

# PostScript

## LETTERS TO THE EDITOR

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### Atopic cough

The correspondence on atopic cough between McGarvey/Morice and Fujimura/Ogawa<sup>1,2</sup> raises a number of very important issues regarding the diagnosis and treatment of chronic cough. These issues warrant careful consideration, not only because of the huge illness burden posed by the frequency of chronic cough but also because issues of terminology and recommended treatment continue to be unclear and irregularly applied.

The "3Rs" of chronic cough—rhinitis, reflux and reactive airways (asthma)—have a certain appeal. They are recognised, often repeated (primary research articles were outnumbered by reviews, letters and case reports on chronic cough in 2002–2003), and easily retained in the short term memory of busy clinicians. In clinical practice they are useful. But there are a number of crucial issues that remain to be addressed. The 3Rs frequently coexist in patients with chronic cough, which means there are more diseases than there are patients, and that can't be a good thing. Also, what is the best way to tell if rhinitis/reflux/reactivity is relevant in the patient in front of you? Why do only a subgroup of people with rhinitis/reflux/reactive airways present with chronic cough?

Furthermore, the 3Rs denote a single disease mechanism—namely, activation of the afferent limb of the cough reflex at the site of the disease process (nose, airway, oesophagus, respectively) which is increasingly ignorant of other relevant mechanisms in chronic cough such as eosinophilic inflammation of the airway,<sup>3</sup> extrathoracic airway hyperresponsiveness,<sup>4</sup> oesophageal dysmotility,<sup>5,6</sup> and airway protussive mediator release, possibly a reflection of neurogenic inflammation.<sup>7</sup>

Problems also exist in relation to eosinophilic bronchitis, a descriptive term which indicates the pattern of airway inflammation present. When first described in chronic cough, eosinophilic bronchitis was reported as a disease mechanism and a marker of a good response to corticosteroid treatment.<sup>3</sup> Recently, the term eosinophilic bronchitis has been used as a disease label in chronic cough—that is, a diagnosis in itself.<sup>8–10</sup> In

this way, eosinophilic bronchitis has been incorporated into the anatomic-diagnostic protocol as a cause of idiopathic cough to be considered when all other avenues have failed. This is problematic since eosinophilic bronchitis occurs in all three of the "Rs"<sup>11</sup> and is also present in most patients labelled as having atopic cough. It also ignores the excellent and prompt response to corticosteroid treatment that occurs in eosinophilic bronchitis. It is less useful to consider eosinophilic bronchitis as a disease or a diagnosis of exclusion. Rather, it is a pattern of airway inflammation that is present in a number of common diseases and, when symptomatic, indicates a good response to an accessible treatment (inhaled corticosteroid). After serious diseases have been ruled out, maybe the first approach to chronic cough should be a supervised trial of "Roids (steroids) and, if that fails, then go for the 3Rs.

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### Interrupter resistance

Sly and Lombardi<sup>1</sup> in their recent editorial suggest that interrupter resistance (Rint) measurements are useful in the management of lung disease in young children. We believe this claim needs further consideration.

Rint measurements can be helpful when change following an intervention—such as the administration of a bronchodilator—is greater than its within-occasion repeatability

but, for a measurement to be useful for following change with time in the individual, it must have acceptable between-occasion repeatability. In the same issue, Beelen *et al*<sup>2</sup> reported between-occasion variability of 0.38 kPa/Ls (2 SD of the differences between measurements) in 25 healthy children. This figure is similar to that of Chan *et al*<sup>3</sup> who reported 72 measurements in healthy children and 95 measurements in children with stable mild asthma. In the healthy children the between-occasion repeatability was 32% expected for age, but in the asthmatic children this rose to 52%. As a hallmark of asthma is bronchial lability, this is not unexpected. These figures need to be compared with the change expected with treatment. Pao *et al*<sup>4</sup> showed that, in an identical group of asthmatic children, a change in mean Rint of 16% occurred with treatment with inhaled corticosteroids. Although this change was demonstrated in a group of children, it would not be picked up easily in the individual because the between-occasion repeatability of Rint is much greater than the change expected.

Rint seems to be a good tool for research and, for that reason, measurements should be standardised. However, we believe its usefulness for the practising clinician is quite limited as measurements in the individual are not sufficiently reliable on a day to day basis. It is difficult to imagine that further refinement and standardisation of the method will improve this.

