The Journal of Laryngology & Otology (2008), ***122***, *11–15*.

doi:10.1017/S0022215107009140
Printed in the United Kingdom
First published online 25 June 2007

Review Article

Bronchiectasis and sino-nasal disease: a review

C M Philpott, D C McKiernan*

Abstract

The 'one airway' model for upper and lower respiratory tract disease is a concept gaining increasing momentum in both respiratory medicine and otorhinolaryngology. The specific common aetiology and pathophysiology of concomitant bronchiectasis and sino-nasal disease, such as chronic rhinosinusitis, are discussed here, as well as the clinical manifestations, along with a review of all the relevant literature in the field.

Key words: Bronchiectasis; Sinusitis; Rhinitis; Ciliary Motility Disorders

Introduction

Rhinitis is a common sino-nasal pathology which affects many individuals and causes a significant reduction in workplace productivity.[1] The association between rhinitis and asthma is well known and documented, and the need to treat both conditions is being increasingly recognised. The role of sino-nasal disease in bronchiectasis is, however, less well documented and has relatively little coverage in the literature. This article will discuss the disease processes and the links between the two sites of airway inflammation.

Bronchiectasis

Bronchiectasis is a condition that receives less attention in respiratory texts than conditions such as asthma and chronic obstructive airways disease. This is primarily owing to the fact that bronchiectasis represents a disease process rather than a specific entity and can commonly occur as part of a systemic disorder, as discussed below. It is defined as the abnormal dilation of proximal, medium-sized bronchi (>2 mm diameter) due to lysis of the elastic and muscular components of their walls.[2,3] This lysis is mediated by the enzymes collagenase and elastase, released from neutrophils that are chemotactically attracted to the area.[4,5] The cytokines that attract the neutrophils include interleukin-8 and leukotriene-B from macrophages and mucosal cells.[6] Sometimes, this dilation is associated with chronic bacterial infection and the consequent expectoration of large quantities of offensive sputum. The condition may however be 'dry', when the upper lobes of the lung are involved, as these have dependant drainage. The pathological process is usually found to be irreversible, but there are a few exceptions, such as after acute pneumonia.[7] There may also be overlap with other clinical entities such as chronic bronchitis, especially when the aetiologies are common.[8]

Several classifications for bronchiectasis have been produced, including a morphological one by Reid, published in 1950, which is as follows.[9] 'Cylindrical bronchiectasis' denotes consistent widening of sections of the bronchi. 'Varicose bronchiectasis' denotes local, cylindrical constrictions, causing an irregularity which resembles varicose veins. 'Saccular or cystic bronchiectasis' denotes dilation increasing towards the lung periphery, with resulting ballooning of the terminal bronchi.

These classifications are useful radiologically but have little bearing clinically or pathophysiologically. That said, bronchiectasis is essentially a radiological diagnosis, and although clinical signs such as an expectorant cough may give clues, the gold standard investigation is a high resolution computed tomography (CT) scan of the chest.[10–12]

Rhinitis and rhinosinusitis

Rhinitis is defined as an inflammatory disorder of the nasal mucosa, characterised by two or more of the following symptoms: rhinorrhoea (anterior and/or posterior), blockage, and itching or sneezing.[13] Rhinitis is a term that encompasses a variety of aetiologies. Allergic rhinitis has now been reclassified by the Allergic Rhinitis and its Impact on Asthma workshop into mild or moderate/severe and intermittent or persistent. The defining features

From the Department of Otorhinolaryngology, Essex Rivers Healthcare NHS Trust, Colchester, and the *Department of Otorhinolaryngology, Cambridge University Hospitals NHS Foundation Trust (West Suffolk Hospital and Addenbrookes Hospital), Cambridge, UK.
Accepted for publication: 22 March 2007.

