

Indoor pollutants and asthma in children

The great indoors

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Further evidence for the role of indoor pollutants in the development of childhood asthma

The prevalence of asthma (especially childhood asthma) is high, and children in particular spend a lot of time in their homes. In addition, our homes contain many pollutants so, understandably, we'd like to know to what extent pollutants in the home environment cause and/or worsen asthma in our children.

WHAT DO WE KNOW?

In many children asthma is closely associated with allergy, and many asthmatic children are allergic to dust mite and pet allergens. For them, reduction of exposure is likely to be beneficial. But does this mean that mite and pet exposure causes asthma? This issue is surprisingly complex. Whereas studies suggest that exposure to specific allergens increases sensitisation to those allergens, this does not necessarily mean that such exposures also increase the incidence of asthma.^{1,2} Some studies even suggest that early life exposure to pets (and other animals) may reduce the incidence of asthma.³⁻⁷

Compared with the already complex role of exposure to allergens and other biological contaminants, the evidence with respect to chemicals such as nitrogen oxides, sulfur oxides, and particles produced by combustion appliances, environmental tobacco smoke, and volatile organic compounds (VOCs) is even less clear.

In this issue of *Thorax* two new studies from Australia attempt to provide further evidence for the role of unvented heating appliances and of VOCs, respectively. Phoa *et al*⁸ retrospectively collected data on unvented heater exposure in a sample of children aged 8–11 years. Early—but not current—exposure to unvented space heaters was found to be associated with airway hyperresponsiveness and wheeze. Rumchev *et al*⁹ conducted a case-control study in young children and found that children aged 6–36 months, discharged from a hospital emergency department with a diagnosis of asthma, had higher concentrations of VOCs in their homes than control children living in the same community.

WHAT EVIDENCE CAN WE GLEAN FROM THESE NEW STUDIES?

Effect of gas heaters on development of childhood asthma

The study by Phoa *et al* was questionnaire based and grouped all sorts of “fume emitting” space heaters into one category—including gas heaters, kerosene heaters, open fireplaces, and wood stoves, each of which have distinctly different patterns of emissions of noxious substances. No measurements of pollutants were performed in the homes. Flued gas heaters, open fires, and wood stoves were all included in the fume emitting category, whereas it is likely that these are connected to chimneys and flues which would prevent most of the emissions from entering the indoor space. Adjustment for socioeconomic status (a likely covariate of flueless heater use) was not attempted, so some uncertainty remains about the extent to which the findings could be attributed in part to differences in socioeconomic status. The authors reported no association between asthma and *current* use of flueless heaters, but the analysis presented adjusted for the use of flueless heaters *early* in life. If there was a substantial correlation between early and current use of flueless heaters, this may mean that the lack of association with current heater use is to some extent due to overadjustment.

Unvented space heaters, fireplaces, and wood stoves have been studied before by several investigators. In a small study Cooper and Alberti¹⁰ found no effect on the lung function of healthy residents of homes with kerosene heaters. In a study in small children Triche *et al*¹¹ found a slight increase in cough with the use of kerosene heaters and wood stoves and slightly more wheeze with the use of unvented gas heaters in the home. In a study from Seattle neither asthma nor wheeze in 5–9 year old children was found to be related to the use of either gas heaters, wood stoves or kerosene heaters.¹² A prospective study from Tasmania did find a relationship between gas heater usage in the first year of life and asthma at the age of 7 years.¹³ A large study from Finland found a *negative* association

between the use of wood stoves and asthma outcomes, but argued that this was because wood stoves were used more on traditional farms. The association disappeared after adjustment for living on a farm.¹⁴ Wood smoke is a well known respiratory irritant, and the use of wood stoves was found to be related to lower respiratory tract illness in a case-control study in small children.¹⁵ A study conducted among a panel of asthmatics found that subjects had more symptoms of cough and shortness of breath on days with reported use of gas stoves, fireplaces or wood stoves.¹⁶ Although the evidence is not entirely consistent, it is clear that unvented combustion appliances increase the exposure of inhabitants to combustion products to a sufficient extent to cause exacerbations and, perhaps, induction of respiratory diseases and symptoms. The study by Phoa *et al* adds to this evidence, albeit with less specificity than previous studies.

