DOI: 10.2169/internalmedicine.46.1775

JC and colleagues have suggested an association between latent adenoviral infection with expression of the adenoviral E 1A gene and COPD (24, 25). The present study focuses on how the adenoviral E1A gene could alter expression of growth factors by human bronchial epithelial (HBE) cells. The data show that connective tissue growth factor (CTGF) and transforming growth factor (TGF)-beta 1 mRNA and protein expression were upregulated in E1A-positive HBE cells. The latent infection of epithelial cells by adenovirus E 1A could contribute to airway remodeling in COPD by the viral E1A gene, inducing TGF-beta 1 and CTGF expression and shifting cells to a more mesenchymal phenotype.

Conclusion and Implication

Chronic obstructive pulmonary disease (COPD) is the collective term describing two separate chronic lung disease diseases: emphysema and chronic bronchitis. Results of many studies have suggested that the genetic susceptibility to COPD is dependent on the action of several gene polymorphisms operating in concert. Polymorphisms in an individual gene may impart only a small relative risk of COPD, and it is likely that the cumulative effect of many polymorphisms will be important in its pathogenesis. Before these associations are generally accepted, they must be subjected to scrutiny with further association studies in terms of ethnicity and COPD phenotypes.

Acknowledgements: This work was supported by a grant from Mitsui Life Social Welfare Foundation.

References

1. Murray CJL, Lopez AD. Evidence-Based Health Policy-Lessons from the Global Burden of Disease Study. Science **274**: 740-743, 1996.
2. Teramoto S, Yamamoto H, Yamaguchi Y, Matsuse T, Ouchi Y. Global burden of COPD in Japan and Asia. Lancet **362**: 1764-1765, 2003.
3. Sandford AJ, Weir TD, Pare PD. Genetic risk factors for chronic obstructive pulmonary disease. Eur Respir J **10**: 1380-1391, 1997.
4. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet **364**: 613-620, 2004.
5. Molfino NA. Gentics of COPD. Chest **125**: 1929-1940, 2004.
6. Teramoto S, Ishii T, Yamamoto H, et al. Xenobiotic enzymes and genetics of COPD. Chest **127**: 408-409, 2005.
7. Falk GA, Briscoe WA. Alpha-1-antitrypsin deficiency in chronic obstructive pulmonary disease. Ann Intern Med **72**: 427-429, 1970.
8. Ishii T, Matsuse T, Teramoto S, et al. Association between alpha-1-antichymotrypsin polymorphism and susceptibility to chronic obstructive pulmonary disease. Eur J Clin Invest **30**: 543-548, 2000.
9. Joos L, He JQ, Shepherdson MB, et al. Therole ofmatrix metalloproteinase polymorphisms in the rate of decline in lung function. Hum Mol Genet **11**: 569-576, 2002.
10. Sandford AJ, Chagani T, Weir TD, et al. Susceptibility genes for rapid decline of lung function in the Lung Health Study. Am J Respir Crit Care Med **163**: 469-473, 2001.
11. Hirano K, Sakamoto T, Uchida Y, et al. Tissue inhibitor of metalloproteinases-2 gene polymorphisms in chronic obstructive pulmonary disease. Eur Respir J **18**: 748-752, 2001.
12. Minematsu N, Nakamura H, Tateno H. Genetic polymorphism in matrix metalloproteinase-9 and pulmonary emphysema. Biochem Biophys Res Commun **289**: 116-119, 2001.
13. Hautamaki RD, Kobayashi DK, Senior RM, Shapiro SD. Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. Science **277**: 2002-2004, 1997.
14. Foronjy RF, Okada Y, Cole R, D'Armiento J. Progressive adult-onset emphysema in transgenic mice expressing human MMP-1 in the lung. Am J Physiol **284**: L727-L737, 2003.
15. Yamada N, Yamaya M, Okinaga S, et al. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to emphysema. Am J Hum Genet **66**: 187-195, 2000.
16. He JQ, Ruan J, Connett JE, et al. Antioxidant gene polymorphisms and susceptibility to a rapid decline in lung function in smokers. Am J Respir Crit Care Med **166**: 323-328, 2002.
17. Ishii T, Matsuse T, Teramoto S, et al. Glutathione S-transferase P1 (GSTP1) polymorphism in patients with chronic obstructive pulmonary disease. Thorax **54**: 693-696, 1999.
18. Smith CA, Harrison DJ. Association between polymorphism in gene for microsomal epoxide hydrolase and susceptibility to emphysema. Lancet **350**: 630-633, 1997.
19. Koyama H, Geddes DM Genes. oxidative stress, and the risk of chronic obstructive pulmonary disease. Thorax **53** (Suppl): S10-S 14, 1998.
20. Minematsu N, Nakamura H, Iwata M, et al. Association of CYP2 A6 deletion polymorphism with smoking habit and development of pulmonary emphysema. Thorax **58**: 623-628, 2003.
21. Sakao S, Tatsumi K, Igari H, et al. Association of tumor necrosis factor {alpha} gene promoter polymorphism with the presence of chronic obstructive pulmonary disease. Am J Respir Crit Care Med **163**: 420-422, 2001.
22. van der Pouw Kraan TC, Kucukaycan M, Bakker AM, et al. Chronic obstructive pulmonary disease is associated with the -1055 IL-13 promoter polymorphism. Genes Immun **3**: 436-439, 2003.
23. Schellenberg D, Pare P, Weir T, et al. Vitamin D binding protein variants and therisk of COPD. Am J Respir Crit Care Med **157**: 957-961, 1998.
24. Hogg JC. Role of latent viral infections in chronic obstructive pulmonary disease and asthma. Am J Respir Crit Care Med **164**: S 71-S75, 2001.
25. Teramoto S, Kume H. The role of nuclear factor-kappa B activation in airway inflammation following adenovirus infection and COPD. Chest **119**: 1294-1295, 2001.

that these changes became more convincing with time, so that a longer term study with higher doses is rational. Finally, the measurement of cytokines, such as TNF-α, in induced sputum might be a useful way to select those patients who may respond to therapy directed against TNF-α, and could have utility in monitoring therapeutic responses.

Conflict of Interest Statement: E.M.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. O.M.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.J.B. has received funding and has served on scientific advisory boards for GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, Novartis, Altana, Pfizer, and Millennium. T.T.H. has received research grants in 2004 to May 2006 from GlaxoSmithKline ($250,000), Novartis ($500,000), and Oxogen ($360,000).

EDWARD M. ERIN
ONN MIN KON
PETER J. BARNES
TREVOR T. HANSEL
National Heart and Lung Institute
Royal Brompton Hospital
London, United Kingdom

References

1. Erin EM, Leaker BR, Nicholson GC, Tan AJ, Green LM, Neighbour H, Zacharasiewicz AS, Turner J, Barnathan ES, Kon OM, *et al.* The effects of a monoclonal antibody directed against tumor necrosis factor-α in asthma. *Am J Respir Crit Care Med* 2006;174:753–762.
2. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, Bradding P, Brightling CE, Wardlaw AJ, Pavord ID. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med* 2006;354:697–708.
3. Howarth PH, Babu KS, Arshad HS, Lau L, Buckley M, McConnell W, Beckett P, Al Ali M, Chauhan A, Wilson SJ, *et al.* Tumour necrosis factor (TNFalpha) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012–1018.
4. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della CG. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18: 254–261.
5. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184–190.
6. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedgecock S, *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309–316.
7. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, Bousquet J, Kerstjens HA, Fox H, Thirlwell J, *et al.* Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34:632–638.
8. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 2004;59:701–708.
9. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, Fox H, Hedgecock S, Blogg M, Cioppa GD. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005;60:302–308.

Aging, the Aging Lung, and Senile Emphysema Are Different

To the Editor:

In his recent editorial, Tuder implicated the pathophysiologic interrelationship between aging and cigarette smoke in the development of chronic obstructive pulmonary disease (COPD) (1). We believe that some of the points in this editorial are misleading.

First, aging is a process leading to death and is characterized by universal progressive, deleterious, and irreversible alterations. But aging is not a disease. We can treat the age-related phenomena, but not aging itself. Tuder is commenting on the article by Sato and coworkers in the same issue, which is entitled "Senescence Marker Protein-30 Protects Mice Lungs from Oxidative Stress, Aging, and Smoking" (2). Sato and coworkers' title is incorrect. Importantly, previous studies have described physiologic changes of the lungs due to aging alone as aging lung or senile lung, but not as senile emphysema (3, 4). Here, the lungs were characterized as undergoing airspace enlargement without alveolar wall destruction (3, 4). Also, Janssens and coworkers' review, which was cited by Tuder, did not correctly differentiate the difference between aging lung and senile emphysema (5). Thus, age itself is known to be a risk for COPD, but not necessary for the development of COPD.

Second, gene regulation of aging is complex. The master gene of aging has not been determined, although the Klotho gene is a candidate (6). Klotho gene–deficient mice develop the airspace enlargement without cigarette smoke exposure. Although mouse models of COPD often exhibited homogeneous alterations of lung structures, age-related changes of the lungs are heterogeneous in humans. The role of a single gene on the functional and morphologic changes of the lungs may be limited in humans. The redundancy of multiple genes associated with aging may substitute for the impaired cell function of lungs in humans due to a single gene defect.