for this classification are whether symptoms occur more or less than four days a week or four weeks a year, and the presence of sleep disturbance or interruption of normal daily activities.[14–16] The importance of rhinitis in asthmatic patients is well documented, although the two are often tackled separately by respiratory physicians and otorhinolaryngologists, respectively. Allergic rhinitis is by far the most common form of nasal mucosal inflammation, and, despite being a benign disease with no systemic manifestations, its high prevalence (20 per cent of the adult population) means that it has a significant socio-economic impact due to reduced workplace productivity.[1,17] It follows that allergic rhinitis can predispose towards infective sino-nasal pathology, and it is not uncommon to find atopy in patients with chronic rhinosinusitis with or without nasal polyposis.[18]

Chronic rhinosinusitis has its own diagnostic criteria, as decided in August 1996 by the multidisciplinary rhinosinusitis task force, on behalf of the American Academy of Otolaryngology–Head and Neck Surgery.[19] The resulting article, 'Adult rhinosinusitis defined', was published in 1997 and endorsed by the American Academy of Otolaryngology–Head and Neck Surgery, the American Academy of Otolaryngic Allergy and the American Rhinologic Society.[20,21] The main defining marker is the presence of symptoms for at least 12 weeks. Along with this, the patient should have at least two major factors present or one major factor and at least two minor factors, or nasal purulence on examination (see Table I).[22]

Any rhinitis of an allergic nature involves an immunoglobulin E mediated response to inhaled allergens on the nasal mucosa. The aetiology of rhinosinusitis can be broadly divided into infective and non-infective causes, but it is infection that is most important in bronchiectasis. *Staphylococcus aureus*, coagulase-negative staphylococcus, and anaerobic and gram-negative bacteria are the predominant organisms in chronic rhinosinusitis, as reflected by the common prescribing habits of otorhinolaryngologists, and beneficial outcomes have been noted in controlled circumstances over short periods.[23,24] What remains uncertain is the actual pathophysiological role which bacteria play in chronic rhinosinusitis; it may be that they are present by association only. Further research will no doubt be ongoing in this area.

To date, there have been suggestions in the literature of a non-infective – or specifically, a non-bacterial – aetiology evident in chronic rhinosinusitis.[25] The sinus mucosa inflammatory infiltrate has been shown to be similar in composition to that of asthmatic patients, with typical cells including lymphocytes, mast cells, eosinophils, fibroblasts, plasma cells and goblet cells. The evidence for an immunological mechanism is underlined by the finding of an increased number of T_H2 lymphocytes positive for interleukins 5 and 13 and interferon-γ in the sinus mucosa of patients with chronic rhinosinusitis; this is despite less than 40 per cent being atopic.[26] It may be that bacterial and fungal colonisation provoke this immunological response without direct pathogenesis, but it remains that histological and radiological changes are evident in the presence of both bacteria and fungi.[27,28] The demoralising reality of endoscopic sinus surgery is that a small proportion of patients return to the clinic with purulent discharge, despite their widened middle meati and beautifully opened ethmoid cavities.[22]

TABLE I

DIAGNOSTIC FACTORS FOR CHRONIC RHINOSINUSITIS

Major factors	Minor factors
Nasal obstruction or blockage	Headache
Nasal discharge or purulence or discoloured postnasal drainage	Fever (all non-acute)
Hyposmia or anosmia	Halitosis
Purulence in nasal cavity on examination	Fatigue
Fever (acute rhinosinusitis only)*	Dental pain
Facial pain or pressure†	Cough
	Ear pain or pressure or fullness

*Fever in acute sinusitis alone does not constitute a strongly suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign. †Facial pain or pressure alone does not constitute a suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign.

Evidence for interaction between bronchiectasis and sino-nasal disease

Kartagener's syndrome typifies the link between chronic rhinosinusitis and bronchiectasis, with the added component of situs inversus.[29] The underlying problem in this syndrome is absent or possibly severely impaired ciliary motility. This scenario can also occur without situs inversus, and in this circumstance is known as primary ciliary dyskinesia.[30,31] As the name suggests, it is primarily a dysfunction of cilial motility rather than a loss of their function outright. Primary ciliary dyskinesia is usually a recessive condition, but there can be genetic heterogenicity. Cilial function is vital to the effective clearing of microscopic particulate matter in the respiratory tract.[32] The motile cilia of the respiratory tract have a nine plus two arrangement of the microtubules and associated proteins that make up the core of the cilia, known as the axoneme (Figure 1).