Effect of VOCs on development of childhood asthma

Rumchev *et al* found differences in indoor VOC concentrations between children with asthma and controls. This was a study in very young children at an age when the diagnosis of asthma is notoriously difficult. Measurements of VOCs were of short duration only (8 hours), but this is likely to lead to random misclassification primarily which would reduce differences between cases and controls. More “asthma” cases than controls reported recent indoor painting which probably shifted the VOC concentrations upwards, and no attempt was made to investigate differences between cases and controls after exclusion of subjects reporting recent indoor painting.

Few studies have addressed the effects of indoor exposure to VOCs on respiratory health. The focus in experimental studies has mostly been on sensory and neurological effects, observed at rather higher concentrations than those measured by Rumchev *et al* (median 36 µg/m³, maximum 600 µg/m³). In the experimental studies by Molhave and others, the concentrations tested have typically been in the range 3–25 mg/m³ and, more often than not, no effects were seen at the lower end of this range.^{17,18} Occupational studies among painters other than spray painters (who may be exposed to isocyanates) have provided evidence of increased asthma rates.¹⁹ However, a study comparing painters using water based paints with VOC exposures in the 1–3 mg/m³ range with painters using solvent based paints with VOC exposures in the 100–380 mg/m³ range

found evidence of increased airway symptoms in the latter group only.²⁰ A recent large study from the UK²¹ failed to document any effects of VOCs on persistent wheezing illness in school children at total VOC concentrations that were higher than in the study by Rumchev *et al*, but a study from Leipzig found that early life exposure to low concentrations of 25 selected VOCs related to house painting was associated with increased respiratory infections in infants.²² Other studies have suggested that VOC emissions from recent house redecorations and floorings might be related to asthma-like symptoms.^{23–24} Whether such associations reflect direct effects of indoor VOCs at low concentrations or, for example, confounding by traffic related pollutants covarying with indoor VOCs²⁵ remains to be seen.

The issue of whether indoor VOCs are a risk factor for asthma in children therefore seems still to be largely undecided. In view of the methodological difficulties outlined above, prospective studies are more likely to produce progress in deciding whether we need to worry about indoor VOCs as determinants of asthma at the relatively low concentrations typically encountered in the home environment.

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TRPV1 and cough

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G P Anderson

Iodo-resiniferatoxin, a new TRPV1 inhibitor, shows promising antitussive activity in an animal model

Cough is one of the most common respiratory complaints and intractable cough remains one of the most distressing and difficult to treat conditions of the lung. It is ironical that the billions of dollars spent worldwide on proprietary over the counter remedies of questionable efficacy¹ for cough exceeds, by orders of magnitude, the money spent on basic cough research. It is therefore not surprising that the cough pharmacopoeia has altered little in the last 50 years, with no important advances over opiate based compounds and cro-

mones. However, basic researchers have not been idle. In this issue of *Thorax* Trevisani and colleagues² present new information pointing to a causative role for an ion channel called transient receptor potential vanilloid-1 (TRPV1) in cough. They show that the highly selective and potent TRPV1 inhibitor iodo-resiniferatoxin, derived from a plant toxin found in *Euphorbia* species, strongly suppresses cough induced by inhaled capsaicin or citric acid in conscious guinea pigs, a widely used animal cough model.

The basis of this work is careful molecular dissection of precisely why coughing occurs when irritants are inhaled. It has been known for years that irritants such as citric acid and capsaicin (the pungent tongue burning constituent of hot chilli peppers) trigger coughing. It has also been known for decades from electrophysiological studies that such irritants activate respiratory tract sensory fibres—especially unmyelinated C fibres—to discharge information via the vagus to the medullary cough centre.³ From this early work it was inferred that the cough receptor on sensory fibres might be an ion channel able to rapidly depolarise afferent nerve membranes and hence trigger cough inducing impulses. This view was reinforced by the inhibitory activity of crude agents such as the dye ruthenium red. The discovery that capsazepine, a capsaicin derivative and a known ion channel blocker, had antitussive activity in animal models⁴ focused attention on the vanilloid receptor family as candidate ion channels.

