partnerships with patients within an evolving team-based primary care structure.

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References

1. Brannan J. Bronchial Hyperresponsiveness in the assessment of asthma control: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010;**138**:115-175. <http://dx.doi.org/10.1378/chest.10-0231>
2. Turton J, Glasgow N, Brannan J. Feasibility and acceptability of using bronchial hyperresponsiveness to manage asthma in primary care: a pilot study. *Prim Care Respir J* 2012;**21**:28-34. <http://dx.doi.org/10.4104/pcrj.2011.00079>
3. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. The AMPUL Study Group. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. *Am J Respir Crit Care Med* 1999;**159**:1043-51.
4. Nuijsink M, Hop WC, Sterk PJ, Duiverman EJ, de Jongste JC. Long-term asthma treatment guided by airway hyperresponsiveness in children: a randomised controlled trial. *Eur Respir J* 2007;**30**(3):457-66. <http://dx.doi.org/10.1183/09031936.00111806>
5. Koenig SM, Murray JJ, Wolfe J, et al. Does measuring BHR add to guideline derived clinical measures in determining treatment for patients with persistent asthma? *Respir Med* 2008;**102**(5):665-73. <http://dx.doi.org/10.1016/j.rmed.2007.12.023>
6. Harris MF, Jayasinghe U, Taggart J, et al. Multi-disciplinary Team Care Plans in the management of patients with chronic disease in Australian general practice. *Med J Aust* 2011;**194**(5):236-9.
7. Australian Government Department of Health and Ageing. MBS Primary Care Items. Chronic Disease Management (CDM) Medicare Item numbers . <http://www.health.gov.au/internet/main/publishing.nsf/content/mbsprimarycare-chronicdiseasemanagement>
8. Lin CCW, Hass M, Maher C, Machado L, van Tulder M. Cost-effectiveness of general practice care for low back pain. A systematic review. *Eur Spine J* 2011;**20**:1012-23. <http://dx.doi.org/10.1007/s00586-010-1675-4>
9. Utens C, Gossens L, Smeenk L, et al. Effectiveness and cost-effectiveness of early assisted discharge for Chronic Obstructive Pulmonary Disease exacerbations: the design of a randomised controlled trial. *BMC Public Health* 2010;**10**:618. <http://biomedcentral.com/1471-2458/10/618> <http://dx.doi.org/10.1186/1471-2458-10-618>
10. Gialamas A, Yelland L, Ryan P, et al. Does point of care testing lead to the same or better adherence to medication? A randomised control trial. The POCT in General Practice Trial in General Practice. *Med J Aust* 2009;**191**:487-91.

Statins for COPD: a challenge to conventional beliefs?

See linked article by Lawes *et al.* on pg 35

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Every now and then a paper comes along which challenges the mould. Chronic obstructive pulmonary disease (COPD) is an airway condition that results from inhaling “dusts” (particularly the tar of cigarettes). So when a paper suggests that a drug affecting the vascular system may alter outcome, it questions our standard beliefs. In this issue of the *PCRJ* is a paper from Lawes *et al.* describing how statin use is associated with a 30% reduction in mortality in COPD over 4 years¹ - an outcome effect that is an order of magnitude greater than the current mainstays of COPD drug treatments, inhaled steroids and long-acting bronchodilators. Indeed, these have disappointingly little or no effect on disease progression, although they do reduce exacerbation rates and improve quality of life. Only oxygen in the late hypoxic phase is disease modulating. So, even a hint of a disease modifying effect by statins has to provoke interest.

But could this paper be wrong? It is observational and thus cannot prove causality, and the authors are appropriately cautious in their inferences, especially with neither smoking nor lung function data.

However, it is a large study, subject inclusion was unselected – i.e. all acute COPD admissions in New Zealand, the prescribing of statins in primary care was independent of the admission and collected via an automated link, and death is an unequivocal outcome.