Within the axoneme, the microtubules in the peripheral pairs differ from one another and are known as A and B tubules. The B tubules are incomplete with respect to the A tubules, in that they contain only two rather than 13 parallel protofilaments. The A microtubules also have an inner and outer row of dynein arms. In primary ciliary dyskinesia, the motile cilia are found to contain abnormalities of the dynein arms and the radial spokes. However, they also lack a central pair of doublets, and therefore have an eight plus one configuration. Occasionally, patients may have an abnormal cilial beat frequency in the presence of a normal structural configuration. Disordered orientation of the cilia

https://doi.org/10.1017/S0022215107009140 Published online by Cambridge University Press

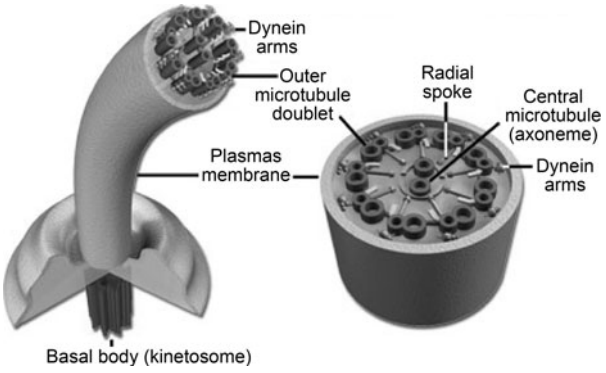

FIG. 1
Cilia and flagella structure.

(when beating) can also occur. Thus far, three genetic defects have been discovered which affect the dynein arms of the axoneme.[33–35]

Atypical cilia have also been found in normal subjects without respiratory disease, but there is some doubt as to their validity.[36–40] However, a study of cilial ultrastructure and function demonstrated that patients with primary ciliary dyskinesia had a significantly greater proportion of cilial abnormalities than did normal subjects.[41] This same study also found that the patient sub-group with allergic rhinitis had a significantly higher ciliary beat frequency than the other, non-primary ciliary dyskinesia sub-groups. Another study assessing cilial orientation found that primary ciliary dyskinesia patients had a high incidence of ciliary disorientation.[42]

However, the effect of abnormal cilial structure and function may not account for the entire problem. Abnormal mucus could also have a role to play in the process,[43] as was concluded by Stanley *et al.*[44] following their study of mucociliary clearance in patients with chronic rhinitis and concomitant chest disease. Mucociliary clearance time was prolonged in patients with both allergic and non-allergic rhinitis. Furthermore, although concomitant asthma did not significantly increase it, 57 per cent of patients with chronic rhinosinusitis and bronchiectasis had mucociliary clearance times greater than 60 minutes.[44] Another study of nasal mucociliary clearance in asthmatics and bronchiectatics, using 68 subjects including controls, showed a significantly impaired clearance time in both groups. These authors stated that this was due to a combination of impaired ciliary function and mucus abnormality,[45] and this finding has been echoed by other studies.[44,46,47]

Clinical pattern of disease

Clinically, patients with Kartagener's syndrome or primary ciliary dyskinesia generally report symptoms of rhinorrhoea and/or mucopus discharge from birth.[29] Not surprisingly, more than a third of patients with this syndrome are found to have nasal polyposis, and all patients fail the saccharin clearance test.[48] *Haemophilus influenzae* was the most common organism found in nasal cultures taken from the inferior turbinates in a study of Kartagener's syndrome patients.[29] Otitis media with effusion is also a common manifestation in these patients, and may cause them to present with conductive deafness. Primary ciliary dyskinesia may be missed in children thought to be atopic with rhinitis and asthma, but microbiological analysis of nasal discharge will usually help to clear up any confusion.[49] These patients can also suffer infertility, and cases have been reported in which this occurs in the absence of any respiratory disease.[50]