Third, there is no association of apoptosis and aging in human lungs. In particular, apoptotic cell death is not directly related to the aging process. Because apoptosis is an active process, it is not related to a degenerative process such as aging.

We realized that the senescence marker protein-30 (SMP-30) gene is a good candidate gene for exploring the aging process and age-related diseases. However, the pathologic interaction between the aging process and COPD may not be solved by analyzing the SMP-30 gene and its protein products. We should differentiate physiologic aging, such as the aging/senile lung, from pathologic aging, as in senile emphysema (4). Furthermore, the resemblances and differences between senile emphysema and adult COPD should be better clarified.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

SHINJI TERAMOTO
MASAKI ISHII
University of Tokyo
Tokyo, Japan

References

1. Tuder RM. Aging and cigarette smoke: fueling the fire. *Am J Respir Crit Care Med* 2006;174:490–491.
2. Sato T, Seyama K, Sato Y, Mori H, Souma S, Akiyoshi T, Kodama Y, Mori T, Goto S, Takahashi K, *et al.* Senescence marker protein-30 protects mice lungs from oxidative stress, aging, and smoking. *Am J Respir Crit Care Med* 2006;174:530–537.
3. Teramoto S, Fukuchi Y, Uejima Y, Teramoto K, Oka T, Orimo H. A novel model of senile lung: senescence-accelerated mouse (SAM). *Am J Respir Crit Care Med* 1994;150:238–244.
4. Teramoto S. Age-related changes in lung structure and function in the senescence-accelerated mouse (SAM): SAM-P/1 as a new model of senile hyperinflation of lung. *Am J Respir Crit Care Med* 1997;156:1361.
5. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999;13:197–205.

6. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, *et al.* Mutation of the mouse Klotho gene leads to a syndrome resembling ageing. *Nature* 1997;390:45–51.

From the Author:

My editorial's intent was to highlight the cellular and molecular events that mechanistically link aging and chronic obstructive pulmonary disease (COPD), and to stimulate further research on this important topic (1). Such studies may help resolve the controversies raised by Drs. Teramoto and Ishii regarding the definition of aging, whether aging should be interpreted as a physiologic or pathologic process, and the relationship between lung alterations due to aging vis-à-vis senile emphysema. It is apparent that the concept of a so-called physiologic lung aging, as argued by Drs. Teramoto and Ishii, deserves careful revaluation. Significant pathologic processes are evident with the onset of aging, such as excessive oxidative stress, DNA damage, enhanced inflammation, and decreased immunity, all of which might contribute to a significantly higher incidence of cancer and degenerative diseases compromising the heart (with heart failure), muscle (with muscle wasting), and joints (with osteoporosis), among others (2).

Why should the lung be different from the heart, brain, or immune system? It is conceivable that age-related molecular and cellular injuries may be of significant pathophysiologic importance in the causation of many pulmonary diseases, including COPD or lung cancer. Indeed, prior work by Dr. Teramoto acknowledges the close resemblance of lung alterations due to aging to those related to environmental injuries (including cigarette smoke inhalation). He raises similar considerations regarding the effect of age on cigarette smoke–induced emphysema to those posed in my editorial and the accompanying article by Sato and coworkers (3).

Aging alters fundamental controls involved in cell growth, maintenance, and death. Accumulation of stresses over the life span shortens telomeres, a hallmark of senescent cells (4). Telomere shortening was recently recognized to be present in COPD lungs in association with increased expression of Ink4a/Arf (5), a biomarker of aging (6). These advances and the recognition of alveolar cell apoptosis, oxidative stress, and senescence have been linked to emphysematous lung destruction (5, 7), warranting the revaluation of prior definitions of alveolar enlargement in both diseased (i.e., COPD) and aging lung (8). Transgenic mice provide important and useful tools for exploring how candidate genes, such as SMP-30 and the Klotho protein, trigger pathogenetic mechanisms involved in destructive alveolar enlargement. These studies will enrich the list of candidate genes potentially involved in aging and in COPD in humans. In addition, these discoveries will further clarify how COPD risk factors, including sex, childhood diseases, cigarette pack-years, and infections might also enhance the susceptibility to the disease.

RUBIN M. TUDER
Johns Hopkins University School of Medicine
Baltimore, Maryland

Conflict of Interest Statement: R.M.T. has received $2,500 for a lecture given in a meeting on COPD sponsored and organized by AstraZeneca. He has received an unrestricted gift of $100,000 from Quark Biotech to conduct research in the pathogenesis of emphysema, particularly of the pathway involving RTP-801.

References

1. Tuder R. Aging and cigarette smoke: fueling the fire. *Am J Respir Crit Care Med* 2006;174:490–491.
2. Chien KR, Karsenty G. Longevity and lineages: toward the integrative biology of degenerative diseases in heart, muscle, and bone. *Cell* 2005; 120:533–544.
3. Sato T, Seyama K, Sato Y, Mori H, Souma S, Akiyoshi T, Kodama Y, Mori T, Goto S, Takahashi K, *et al.* Senescence marker protein-30 protects mice lungs from oxidative stress, aging, and smoking. *Am J Respir Crit Care Med* 2006;174:530–537.
4. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci USA* 2004;101:17312–17315.
5. Tsuji T, Aoshiba K, Nagai A. Alveolar cell senescence in patients with pulmonary emphysema. *Am J Respir Crit Care Med* 2006;174:886–893.
6. Krishnamurthty J, Torrice C, Ramsey MR, Kovalev GI, Al-Regaiey K, Su LS, Sharpless NE. Ink4a/Arf expression is a biomarker of aging. *J Clin Invest* 2004;114:1299–1307.
7. Muller KC, Welker CL, Paasch K, Feindt B, Erpenbeck VJ, Hohlfeld JM, Krug N, Nakashima M, Branscheid D, Magnussen H, *et al.* Lung fibroblasts from patients with emphysema show markers of senescence in vitro. *Respir Res* 2006;7:32.
8. Snider GL, Kleinerman LJ, Thurlbeck WM, Bengali ZH. The definition of emphysema: report of a National, Heart, Lung and Blood Institute, Division of Lung Diseases Workshop. *Am Rev Respir Dis* 1985;131: 182–185.

Should Individuals Who Are Tuberculin Skin Test Negative and Positive to RD1–IFN-γ Assay Receive Preventive Therapy?

To the Editor:

We read with interest the recent pulmonary perspective by Luca Richeldi about the use of blood tests for the diagnosis of tuberculosis infection (1). Richeldi reviews the evidence suggesting that tests based on *in vitro* release of IFN-γ in response to *Mycobacterium tuberculosis* region of difference 1 (RD1)-antigens, in particular those based on the enzyme-linked immunospot (ELISpot) technique, may be more sensitive than the tuberculin skin test (TST) for the diagnosis of tuberculosis infection. He also argues that routine use of these tests may result in short-term increased costs due to more diagnosis of and treatment for tuberculosis infection. In our opinion, if the preliminary evidence on ELISpot sensitivity is confirmed, other issues, besides that of costs, need also to be addressed before replacing TST in screening programs for latent tuberculosis with more sensitive blood tests.

Lord and coworkers recently analyzed the level of evidence needed to accept a new diagnostic test in routine practice (2). These authors argue that when a new test is more sensitive than an old one, the extra cases detected by the new test may represent a different spectrum of disease compared with those detected by the old test. Thus, the information about the effect of treatment of cases diagnosed by the old test may not necessarily apply to extra cases detected by the new test. The recent paper by Ewer and coworkers (3) suggests that new blood tests for tuberculosis infection may indeed produce a shift in the spectrum of infection detected. These authors identified 14 students who were TST-negative and ELISpot-positive among contacts in a school tuberculosis outbreak. None of them received preventive therapy, and seven became ELISpot-negative during follow-up. In contrast, no change in ELISpot response was observed in the ELISpot-positive, but untreated TST-positive staff. The authors suggested that individuals who were ELISpot-positive only may have been infected with a lower dose of *M. tuberculosis*, insufficient to induce a cutaneous response to PPD.

Available data on the benefit of treatment of latent tuberculosis infection are based on trials using TST-positive individuals (4). It remains to be demonstrated that a similar benefit could be found in TST-negative individuals who are positive to IFN-γ

A.A. El Solh
Division of Pulmonary, Critical Care and Sleep Medicine, Dept of Medicine, University at Buffalo School of Medicine and Biomedical Sciences, Buffalo, NY, USA.

REFERENCES

1 El Solh AA, Saliba R, Bosinski T, Grant BJ, Berbary E, Miller N. Allopurinol improves endothelial function in sleep apnea: a randomised controlled study. *Eur Respir J* 2006; 27: 997–1002.

2 Moens AL, Goovaerts I, Claeys MJ, Vrints CJ. Flow-mediated vasodilation: a diagnostic instrument, or an experimental tool? *Chest* 2005; 127: 2254–2263.

3 Sorensen KE, Dorup I, Hermann AP, Mosekilde L. Combined hormone replacement therapy does not protect women against the age-related decline in endothelium-dependent vasomotor function. *Circulation* 1998; 97: 1234–1238.