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### Authors' reply

We thank Drs Dundas and McKenzie for their comments. We agree with them that the interrupter resistance (Rint) is able to detect short term changes in airway calibre after bronchodilator inhalation. However, we must disagree with their comment that Rint has a poor long term repeatability and their consequent conclusion that Rint is not useful for routine clinical purposes. The long term repeatability (38 days apart) of Rint measurements (2 SD of the difference between two sets of measurements) reported by Beelen *et al*<sup>1</sup> in healthy preschool children was actually 0.37 kPa/Ls in 25 children under field conditions and 0.28 kPa/Ls in 15 children under laboratory conditions. This value is very similar to the long term repeatability

(3 weeks apart, 2 SD of the difference between two sets of measurements) reported by Chan *et al*<sup>2</sup> in 72 healthy preschool children (0.23 kPa/l.s) and the long term repeatability (2.5 months apart, 2 SD of the difference between two sets of measurements) that we found in children with a history of wheezing or cough (0.21 kPa/l.s).<sup>3</sup> In our study the potential effects of the disease or treatment on long term Rint variability were carefully avoided and only clinically stable children with no change in treatment were recruited. Assessment of the long term variability of a lung function test must be undertaken under circumstances in which the true lung function can reasonably be expected not to have changed. This is unlikely to be the case in children with asthma where lung function is expected to vary with time. The fact that Chan *et al*<sup>2</sup> found a much higher long term Rint variability in 95 children with doctor observed wheeze in the previous 4–6 weeks and on no long term treatment should not lead to the conclusion that Rint is not useful in clinical practice. On the contrary, it provides evidence that Rint is able to detect long term changes in airway calibre in children with a recent history of respiratory symptoms. If we add that Rint is also feasible in preschool children,<sup>1–3</sup> we can conclude that it is a potentially useful tool in routine clinical practice.

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## Atrial septostomy in the treatment of severe pulmonary arterial hypertension

In their recent paper on atrial septostomy as a treatment for severe pulmonary arterial hypertension, Reichenberger *et al*<sup>1</sup> measured cardiac output before and after this intervention using both the thermal dilution and Fick methods. We were interested by their choice of dilution technique. In these patients atrial septostomy was intended to produce a right to left interatrial shunt, as evidenced by the fall in arterial oxygen saturation following the procedure. Cardiac output measurement by the thermal dilution method described in their paper relies upon calculation of the area under the temperature curve, measured by a thermistor placed in the pulmonary artery, following an injection of cold saline into the right atrium or superior vena cava. In simple

terms, the greater the area under the curve (purists would perhaps say “over the curve” since the injectate produces a transient fall in blood temperature in the pulmonary artery), the lower the derived cardiac output. It is unclear why the authors would choose such a method to estimate cardiac output following atrial septostomy when it would be expected that a proportion of the injectate would pass directly into the left atrium through the interatrial septal defect, producing an erroneous overestimate of cardiac output. A reliable method of measuring blood flow within the pulmonary artery after the procedure might be expected, at least initially, to show exactly the opposite result—namely, a fall in pulmonary arterial flow caused by the right to left shunt. We postulate that the explanation for their observed good correlation between the thermodilution and Fick cardiac outputs is that, before the procedure, both were reliable methods and that, after the procedure, the true cardiac output increased and was correctly measured by the indirect Fick method but was artefactually increased, despite a fall in pulmonary arterial blood flow, when measured by thermodilution.

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## Reference

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## Authors' reply

We thank Dr McCann and colleagues for their comments on our paper in which cardiac output measurements were performed using thermodilution methods following creation of an atrial shunt after atrial septostomy in patients with severe pulmonary hypertension.<sup>1</sup>

We agree with the authors that cardiac output measured with the thermodilution method can give overestimated readings in the presence of an existing intercardiac shunt and that the Fick method is the method of choice. We have therefore calculated the cardiac output using both methods and, interestingly, found a very good correlation in our patient population between both methods before and after shunt creation ( $r = 0.83$  and  $r = 0.78$ , respectively), allowing us to present data measured with the thermodilution method. However, cardiac output measured by thermodilution was significantly lower than the calculation based on the Fick method. This has been described in tricuspid regurgitation.<sup>2,3</sup> In our patient population the mean cardiac index increased by 31% after atrial septostomy measured with the thermodilution method and by 29% when measured with the Fick method.

The most important message of our paper is that creation of the small interatrial shunt improves cardiac output independently of the method used for its calculation. This is accompanied by a significant reduction in oxygen saturation (from 93.2% to 87.4%), but systemic oxygen transport is increased. This improves the patients' symptoms and has the

potential to influence prognosis in this selected population of patients with severe pulmonary arterial hypertension.