A 1991 Japanese study found that 5 per cent of patients with chronic rhinosinusitis had bronchiectasis. However, conversely, the same study found that 45 per cent of patients with idiopathic bronchiectasis had chronic rhinosinusitis, thus demonstrating that the presence of lower airway disease predisposed towards a much increased risk of upper airway disease.[51] This same study also reported that 70 patients with chronic rhinosinusitis had a high incidence of fibro-nodular shadowing in the lungs on a chest X-ray, compared with 70 controls. Another study of patients with primary ciliary dyskinesia showed an even greater correlation between bronchiectasis and chronic rhinosinusitis, with 79 per cent of patients demonstrating both pathologies either clinically or radiologically.[52]

As mentioned above, the mucociliary (saccharin) clearance test is the investigation used to confirm the diagnosis, although sometimes further confirmation will be necessary from electron microscopy of nasal biopsies or bronchial brush biopsies.[53] Traditionally, the diagnostic feature on electron microscopy was dynein deficiency. However, more recently, this has been challenged by the introduction of ciliary function analysis following ciliogenesis, which appears to have a high specificity and sensitivity.[54] In the UK, the centres which currently have a diagnostic service performing nasal brushing for primary ciliary dyskinesia assessment are the Royal Brompton Hospital, London, the Leicester Royal Infirmary and the Southampton General Hospital. In addition, genetic counselling will often be important, as the condition is predominantly inherited as an autosomal recessive trait. These patients will also often require regular chest physiotherapy in order to ensure drainage of dependent areas of the lungs; parents of affected children are often encouraged to learn the techniques themselves.

Conclusions

The evidence from the literature to date leaves no doubt about the common pathological pathway which leads to disease of the lower and upper respiratory tract due to cilial and mucus abnormalities. However, many of these studies are now 20 years old, and as a better understanding of cilial disease is obtained at a molecular and genetic level, so further studies may well enhance the current knowledge and bring the possibility of improved therapeutic options. There is undeniably a need for

https://doi.org/10.1017/S0022215107009140 Published online by Cambridge University Press

clinicians, within both respiratory medicine and otorhinolaryngology as well as in general practice, to consider the 'combined airway' model[55] when treating patients. Thus, the role for combined airways clinics is ever clearer, in the age of the multi-disciplinary team.