DOI: 10.1183/09031936.00111906

ACE inhibitors prevent aspiration pneumonia in Asian, but not Caucasian, elderly patients with stroke

To the Editors:

In a recent issue of the *European Respiratory Journal*, VAN DE GARDE *et al.* [1] demonstrated that the use of angiotensin-converting enzyme (ACE) inhibitors is not associated with a decreased risk of hospitalisation for community-acquired pneumonia (CAP) in a general, essentially white population. Their conclusion that the beneficial effect of ACE inhibitors on pneumonia risk is not observed in a general white population is in contrast with previous findings in Asian populations [1]. This was an excellent good study examining the association of ACE inhibitor treatment of cardiovascular disease with a risk reduction of CAP using a large sample size. The results are acceptable and not surprising; however, the discussion and conclusion are misleading.

As shown in table 1, there are controversies regarding the ACE inhibitor effects on the risk reduction of pneumonia even in Asian countries; furthermore, the study samples are very different among the studies. In a prospective study by SEKIZAWA *et al.* [2], ACE inhibitor use reduced pneumonia incidence for 2 yrs. They did not examine the general population; subjects were hypertensive elderly patients with a history of stroke or lacuna infarction, and a mean age 10 yrs older than that of the study by VAN DE GARDE *et al.* [1]. However, the study by ARAI *et al.* [3] examined the association of ACE inhibitors and the risk reduction of pneumonia in the general hypertensive elderly without stroke in Japan [3]. Surprisingly, they had an 8.3–8.9% incidence of pneumonia over 3 yrs, an incidence twenty times higher than the previous data [6, 7]. It is hard to believe that ~3% of hypertensive elderly outpatients without major complications suffered from pneumonia. We have previously presented data showing no association of ACE inhibitor use with pneumonia risk in elderly hypertensive subjects without stroke history [4]. Since ACE inhibitors, through the inactivation substance P, improve upper airway reflexes such as swallowing and cough, resulting in the reduction of aspiration pneumonia in elderly patients, they may not reduce the CAP in those patients without deglutition problems. Current evidence indicates that ACE inhibitors play a significant role in the prevention of aspiration pneumonia in the elderly, but not in common CAP in healthy adults. This was confirmed by the sub-analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). OHKUBO *et al.* [5] re-analysed the PROGRESS data concerning the incidence of pneumonia. ACE inhibitor-active treatment significantly reduced the risk of pneumonia among participants of Asian ethnicity (mean (95% confidence interval) 47% (14–67%), p=0.01), with no significant effect among non-Asian participants (5% (-27–29%), p=0.7; p for homogeneity=0.04). These findings add to the body of

TABLE 1 The association of angiotensin-converting enzyme (ACE) inhibitor use and the rate of pneumonia in different trials

	VAN DE GARDE [1]	SEKIZAWA [2]	ARAI [3]	TERAMOTO [4]	OHKUBO [5]	OHKUBO [5]
Race	Caucasian	Asian	Asian	Asian	Asian	Caucasian
Age yrs	67	76–77	75.3–76.5	>65	64	64
Subjects n	4925	440	576	358	2352	3753
Observation period yrs	6	2	3	3	3.9	3.9
History of stroke	No	Yes	No	No	Yes	Yes
Pneumonia incidence %						
Without ACE inhibitors		9	2.77–2.97	0.25	1.04	1.3
With ACE inhibitors		3.5	1.1	0.56	0.56	1.24
Pneumonia prevention by ACE inhibitors	No	Yes	Yes	No	Yes	No

evidence regarding the effects of these drugs on pneumonia. The randomised design of PROGRESS greatly reduced the likelihood of confounding of the analyses and provided an excellent opportunity to explore the validity of the associations reported in observational studies [2, 3]. Thus, the key issue is the selection of elderly subjects in terms of ethnicity, post-stroke state, performance status, type of ACE inhibitor and swallowing function.

The clinical epidemiology research group of ETMINAN *et al.* [8] recently reported that no association was found between the use of ACE inhibitors or angiotensin II receptor blockers (ARBs) and risk of hospitalisation secondary to CAP. The study further confirmed the limited efficacy of ACE inhibitors on the risk reduction of hospitalisation due to pneumonia in a white population. As we speculated, ARBs did not have any role in the prevention of aspiration pneumonia.

Stroke and post-stroke patients often exhibit a normal cough reflex, but not swallowing reflex, and the small volume of aspirated materials due to impaired swallowing during night is a key factor for the risk of pneumonia [9, 10]. Hence, a ten times higher rate of pneumonia in post-stroke patients without significant neurological deficit, compared with the rate of pneumonia in normal elderly [5]. Furthermore, the age-dependent impairment of upper airway reflexes should be carefully considered for the mechanism of CAP in the elderly irrespective of the history of stroke.

Finally, we emphasise that aspiration and silent aspiration are very important mechanisms of aspiration pneumonia. Silent aspiration is very common in patients with stroke and frail elderly patients, and nasogastric tube feeding without swallowing rehabilitation or oral care cannot reduce the pneumonia risk in patients with swallowing disorders [11].

We believe that angiotensin-converting enzyme inhibitors could prevent aspiration pneumonia in selected elderly patients. Post-stroke and the frail elderly are the best candidates for the pneumonia risk reduction by angiotensin-converting enzyme inhibitors [12]. However, these merits may not be consistently observed in Caucasian elderly patients with or without stroke.

S. Teramoto, H. Yamamoto, Y. Yamaguchi, Y. Hanaoka, M. Ishii, S. Hibi and Y. Ouchi
Dept of Geriatric Medicine, Dept of Urology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

REFERENCES

1 van de Garde EM, Souverein PC, van den Bosch JM, Deneer VH, Leufkens HG. Angiotensin-converting enzyme inhibitor use and pneumonia risk in a general population. *Eur Respir J* 2006; 27: 1217–1222.
2 Sekizawa K, Matsui T, Nakagawa T, Nakayama K, Sasaki H. ACE inhibitors and pneumonia. *Lancet* 1998; 352: 1069.
3 Arai T, Yasuda Y, Toshima S, Yoshimi N, Kashiki Y. ACE inhibitors and pneumonia in elderly people. *Lancet* 1998; 352: 1937–1938.
4 Teramoto S, Ouchi Y. ACE inhibitors and prevention of aspiration pneumonia in elderly hypertensives. *Lancet* 1999; 353: 843.
5 Ohkubo T, Chapman N, Neal B, Woodward M, Omae T, Chalmers J. Effects of an angiotensin-converting enzyme inhibitor-based regimen on pneumonia risk. *Am J Respir Crit Care Med* 2004; 169: 1041–1045.
6 Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987; 1: 671–674.
7 Jokinen C, Heiskanen L, Juvonen H, *et al.* Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993; 137: 977–988.
8 Etminan M, Zhang B, Fitzgerald M, Brophy JM. Do angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers decrease the risk of hospitalization secondary to community-acquired pneumonia? A nested case-control study. *Pharmacotherapy* 2006; 26: 479–482.
9 Teramoto S, Ishii T, Yamamoto H, *et al.* Significance of chronic cough as a defence mechanism or a symptom in elderly patients with aspiration and aspiration pneumonia. *Eur Respir J* 2005; 25: 210–211.
10 Teramoto S, Matsuse T, Fukuchi Y, Ouchi Y. Simple two-step swallowing provocation test for elderly patients with aspiration pneumonia. *Lancet* 1999; 353: 1243.
11 Teramoto S, Ishii T, Yamamoto H, Yamaguchi Y, Ouchi Y. Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patients. *Eur Respir J* 2006; 27: 436–437.
12 Teramoto S, Kume H, Fukuchi Y. Antihypertensive drugs in Japan. *Lancet* 2001; 357: 720–721.

DOI: 10.1183/09031936.00115106

From the authors:

I would like to thank S. Teramoto and co-workers for their response to the study my co-workers and I performed on the effects of angiotensin-converting enzyme (ACE) inhibitors on the risk of acquiring pneumonia. Indeed, we could not confirm an association between the use of ACE inhibitors and the risk of pneumonia in a general population. This, however, does not exclude any beneficial effects of ACE inhibitors in specified patient subgroups.

As mentioned in our introduction and by S. Teramoto and co-workers, it is known that patients with a history of stroke do have a higher risk of acquiring pneumonia, which is particularly due to a reduced cough and swallowing reflex [1, 2]. That ACE inhibitors can be beneficial in these patients is already widely reported [3–5]. We aimed to study whether this protective effect can also be extended to the general population. Unfortunately, we were not able to test modification of the association through stroke, as data on stroke history were sparsely available in the database.

Concerning ethnicity, the reason why the association could not be confirmed in the non-Asian participants of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) is still subject to speculation. Genetic differences should certainly be considered. However, OHKUBO *et al.* [4] were unable to show an influence of the ACE I/D polymorphism on the protective

It is not correct to say that "a quarter of centres did not measure height". We reported that: "Out of 42 centres, it was measured in 31, self-reported in five and not recorded whether measured or asked in six." We were being scrupulously honest and in five of the latter it is likely that height was measured. However, study personnel have moved on and definitive information could not be retrieved once we had realised that some centres had not measured height directly. In three of the centres that we classed as "self-reported height", subjects were measured if any doubt was expressed, and gross errors are unlikely to have occurred. Although the over-estimation of height in the study by STEWART *et al.* [3] was nontrivial, that found by NIEDHAMMER *et al.* [4] was <0.5 cm on average. The other reference does not seem relevant.