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## Treatment of severe acute childhood asthma

I am writing in response to Dr South's recent editorial which highlighted how second line treatment for severe acute childhood asthma

### Box 1 Summary of survey results

- IV aminophylline: 159 replies (70.0%):
  - 14 (9%) departments plan to change to IV salbutamol in the future;
  - believe evidence for IV salbutamol not good despite new guidelines;
  - tried to change policy to IV salbutamol but colleagues not keen;
  - practice may be out of date;
  - familiar with aminophylline—safe and effective over many decades;
  - nurses find volumes required to make up IV salbutamol problematic;
  - nurses insist IV salbutamol only administered on PICU due to hypokalaemia.
- IV salbutamol: 34 replies (15.0%):
  - 11 (32%) departments based in London;
  - use IV salbutamol to standardise with other local centres;
  - considering changing back to aminophylline as felt it was more effective.
- IV aminophylline or IV salbutamol: 28 replies (12.3%):
  - choice based on individual doctors and details of individual cases;
  - 5 (18%) departments moving towards IV salbutamol as main choice.
- IV terbutaline: 3 replies (1.3%)
- IV magnesium: 1 reply (0.4%)
- No choice: 2 replies (0.9%):
  - feel unable to state what actually happens in reality in department

is still the subject of debate.<sup>1</sup> I conducted a survey of consultant paediatricians who were clinical leads in asthma at 582 NHS establishments across the UK (details from official published lists) in which they were asked to indicate their department's preferred choice for second line treatment of acute severe asthma not responding adequately to first line treatment with high dose nebulised bronchodilators and corticosteroids. I also invited them to make any additional comments or remarks.

A total of 252 responses were received (43.3% response rate), of which 25 stated that their NHS establishment either did not treat children or did not treat acute asthma. The 227 remaining responses and feedback comments for each treatment choice are summarised in box 1.

The results highlight how clinical practice can sharply contrast with clinical guidelines. It is arguable how the results should be interpreted. Should we standardise with the majority of the UK and use IV aminophylline or should we follow guidelines and use IV salbutamol, despite the evidence being unclear and it only being used by a minority of departments across the UK? It would be interesting to repeat this exercise in 10 years' time to see what direction departments across the UK decide to follow.

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## Reference

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## Author's reply

Dr Vijayadeva's survey of the choice of second line drug treatment for severe acute childhood asthma by UK consultant paediatricians has some very interesting findings. Most of the paediatricians (70.4%) gave IV aminophylline as their preferred choice despite the fact that national guidelines recommend IV salbutamol. Could this be practice change inertia, or is it the result of years of experience with the long established agent aminophylline and the lack of conviction that IV salbutamol is better?

That there is considerable practice variation is not a surprise and may be a healthy situation, given that the evidence for superiority between IV salbutamol and IV aminophylline remains somewhat inconclusive. I was interested to note that some prescribers had switched to salbutamol in accordance with the guidelines but were now considering

changing back to aminophylline as they felt it was more effective.

My conclusion from reading the literature, as outlined in my editorial in *Thorax*,<sup>1</sup> is that the limited evidence suggests that aminophylline has advantages for efficacy in severe cases but at the cost of additional minor adverse effects. The higher rate of use of aminophylline by UK paediatricians sits comfortably with this. It may be the guideline, rather than the prescribing practice, which needs to be updated.

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## Chronic cough in adults

Morice and Kastelik<sup>1</sup> have produced an excellent review of the management of chronic cough in adults. As stated by the authors, cough may arise from anywhere in the distribution of the vagus. One of the less common causes of chronic cough is disease of the ear<sup>2–3</sup> due to stimulation of Arnold's nerve.<sup>4</sup> This nerve is an auricular branch of the vagus nerve which supplies the posterior and inferior parts of the auditory canal. In the absence of auricular symptoms an otoscope is not usually used in the investigation of patients with chronic cough. This diagnostic possibility may therefore be overlooked, resulting in many unnecessary examinations of the upper and lower respiratory tracts.<sup>5</sup>

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## Authors' reply

We thank the authors for their comments on our review of chronic cough in adults.<sup>1</sup> The otoscopic examination of the external auditory meatus forms an important part of the assessment of patients with apparently idiopathic chronic cough. In 1832 Arnold described the ear-cough reflex, consisting of cough produced by a direct stimulation of the deep portion of the posterior wall of the external auditory meatus. In healthy subjects without chronic cough the reflex is present in 2–6% of the population.<sup>2–4</sup> In chronic cough we hypothesised that vagal hypersensitivity might give rise to increased cough reflex sensitivity. However, infusion of capsaicin or citric acid into the external auditory meatus leads to cough only infrequently in our patients.

Cough arising from the ear is rare with only 15 cases having been reported.<sup>5</sup> In some cases surgical treatment may be required. However, foreign bodies and ear wax have been the most commonly reported causes. The diagnostic clue is that other auricular symptoms are frequently reported. However, in apparently idiopathic cough otoscopy should be routinely performed.

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