, T., Yamaya, M., Ohrui, T., Arai, H. & Sasaki, H. (2002) Sitting position to prevent aspiration in bed-bound patients. *Gerontology*, **48**, 194-195.

Nakagawa, T., Ohrui, T., Sekizawa, K. & Sasaki, H. (1995) Sputum substance P in aspiration pneumonia. *Lancet*, **345**, 1447.

Nakagawa, T., Sekizawa, K., Arai, H., Kikuchi, R., Manabe, K. & Sasaki, H. (1997) High incidence of pneumonia in elderly patients with basal ganglia infarction. *Arch. Intern. Med.*, **157**, 321-324.

Nakagawa, T., Wada, H., Sekizawa, K., Arai, H. & Sasaki, H. (1999) Amantadine and pneumonia. *Lancet*, **353**, 1157.

Nakagawa, T., Sekizawa, K., Nakajo, K., Tanji, H., Arai, H. & Sasaki, H. (2000) Silent cerebral infaraction: a potential risk for pneumonia in the elderly. *J. Intern. Med.*, **247**, 255-259.

Nakajoh, K., Satoh-Nakagawa, T., Arai, H., Yanai, M., Yamaya, M. & Sasaki, H. (1999) Longevity may decrease medical costs. *J. Am. Geriatr. Soc.*, **47**, 1161-1162.

Nakajoh, K., Nakagawa, T., Sekizawa, K., Matsui, T., Arai, H. & Sasaki, H. (2000) Relation between incidence of pneumonia and protective reflexes in post-stroke patients with oral or tube feeding. *J. Intern. Med.*, **247**, 39-42.

Nakamura, M., Matsui, T., Ohrui, T., Kida, K., Yamaya, M. & Sasaki, H. (2002) Gender crossover of lung function. *Geriatr. Gerontol. Internat.*, **2**, 127-130.

Nakayama, K., Sekizawa, K. & Sasaki, H. (1998) ACE inhibitor and swallowing reflex. *Chest*, **113**, 1425.

Nakayama, K., Monma, M., Fukushima, T., Ohrui, T. & Sasaki, H. (2000) Tuberculin responses and risk of pneumonia in immobile elderly patients. *Thorax*, **55**, 867-869.

Nakayama, K., Shinkawa, M., Ohrui, T., Hirai, H. & Sasaki, H. (2002) Interferon-gamma responses to mycobacterial antigens in Heaf-positive children. *Lancet*, **360**, 1334-1335.

Nakazawa, H., Sekizawa, K., Ujiie, Y., Sasaki, H. & Takishima, T. (1993) Risk of aspiration pneumonia in the elderly. *Chest*, **103**, 1636-1637.

Ohara, Y., Ohrui, T., Morikawa, T. & Sasaki, H. (2002) Parental attitudes towards passive smoking in Japan. *Lancet*, **359**, 1159.

Ohrui, T., Yamaya, M., Suzuki, T., Sekizawa, K., Funayama, E., Sekine, H. & Sasaki, H. (1997) Mechanisms of gastric juice-induced hyperpermeability of the cultured human tracheal epithelium. *Chest*, **111**, 454-459.

Ohrui, T., Zayasu, K., Satoh, R., Matsui, T., Sekizawa, K. & Sasaki, H. (2000) Pulomonary tuberculosis and serum IgE. *Clin. Exp. Immunol.*, **122**, 13-15.

Ohrui, T., Arai, H., Ichinose, M., Matsui, T., Yamaya, M. & Sasaki, H. (2002) Relationship between ashma severity and progression of Alzheimer's disease. *Thorax*, **57**, 561.

Ohrui, T., Yamaya, M., Kubo, H. & Sasaki, H. (2004a) Survival rates between males and females. *Geriatr. Gerontol. Internat.*, **4**, 64-65.