There was exclusion for non-White ethnicity in only one centre: Melbourne (Australia). Ethnicity was not recorded in any of the other centres, which are listed in table 1 of our paper [1], but this was not raised as an issue.

It was our intention in writing the paper to engender debate and our conclusions are endorsed by S. Stanojevic and co-workers. We believe that current reference curves cannot be guaranteed to give accurate norms of lung health, and that multicentre studies must invest substantially in standardised equipment. However, "statistical models which can adjust for between-centre differences", as advocated by S. Stanojevic and co-workers, do not solve the problem, as differences may be due to genuine variation in health.

S. Chinn, D. Jarvis and P. Burney
Imperial College, London, UK.

REFERENCES

1 Chinn S, Jarvis D, Svanes C, Burney P. Sources of variation in forced expiratory volume in one second and forced vital capacity. *Eur Respir J* 2006; 27: 767–773.
2 Beardsmore CS, Paton J, Thompson JR, *et al.* Standardized lung function laboratories for multicenter trials. *Pediatr Pulmonol* 2006; (In press).
3 Stewart AW, Jackson RT, Ford MA, Beaglehole R. Underestimation of relative weight by use of self-reported height and weight. *Am J Epidemiol* 1987; 125: 122–126.
4 Niedhammer I, Bugel I, Bonefnat S, Goldberg M, Leclerc A. Validity of self-reported weight and height in the French GAZEL cohort. *Int J Obes Relat Metab Disord* 2000; 24: 1111–1118.

DOI: 10.1183/09031936.00125506

Improvement of endothelial function with allopurinol may occur in selected patients with OSA: effect of age and sex

To the Editors:

In a recent issue of the *European Respiratory Journal*, EL SOLH *et al.* [1] demonstrated that allopurinol improves endothelial dysfunction in patients with moderate-to-severe obstructive sleep apnoea (OSA). Because xanthine oxidase inhibition with allopurinol prevents the formation of superoxide free radicals, which leads to better endothelial function, EL SOLH *et al.* [1] speculated that excess activity of xanthine oxidase contributes significantly to vasodilatory impairment in patients with OSA.

The study was a sophisticated prospective, randomised, crossover design, minimising the presence of confounding variables and eliminating inherent individual variations in terms of the generation of free radicals, hyperaemic vascular reactivity or response to treatment. However, a number of arguable assumptions were made in the article of EL SOLH *et al.* [1].

First, endothelial function assessment using hyperaemia-induced flow-mediated vasodilation (FMD) is not always suitable for the assessment of endotheloial function in female obese patients with sleep apnoea. There is a significant relationship between FMD and brachial artery size; therefore, as males have larger arterial diameters, smaller FMD is noted in males [2]. Thus, the changes in FMD in males before and after therapeutic intervention are usually larger than those in females. As the current study did not examine the FMD results of females and males separately, the sex difference may exist in the study. Inversely, the FMD improvement after allopurinol treatment may be clearly indicated, when the males' results were analysed separately from the females' results.

Secondly, FMD of the brachial artery diminished with age [2]. Thus, the age distribution of the study sample affects the results of the FMD alterations after intervention. Because the authors examined subjects aged 29–60 yrs, this wide range of the population may not represent the genuine effects of allopirinol on the FMD in association with oxidative stress due to sleep apnoea itself.

Thirdly, obesity without sleep apnoea also causes endothelial dysfunction [3]. The FMD results should be standardised by the body mass index (BMI) or metabolic variables, when the FMD results are properly assessed. In the study by EL SOLH *et al.* [1], BMI ranged 23–67. We speculate that the FMD results in patients with a normal BMI of 24 might be very different from the extraordinarily obese patients with a BMI of 67. It has also been reported that FMD is associated with systemic inflammation and glucose homeostasis in obese patients, independent of

obesity [4]. Because both obesity and sleep apnoea cause systemic inflammation [5, 6], the association of the inflammatory markers and insulin sensitivity with FMD should be further examined.

Fourthly, the menopause and menstrual cycle significantly affect sleep apnoea and endothelial function [7, 8]. The menopausal transition is significantly associated with an increased likelihood of having sleep-disordered breathing, independent of known confounding factors [7]. FMD increases in menstrual phase, when serum oestradiol level is low and the value is comparable to that in male subjects [8]. Because endothelium-dependent vasodilatation varies during the menstrual cycle, the timing of FMD measurements of female subjects is critical for the precise assessment of allopinol effects.

The incidence of cardiovascular disease is lower in premenopausal females compared with males in the same age group; following menopause, the risk of mortality from cardiovascular disease increases in females [9]. FMD-induced vasodilatation is lower in females aged 55 yrs than those aged 35 yrs [10]. The lower FMD in females aged 55 yrs, compared with those aged 35 yrs, could be due to postmenopausal hormonal changes.

It has been suggested that endothelial function assessment using hyperaemia-induced FMD is adequately reproducible in healthy middle-aged males and females [2]. However, there are many confounding factors including age, sex, obesity, smoking, elevated blood lipids, high blood pressure and systemic inflammation. Thus, FMD measurement may not be an appropriate method for the assessment of the endothelial function in female obese patients with sleep apnoea.

Further study using a large sample size should be carefully assessed by age, obesity and sex differences. The improvement of endothelial function by allopurinol effects on the vascular function in patients with sleep apnoea will then be adequately realised.

S. Teramoto*, H. Kume#, Y. Yamaguchi, H. Yamamoto, Y. Hanaoka, M. Ishii, T. Ishii[1] and Y. Ouchi*
Depts of *Geriatric Medicine and #Urology, Graduate School of Medicine, University of Tokyo, and [1]Dept of Respiratory Medicine, Nippon Medical School, Tokyo, Japan.

REFERENCES

1 El Solh AA, Saliba R, Bosinski T, Grant BJ, Berbary E, Miller N. Allopurinol improves endothelial function in sleep apnoea: a randomised controlled study. *Eur Respir J* 2006; 27: 997–1002.
2 Jensen-Urstad K, Rosfors S. A methodological study of arterial wall function using ultrasound technique. *Clin Physiol* 1997; 17: 557–567.
3 Shechter M, Beigel R, Freimark D, Matetzky S, Feinberg MS. Short-term sibutramine therapy is associated with weight loss and improved endothelial function in obese patients with coronary artery disease. *Am J Cardiol* 2006; 97: 1650–1653.
4 Williams IL, Chowienczyk PJ, Wheatcroft SB, *et al.* Endothelial function and weight loss in obese humans. *Obes Surg* 2005; 15: 1055–1060.
5 Teramoto S, Yamamoto H, Yamaguchi Y, Namba R, Ouchi Y. Obstructive sleep apnea causes systemic inflammation and metabolic syndrome. *Chest* 2005; 127: 1074–1075.
6 Teramoto S, Yamamoto H, Ouchi Y. Increased C-reactive protein and increased plasma interleukin-6 may synergistically affect the progression of coronary atherosclerosis in obstructive sleep apnea syndrome. *Circulation* 2003; 107: E40.
7 Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 2003; 167: 1181–1185.
8 Hashimoto M, Akishita M, Eto M, *et al.* Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation* 1995; 92: 3431–3435.
9 Jensen-Urstad K, Johansson J. Gender difference in age-related changes in vascular function. *J Intern Med* 2001; 250: 29–36.
10 Perregaux D, Chaudhuri A, Mohanty P, *et al.* Effect of gender differences and estrogen replacement therapy on vascular reactivity. *Metabolism* 1999; 48: 227–232.

DOI: 10.1183/09031936.00104806

From the authors:

We thank S. Teramoto and colleagues for their comments on our recent article [1]. We agree that changes in flow-mediated vasodilation (FMD) are influenced by a variety of intrinsic and extrinsic factors such as endogenous, environmental and familial factors [2], of which age, sex and body mass index (BMI) are the classic examples. Indeed, analysis by sex of our data showed that male participants had larger arterial diameters and smaller FMD at baseline compared with female subjects ($6.1 \pm 2.6\%$ in males and $8.0 \pm 1.7\%$ in females). However, in contrast to the remarks of S. Teramoto and colleagues, the median FMD improvement after allopurinol treatment was larger in women (4.3%; 95% confidence interval (CI) 1.0–7.6%) than in their male counterparts (3.4%; 95% CI 1.5–5.4%); although not to a statistically significant degree. Correlation analyses also revealed no significant relationship between changes in FMD (before and after treatment) and either age ($r=0.2$; $p=0.5$) or BMI ($r=0.06$; $p=0.85$). We acknowledge that the power of the study is too small to detect any significant difference and we alluded to this limitation in the manuscript. As pointed out by S. Teramoto and colleagues, FMD is influenced by circulating levels of oestrogen and progesterone, and by the phase of the subject's menstrual cycle [3]. This variability would have been significant had our female participants been of a child-bearing age; however, only one of the four female subjects fell into that category. Finally, we concur with S. Teramoto and colleagues that a larger sample size would be needed to confirm our findings. Now that our randomised clinical trial has shown potential efficacy, we hope it stimulates further long-term research studies to determine the role and side-effects of allopurinol in the treatment of obstructive sleep apnoea-related endothelial dysfunction.