The TRPV1 channel is a so-called receptor operated ion channel. It is moulded from six transmembrane domains that cluster forming a molecular “gate” which regulates the flow of cations across membranes when activated by a soluble ligand. TRPV1 is encoded on chromosome 17p13.3 and is also known as the capsaicin receptor, and the vanilloid receptor subtype 1 (VR1). This channel has been of interest to pain researchers for some time as it is known that the TRPV1 channel can be activated by painful heat (>43°C) and acid (pH <6.5). Its expression, however, is not confined to sensory nerves; TRPV1 has also recently been found on glial cells, endothelium, epithelium and keratinocytes, suggesting that it may have a much broader role in regulating responses to tissue injury. Indeed, as there is no good evolutionary reason why the lower lung should respond to hot pepper extracts, it has been strongly suspected that there must be one or more endogenous ligands for TRPV1. To date, three putative “endovanilloids” including N-acyldopamines, arachidonic acid lipxygenase metabolites, and anandamide (the endogenous ligand for cannabis receptors) have been identified.⁵ It is quite conceivable that these endoligands may be upregulated—together with kinins, histamine, and other known cough triggers—in lung diseases, but their specific relationship to cough is unknown.

TRPV1 therefore has the attraction of being a common activation point for coughing induced by different stimuli. As always, there are caveats. The cough reflex has important survival benefits

and it is likely that multiple cough pathways have co-evolved. Mice breathe too rapidly and too shallowly to generate the airflow turbulence necessary to clear mucus by coughing, but they have a highly conserved afferent fibre TRPV1 which has strong homology with the human form. Elegant research by Kollarik and Udem⁶ has very recently identified TRPV1 independent discharges in bronchopulmonary vagal afferent fibres to bradykinin and acid in TRPV1 knock-out mice, indicating that at least one “back up” mechanism must exist. These findings are consistent with earlier studies showing that capsazepine did not block all cough inducing stimuli.⁴ It is also clear that patients with chronic cough have a reduced threshold for stimulation of cough, most probably because their afferent sensory fibres have become sensitised in a manner analogous to hyperalgesia in chronic pain. It is thought that this sensitisation may have both a peripheral and a CNS component. The role of TRPV1 in the induction or reversal of sensitisation—which may underlie very intractable cough—remains unknown. Moreover, the causes of cough in humans range from the physiological to the existential. While it is reasonable to hope that TRPV1 targeted treatments might benefit cough in very common clinical settings such as chronic obstructive pulmonary disease, post-viral cough syndromes, and cough associated with gastro-oesophageal reflux disease, it seems unlikely that the concept would benefit “psychogenic” cough at all.

Notwithstanding these limitations, the work of Trevisani and coworkers showing a therapeutic benefit of inhibiting TRPV1 with iodo-resiniferatoxin (and the more than 60 patents already filed in this field) suggests that there may soon be safer and more effective agents to deal with this perennial problem.

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Pneumocystis jirovecii infection

Pneumocystis jirovecii infection

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A review of *Pneumocystis* and the rationale for renaming it

The organism *Pneumocystis* causes severe pneumonia in individuals with immune systems impaired by HIV, transplantation, malignancy, connective tissue disease, and the treatment thereof. In HIV infected patients it remains a major pathogen in those who are unaware of their HIV serostatus, or who decline to take or are intolerant of highly active antiretroviral therapy. *Pneumocystis* also infects a wide

variety of mammals and causes pneumonia in those that are immunosuppressed or immunodeficient. Originally *Pneumocystis* was thought to be a single species of protozoa. Study of the organism has been severely hampered by the fact that it cannot be cultured in vitro. Over the last 20 years, using molecular biological, immunological and other techniques, *Pneumocystis* has been shown to be a fungus, to be genetically

diverse, host species specific, transmissible from animal to animal, to colonise individuals with minor degrees of immunosuppression, and to cause clinical disease by “new” infection in addition to reactivation of latent childhood acquired infection. More recently the organism causing disease in humans has been renamed *Pneumocystis jirovecii*. This article highlights some of these recent developments and provides a rationale for the renaming of the organism.

WHAT IS PNEUMOCYSTIS?