Ohrui, T., Matsui, T., Yamaya, M., Arai, H., Ebihara, S., Maruyama, M. & Sasaki, H. (2004b) Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *J. Am. Geriatr. Soc.*, **52**, 649-650.

Ohrui, T., Matsui, T., Yamaya, M., Kubo, H., Arai, H. & Sasaki, H. (2004c) A new therapy for Alzheimer's disease. *Geriatr. Gerontol. Internat.*, **4**, 123-125.

Ohrui, T., Tomita, N., Sato-Nakagawa, T., Matsui, T., Maruyama, M., Niwa, K., Arai, H. & Sasaki, H. (2004d) Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology*, **63**, 1324-1325.

Ohrui, T., Matusui, T., He, M., Ebihara, S. & Sasaki, H. (2004e) Relation between retirement and subsequent health status in highly educated older men. *J. Am. Geriatr. Soc.*, **52**, 2145-2147.

Okamura, N., Maruyama, M., Ebihara, T., Matsui, T., Nemoto, M., Arai, H., Sasaki, H. & Yanai, K. (2004) Aspiration pneumonia and insular hypoperfusion in patients with cerebrovascular disease. *J. Am. Geriatr. Soc.*, **52**, 645-646.

Osler, W. (1898) *The Principles and Practice of Medicine*. New York, D. Appleton and CO.

Pinto, A., Yanai, M., Nakagawa, T., Sekizawa, K. & Sasaki, H. (1994) Swallowing reflex in the night. *Lancet*, **344**, 820-821.

Sasaki, H., Sekizawa, K., Yamaya, M., Arai, H. & Ohrui, T. (1996) Will aging of the population make Japan less productive? *J. Am. Geriatr. Soc.*, **44**, 1013-1014.

Sasaki, H., Sekizawa, K., Yanai, M., Arai, H., Yamaya, M. & Ohrui, T. (1997) Elongation of life expectancy may accompany shift of medical cost to older adults. *J. Am. Geriatr. Soc.*, **45**, 254-255.

Sato, E., Ohrui, T., Matsui, T., Arai, H. & Sasaki, H. (2001) Folate deficiency and risk of pneumonia in older people. *J. Am. Geriatr. Soc.*, **49**, 1739-1740.

Seki, T., Kurusu, M., Tanji, H., Arai, H. & Sasaki, H. (2003) Acupuncture and swallowing reflex in poststroke patients. *J. Am. Geriatr. Soc.*, **51**, 726-727.

Sekizawa, K., Ujiie, Y., Itabashi, S., Sasaki, H. & Takishima, T. (1990) Lack of cough reflex in aspiration pneumonia. *Lancet*, **355**, 1228-1229.

Sekizawa, K., Jia, Y.X., Ebihara, T., Hirose, Y., Hiragawa, Y. & Sasaki, H. (1997) Role of substance P in cough. *Pulm. Pharmacol.*, **9**, 323-328.

Sekizawa, K., Matsui, T., Nakagawa, T., Nakayama, K. & Sasaki, H. (1998) ACE inhibitors and pneumonia. *Lancet*, **352**, 1069.

Sekizawa, K., Yanai, M., Yamaya, M., Arai, H. & Sasaki, H. (1999) Amantadine and pneumonia in elderly stroke patients. *Lancet*, **353**, 2156-2157.

Shinkawa, M., Yanai, M., Yamaya, M., Matsui, T. & Sasaki, H. (2000) Depressive state and common cold. *Lancet*, **356**, 942.

Shinkawa, M., Yamaya, M., Ohrui, T., Arai, H. & Sasaki, H. (2002a) Depression in older people. *Geriatr. Gerontol. Internat.*, **2**, 215-216.

Shinkawa, M., Nakayama, K., Hirai, H., Monma, M. & Sasaki, H. (2002b) Depression and immunoreactivity in disabled older patients. *J. Am. Geriatr. Soc.*, **50**, 198.

