regimens (simulating a clinical trial) for our patients. In a study evaluating metered dose inhaler compliance in COPD, use of an electronic medication monitor with feedback on the accuracy of medication use improved compliance.11 This type of methodology could be used to improve adherence in COPD outside a clinical trial. Clearly, further research is needed to better understand the factors driving the phenomenon of improved outcomes in adherers. While it is disappointing that neither treatment with active drug nor disease severity had an impact on adherence, study participation was better in the combination treatment arm of the TORCH study which suggests that symptomatic improvement may positively affect the likelihood of compliance of a patient with COPD in the more global sense. This would be good news for our patients as the current analysis also

suggests that the association between adherence and mortality risk reduction with combination therapy was even greater when only those in the treatment arm were analysed.

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# Airways disease: just nosing around?

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The airway is a continuous structure extending from the nasal vestibule to the alveoli, with the same pseudostratified ciliated columnar epithelium along much of its length. While an arbitrary line at the level of the vocal cords divides the airway into upper and lower subdivisions-a concept introduced in medical school anatomy tutorials and continued in patient care-airways disease does not conform to such specific anatomical regions. Upper and lower airway disease often coexist, with upper airway involvement often preceding that of the lower airway and even determining severity of disease and quality of life.1 This recognition has led to the development of the terms "united airways" and "one airway, one disease".

The nose is an air conditioner—filtering, warming and humidifying over 10 000 litres of air daily before it progresses to the lungs. The nasal passages and associated structures bear the brunt

of environmental contact, being the first site of allergen, microbial and particle deposition. As a consequence, the upper airway is the location of a highly-developed innate and adaptive immune system. Effective mucociliary clearance is vital for respiratory health, as evidenced by the effects of defects such as primary ciliary dyskinesia (PCD) and cystic fibrosis. Sinus disease is almost universal in these patients, and even the subgroup of idiopathic bronchiectasis demonstrates high rates of chronic sinus infection, polyps and inflammation.<sup>2</sup> Simple measures such as nasal douching can help with symptoms and quality of life. Measurement of nasal nitric oxide is simple and quick,<sup>3</sup> and very low levels can alert the physician to the possibility of PCD before major lung damage is sustained, thus allowing the benefit of early physiotherapy.

An important lymphoid tissue mass (tonsils and adenoids) collectively termed Waldeyer's ring and prominent in childhood is a unique immunological organ surrounding the upper airway. It supports development and maturation of the immune system. A defective or compromised immune response often manifests initially with recurrent upper airway infection before involving the lungs or other organs. The upper airway epithelium can rapidly generate an array of immunomodulatory cytokines, chemokines and growth factors in response to injury, allergen or pathogen contact that can activate and sustain an airway inflammatory response. The submucosal tissue is rich in antigen presenting cells that can sample the environment, process material and subsequently navigate an immune response via induction of T cell function and immunoglobulin production. An over-excessive or dysregulated immune response can lead to allergic disease, predominantly Th2-mediated and possibly predisposed to by the presence of thymic stromal lymphopoietin in nasal epithelium.4 5 Alternatively, Th1 mechanisms give rise to serious systemic disorders such as Wegener's granulomatosis in which, again, upper airway manifestations usually appear first.6 Early diagnosis and rapid treatment can prevent further organ involvement such as renal disease and improve prognosis. The upper airway is also a site of manifestation of rheumatological disease such as Sjogren's syndrome or disorders of vascular remodelling impairment such as hereditary haemorrhagic telangiectasia. It is therefore evident that a broad spectrum of disease can present at the nasal level before involving the remainder of the airways, allowing a window of opportunity for diagnosis and early intervention.

Rhinitis means inflammation of the nasal lining, but the term is used to define a constellation of symptoms—nasal obstruction or congestion, rhinorrhoea

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(anterior and/or posterior), sneezing and nasal itch. Rhinitis, whether allergic or non-allergic, predisposes to asthma with an odds ratio of 3.7 Certain forms of rhinitis exhibit even higher risks of developing asthma-for example, occupational rhinitis in wood workers, farmers8 and those allergic to house dust mite. Early diagnosis with either removal from allergen exposure or immunotherapy could prevent asthma, as has been shown for children allergic to grass pollen.9 10 Most subjects with asthma have rhinitis, and even in those without nasal symptoms, upper airways inflammation is demonstrable.<sup>11</sup> The reverse is also true—findings now explicable by the elegant studies of Wytske Fokkens and her colleagues who challenged the nose with allergen and showed eosinophil ingress to both nose and bronchi and vice versa.<sup>12 13</sup>

Seasonal allergic rhinitis is associated with increased airway hyperresponsiveness (AHR)<sup>14</sup> which is treatable by reducing nasal inflammation.<sup>15</sup> In fact, the same dose of corticosteroid is more effective in reducing AHR when applied nasally than when inhaled.<sup>16 17</sup> This may account for the discrepancy between lower airways inflammation and bronchial hyperreactivity which is becoming apparent from recent human trials of anti-interleukin (IL)-5 in which reduction of blood and sputum eosinophils failed to affect forced expiratory volume in 1 s while reducing exacerbations.

