

REFERENCES

- 1 Ackerknecht EH. The history of psychosomatic medicine. *Psychol Med* 1982;**12**:17–24.
- 2 Biondi M, Zannino LG. Psychological stress, neuroimmunomodulation, and susceptibility to infectious diseases in animals and man: a review. *Psychother Psychosom* 1997;**66**:3–26.
- 3 Kubzansky LD, Sparrow D, Jackson B, et al. Angry breathing: a prospective study of hostility and lung function in the Normative Aging Study. *Thorax* 2006;**61**:863–8.
- 4 Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. *Annu Rev Public Health* 2005;**26**:469–500.
- 5 Kiecolt-Glaser JK, McGuire L, Robles TF, et al. Psychoneuroimmunology: psychological influences on immune function and health. *J Consult Clin Psychol* 2002;**70**:537–47.
- 6 Lehrer P, Feldman J, Giardino N, et al. Psychological aspects of asthma. *J Consult Clin Psychol* 2002;**70**:691–711.
- 7 Pickering TG. Mental stress as a causal factor in the development of hypertension and cardiovascular disease. *Curr Hypertens Rep* 2001;**3**:249–54.
- 8 Cohen S, Hamrick N, Rodriguez MS, et al. Reactivity and vulnerability to stress-associated risk for upper respiratory illness. *Psychosom Med* 2002;**64**:302–10.
- 9 Kimyai-Asadi A, Usman A. The role of psychologic stress in skin disease. *J Cutaneous Med Surg* 2001;**5**:140–5.
- 10 Abbey SE, Garfinkel PE. Chronic fatigue syndrome and depression: cause, effect, or covariate? *Rev Infect Dis* 1991;**13**(Suppl 1):S73–83.
- 11 Bennett EJ, Tennant CC, Piesse C, et al. Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. *Gut* 1998;**43**:256–61.
- 12 Engel GL. Psychologic stress, vasodepressor (vasovagal) syncope, and sudden death. *Ann Intern Med* 1978;**89**:403–12.
- 13 Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. *Curr Opin Allergy Clin Immunol* 2005;**5**:23–9.
- 14 Hasler G, Gergen PJ, Kleinbaum DG, et al. Asthma and panic in young adults: a 20-year prospective community study. *Am J Respir Crit Care Med* 2005;**171**:1224–30.
- 15 Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. *Arch Gen Psychiatry* 2003;**60**:1125–30.
- 16 Isenberg SA, Lehrer PM, Hochron S. The effects of suggestion and emotional arousal on pulmonary function in asthma: a review. *Psychosom Med* 1992;**54**:192–216.
- 17 Sarafino EP, Gates M, DePaulo D. The role of age at asthma diagnosis in the development of triggers of asthma episodes. *J Psychosom Res* 2001;**51**:623–8.
- 18 Carr RE, Lehrer PM, Hochron S. Effect of psychological stress on airway impedance in asthma and panic disorder. *J Abnormal Psychol* 1996;**105**:137–41.
- 19 Hock RA, Rodgers CH, Reddi C, et al. Medico-psychological interventions in male asthmatic children: an evaluation of physiological change. *Psychosom Med* 1978;**40**:210–5.
- 20 Ritz T, Steptoe A. Emotion and pulmonary function in asthma: reactivity in the field and relationship with laboratory induction of emotion. *Psychosom Med* 2000;**62**:808–15.
- 21 Suarez EC, Saab PG, Llabre MM, et al. Ethnicity, gender, and age effects on adrenoceptors and physiological responses to emotional stress. *Psychophysiology* 2004;**41**:450–60.
- 22 Goldstein HS, Edelberg R, Meier CF, et al. Relationship of expressed anger to forearm muscle vascular resistance. *J Psychosom Res* 1989;**33**:497–504.
- 23 Donker FJS, Bretelet MHM. Blood lipids: A shortcut from hostility to CHD? *Psychol Health* 2004;**19**:197–212.
- 24 Costanzo ES, Lutgendorf SK, Kohut ML, et al. Mood and cytokine response to influenza virus in older adults. *J Gerontol Series A: Biol Sci Med Sci* 2004;**59**:1328–33.
- 25 Suarez EC, Lewis JG, Kuhn C. The relation of aggression, hostility, and anger to lipopolysaccharide-stimulated tumor necrosis factor (TNF)-alpha by blood monocytes from normal men. *Brain Behav Immun* 2002;**16**:675–84.
- 26 Eckberg DL, Sleight P. *Human baroreflexes in health and disease*. Oxford: Clarendon Press, 1992.
- 27 Ogawa Y, Kanbayashi T, Saito Y, et al. Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. *Sleep* 2003;**26**:986–9.
- 28 Hasday JD, McCrea KA, Meltzer SS, et al. Dysregulation of airway cytokine expression in chronic obstructive pulmonary disease and asthma. *Am J Respir Crit Care Med* 1994;**150**(5 Pt 2):S54–8.
- 29 Udem BJ, Kollarik M. The role of vagal afferent nerves in chronic obstructive pulmonary disease. *Proc Am Thor Soc* 2005;**2**:355–60.
- 30 Garrard CS, Seidler A, McKibben A, et al. Spectral analysis of heart rate variability in bronchial asthma. *Clin Auton Res* 1992;**2**:105–11.
- 31 Lehrer PM, Isenberg SA, Hochron S. Asthma and emotion: a review. *J Asthma* 1993;**30**:5–21.