Suzuki, T., Yanai, M., Yamaya, M., Satoh-Nakagawa, T., Sekizawa, K., Ishida, S. & Sasaki, H. (2001a) Erythromycin and Common Cold in COPD. *Chest*, **120**, 730-733.

Suzuki, T., Arai, H., Iwasaki, K., Tanji, H., Higuchi, M., Okamura, N., Matsui, T., Maruyama, M., Yabe, T., Toriizuka, K., Yamada, H., Hanawa, T., Ikarashi, Y. & Sasaki, H. (2001b) A Japanese herbal medicine (Kami-Untan-To) in the treatment of Alzheimer's disease: A pilot study. *Alzheimer's Reports*, **4**, 177-182.

Ujiie, Y., Sekizawa, K., Aikawa, T. & Sasaki, H. (1993) Evidence for Substance P as an endogenous substance causing cough in guinea pigs. *Am. Rev. Respir. Dis.*, **148**, 1628-1632.

Wada, H., Nakajoh, K., Satoh-Nakagawa, T., Suzuki, T., Ohrui, T., Arai, H. & Sasaki, H. (2001) Risk factors of aspiration pneumonia in Alzheimer's disease patients. *Gerontology*, **47**, 271-276.

Wang, H.D., Nakagawa, T., Sekizawa, K., Kamanaka, M. & Sasaki, H. (1998) Cough reflex in the night. *Chest*, **114**, 1496-1497.

Watando, A., Ebihara, S., Ebihara, T., Okazaki, T., Takahashi, H., Asada, M. & Sasaki, H. (2004a) Effect of temperature on swallowing reflex in elderly patients with aspiration pneumonia. *J. Am. Geriatr. Soc.*, **52**, 2143-2144.

Watando, A., Ebihara, S., Ebihara, T., Okazaki, T., Takahashi, H., Asada, M. & Sasaki, H. (2004b) Daily oral care and cough reflex Sensitivity in elderly nursing home patients. *Chest*, **126**, 1066-1070.

White, H.D., Simes, R.J., Anderson, N.E., Hankey, G.J., Watson, J.D.G., Hunt, D., Colquhoun, D.M., Glasziou, P., MacMahon, S., Kirby, A.C., West, M.J. & Tonkin, A.M. (2000) Pravastation therapy and the risk of stroke. *N. Engl. J. Med.*, **343**, 317-326.

Yamaya, M., Yanai, M., Ohrui, T., Arai, H. & Sasaki, H. (2001a) Progress in geriatrics: interventions to prevent pneumonia among older adults. *J. Am. Geriatr. Soc.*, **49**, 85-90.

Yamaya, M., Yanai, M., Ohrui, T., Arai, H., Sekizawa, K. & Sasaki, H. (2001b) Antithrombotic therapy for prevention of pneumonia. *J. Am. Geriatr. Soc.*, **49**, 687-688.

Yoneyama, T., Yoshida, M., Matsui, T. & Sasaki, H. (1999) Oral care and pneumonia. *Lancet*, **354**, 515.

Yoneyama, T., Yoshida, M., Ohrui, T., Mukaiyama, H., Okamoto, H., Hoshiba, K., Ihara, S., Yanagisawa, S., Ariumi, S., Morita, T., Mizuno, Y., Ohsawa, T., Akagawa, Y., Hashimoto, K. & Sasaki, H. (2002) Oral care reduces pneumonia in older patients in nursing homes. *J. Am. Geriatr. Soc.*, **50**, 430-433.

Yoshino, A., Ebihara, T., Ebihara, S., Fuji, H. & Sasaki, H. (2001) Daily oral care and risk factors for pneumonia among elderly nursing home patients. *J. Am. Geriatr. Soc.*, **286**, 2235-2236.

Zheng, S., Yanai, M., Matsui, T., Sekizawa, K. & Sasaki, H. (1997) Noctunal cough in patients with sputum production. *Lancet*, **350**, 864-865.