Respirology (2006) **11**, 669–670 doi: 10.1111/j.1400-1843.2006.00914.x

LETTER TO THE EDITOR

Reference values for 6-min walk distance in Asian adults may not be different from that of Caucasian adults

SHINJI TERAMOTO,[1] HARUKI KUME,[2] TAKEO ISHII,[1] HIROSHI YAMAMOTO,[1] YASUHIRO YAMAGUCHI,[1] MASAKI ISHII,[1] YOKO HANAOKA[1] AND YASUYOSHI OUCHI[1]

Departments of [1]Geriatric Medicine and [2]Urology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

In a recent issue of *Respirology*, Poh and coworkers demonstrated that the 6-min walk distance (6MWD) in healthy Singaporean adults cannot be predicted using the reference equations derived from Caucasian populations. Published equations derived from Caucasian subjects overestimated 6MWD in Singaporean Chinese.[1] This is very important research that will assist in the interpretation of 6MWD in Asian patients with cardiopulmonary disease, as the 6MWD reference values have mostly been published for healthy Caucasian subjects. We agree with the authors that an adequate reference value for Asian peoples is necessary for assessing physical function in middle-aged and older patients with COPD.

However, the authors did not fully review the published studies on the 6MWD reference values in Japanese people.[2,3] The 10-min walk distance (10MWD) test was developed by the Japanese Research Group for Chronic Respiratory Failure to determine the 10MWD reference values for healthy male and female Japanese adults.[2] From these values, the mean 6MWD value for healthy Japanese men and women are approximately 572 m and 504 m, respectively. One hundred and fifty-eight healthy subjects were also evaluated for 6MWD using three walking tests with a standardized protocol. Mean values of 6MWD for healthy male and female Japanese adults are 624 m and 541 m, respectively. These data are not all that different from the authors' data or from Enright and Sherrill's data.[4] As such we do not think that the reference values show a big difference between Asian and Caucasian populations (Table 1).

Moreover, there are considerable variations of 6MWD references even in the Caucasian population. Enright and coworkers have reported that the mean 6MWD in a healthy subset of participants was 367 m for elderly women and 400 m for elderly men using a sample from the Cardiovascular Health Study.[5] The equations predict distances of 430 m and 464 m for a 67-year-old white woman and man of average height and weight, respectively. This reference equation gives predicted (mean) 6MWDs that are substantially lower than those published by previous investigators on Caucasian populations.[6–8]

Troosters and coworkers have reported that the mean values for 6MWD for healthy elderly men and women are 673 m and 589 m, respectively.[6] A study of 290 healthy adults in Tucson, USA predicts distances of 466 m and 544 m for women and men, respectively.[4] Rikli and Jones have examined 6MWD in 7183 older adults. Their predicted values are approximately 50% greater than Enright's data.[7]

The reasons why these reference equations are so different in healthy volunteers in either Caucasian or Asians are not clear. Differences in participant recruitment and test instructions may account for the variations among different studies. The American Thoracic Society has published detailed guidelines for 6MWD procedures that should be followed by investigators studying carefully selected healthy people.[8] It has been also cautioned that the reference equations obtained from this model explained only 20% of the variation in 6MWD.[5] According to the American Thoracic Society review of previously published 6MWD studies, the increases due to the learning effect ranged from a mean of zero to 17%. Performance usually reaches a plateau after two tests performed within a week. The reproducibility results from one study of 112 patients with stable, severe COPD suggest that an improvement of >70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant.[9]

Considered together with the data between test variation and intra-test variation there is no definite reference value of 6MWD in either Caucasian or Asians.

The 6MWD testing should be useful for measuring changes in functional status in the clinical setting, but considerable caution is needed when using currently available reference equations to determine if a given

Correspondence: Shinji Teramoto, Department of Geriatric Medicine, The University of Tokyo Hospital, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-8655, Japan.
Email: shinjit-tky@umin.ac.jp

Table 1 The mean value of 6-min walking distance in male and female Asians and Caucasians

Author (ref. no)	Poh (1)	Takishima (2)	Teramoto (3)	Enright (4)	Enright (5)	Troosters (6)	Rikli (7)
Race	Asian	Asian	Asian	Caucasian	Caucasian	Caucasian	Caucasian
Mean age (years)	61	65	65	60	67	65	
Male							
6MWD (m)	580	572	624	576	464	673	689
Subjects (*n*)	16	34	80	117	715	54	7183†
Female							
6MWD (m)	538	504	541	494	430	589	624
Subjects (*n*)	19	38	78	173	1094	54	

†Total number of subjects of male and female.
6MWD, 6-min walking distance.

patient's 6MWD is normal or low. Expected values should be adjusted for the patient's age, gender, height and weight.

In summary, there is considerable variation in the normal values of 6MWD even in healthy people. The published reference equations may help in the assessment of functional status in patients with cardiopulmonary diseases, but not necessarily determine the absolute exercise capacity in these patients. The variation in 6MWD is affected by a number of factors that are not solely due to race and ethnicity.

REFERENCES

1 Poh H, Eastwood PR, Cecins NM, Ho KT, Jenkins SC. Six-minute walk distance in healthy Singaporean adults cannot be predicted using reference equations derived from Caucasian populations. *Respirology* 2006; **11**: 211–16.

2 Takishima T. *Exercise Testing*. Annual Report of Japanese Respiratory Failure Research Working Group. Ministry of Health and Welfare of Japan, Tokyo, 1986; 8–13.

3 Teramoto S, Ohga E, Ishii T, Yamaguchi Y, Yamamoto H, Mastsuse T. Reference value of six-minute walking distance in healthy middle-aged and older subjects. *Eur. Respir. J.* 2000; **15**: 1132–3.

4 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am. J. Respir. Crit. Care Med.* 1998; **158**: 1384–7.

5 Enright PL, McBurnie MA, Bittner V *et al.* Cardiovascular Health Study. The 6-min walk test: a quick measure of functional status in elderly adults. *Chest* 2003; **123**: 387–98.

6 Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur. Respir. J.* 1999; **14**: 270–4.

7 Rikli RE, Jones CJ. Functional fitness normative scores for community-residing older adults, ages 60–94. *J. Aging Phys. Act.* 1999; **7**: 162–81.

8 American Thoracic Society. Guidelines for the six minute walk test. *Am. J. Respir. Crit. Care Med.* 2002; **166**: 111–17.

9 Redelmeier DA, Bayoumi AM, Goldstein RS *et al.* Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am. J. Respir. Crit. Care Med.* 1997; **155**: 1278–82.

complaints were diagnosed with bronchitis. This resulted in a more frequent use of inhaled steroids and bronchodilators in Dutch children as compared with German children [2].

We cannot exclude the fact that a possible geographically heterogeneous worldwide *Chlamydia pneumoniae* pandemic could contribute to changes in asthma prevalences in different countries. However, it seems unlikely to us that this would be the sole explanation, as not all asthmatics (established or newly diagnosed) have *C. pneumoniae* present in bronchoalveolar lavage fluid. Moreover, the widespread use of (macrolide) antibiotics has not prevented a clear increase in asthma prevalence. On the contrary, it seems that a decrease in hospitalisation and mortality is strongly associated with an increase in the use of inhaled steroids [3], and there is no indication that this is associated with the use of antibiotics.

However, it is certainly worthwhile to pay attention to the so-called Chlamydia-asthma theory proposed by D.L. Hahn and to investigate the presence of *Chlamydia pneumoniae* or other infectious organisms in new asthma patients.

C.P. van Schayck, M. Mommers and E.D. Dompeling
Care and Public Health Research Institute (CAPHRI), University Maastricht, Maastricht, The Netherlands.

REFERENCES

1 van Schayck CP, van der Heijden FM, van den Boom G, Tirimanna PRS, van Herwaarden CL. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. *Thorax* 2000; 55: 562–565.
2 Mommers M, Swaen GMH, Weishoff-Houben M, Dott W, van Schayck CP. Differences in asthma diagnosis and medication use in children living in Germany and the Netherlands. *Prim Care Respir J* 2005; 14: 31–37.
3 Haahtela T, Klaukka T, Koskela K, Erhola M, Laitinen LA. Asthma programme in Finland: a community problem needs community solutions. *Thorax* 2001; 56: 806–814.

DOI: 10.1183/09031936.06.00129205

Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patients

To the Editors:

In a recent issue of the *European Respiratory Journal*, KOSTADIMA *et al.* [1] reported that early gastrostomy is associated with a lower frequency of ventilator-associated pneumonia (VAP) compared with nasogastric tube (NGT) feeding in patients who are mechanically ventilated due to stroke or head injury. Since VAP is the most frequent and serious intensive care unit (ICU)-acquired infection among patients undergoing mechanical ventilation, and is associated with a 20–30% increase in the risk of death, the preventive strategy for VAP in mechanically ventilated patients is important to reduce the length of an ICU stay and overall mortality [2].