Chagas first identified *Pneumocystis* organisms in humans in 1909, but they were mistaken for a new stage of the life cycle of the protozoan *Trypanosoma cruzi*.¹ Within a very short time it became apparent that the organism infected other host species, was not a trypanosome, and was named

Pneumocystis carinii in honour of Carini, a colleague of Chagas.² For many years the organism continued to be widely viewed as a protozoan, based on the observations that it had morphological features of protozoa and lacked some phenotypic features typical of fungi, and that antiprotozoal but not antifungal drugs were effective. In 1988 DNA sequence analysis showed that *Pneumocystis* was a fungus.^{3,4} Subsequently, additional DNA analysis at many loci has shown that *Pneumocystis* organisms from different mammalian hosts are quite different.⁵⁻⁷ It is also apparent that *Pneumocystis* shows strong host species specificity—for example, it is not possible to cross infect a mouse with *Pneumocystis* from a rat⁸ yet, if *Pneumocystis* obtained from the lungs of one rat is transferred to another rat, it will cause severe pneumonia. One explanation for these observations is that *Pneumocystis* is an obligate parasite which has co-evolved in a particular host in order to survive.⁹ The above data further indicate that human *Pneumocystis* infection is not a zoonosis. DNA sequence analysis of human *Pneumocystis* at several different loci has demonstrated genetic diversity in the organism^{7,10,11} and has shown that two or more types of organism infect some patients with *Pneumocystis* pneumonia.^{7,11}

HOW DOES HUMAN INFECTION ARISE?

It was originally thought that *Pneumocystis* organisms were acquired during childhood and persisted in the lungs in adult life in a dormant phase. Immunosuppression of the individual—for example, by transplantation or by HIV infection—allowed the organism to propagate and cause pneumonia. The finding of antibodies to *Pneumocystis* in the majority of healthy children¹² and the strong association of disease with immunosuppression support this “latency” hypothesis. This hypothesis has been challenged by studies showing a lack of *Pneumocystis* in the lungs of healthy individuals¹³ and by studies which showed that *Pneumocystis* organisms are frequently acquired and cleared by the immune system of immune competent humans.¹⁴ Animal studies also challenge the “latency” hypothesis. In rat and severe combined immunodeficiency (SCID) mice models of infection, *Pneumocystis* organisms are eliminated from the lungs after *Pneumocystis* pneumonia and persistence of latent organisms is limited.^{15,16} Limited asymptomatic carriage of *Pneumocystis* has been demonstrated in some HIV immunosuppressed adults; during carriage a change in genotype

was observed, strongly supporting a hypothesis of “recent infection”.¹⁷ Further support for the “recent infection” model comes from studies of patients with recurrent episodes of *Pneumocystis* pneumonia in which a different genotype of *Pneumocystis* was associated with each episode.^{18,19} Recent infection is suggested by the finding that allelic variation patterns in isolates of *Pneumocystis* are correlated with patient’s place of diagnosis and not their place of birth.²⁰ The target enzyme for sulpha drugs (sulphamethoxazole, dapsone, etc) is dihydropyrimidine synthase (DHPS). In many organisms, including protozoa such as *Plasmodium falciparum* and bacteria such as *Streptococcus pneumoniae*, mutations in the DHPS gene confer resistance to sulpha drugs. Several studies have shown a significant association between patients’ receipt of sulpha drug prophylaxis and the presence of mutations in the DHPS gene of *Pneumocystis*.^{21,22} These mutations also correlate with geographical location^{22,23} and may additionally be found in *Pneumocystis* from patients who have not received sulpha drug prophylaxis, suggesting that recent transmission has occurred, either directly person to person or via a common environmental source.²³⁻²⁵

In animal models airborne transmission of *Pneumocystis* has been demonstrated²⁶ but the route of transmission of human *Pneumocystis* is unclear. Human *Pneumocystis* DNA has been identified in air spores from both rural²⁷ and hospital environments,²⁸ and it is likely that transmission between humans occurs via the airborne route. This hypothesis is supported by reports of case clusters of *Pneumocystis* pneumonia among immunosuppressed patients,²⁹ transmission of *Pneumocystis* DNA from immunosuppressed patients to immune competent healthcare workers,^{14,30} and mother to child transmission of *Pneumocystis* infection.³¹