Spirometric screening

Spirometric screening: does it work?

D M Mannino

Role of spirometric testing in smoking cessation

Pulmonary function testing offers an easy, inexpensive, and non-invasive means of diagnosing and staging chronic lung disease.^{1,2} It provides information on both the presence of obstructive lung disease and restrictive lung disease and can provide insights on how patients might respond to treatment.^{3,4} Spirometric testing also provides prognostic information, with lung function measures predicting mortality and the development of lung cancer.^{5,6}

Despite the valuable information that spirometric testing provides, it is underused in medical practices in much of the world. There are several reasons for this, including (1) problems with doing the procedure,⁷ (2) problems related to compensation, and (3) the absence of “evidence” that spirometric testing actually makes a difference in the diagnosis and treatment of patients. Advances in the design of spirometric

tests that provide quality control feedback are addressing the first reason. The second reason varies between locales and health plans. Addressing the final reason is critical to increasing the use of spirometry in a general medical practice.

A recent review commissioned by the United States’ Agency for Health Research and Quality by Wilt *et al*⁸ concluded that “the evidence does not support widespread use of spirometry in primary care settings for all adults with persistent respiratory symptoms or having a history of exposure to pulmonary risk factors for case-finding, improving smoking cessation rates, monitoring the clinical course of COPD, or adjusting COPD interventions”. With specific regard to smoking cessation, the report’s review of four studies in the literature concluded the following:

“Spirometric testing as a motivational tool to improve smoking cessation rates is unlikely

to provide more than a small benefit. Results from observational studies of spirometry are mixed. RCT of other biomarkers used as motivational tools for smoking cessation are generally negative. The only randomized controlled trial that assessed the independent contribution of spirometry and counseling on smoking cessation rates reported a nonsignificant 1 percent greater quit rate at 12 months in the group assigned to receive spirometry ...”⁸

The paper in this issue of *Thorax* by Bednarek *et al*,⁹ which is observational and not a randomised clinical trial, would not have been included in the review by Wilt *et al* and thus would not have changed the conclusion. The information in the study by Bednarek *et al* is, however, compelling. Their evidence suggests that spirometric testing, with a very quick and simple feedback consisting of a lung function decline curve marked with the patient’s value, improved smoking cessation. In the world of smoking cessation, the validated cessation rates at 1 year of 16.3% in the overall group was higher than the expected 4–6%,^{10,11} and there was evidence that lower lung function at baseline resulted in higher cessation rates. Even though this was not a randomised trial, these results are remarkable and should be a model for designing a study to determine whether this quick and

simple intervention can improve cessation in other populations.

Does spirometric screening work? For this group of men from Poland, the answer—with regard to increasing smoking cessation—appears to be a qualified yes. Those of us interested in decreasing the most preventable cause of death and disease in the developed world now have a road map to help us design studies for implementation in our own populations.

Thorax 2006;**61**:834–835.
doi: 10.1136/thx.2006.061317

Correspondence to: Dr D M Mannino, Division of Pulmonary, Critical Care and Sleep Medicine, University of Kentucky Medical Center, 800 Rose Street, MN 614, Lexington, KY 40536, USA; dmannino@uky.edu

Competing interests: none declared.