A further caveat is that absolute numbers of deaths in the two groups, i.e. those prescribed and not prescribed statins, were similar at 4 years. The differences are only seen when statistical controls are added. However, to argue that those with cardiovascular or diabetes co-morbidity should have similar outcomes to those without flies in the face of every known epidemiological study. An odds ratio showing 30% fewer deaths puts statin therapy into the same league as oxygen, but with applicability to a wider range of patients. The changes in the study are not explained by the expected lipid or cardiovascular effects, leading to the implication that statins may be altering the underlying COPD. Until this hypothesis is formally tested it remains exciting but unproven – but for a moment let us follow the potential trail of what it might mean.

Statins were introduced for their lipid-lowering effect which, by reducing deposition of cholesterol in arteries, is cardio-protective. But they also act on platelets and clotting^{2,3} and perhaps vasculitis.⁴ These non-lipid effects are debated⁵ but some are claiming that the effects of statins go beyond fat metabolism such that cardiovascular patients obtain a double benefit.⁶ Those arguing for a polypill⁷ suggest that statin benefits are independent of cholesterol levels, which may imply that the primary effect of statins is on non-lipid mechanisms.

Yet there are no suggestions that statins act to reduce or block the effect of inflammation due to smoke deposits or other dusts in the lung, or on elastases. While it is possible that this is because no one has looked, the alternative is to ask more radical questions:

- Could COPD be a vascular disease in which the small airway disease is due to a failure of vascular supply leading to airway loss? Could COPD be Buerger's disease of the lung?
- Is it possible that the tars with all their active chemicals depositing on major bifurcations are the main agent for cancer, while it is the vasoconstriction of the nicotine that is responsible for the small airway disease of COPD?

Despite two decades of active research, the causal mechanisms of COPD remain unclear. The emphysema-elastin degradation story applies to some patients, but many have physiologically fixed obstruction with little or no emphysema on scans or at post mortem. The inflammation of COPD includes neutrophils and CD8 lymphocytes, which overlaps with the pattern seen in post-transplantation bronchoalveolitis obliterans when the bronchial arterial supply is damaged.⁸ Chronic ischaemia of the brain⁹ and of the heart¹⁰ has some similar features – so is there a possibility that the COPD inflammation results from failure of the bronchial artery supply to the small airways?

Cigarette smoke consists of very fine particulates (mostly < 0.1 µm in diameter) that cool and aggregate as they pass into the airway, but they still contain many active chemicals when the particles deposit at airway bifurcations where there is most turbulence.¹¹ Deposition is relatively higher in the upper lobes where both emphysema and tumours are most common. The irritant chemicals would be expected to lead to local inflammation and mucus production. The relationship to cancer would stand, but is it the tar and chemicals that causes the COPD? Or could it be the nicotine? – a known vasoconstrictor that will be present in concentrations higher than the peak cerebral levels that lead to addiction – in which case the bronchial arterial supply could be affected leading to ischaemic damage of the airways. The bronchial arteries are complex structures with an interlacing network of vessels that are within and without the bronchial wall. Most of the anatomic work on the bronchial circulation is more than 30 years old, and current textbooks simply state that, because of the multiple anastomotic branching, damage is unlikely. But as vessels become smaller their vulnerability is likely to increase, and if with each cigarette just one or two vessels were damaged and the tissue supplied did not have adequate collateral supply, then localised infarction might result in cell death and a space appearing in the centre of the lobule. Such speculation might seem fanciful, but a seminal recent paper¹² describes how small airways of 2mm diameter or less are reduced in number – i.e. somehow airways have been destroyed – and also suggests that the reduction in numbers may precede the development of centri-lobular emphysema.

There are other observations that might fit. Most respiratory physicians have a few patients who have inhaled cocaine and then present with severe COPD perhaps two decades earlier than cigarette smokers. Cocaine is a potent vaso-constrictor. The addictive “high” from cigarettes arises from the very high peak cerebral nicotine level – implying even higher levels in the bronchioles – and the switch to low tar cigarettes does not reduce disease as patients puff harder to obtain the cerebral nicotine which thus goes to the bronchioles.