COLONISATION AND THE HUMAN RESERVOIR OF INFECTION

Increasingly sensitive techniques have been developed for detecting *Pneumocystis* DNA in human respiratory samples (bronchoscopic alveolar lavage fluid, induced sputum, and oropharyngeal washes) using the polymerase chain reaction.^{11,13,14,32} This sensitivity has enabled detection of very low levels of *Pneumocystis*, not detectable by conventional histochemical staining, in respiratory samples from individuals in whom it was not expected. Molecular detection techniques have shown that

Pneumocystis is carried in the lungs of asymptomatic individuals with mild immunosuppression induced by HIV or malignancy,³³⁻³⁶ in immune competent patients³⁷ with primary pulmonary disorders,³⁸ in patients receiving long term corticosteroid therapy for malignancy or connective tissue disorders,^{39,40} and in pregnant women.⁴¹ It is thought that detection of *Pneumocystis* in respiratory samples from these asymptomatic patient groups represents colonisation with the organism. It is further hypothesised that these groups of patients may be important in the person to person transmission of *Pneumocystis* and that they may be a reservoir for future *Pneumocystis* infection in other susceptible (immunosuppressed) individuals.¹⁷

WHY RENAME PNEUMOCYSTIS CARINII?

In 1994, in response to the accumulation of molecular biological data demonstrating genetic diversity among isolates of *Pneumocystis* from different host species together with data from cross infection studies suggesting host species specificity, an interim renaming of *Pneumocystis carinii* occurred using a trinomial system.⁴² Thus the organism causing infection in humans was named *Pneumocystis carinii* f. sp. *hominis* and that causing infection in rats was called *Pneumocystis carinii* f. sp. *carinii*. In 1999 a binomial system was proposed for naming the organism.⁴³ The organism producing human disease is now known as *Pneumocystis jirovecii* (pronounced “yee-row-vetsee”) in honour of the Czech parasitologist Otto Jirovec who was one of the first researchers to study *Pneumocystis* in humans.^{44,45} This renaming not only recognises the host specificity of different species of *Pneumocystis* for different mammalian hosts, but also the significant differences that exist among different species of *Pneumocystis* at a DNA sequence level. *Pneumocystis carinii* is now the name used to describe infection in rats and is not infectious to humans.^{44,45} The acronym “PCP” which is used to describe the clinical syndrome of pneumonia in both humans and other mammals is still used, but it now represents **P**neumo**C**ystis **P**neumonia. Physicians and patients will be reassured by the knowledge that human infection does not arise in—nor can it be transmitted to—domestic animals, and by the fact that, despite the name change, the clinical disease remains “PCP”.

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Location, location, location: microlocalisation of inflammatory cells and airway dysfunction

C E Brightling, I D Pavord

Role of inflammatory cell location in the pathogenesis of asthma, COPD, and cough

Most inflammatory mediators are rapidly inactivated once they leave the cell so that they act across distances of only a few microns. It is therefore likely that microlocalisation between inflammatory and structural cells is a fundamental organising principle of airway inflammation and repair.

Enthusiasm for the view that microlocalisation is important in obstructive airway diseases has been fuelled by studies which showed inflammatory cells within the airway smooth muscle in asthma and chronic obstructive pulmonary disease (COPD) but not in normal controls. In asthma the airway smooth muscle is infiltrated by mast cells, predominantly of the chymase positive phenotype. Mast cell numbers correlate inversely with airway responsiveness,¹ which suggests that interactions between mast cells and smooth muscle cells are central in the development of the disordered physiology in asthma. The strength of this assertion is underpinned by the paucity of mast cells within the airway smooth muscle in eosinophilic bronchitis, a condition that presents with chronic cough and shares many of the immunopathological features of asthma but is not associated with airflow obstruction or airway hyperresponsiveness.¹⁻³ Importantly, there is evidence that mast cells infiltrating the airway smooth muscle bundle are activated; a necroscopic study of fatal and non-fatal asthma has shown that there is a marked increase in mast cell degranulation in the airway smooth muscle in both the large and small airways.⁴