Although the classic theories, including the gastropulmonary hypothesis, are important to understand the mechanisms of VAP, the recent advancement of the pathophysiology of nosocomial pneumonia and aspiration pneumonia are not fully discussed in the paper by KOSTADIMA *et al.* [1].

There is growing evidence that oropharyngeal dysphagia plays a critical role in aspiration pneumonia and VAP in mechanically ventilated patients [3, 4]. Brain injury, severe stroke and unconsciousness, due to sedatives and hypnotics, disturb the swallowing reflex. This results in the development of aspiration pneumonia in humans and animals [5]. However, nosocomial pneumonia and aspiration pneumonia are prevented by the improvement of the swallowing reflex after administration of angiotensin-converting enzyme (ACE) inhibitors [6]. The elevated levels of bradykinin and substance P by ACE inhibitors play a role in setting the threshold for the cough and swallowing reflex in humans, resulting in the reduction of occurrence of pneumonia. Although KOSTADIMA *et al.* [1] speculated about the underlying mechanisms of risk of VAP in the patients with NGT feeding, they did not assess the swallowing reflex and cough reflex. We have developed a novel diagnostic test for the risk of aspiration pneumonia [7, 8]. The simple swallowing provocation test can be applied for all the ventilated patients as it is very easy and can be performed on bedridden patients without requiring their cooperation. The assessment of the swallowing reflex is the clue to the underlying mechanisms of VAP in critically ill patients. As it has been suggested that nosocomial maxillary sinusitis increases the occurrence of VAP, microaspiration of oropharyngeal materials, including maxillary sinus, is a significant cause of VAP [9].

NGT feeding is known to be a significant cause of aspiration pneumonia in stroke patients [10]. Since the NGT bypasses the small amount of gastric contents through to the oropharynx, the materials can be easily aspirated into lower airways in dysphagic patients with stroke. The mechanism is not related to the percutaneous endoscopic gastrostomy (PEG). This evidence supports the fact that NGT feeding, but not PEG, is a significant cause of VAP in critically ill patients. Although feeding *via* PEG is a very straightforward way to reduce aspiration and aspiration-associated pneumonia, the improvement of the swallowing reflex must be a fundamental approach to reduce VAP in patients. As the PEG procedure using gastroscopic fibre may also be a risk for aspiration in unconscious patients, the indication of early gastrostomy for

the patients should be very carefully assessed. The PEG feeding patients with dysphagia may be suffering from aspiration pneumonia [11].

Considered together, we believe that the prevention of aspiration by using oral care, angiotensin-converting enzyme inhibitors and swallowing rehabilitation may be an alternative approach in reducing the risk of ventilator-associated pneumonia in patients.

S. Teramoto*, T. Ishii#, H. Yamamoto*, Y. Yamaguchi* and Y. Ouchi*

*Dept of Geriatric Medicine, University of Tokyo, Tokyo, and #Pulmonary Medicine, Yokohama City University, Yokohama, Japan.

REFERENCES

1 Kostadima E, Kaditis AG, Alexopoulos EI, Zakynthinos E, Sfyras D. Early gastrostomy reduces the rate of ventilator-associated pneumonia in stroke or head injury patients. *Eur Respir J* 2005; 26: 106–111.
2 Povoa P, Coelho L, Almeida E, *et al.* C-reactive protein as a marker of ventilator-associated pneumonia resolution: a pilot study. *Eur Respir J* 2005; 25: 804–812.
3 Teramoto S, Yamamoto H, Yamaguchi Y, Kawaguchi H, Ouchi Y. Nosocomial infections in adult intensive-care units. *Lancet* 2003; 362: 493.
4 Teramoto S. The causes of aspiration pneumonia in mechanically ventilated patients: a possible pathological link with upper airway bacterial colonization. *Br J Anaesth* 2000; 84: 694.
5 Teramoto S, Matsuse T, Ishii T, Matsui H, Fukuchi Y, Ouchi Y. Investigation of age on the aspiration using LacZ gene transduction of adenovirus vectors. *Am J Respir Crit Care Med* 1998; 158: 1914–1919.
6 Teramoto S, Ouchi Y. ACE inhibitors and prevention of aspiration pneumonia in elderly hypertensives. *Lancet* 1999; 353: 843.
7 Teramoto S, Yamamoto H, Yamaguchi Y, Ouchi Y, Matsuse T. A novel diagnostic test for the risk of aspiration pneumonia in the elderly. *Chest* 2004; 125: 801–802.
8 Teramoto S, Matsuse T, Fukuchi Y, Ouchi Y. Simple two-step swallowing provocation test for elderly patients with aspiration pneumonia. *Lancet* 1999; 353: 1243.
9 Holzapfel L, Chastang C, Demingeon G, Bohe J, Piralla B, Coupry A. A randomized study assessing the systematic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Influence of nosocomial maxillary sinusitis on the occurrence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1999; 159: 695–701.
10 Ferrer M, Bauer TT, Torres A, Hernandez C, Piera C. Effect of nasogastric tube size on gastroesophageal reflux and microaspiration in intubated patients. *Ann Intern Med* 1999; 130: 991–994.
11 Carnes ML, Sabol DA, DeLegge M. Does the presence of esophagitis prior to PEG placement increase the risk for aspiration pneumonia? *Dig Dis Sci* 2004; 49: 1798–1802.

DOI: 10.1183/09031936.06.00113405

From the authors:

We read with interest the letter from S. Teramoto and coworkers regarding the role of oropharyngeal dysphagia in the pathogenesis of ventilator-associated pneumonia (VAP). The presence of a nasogastric tube has been identified as an independent risk factor for VAP, mainly because of gastro-oesophageal reflux and aspiration [1, 2]. Aspiration is probably due to loss of anatomical integrity of the lower oesophageal sphincter, increased frequency of transient sphincter relaxation and oropharyngeal dysphagia *via* desensitisation of the pharyngoglottal adduction reflex [3, 4].

We speculate that the advantage of performing an early gastrostomy is the possibility of avoiding dysfunction of lower oesophageal sphincter due to the presence of a nasogastric tube [5]. JOHNSON *et al.* [6] have demonstrated an increase in lower oesophageal sphincter pressure following performance of percutaneous endoscopic gastrostomy and a decrease in gastro-oesophageal reflux score. Prevention of oropharyngeal dysphagia induced by the nasogastric tube may be another mechanism in reducing the risk of aspiration.

Of note, percutaneous endoscopic gastrostomy does not eliminate gastro-oesophageal reflux, mainly in patients with a pre-existing nasogastric tube [7]. For this reason, we selected the performance of early gastrostomy in our study. In a recent report, MCCLAVE *et al.* [8] found a decrease in the incidence of regurgitation in intensive care unit patients with early gastrostomy compared with those with a nasogastric tube.

E. Kostadima, A. Kaditis, E. Alexopoulos, E. Zakynthinos and D. Sfyras

University of Thessaly School of Medicine and Larissa University Hospital, Larissa, Greece.

REFERENCES

1 Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of the CDC and the Health-care Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004; 53: 1–36.
2 Chastre J, Fagon J-Y. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165: 867–903.
3 Gomes GF, Pisani JC, Macedo ED, Campos AC. The nasogastric feeding tube as a risk factor for aspiration and aspiration pneumonia. *Curr Opin Clin Nutr Metab Care* 2003; 6: 327–333.
4 Nind G, Chen W, Protheroe R, *et al.* Mechanisms of gastroesophageal reflux in critically ill mechanically ventilated patients. *Gastroenterology* 2005; 128: 600–606.
5 Kostadima E, Kaditis AG, Alexopoulos EI, Zakynthinos E, Sfyras D. Early gastrostomy reduces the rate of ventilator-associated pneumonia in stroke or head injury patients: a preliminary study. *Eur Respir J* 2005; 26: 106–111.
6 Johnson DA, Hacker JF, Benjamin SB, *et al.* Percutaneous endoscopic gastrostomy effects on gastroesophageal reflux

today, according to data from the United Network for Organ Sharing.

Daniel C. Brennan, M.D.
Washington University School of Medicine
St. Louis, MO 63110
dbrennan@wustl.edu

Paula Buchanan, M.P.H.
Mark A. Schnitzler, Ph.D.
Saint Louis University Center for Outcomes Research
St. Louis, MO 63104

Dr. Buchanan reports receiving a grant from the American Society of Transplantation. Dr. Schnitzler reports receiving consulting fees from Novartis Pharma, lecture fees from Genzyme, and grant support from Genzyme, Novartis Pharma, Astellas, and TransMedics.

1. Humar A, Johnson EM, Payne WD, et al. Effect of initial slow graft function on renal allograft rejection and survival. Clin Transplant 1997;11:623-7.

DHEA and Testosterone in the Elderly

TO THE EDITOR: In their report on the effects of dehydroepiandrosterone (DHEA) and testosterone when used as antiaging supplements, Nair et al. (Oct. 19 issue)[1] conclude that low-dose testosterone replacement in elderly men has no "physiologically relevant beneficial effects on body composition, physical performance, [or] insulin sensitivity." However, this conclusion is premature, since the testosterone replacement administered failed to achieve physiologic testosterone levels throughout the study period (Fig. 2 of the article). Moreover, despite the marginal increase in testosterone levels achieved, improvements in fat-free mass, fasting insulin levels, and bone mineral density were observed.