However, we are left with some difficulty in explaining the dust pollution story, since the PM₁₀ particulates inhaled from air pollution

and the coal dust from mining are neither highly irritant nor vasoconstrictor in nature. Perhaps the indoor smoke of indoor cooking pollution may be different? The claimed effects of the pollution and industrial dust studies have been markedly less than for smoking, and it has been difficult to separate out potential competing effects, particularly as almost all the studies are cross-sectional or do not include the same individuals longitudinally. It is fair to state that many have been convinced by the collective body of papers, but this author has always retained doubts, largely because of the dependence on statistics to describe small effect sizes (an order of magnitude less than the effects of smoking) and the potential for uncontrolled co-variation. Space does not allow a fuller discussion, but a thoughtful recent paper describes how the complexities of the statistics may mislead when there are several co-variate factors – e.g. ageing, cohort effects, cumulative smoking, and cumulative pollution/work exposures, all of which increase with time.¹³ This statins paper¹ also depends on statistical control, so an open mind is important. But if the vascular pathogenesis theory holds up, we may need to re-examine the putative roles of air pollution, coal dust and other agents with fresh eyes.

What might this mean for COPD patients? An urgent prospective study to test whether or not statins have a significant effect on COPD is needed. If that study were positive, it would significantly alter the prescribing advice for all COPD patients. Bronchodilators, pulmonary rehabilitation, and oxygen in established symptomatic disease will remain treatment mainstays, but would we still feel as passionate about the inhaled steroids?

Stopping smoking will remain the first choice for preventing disease progression, but is it possible that statins might slow disease progression even in continuing smokers by preventing local thrombi and preserving oxygenation of the small airway tissues? Perhaps the nicotine substitutes used to assist smokers to quit should be reconsidered; could they be making things worse, albeit leading to less nicotine in the longer term? – or are the relatively low peak doses safe?

This statins paper from Lawes *et al.*¹ may be an observational study to be interpreted cautiously, but given the paucity of therapy available for COPD it is quite exciting to speculate about something that might improve outcomes significantly. It would be even more exciting if this were to lead to a new understanding of COPD disease mechanisms and thus accelerate progress. But there have been false dawns before...

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References

1. Lawes CMM, Thornley S, Young R, *et al.* Statin use in COPD patients is associated with a reduction in mortality: a national cohort study. *Prim Care Respir J* 2012; 21(1):35-40. <http://dx.doi.org/10.4104/pcrj.2011.00095>

2. Paraskevas KI, Bessias N, Perdikides TP, Mikhailidis DP. Statins and venous thromboembolism: A novel effect of statins? *Current Medical Research and Opinion* 2009; **25**(7):1807-09. <http://dx.doi.org/10.1185/03007990903052591>
3. Waters DD. Exploring new indications for statins beyond atherosclerosis: Successes and setbacks. *J Cardiol* 2010; **55**(2):155-62. <http://dx.doi.org/10.1016/j.jcc.2009.12.003>
4. Muscal E, Brey RL. Antiphospholipid syndrome and the brain in pediatric and adult patients. *Lupus* 2010; **19**(4):406-11. <http://dx.doi.org/10.1177/0961203309360808>
5. Pedersen TR. Pleiotropic effects of statins: evidence against benefits beyond LDL-cholesterol lowering. *Am J Cardiovasc Drugs* 2010; **10**(Suppl 10).
6. Morales-Villegas EC, Di Sciascio G, Briguori C. Statins: Cardiovascular Risk Reduction in Percutaneous Coronary Intervention—Basic and Clinical Evidence of Hyperacute Use of Statins. *Int J Hypertens* 2011;904742.
7. Wald DS, Wald NJ. The Polypill in the prevention of cardiovascular disease. *Prev Med* 2011; **52**(1):16-17. <http://dx.doi.org/10.1016/j.ypmed.2010.11.015>
8. Dark J, Corris PA. Lung Transplantation in Respiratory Medicine. Eds Gibson J, Geddes D, Costabel U *et al.* Saunders, London 2003 pp496
9. Schwab JM, Nguyen TD, Meyermann R, Schluesener HJ. Human focal cerebral infarctions induce differential lesional interleukin-16 (IL-16) expression confined to infiltrating granulocytes, CD8+ T-lymphocytes and activated microglia/macrophages. *Journal of Neuroimmunology* 2001; **114**:232-24. [http://dx.doi.org/10.1016/S0165-5728\(00\)00433-1](http://dx.doi.org/10.1016/S0165-5728(00)00433-1)
10. Heart Stable E, Kinnaird T, la Sala A, *et al.* CD8+ T Lymphocytes Regulate the Arteriogenic Response to Ischemia by Infiltrating the Site of Collateral Vessel Development and Recruiting CD4 Mononuclear Cells Through the Expression of Interleukin-16. *Circulation* 2006; **113**:118-24. <http://dx.doi.org/10.1161/CIRCULATIONAHA.105.576702>
11. National Research Council. "10 Tobacco Smoke and Toxicology." Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington, DC: The National Academies Press, 2001.)
12. McDonough JE, Yuan R, Suzuki M. Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2011; **365**:1567-75. <http://dx.doi.org/10.1056/NEJMoa1106955>
13. Schwartz J. A spine for our time. *Thorax* 2011; **66**:841-2. <http://dx.doi.org/10.1136/thx.2010.154195>