Most asthma exacerbations begin in the upper airway, often with a viral cold.18 Synergy exists between viral and allergic inflammation such that there is a nearly 20-fold risk of hospitalisation for asthma in the allergic child exposed to both relevant allergen plus rhinovirus.19 Our work on rhinitis co-morbidities such as otitis media with effusion suggests that, by reducing nasal inflammation in allergic children by regular intranasal corticosteroids, the effects of intermittent colds can be ameliorated.<sup>20 21</sup> This approach needs to be extended to asthma both in adults and children with large well-designed prospective studies and also to chronic obstructive pulmonary disease (COPD). Large-scale retrospective series do show benefits to asthma by treatment of associated rhinitis, including reduced emergency visits, hospitalisation or both,<sup>22-24</sup> although one would not appreciate this from reading the present national asthma guidelines.<sup>25</sup>

Severe or difficult asthma remains a clinical challenge with significant utilisation of health resources. In several recent studies, poor asthma control is associated with rhinitis.<sup>26 27</sup> In a UK general practice study of 4429 patients with asthma, bothersome rhinitis gave an odds ratio of >4 for poor asthma control (as defined by an Asthma Control Questionnaire of >1.25), similar to that for smoking. Mild rhinitis was more likely to worsen asthma (odds ratio 1.97) than poor adherence to treatment (odds ratio 1.29).<sup>28</sup> Yet in asthma clinics it is routine to ask about smoking and adherence but to ignore rhinitis.

Chronic rhinosinusitis is a concept possibly less familiar than rhinitis to chest physicians. It implies inflammation of the nose and of the sinus linings and can include nasal polyposis.29 30 It is consistently associated with increasing severity of asthma.31 32 Asthmatic patients with nasal polyposis and aspirin intolerance have the highest rates of exacerbation and hospital admissions.<sup>33</sup> Again this disorder begins in the upper airway-often in young adults with symptoms of a severe cold which fails to resolve. Nasal polyps, asthma and aspirin sensitivity develop over the following few years.<sup>34</sup> The upper airway, because of its accessibility, has proved invaluable in investigating the pathophysiology of this disease, in diagnosing it safely by nasal aspirin challenge<sup>35</sup> and as a route of treatment using topical aspirin desensitisation.<sup>36</sup>

Staphylococcus aureus is present in nasal polyps and *S* aureus enterotoxin B further shifts the local cytokine pattern toward Th2 cytokines but disfavours the T regulatory cytokines IL-10 and transforming growth factor- $\beta_1$ . Furthermore, *S* aureus-derived enterotoxins influence local immunoglobulin synthesis and induce polyclonal immunoglobulin E production which may contribute to severe inflammation via activation of mast cells.<sup>37</sup> This observation has been extended to the bronchial mucosa<sup>38</sup> and may be relevant to intrinsic asthma.<sup>39</sup>

Studies in animal models have shown that localised allergen provocation is associated with a systemic inflammatory response with bone marrow increases in inflammatory cell progenitors.<sup>40</sup> The demonstration that antigen stimulation of any part of the respiratory mucosa leads to a ripple effect along the entire airway<sup>12 13</sup> must suggest that other mechanisms of nasal mucosal activation and damage-for example, infection or particulate stress such as tobacco smokehave the potential to exacerbate lower airway disease. While studies in COPD are currently limited, the nasal airway in patients with stable COPD has increased inflammation<sup>41 42</sup> and a rapid response to

local histamine provocation with neutrophil activation and mucin secretion.<sup>43</sup> The suggestion is that an immunologicallyprimed upper airway is present in COPD and can recognise and initiate a rapid local immune response to microbial and particulate activation which contributes to the increase in bronchial inflammation found at exacerbation. Further studies are needed to evaluate such mechanisms, as there may be important implications for intervention in COPD exacerbations at the nasal level.

In this issue of Thorax a series of focused reviews is initiated which evaluate the current evidence that supports an important role for the upper airway in the initiation, maintenance and exacerbation of respiratory diseases (see page 999). The importance of assessing the upper airway in a respiratory clinic is highlighted. It is obvious that much work is still needed to broaden our understanding of the mechanistic interactions of airway disease and how intervention at the level of the upper airway will impact on overall disease response and quality of life. Given that the nasal mucosa is an easily accessible site for tissue sampling and delivery of interventions, development of nasal models of disease must be considered. Prospective studies to evaluate the benefits of nasal intervention in specific disease settings are a priority; any trial of treatment for asthma should automatically include assessment of upper airway changes and vice versa. The American Thoracic Society and the European Respiratory Society have recently released official standards regarding asthma evaluation for clinical trials and practice which are disappointingly parochial. Future asthma guidelines should incorporate guidance on the evaluation of upper airway manifestations of disease and intervention strategies. Asthma control needs replacing with airways control. A multidisciplinary approach with respiratory physicians working with ENT surgeons with training in rhinology is ideal, but probably unlikely in light of present financially-driven health care. The future respiratory physician should therefore be trained in upper as well as lower airways medicine since, by assessing the whole airway, it is anticipated that better disease understanding, control, improved quality of life and possibly prevention will be achieved with ultimate benefits for patients.

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