Other studies of testosterone replacement, including those cited to support the authors' conclusions,[2] have shown a decrease in fat mass (12.5%) and an increase in lean mass (4%) when physiologic testosterone levels are achieved in elderly men. Studies of standard doses of testosterone in the treatment of testicular failure[3] have shown additional positive effects on muscle strength, physical performance,[4] and bone mineral density.[5] Large, long-term trials are clearly needed to assess the risks and benefits of testosterone replacement in elderly men, and caution should be exercised regarding the treatment of andropause in men. However, the serum testosterone level achieved should be within the normal range to assess the effect on outcome measures adequately.

Stephanie T. Page, M.D., Ph.D.
University of Washington
Seattle, WA 98195
page@u.washington.edu

Alvin M. Matsumoto, M.D.
Veterans Affairs Puget Sound Health Care System
Seattle, WA 98108

William J. Bremner, M.D., Ph.D.
University of Washington
Seattle, WA 98195

1. Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. N Engl J Med 2006; 355:1647-59.
2. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999;84:2647-53.
3. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995-2010. [Erratum, J Clin Endocrinol Metab 2006;91:2688.]
4. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005;90:1502-10.
5. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004;89:503-10.

TO THE EDITOR: The findings of Nair et al. cannot be generalized, because the study included relatively healthy subjects. To investigate the benefits and risks of androgen-replacement therapy, it is essential to make judicious choices regarding the subjects to be included in the research. In this study, the average baseline scores for the quality of life (on the Health Status Questionnaire [HSQ] and the Medical Outcomes Study 36-item Short-Form General Health Survey [SF-36]) of all the subjects were above 50 for both the physical and mental components. The average score on both instruments in the general U.S. population is 50.[1] The high scores of these subjects suggest that the

study included healthier elderly persons than those who would be representative of the general elderly population.

Moreover, physical exercise is expected to improve and maintain physical functioning in older people.[2,3] Not only androgen administration but also well-designed physical training is needed to improve the physical performance of elderly persons. The androgen level might be a mediator that could be elevated by exercise training, which would then increase physical performance. The administration of androgen in the absence of exercise may not be enough to improve physical performance among the elderly.

Mitsuko Yasuda, M.D., Ph.D.
Shigeo Horie, M.D.
Teikyo University
Tokyo 173-8605, Japan
shorie@med.teikyo-u.ac.jp

1. van Hooren SA, van Boxtel MPJ, Valentijn SAM, Bosma H, Ponds RW, Jolles J. Influence of cognitive functioning on functional status in an older population: 3- and 6-year follow-up of the Maastricht Aging Study. Int J Geriatr Psychiatry 2005;20:883-8.
2. Mian OS, Thom JM, Ardigo LP, et al. Effect of a 12-month physical conditioning programme on the metabolic cost of walking in healthy older adults. Eur J Appl Physiol (in press).
3. Tsuji I, Tamagawa A, Nagatomi R, et al. Randomized controlled trial of exercise training for older people (Sendai Silver Center Trial: SSCT): study design and primary outcome. J Epidemiol 2000;10:55-64.

TO THE EDITOR: DHEA was banned in 1985 by the Food and Drug Administration because clinical safety and efficacy data were lacking to support claims of cures for cardiovascular disease and aging. After the passage of the Dietary Supplement Health and Education Act in 1994, DHEA, which had not previously been labeled as a drug, again became available. It is amazing that a previously banned substance can now be sold directly to the public, and it speaks to the lack of oversight and protection afforded by the Dietary Supplement Health and Education Act.

Hormones have long been equated with youth by the public and are thus a favorite type of substance for marketing by the antiaging industry.[1] As one substance falls out of favor, another quickly replaces it: the miracle of melatonin[2] was replaced by the superhormone promise[3] of DHEA. The heir apparent now seems to be growth hormone, which, paradoxically, is illegal to distribute for antiaging uses but constitutes a market estimated at more than $600 million per year in the United States alone.[4]

Thomas T. Perls, M.D.
Boston University Medical Center
Boston, MA 02118
thperls@bu.edu

1. U.S. Senate Special Committee on Aging. Swindlers, hucksters and snake oil salesman: hype and hope marketing anti-aging products to seniors. 107th Congress, 1st session. Washington, DC: Government Printing Office, September 10, 2001.
2. Pierpaoli W, Regelson W. The melatonin miracle: nature's age-reversing, disease-fighting, sex-enhancing hormone. New York: Pocket Books, 1995.
3. Regelson W, Colman C. The superhormone promise. New York: Pocket Books, 1996.
4. Perls TT, Reisman NR, Olshansky SJ. Provision or distribution of growth hormone for "antiaging": clinical and legal issues. JAMA 2005;294:2086-90.

TO THE EDITOR: The study by Nair et al. may be misleading. One problem arises from the age of the persons involved in the study. Women older than 60 years rarely have postmenopausal symptoms. In the absence of symptoms, how are the beneficial effects of treatment on the quality of life to be demonstrated? Similarly, one may question the use of testosterone in men older than 60 years.

The principal problem, however, is that Nair et al. treated laboratory values (low values of DHEA and testosterone), not — as is usual medical practice — symptoms. To return to the example of postmenopausal care for women older than 60 years, such an approach could be equated with indiscriminately treating unselected postmenopausal women, all of whom, of course, have low estradiol levels, with estrogen replacement, whether or not they are symptomatic. Whether such an unselected approach to treatment would ever reveal clinical benefits regarding the quality of life is questionable.

That DHEA can indeed positively affect certain physiological processes of aging has been suggested with regard to ovarian function.[1-3] Thus, nothing in the study by Nair et al. contradicts the value of further investigation of DHEA in specific conditions of aging.

Norbert Gleicher, M.D.
David Barad, M.D.
Center for Human Reproduction
New York, NY 10021
ngleicher@thechr.com

The prevalence of depressive symptoms and their variables among frail aging men in New York City's Personal Care Services

Mitsuko Yasuda[1], M.D., Ph.D, M.P.H., Shigeo Horie[1], M.D., Steven M. Albert[2], Ph.D, M.Sc., Bridget Simone[3], Dr.P.H.

[1] Department of Urology, Teikyo University; [2] Department of Sociomedical Sciences, Columbia University; [2] Department of Behavioral and Community Health Sciences, University of Pittsburgh; [3] New York City Human Resources Administration

Correspondence:
Mitsuko Yasuda, M.D., Ph.D., M.P.H
Department of Urology, Teikyo University School of Medicine
Address: 2-11-1 Kaga, Itabashi, Tokyo 173-8606 Japan
telephone number: +81-3-3964-2497
facsimile number: +81-3-3964-8934
myasuda@med.teikyo-u.ac.jp

ABSTRACT

Background

New York City's Personal Care Service Program provides service-rich assistance to the frail elderly who would not be able to live at home without such support. Depressive symptoms are common among elderly people. We conducted a cross-sectional study in order to investigate the prevalence of depressive symptoms and to determine variables among frail elderly men receiving personal care services.

Methods

Data were collected from administrative data available in the Human Resources Administration's computer system. Two hundred men aged 65 or older were randomly selected. We defined depressive symptoms by tracking the recording of depressed mood in the data system. We examined statistical differences in a variety of indicators between elderly men with- and without depressive symptoms. Multiple logistic regression analysis was performed to determine independent variables of depressive symptoms.

Results

10.5 % of all cases had depressive symptoms. In multiple logistic regression models, the duration of services and hearing impairment were independently associated with depressive symptoms among frail elderly men.

Conclusion

The results of this study indicate the low prevalence of depressive symptoms among frail elderly men compared with previous studies. The duration of services was a protective factor of depressive symptoms. That is, personal care services provided a high quality of ADL support that keeps frail elderly men living at home as long as possible. The significance of hearing impairment that can induce social isolation also needs to be stressed as an indicator of depressive symptoms.

INTRODUCTION

Personal care services provide individuals in need of assistance with ADL and household support, which are prerequisite to health and safety in their own homes. While personal care services — the Medicaid Optional Program — have been adopted by 26 states, 15 states have set limits on the hours of services made available and 10 states have set cost caps[1,2]. New York is the only state that has not placed limits on service benefits. The program currently serves approximately 53,000 clients daily through 969 vendors. The high intensity of services, including 24-hour day personal assistance care, allows individuals who are medically eligible for nursing home placement to live in their homes. Elderly clients are more likely to be disabled than older community residents who do not participate in personal care services[3]. Depressive symptoms affected 8% to 20% of elderly individuals in the community[4]. Older adults with medical illness, somatic impairment and social isolation are more likely to be depressed[5]. We hypothesized that medical illness, physical impairment, and social isolation would be associated with administrative reports of depressive symptoms in elderly men. We sought to investigate the prevalence of depressive symptoms among the men aged 65 or older who received personal care services from New York City for more than one year, and to examine the relationships between depressive symptoms and a variety of indicators, such as age, medical and functional indicators, use of personal care services and caregiver support, in order to determine the variables of depressive symptoms. We used administrative data, such as Medicaid administrative claims, medical requests (M11Q) and social assessments (M11S).