Oral immunotherapy for peanut allergy: an evidence-based medicine assessment

See linked article by Sheikh *et al.* on pg 41

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Food-induced allergic disorders mediated by IgE represent a major health problem, affecting children and adults worldwide.¹ Even though the exact prevalence of food allergy is difficult to determine, it has been reported that in some countries IgE-mediated food allergy affects up to 6-8% of children and up to 2-4% of adults.¹⁻³ Some food allergies such as egg, milk, soy and wheat may be outgrown within the first decade of life, whilst others such as peanut, tree nuts, fish and shellfish are often lifelong.⁴ Food allergy has different clinical manifestations involving many body systems including the skin, the gastrointestinal and respiratory tracts, and the cardiovascular system. Furthermore, the incidence of food-related anaphylaxis primarily in children seems to be increasing globally. Individuals with both severe or difficult asthma and a history of food allergy are those at highest risk of developing life-threatening anaphylactic reactions.

One of the major food allergens in many countries is peanut.^{5,6}

Peanuts are widely used as a nutritious oral aliment (providing protein, vitamins and minerals) and are the most common food-related cause of IgE-mediated allergic reactions.⁷ Patients with atopic dermatitis can increase their risk to sensitisation to peanuts and subsequently the development of peanut allergy due to cutaneous exposure to peanut oil-containing creams.⁸ Reactions to peanuts are immediate and can be severe, even life-threatening. Symptoms range from a relatively mild urticarial rash, vomiting, diarrhoea, wheezing, and dyspnoea, to severe throat angioedema, cardiovascular collapse or fulminant anaphylaxis.⁹ Patients with well-documented peanut allergy often have to carry rescue medication such as adrenaline auto-injectors to treat themselves if severe reactions occur.⁹ Measures to prevent (or even cure) food allergies such as peanut allergy are therefore a high scientific priority in the field of allergic disease, and many attempts to induce tolerance to peanut are under way.

In this issue of the *Primary Care Respiratory Journal*, Sheikh and colleagues present a timely systematic review¹⁰ of studies that have attempted to induce desensitisation and tolerance to peanut by oral immunotherapy in patients with such allergy. A thorough search of the major biomedical databases was conducted using a previously designed study protocol. In total, 1,672 potentially eligible studies were identified. After a systematic evaluation, only six studies met the study inclusion criteria, enrolling 85 patients in total. Surprisingly, the duration of oral immunotherapy treatment varied between studies, ranging from 6 days to 36 months. Four studies were multicentre and two single centre. Four studies were conducted in the USA and two in Europe. All studies used a "case series" design, and so this systematic review lacks the strength that can be provided by randomised prospective placebo-controlled studies. This situation was stated by the authors to be at high risk of bias. Regardless, the studies overall argue that oral immunotherapy may have some future, since the treated patients tolerated higher doses of peanut after the