References

1 Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol* 1994; **94**:182–8
2 Lode H. Respiratory infection: the disease. *Clin Ther* 1985; **7**:1–18
3 Murray JF. New presentations of bronchiectasis. *Hosp Prac* 1991;**26**:55–8
4 Schuster A, Ueki I, Nadel JA. Neutrophil elastase stimulates tracheal submucosal gland secretion that is inhibited by ICI 200,355. *Am J Physiol* 1992;**262**:86–91
5 Sepper R, Konttinen YT, Ding Y, Takagi M, Sorsa T. Human neutrophil collagenase (MMP-8), identified in bronchiectasis BAL fluid, correlates with severity of disease. *Chest* 1995;**107**:1641–7
6 Mikami M, Llewellyn-Jones CG, Bayley D, Hill SL, Stockley RA. The chemotactic activity of sputum from patients with bronchiectasis. *Am J Respir Crit Care Med* 1998;**157**:723–8
7 Lander F. Bronchiectasis and atelectasis: temporary and permanent changes. *Thorax* 1946;**1**:198–210
8 Mysliwiec V, Pina JS. Bronchiectasis: the 'other' obstructive lung disease. *Postgrad Med* 1999;**106**:123–6
9 Reid L. Reduction in bronchial subdivision in bronchiectasis. *Thorax* 1950;**5**:233–47
10 McGuinness G, Naidich DP. CT of airways disease and bronchiectasis. *Radiol Clin North Am* 2002;**40**:1–19
11 Ooi GC, Khong PL, Chan-Yeung M, Ho JC, Chan PK, Lee JC *et al*. High-resolution CT quantification of bronchiectasis: clinical and functional correlation. *Radiology* 2002;**225**: 663–72
12 Remy-Jardin M, Amara A, Campistron P, Mastora I, Delannoy V, Duhamel A *et al*. Diagnosis of bronchiectasis with multislice spiral CT: accuracy of 3-mm-thick structured sections. *Eur Radiol* 2003;**13**:1165–71
13 Scadding G, Lund V. *Investigative Rhinology*, 1st edn. London: Taylor & Francis, 2004
14 Pawankar R. Allergic rhinitis and asthma: the link, the new ARIA classification and global approaches to treatment. *Curr Opin Allergy Clin Immunol* 2004;**4**:1–4
15 Bachert C, van Cauwenberge P. The WHO ARIA (allergic rhinitis and its impact on asthma) initiative. *Chem Immunol* 2003;**82**:119–26
16 Bousquet J, Van Cauwenberge P, Bachert C, Canonica GW, Demoly P, Durham SR *et al*. Requirements for medications commonly used in the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA). *Allergy* 2003;**58**:192–7
17 Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(suppl 5):147–334
18 Pelikan Z, Pelikan-Filipek M. Role of nasal allergy in chronic maxillary sinusitis – diagnostic value of nasal challenge with allergen. *J Allergy Clin Immunol* 1990;**86**: 484–91
19 Anonymous. Report of the Rhinosinusitis Task Force Committee Meeting. Alexandria, Virginia, August 17 1996, *Otolaryngol Head Neck Surg* 1997;**117**:1–68
20 Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997;**117**:1–7
21 Lund VJ, Kennedy DW. Staging for rhinosinusitis. *Otolaryngol Head Neck Surg* 1997;**117**:35–40
22 Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW *et al*. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 2003;**129**(suppl 3):s1–32
23 Fairbanks DN. Inflammatory diseases of the sinuses: bacteriology and antibiotics. *Otolaryngol Clin North Am* 1993;**26**:549–59
24 Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. *Am J Rhinol* 2002;**16**:303–12
25 Statham MM, Seiden A. Potential new avenues of treatment for chronic rhinosinusitis: an anti-inflammatory approach. *Otolaryngol Clin North Am* 2005;**38**: 1351–65, xi
26 Shin SH, Ponikau JU, Sherris DA, Congdon D, Frigas E, Homburger HA *et al*. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. *J Allergy Clin Immunol* 2004;**114**:1369–75
27 Abraham C, Faddis B, Chole R. Chronic bacterial rhinosinusitis: description of a mouse model. *Arch Otolaryngol Head Neck Surg* 2001;**127**:657–64
28 Ponikau JU, Sherris DA, Kita H, Kern EB. Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2002;**110**:862–6
29 Pedersen M, Mygind N. Rhinitis, sinusitis and otitis media in Kartagener's syndrome (primary ciliary dyskinesia). *Clin Otolaryngol* 1982;**7**:373–80
30 Eliasson R, Mossberg B, Camner P, Afzelius BA. The immotile-cilia syndrome. A congenital ciliary abnormality as an etiologic factor in chronic airway infections and male sterility. *N Engl J Med* 1977;**297**:1–6
31 Sleigh MA. Primary ciliary dyskinesia. *Lancet* 1981;**ii**:29
32 Eley L, Yates LM, Goodship JA. Cilia and disease. *Curr Opin Genet Dev* 2005;**15**:308–14
33 Olbrich H, Haffner K, Kispert A, Volkel A, Volz A, Sasmaz G *et al*. Mutations in DNAH5 cause primary ciliary dyskinesia and randomization of left-right asymmetry. *Nat Genet* 2002;**30**:143–4
34 Pennarun G, Escudier E, Chapelin C, Bridoux AM, Cacheux V, Roger G *et al*. Loss-of-function mutations in a human gene related to *Chlamydomonas reinhardtii* dynein IC78 result in primary ciliary dyskinesia. *Am J Hum Genet* 1999;**65**:1508–19
35 Bartoloni L, Blouin JL, Pan Y, Gehrig C, Maiti AK, Scamuffa N *et al*. Mutations in the DNAH11 (axonemal heavy chain dynein type 11) gene cause one form of situs inversus totalis and most likely primary ciliary dyskinesia. *Proc Nat Acad Sci USA* 2002;**99**:10282–6
36 McDowell EM, Barrett LA, Harris CC, Trump BF. Abnormal cilia in human bronchial epithelium. *Arch Pathol Lab Med* 1976;**100**:429–36
37 Takasaka T, Sato M, Onodera A. Atypical cilia of the human nasal mucosa. *Ann Otol Rhinol Laryngol* 1980;**89**: 37–45
38 Fox B, Bull TB, Makey AR, Rawbone R. The significance of ultrastructural abnormalities of human cilia. *Chest* 1981; **80**(suppl 6):796–9
39 Fox B, Bull TB, Arden GB. Variations in the ultrastructure of human nasal cilia including abnormalities found in retinitis pigmentosa. *J Clin Pathol* 1980;**33**:327–35
40 Kollberg H, Mossberg B, Afzelius BA, Philipson K, Camner P. Cystic fibrosis compared with the immotile-cilia syndrome. A study of mucociliary clearance, ciliary ultrastructure, clinical picture and ventilatory function. *Scand J Respir Dis* 1978;**59**:297–306
41 Rossman CM, Lee RM, Forrest JB, Newhouse MT. Nasal ciliary ultrastructure and function in patients with primary ciliary dyskinesia compared with that in normal subjects and in subjects with various respiratory diseases. *Am Rev Respir Dis* 1984;**129**:161–7
42 De Iongh R, Rutland J. Orientation of respiratory tract cilia in patients with primary ciliary dyskinesia, bronchiectasis, and in normal subjects. *J Clin Pathol* 1989;**42**: 613–19
43 Eliezer N, Sade J, Silberberg A, Nevo AC. The role of mucus in transport by cilia. *Am Rev Respir Dis* 1970;**102**: 48–52
44 Stanley PJ, Wilson R, Greenstone MA, Mackay IS, Cole PJ. Abnormal nasal mucociliary clearance in patients with rhinitis and its relationship to concomitant chest disease. *Br J Dis Chest* 1985;**79**:77–82