A recent study has investigated whether a similar phenomenon occurs in COPD. Baraldo *et al*⁵ found increased numbers of neutrophils and CD8+ cells—but not mast cells—in the small airways of smokers with COPD, and the neutrophil number was inversely related to percentage predicted forced expiratory volume in 1 second (FEV₁). This is consistent with an earlier study which

showed that the number of neutrophils in the airway smooth muscle in smokers is related to air trapping as determined by CT scanning.⁶ However, in this study Berger *et al* found that the number of chymase positive mast cells was more closely related with air trapping. Most of the subjects in these studies had undergone lung resection for cancer so, although the airways studied were considered to be from unaffected areas, there remains the possibility that the underlying lung cancer contributed to the inflammatory changes. Nevertheless, the body of evidence strongly suggests that microlocalisation of inflammatory cells within the airway smooth muscle bundle is an important feature of obstructive airway diseases. This raises two key questions:

- Why do specific inflammatory cells accumulate in the airway smooth muscle in asthma and COPD?
- How do interactions between these inflammatory cells and airway smooth muscle cells lead to disordered airway function?

WHY DO SPECIFIC INFLAMMATORY CELLS ACCUMULATE IN THE AIRWAY SMOOTH MUSCLE IN ASTHMA AND COPD?

Selective recruitment of inflammatory cells to the airway smooth muscle is likely to be mediated by smooth muscle derived chemoattractants and by maintenance of the correct microenvironment to maintain cell differentiation and survival. Airway smooth muscle has a significant secretory capacity, so it clearly has the potential to recruit inflammatory cells.⁷ For example, CXCL8 (IL-8) and CXCL10 (IP-10) released by activated airway smooth muscle in COPD may mediate neutrophil and CD8+ cell migration into the airway smooth muscle bundle.^{8,9} A plethora of chemotactic factors for mast cells are released by airway smooth

muscle—notably, stem cell factor (SCF),¹⁰ CCL11 (eotaxin),¹¹ CXCL8 (IL-8),⁸ and transforming growth factor (TGF)- β .¹⁰ We have recently shown that CXCR3 is the most abundantly expressed chemokine receptor on human lung mast cells within airway smooth muscle, that human lung mast cell migration is induced by the CXCR3 ligand CXCL10, and that CXCL10 is released preferentially from asthmatic airway smooth muscle cells compared with those from healthy controls.¹² Future studies investigating the effects of inhibiting this pathway will be of particular interest.

It is likely that a number of other chemokines play a role in the recruitment of inflammatory cells into the airway and it may be that the release of chemotaxins by airway smooth muscle varies in response to different stimuli such as cigarette smoke, infection, or allergen exposure. Future studies should explore the relative importance of these triggers and the associated chemotaxins that are released in promoting inflammatory cell infiltration into the airway smooth muscle. It is also important to investigate why some inflammatory cells, notably eosinophils, are rarely seen in the airway smooth muscle in spite of appropriate chemotactic signals.

HOW DO INTERACTIONS BETWEEN THESE INFLAMMATORY CELLS AND AIRWAY SMOOTH MUSCLE CELLS LEAD TO DISORDERED AIRWAY FUNCTION?

Activation of the inflammatory cells within the airway smooth muscle bundle would be predicted to have important consequences on airway smooth muscle function. Following mast cell degranulation the mediators histamine, PGD₂ and LTC₄ are released which are all potent agonists for airway smooth muscle contraction.¹³ Mast cell cytokines may further contribute to airway hyperresponsiveness. The mast cells in the airway smooth muscle bundles in asthma express IL-13,¹⁴ and IL-13 has been shown to attenuate relaxation to β agonists and to augment contractility to acetylcholine.^{15,16} The effect of neutrophil derived mediators on airway smooth muscle function is less clear, with conflicting reports from animal studies showing that elastase can increase and diminish smooth muscle responsiveness.^{17,18}