REFERENCES

- 1 **Petty TL**. Benefits of and barriers to the widespread use of spirometry. *Curr Opin Pulm Med* 2005;**11**:115–20.
- 2 **Pauwels RA**, Buist AS, Calverley PM, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001;**163**:1256–76.
- 3 **Mannino DM**, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the Third National Health and Nutrition Examination. *J Intern Med* 2003;**254**:540–7.
- 4 **Celli BR**, Cote CG, Marin JM, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:1005–12.
- 5 **Mannino DM**, Buist AS, Petty TL, *et al*. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003;**58**:388–93.
- 6 **Mannino DM**, Aguayo SM, Petty TL, *et al*. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003;**163**:1475–80.
- 7 **Eaton T**, Withy S, Garrett JE, *et al*. Spirometry in primary care practice: the importance of quality assurance and the impact of spirometry workshops. *Chest* 1999;**116**:416–23.
- 8 **Wilt TJ**, Niewoehner D, Kim C, *et al*. Use of spirometry for case finding, diagnosis, and management of chronic obstructive pulmonary disease (COPD). *Evid Rep Technol Assess (Summ)* 2005:1–7.
- 9 **Bednarek M**, Gorecka D, Wielgomas J, *et al*. Smokers with airflow obstruction are more likely to quit smoking. *Thorax* 2006;**61**:869–73.
- 10 **Segnan N**, Ponti A, Battista RN, *et al*. A randomized trial of smoking cessation interventions in general practice in Italy. *Cancer Causes Control* 1991;**2**:239–46.
- 11 **Risser NL**, Belcher DW. Adding spirometry, carbon monoxide, and pulmonary symptom results to smoking cessation counseling: a randomized trial. *J Gen Intern Med* 1990;**5**:16–22.

IL-10 and IPF

IL-10: another therapeutic target in idiopathic pulmonary fibrosis?

A B Millar

The need for appropriately designed clinical trials in IPF

These are exciting and hopeful times for those involved in the treatment of idiopathic pulmonary fibrosis (IPF). Despite the ever expanding wealth of cellular and molecular biology, translation into clinical trials for IPF has been limited.¹ However, in the last 2 years results on three potential therapeutic agents have been published, albeit with limited benefit, with others imminent.^{2–4} The study by Nakagome *et al*⁵ in this issue of *Thorax* gives further support to the concept of interleukin (IL)-10 as an additional biological therapeutic agent.

In the last 20 years the ability of the scientific community to analyse the biological interactions between cells has led to an information explosion. This has been exemplified by the analysis of cytokine (and growth factor) networks.⁶ Typically, the initial identification of a protein is followed by its receptor(s), its inhibition or induction by lipopolysaccharide and dexamethasone, and then a cascade of publications on interactions with other biologically active proteins. Unfortunately for the lung biologist, despite its relative inaccessibility, the unique role of the lung makes the requirement for cell and

organ specificity even more crucial than in other tissues when dissecting these networks. This is exemplified by the constitutive secretion of the anti-inflammatory IL-10 by human lung alveolar macrophages, contrasting with tissue macrophages from other organ sites.⁷

In vitro or ex vivo studies of individual cytokines and growth factors lead to the identification of molecules with potential useful biological activity. In the case of IL-10, it was identified as an anti-inflammatory agent.⁸ In the context of the lung, IL-10 has been shown to be expressed by alveolar macrophages constitutionally and stimulated by lipopolysaccharide, both directly and indirectly by tumour necrosis factor (TNF)—effectively controlling inflammation in a homeostatic feedback loop. Its role in inflammation has been explored in a number of inflammatory conditions including sarcoidosis, asthma, and acute respiratory distress syndrome (ARDS).^{9–11} Similar studies in IPF have been limited and conflicting.^{12–13} This may be related to the change in view of IPF from a condition with an inflammatory basis to that of “dysregulated repair” based on the epidermo-mesenchymal unit.¹⁴

The latter view of IPF has led to a much greater focus on fibroblast function and fibrogenic cytokines, in particular transforming growth factor (TGF)- β . This cytokine has been shown to induce fibroblast proliferation, chemotaxis, and collagen production.¹⁵ In the context of IPF, it is mainly produced by the alveolar macrophages and expressed in fibroblastic foci.¹⁶ There is a paucity of studies on the potential interaction between IL-10 and TGF- β , but some recent work has suggested potential interactions.¹⁷ All such studies are limited by the isolation of cells from the tissue milieu, albeit facilitating clear cut answers. The evaluation of animal models of disease provides an alternative method of investigation.

Nakagome *et al*⁵ have used the bleomycin mouse model for their work, recognising its limitations—in particular the observation that fibrosis can resolve with withdrawal of bleomycin, in contrast to the human condition. A significant number of potential biological treatments have previously been shown to ameliorate fibrosis in this model, including TGF inhibition.^{18–19} However, in such studies the agent has been given either prior to or synchronously with the inducing agent. In the well controlled study by Nakagome *et al* the administration of IL-10 2 weeks after induction led to amelioration of fibrosis. This is a crucial finding for a condition such as IPF in which presentation is invariably that of established disease. The authors used an intravenously delivered IL-10 plasmid which resulted in increased systemic production of IL-10 perfusing all organs and was shown to be increased in the lung. The use of genetically modified animals has been a further step forward for this type of