45 Awotedu AA, Babalola OO, Lawani EO, Hart PD. Abnormal mucociliary action in asthma and bronchiectasis. *Afr J Med Med Sci* 1990;**19**:153–6
46 Rutland J, Cole PJ. Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. *Thorax* 1981;**36**:654–8
47 Varpela E, Laitinen LA, Keskinen H, Korhola O. Asthma allergy and bronchial hyper-reactivity to histamine in patients with bronchiectasis. *Clin Allergy* 1978;**8**:273–80
48 Eccles R. Physiology of the nose. In: Jones A, Phillips D, Hilgers F, eds. *Diseases of the Head and Neck, Nose and Throat*. London: Arnold, 1998:675–6
49 Williams RB 3rd, Gwaltney JM Jr. Allergic rhinitis or virus cold? Nasal smear eosinophilia in differential diagnosis. *Ann Allergy* 1972;**30**:189–94
50 Moryan A, Guay AT, Kurtz S, Nowak PJ. Familial ciliary dyskinesis: a cause of infertility without respiratory disease. *Fertil Steril* 1985;**44**:539–42
51 Shirahata Y. Correlation between upper airway tract and lower airway tract in the break down of sinobronchiectasis [in Japanese]. *Nippon Jibiinkoka Gakkai Kaiho* 1991;**93**: 1991–8
52 Mossberg B, Camner P, Afzelius BA. The immotile-cilia syndrome compared to other obstructive lung diseases: a clue to their pathogenesis. *Eur J Respir Dis Suppl* 1983; **127**:129–36
53 Biggart E, Pritchard K, Wilson R, Bush A. Primary ciliary dyskinesia syndrome associated with abnormal ciliary orientation in infants. *Eur Respir J* 2001;**17**:444–8
54 Jorissen M, Willems T, Van der Schueren B. Ciliary function analysis for the diagnosis of primary ciliary dyskinesia: advantages of ciliogenesis in culture. *Acta Oto-laryngol* 2000;**120**:291–5
55 Hens G, Hellings PW. The nose: gatekeeper and trigger of bronchial disease. *Rhinology* 2006;**44**:179–87

Address for correspondence:
Mr Carl M Philpott,
The Cottage,
Debenham Road,
Middlewood Green,
Stowmarket IP14 5EZ, UK.

E-mail: carl.philpott@btinternet.com

Mr C M Philpott takes responsibility for the integrity of the content of the paper.
Competing interests: None declared