The interactions between inflammatory cells and airway smooth muscle cells may have more long term consequences. A number of mast cell mediators including histamine,¹⁹ tryptase,²⁰ and LTD₄,²¹ as well as the neutrophil product elastase,²² promote airway smooth muscle proliferation. Increased

airway smooth muscle mass is a well established feature of both asthma²³ and COPD.²⁴ In asthma this occurs predominantly in the large airway and in COPD in the small airways. A study using a computational model of the effects of increased muscle mass has suggested that it is the most important abnormality responsible for the increased airflow resistance observed in response to bronchoconstricting stimuli in both asthma and COPD.²⁵ The relative contribution of airway wall smooth muscle mass to overall airway wall thickness in the small airways is much greater than that in the large airways. Thus, increased smooth muscle mass in the small airways is likely to make a significant contribution to the development of fixed airflow obstruction characteristic of COPD and sometimes seen in persistent chronic severe asthma. The role of interactions between inflammatory cells and smooth muscle cells in the development of airway wall remodelling in asthma and COPD offers exciting opportunities for future research.

FUTURE STUDIES

The recognition of the importance of microlocalisation is not confined to inflammatory cells and airway smooth muscle cells but is probably equally critical in interactions with other structural cells such as the epithelium, fibroblasts, mucosal glands, and nerve cells. Eosinophilic bronchitis, cough variant asthma, and idiopathic chronic cough are associated with increased concentration of mast cell products in sputum,²⁶⁻²⁷ and we have suggested that localisation of mast cells to sensory nerve endings might be important in the development of cough reflex hypersensitivity and cough. A rather similar interaction is thought to be important in the genesis of itch.²⁸⁻²⁹ Understanding the fundamental steps that are involved in the migration of inflammatory cells towards structural cells such as the airway smooth muscle and the interactions between these cells may provide us with novel targets for the future treatment of asthma, COPD, and cough.

Researchers interested in the immunopathology of airway diseases therefore need to be mindful of the importance of "location, location, location".

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Impact factor

Journal impact factors for 2003: *Thorax* increases

J A Wedzicha, S L Johnston, D M Mitchell

The impact factor for *Thorax* is rising

Impact factors for journals for the year 2003 have recently been published and we are delighted that the impact factor for *Thorax* has risen to 4.188. It is now the second highest ranked conventional respiratory journal in terms of impact factor, behind the *American Journal of Respiratory and Critical Care Medicine*, and has overtaken the *American Journal of Respiratory Cell and Molecular Biology*. The impact factors for the main respiratory journals are listed in table 1.

The journal impact factor for 2003 reflects the number of citations in 2003 to papers published in *Thorax* in 2001 and 2002. *Thorax* is very fortunate in having received excellent papers for publication and this is reflected in the rise in the impact factor over the last few years.¹ However, in addition to original papers in 2001 and 2002, *Thorax* published a number of high quality review articles such as the Year in Review supplement,² critical care series,³ we started a series on COPD⁴ and one on lung cancer.⁵ In 2001 and 2002 we also published a number of guidelines which have important implications for clinical practice—such as guidelines for the management of community acquired pneumonia in adults and children,^{6,7} the use of non-invasive ventilation in acute respiratory failure,⁸ selection of patients with lung cancer for surgery,⁹ guidelines for flexible

bronchoscopy,¹⁰ and on air travel.¹¹ We would like to thank the previous *Thorax* editors, John Britton and Alan Knox, for their hard work¹² and for their immense contribution to the current success of the journal.

The rise in impact factor reflects the continuing success of *Thorax*. Over the past year we have seen a marked rise in submissions, especially of high quality papers,¹³ and we very much urge you to continue to send us your best papers. The online submission Bench>Press system means that the peer review process in the journal is now faster and our publication lag time is short. Thus, over the next few years we are

Table 1 Impact factors for respiratory journals: 2003

<i>American Journal of Respiratory and Critical Care Medicine</i>	8.876
<i>Thorax</i>	4.188
<i>American Journal of Respiratory Cell and Molecular Biology</i>	4.015
<i>American Journal of Physiology: Lung Cellular and Molecular Pathology</i>	3.735
<i>Journal of Thoracic and Cardiovascular Surgery</i>	3.319
<i>Chest</i>	3.264
<i>European Respiratory Journal</i>	2.999
<i>Journal of Heart and Lung Transplantation</i>	2.843
<i>Respiratory Medicine</i>	1.419

confident that the impact factor for *Thorax* will rise further, with the journal enjoying an increasing international profile while at the same time maintaining its important educational role.

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