METHODS

Data collection

To receive personal care services, people need to submit a medical request form (M11Q) filled out by their physicians, a social assessment (M11S) performed by case workers, and a nurse's assessment (M27r) to New York City's Human Resources Administration (HRA). These data are collected at nine Community Alternative System

Agency borough offices (CASA offices) that serve the clients in their geographic areas and are stored in the centralized computer database.

Subjects

Subjects were randomly drawn from the centralized computer database. In addition, we limited the subjects to those who were men aged 65 or older and to those who had been receiving services for at least one year. Finally, we excluded clients who received only "level 1" service (housekeeper services), since they were not receiving personal assistance care. Information on 200 elderly men was included in the this study.

Definition of depressive symptoms

According to DSM-_[6], major depression is defined as the presence of five or more out of nine symptoms, such as depressed mood, loss of interest or pleasure, eating disturbance, sleep disturbance, psychomotor agitation, fatigue, a feeling of worthlessness or guilt, poor concentration and suicidal ideation during the same two week period. At least one of the symptoms is either depressed mood or loss of interest/pleasure. This level of either specificity or sensitivity was unavailable in the administrative data. In the absence of the full set of 9 DSM-IV, the item of depressive mood in the medical report was used as an indicator of depressive symptoms, as depressive mood and anhedonia are two gateway symptoms, one of which is needed to constitute a depressive disorder.

Sociodemographic characteristics

Sociodemographic variables included age, living situation (living alone, living with caregivers or with non-caregivers) and caregiving support.

Administrative claims

The number of service hours that the clients were receiving on July 2005 was assessed as the number of billed service hours. For duration of home care services, we retrieved all service periods of home care services from the initial authorization to July 2005.

Medical status

Overall medical co-morbidity was indicated by the total number of ICD-9 diagnosis.

Cognitive impairment

Three items of mental status indicators in the M11Q, such as disorientation to place/time, short-term memory impairment, and impaired judgment were used to identify cognitive impairment. If the clients had at least one of three impairments, they were categorized as having "dementia". The clients with none of three impairments

were categorized as "no impairment".

ADL status

ADL status was based on the number of needs in six activities of daily living.

Functional Status

Sensory impairment (speech impairment, visual impairment and hearing impairment), muscular impairment (dominant hand, upper extremities, lower extremities), and bladder incontinence were assessed to examine if these impairments were associated with depressive symptoms.

Caregiver support

Data related to caregiver support were obtained from a social assessment (M11S). We investigated whether the clients lived with- or without informal caregivers.

STATISTICAL ANALYSIS

The data were analyzed utilizing an SPSS 13.0 statistics package. Statistical differences in each variable between the clients with and without depressed mood were examined by a t-test or chi-square test. The level of significance was set at $p<0.05$ (two-sided). In order to evaluate the role played by depressive symptoms as indicators, multiple logistic regression analysis was performed considering depressive symptoms as a dependent variable.

RESULTS

The characteristics of groups indicated with- and without depressive symptoms are shown in Table 1. 10.5% of the subjects were defined to have depressive symptoms considering the presence of depressed mood. Differences did not achieve a statistical significance in age, intensity of services (hours of services per week), number of ADL disabilities, number of comorbid conditions, and cognitive impairment. For functional status, elderly men with depressive symptoms were significantly more likely to be visually impaired (66.7 % vs. 44.9%, p=0.49,n=200, df=1) and have hearing impairment (76.2% vs. 43.3%, p=0.004,n=200, df=1), upper extremities impairment (70.0 vs. 43.8%, p=0.026, n=200, df=1) and bladder incontinence (65.0% vs. 38.8%, p=0.024,n=200, df=1). The two groups did not differ in either living situation or caregiver support. Even though the difference did not achieve statistical significance, it should be noted that elderly men without depressive symptoms were more likely to live alone (59.3% vs. 44.4%, p=0.687, n=200, df=2).

The associations between independent variables and depressive symptoms based on logistic regression analysis are shown in Table 2. The probability of having depressive symptoms decreases with duration of services (OR=0.86, 95% CI: 0.75-0.97),

and increased with hearing impairment (OR=3.67, 95% CI: 1.18-11.84).

DISCUSSION

Estimates of depressive symptoms in community-dwelling elderly range from 8% to 20% [4]. Older adults with medical illness, somatic impairment and social isolation are more likely to be depressed [5]. About 30% to 50% of nursing home residents and about 26% to 44% of homebound elderly adults had depressive symptoms [7,8]. In our study, despite the level of their disabilities, the prevalence of depressive symptoms among elderly men was low (10.5%). Instead of administration in nursing homes, living at home as long as possible with home care services, frail elderly men could maintain their self-esteem and internal locus of control that would be associated with depression[9].

The high prevalence of hearing impairment among elderly men in our study (46.7%) was consistent with previous studies whose prevalence ranged from 21% to 72 % [10,11,12]. Hearing impairment leads to withdrawal from social activities and isolation. Previous studies suggested that hearing impairment in elderly people has a significant correlation with depression[13-17]. Our study was consistent with these findings. People with hearing impairment were 3.67 times as likely to have depressive symptoms as people without hearing impairment (p=0.03). Hearing impairment needs to be stressed as an indicator of social isolation and the presence of depressive symptoms. Regular audiological check-ups to detect occult hearing impairment, and to provide mental health screening to people with hearing loss, need to be considered.

For every additional year to the mean duration, elderly male clients were 14% less likely to be depressed. p=0.018 (CI: 0.75, 0.97). It suggested that personal care services programs can mitigate the development of depression by keeping clients at their homes where they prefer to be the most for as long as they can.

In order to improve the quality of personal care services, it is vital to develop interventions to screen and assess depressive symptoms among elderly clients who are at risk and to provide access to specialist mental health services. Intervention focused on elderly men with hearing impairment may be cost-effective, since they are at a high risk of depressive symptoms in later life. We would stress that among various indicators in administrative data, hearing impairment is important as an indicator of social isolation and the presence of depressive symptoms.

References

1) Lebanc AL, Tonner CM, Harrington C. State Medicaid programs offering personal care services. *Health Care Financing Review* 2001; 22:155-173.
2) Weiner JM,Tilly J, Alecxih LMB. Home and community-based services in seven states. *Health care Financing Review* 2002; 23: 89-114.
3) Steven MA, Simone B, Brassard A, Stern Y, Mayeux R. Medicaid Home Care Services and Survival in New York City. *The Gerontologist* 2005; 45(5):609-616
4) Lebowitz BD. Depression and treatment of depression in late life: an overview of the NIH consensus statement. *Am J Geriatr Psychiatry* 1996; 4(suppl 1): 53-56.
5) Ciechanowski P, Wagner E, Schmaling K, Schwarts S, Williams B, Diehr P,et al. Community-Integrated Home-Based Depression Treatment in Older Adults. *JAMA* 2004; 291(13):1569-1577
6) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association, 2004
7) Kurlowicz LH, Evans LK, Strumpf NE, Maislin G. A psychometric evaluation of the Cornell Scale for Depression Dementia In a Frail, Nursing home population. *Am J Geriatr Psychiatry* 2002; 10 (5): 600-608.
8) Loughlin, A. Depression and Social report. *Journal of Gerontological Nursing* 2004; 30(5):11-15.
9) Brarucha AJ, Dew MA, Miller MD. Psychotherapy in long-term care: A view. *J am Med Dir Assoc*. 2006; 7(9):568-80
10) Morre AA, Siu AL. Screening for common problems in ambulatory elderly: Clinical confirmation of a screening instrument. *Am J Med* 1996;100:438-443.
11) Feller BA. *Prevalence of selected impairments*. 1977 Vital and Health Statistics Department of Health and Human Services. National Center for Health Statistics. Washington, US Government Printing Office, 1981: DHHS Publ No (PHS) 81-1562, Series 10, No 134..1981
12) Gates GA, Cooper JC, Kannel WB, Miller NJ. Hearing in the elderly: Framingham cohort 1983-1985. *Ear Hear* 1990;11:247-256.
13) Cacciatore F, Napoli C, Abete P, Marciano E, Triassi M, Rengo F. Quality of Life Determinants and Hearing Function in and Elderly Population:Osservatorio Geriatrico Campano Study Group. *Gerontology* 1999; 45: 323-328.
14) Naramura H, Nakanishi N, Tatara K, Ishikawa M, Shiraishi H, Yamamoto A. Physical and mental correlates of hearing impairment in the elderly in Japan. *Audiology* 1999; 38:24-29.

15) Uhlmann RF, Larson EB., Rees TS., Koepsell TD., Duckert LG. Relationship of hearing impairment to dementia and cognitive dysfunction in older adults. *JAMA* 1989; 261:1916-1919.

16) Tambs K. Moderate effects of hearing loss on mental health and subjective well-being: Results from the nord-Trondelag hearing loss study. *Psychosomatic Medicine* 2004; 66(5): 776-782.

17) Strawbridge WJ., Wallhagen MI, Shema SJ, Kaplan GA. Negative Consequences of Hearing Impairment in Old Age: A Longitudinal Analysis. *The Gerontologist* 2000; 40(3):320-326.