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Evidence that pollution levels within European Community guidelines produce significant respiratory morbidity

S WALTERS, RK GRIFFITHS, JG AYRES *Institute of Public and Environmental Health, Birmingham University; Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* Hospital admission for acute respiratory disease (ARD) is a major public health problem, around 5000 admissions per year occurring in residents of Birmingham, of which almost half are for asthma. Although ambient levels of smoke and sulphur dioxide (SO_2) have fallen since 1960 in the United Kingdom, these pollutants and others associated with motor vehicle exhaust emissions remain a potential cause of respiratory morbidity. This study used Körner inpatient data on residents of Birmingham from 1988–90 together with measurements of smoke, SO_2, and nitrogen dioxide (NO_2) from Birmingham City Council to explore their relation. Age-sex standardised hospitalisation ratios (SHRs) were calculated for all ages and preschool children separately for all electoral wards in Birmingham. When SHRs were related to mean annual ambient pollutant levels in the wards where pollution levels are measured, significant positive correlations were found in adults between admissions for ARD ($R = 0{\cdot}7$) and for asthma ($R = 0{\cdot}56$) and mean ambient NO_2 over the two year period. In preschool children a significant relation was found between mean ambient SO_2 and hospitalisation for ARD ($R = 0{\cdot}67$) and asthma ($R = 0{\cdot}72$) ($p < 0{\cdot}05$). The effect of acute changes in air pollution levels on hospitalisation for ARD and asthma was then studied by examining the relation between mean pollution levels, local peak pollution levels, and subsequent hospitalisation for ARD and asthma on both a daily and weekly basis (four weekly for NO_2). Relations significant at the 0·1% level were found between ARD and asthma and mean daily smoke and SO_2 levels. These relations were strongly seasonal, reaching significance only in winter. Admissions to hospital lagged behind pollution peaks by two days for NO_2 and four days SO_2 and smoke. The relation between weekly mean pollution levels and admissions in the same and succeeding week were non-linear with a threshold effect at around 20 $\mu g/m^3$ for both smoke and SO_2. These relations were significant for both adults and preschool children. The relation between four weekly NO_2 and asthma was significant and linear ($R = 0{\cdot}53$, $p < 0{\cdot}05$) for both adults and children. All relations between acute respiratory admissions and air pollution levels occurred at mean levels of air pollution well within the current European Community daily, monthly, or annual guidelines, suggesting significant morbidity at these presumed safe levels.

Use of information technology in a department of respiratory medicine

C BEECH, AH EVANS, V HILL, N MALI, S BRADBURY, CFA PANTIN *On behalf of all members of the Department of Respiratory Medicine, Stoke-on-Trent* In 1987 a review of the work pattern led to the requirements for an information system for the Department of Respiratory Medicine at Stoke-on-Trent being specified. From these basic requirements, a microcomputer network larger than the original specifications has developed. The system has respiratory function, word processing with coding of diagnoses, nebuliser loaning, diary and resource management modules on network with bronchoscopy audit as a separate system. The system is used to produce letters and discharge summaries, lung function results, bronchoscopy reports, and audit. Guidelines on asthma management for local general practitioners using desk top publishing have been printed. Selective targeting of general practitioners and patients via diagnosis has been organised. The system helps organise the servicing of equipment. The success of the system depends on the involvement of the whole department. A pulmonary function technician is a trained network and technical manager; all secretaries have word processing skills and two are trained in desk top publishing. The system is under continual improvement, and is being integrated into a hospital wide system.

Confidential inquiry into deaths from asthma in Norwich

NJ WAREHAM, BDW HARRISON, PF JENKINS, J NICHOLLS, DE STABLEFORTH *Respiratory Medicine Department, West Norwich Hospital, Norwich* A confidential inquiry into asthma mortality has been established in Norwich by a process of continual review and local feedback. The circumstances of all deaths due to asthma are reviewed by a panel of three chest physicians with data from the hospital and general practitioner records, necropsy reports, and coroners' notes. This paper describes the initial findings of a two year retrospective study of patients dying from asthma between the ages of 16 and 65 in 1988 and 1989. The panel reviewed 16 cases; the mean age at death was 47·4 years and the ratio of men to women 2·2:1. Necropsy data were available in 10 cases, and in the remainder a death certificate had been issued without reference to the coroner. All the patients either died at home or were dead on arrival at hospital. On reviewing the factors that contributed to each patient's death, the panel found significant psychosocial factors in 73% of cases. The routine medical treatment was considered appropriate in 80% of cases and the care given during the final attack was appropriate in 67% of cases. However, evidence of underutilisation of inhaled steroids was found in 25% of cases and 25% of the patients died within four weeks of being discharged from hospital. Patients' understanding of their condition was assessed as good in only 25% of cases, and there was evidence of difficulty in coping with asthma in 87%. The overall level of appropriateness of medical treatment suggests an improvement from earlier studies (*BMJ* 1982;285:1251–5). However, the importance of psychosocial deprivation, poor education, and compliance as factors possibly related to the risk of dying from asthma has important implications for the outpatient monitoring and education of patients with asthma.

General practice survey of acceptability and impact of the 1990 guidelines for management of adult asthma

SR HILTON *GPs in Asthma Group, c/o Department of General Practice, St George's Hospital Medical School, London* This group consists of 330 general practitioners (GPs) nation wide with an expressed interest in the management of asthma. After publication of the 1990 British Thoracic Society guidelines all members were surveyed by postal questionnaire during January 1991, and 242 (73%) responded. They were questioned on the impact of the guidelines—both personally and within their own district—on asthma management. They were asked to comment specifically on five aspects most relevant to general practice. (1) 94% agreed overall with the section on short course oral steroids, although 23% expressed reservations on one or more issues of timing, dosage, or duration of courses; (2) 95% agreed with the early introduction of inhaled anti-inflammatory agents; (3) 91% agreed with guidelines on use of nebulisers, but 12% wanted specific guidelines on use of nebulisers in acute attacks; (4) 91% thought that the criteria for outpatient referral were reasonable, but one in 10 commented that interested GPs need not refer all such patients; and (5) 93% agreed with the section on emergency admission in acute asthma. Most (81%) thought that the guidelines had had a useful personal impact—whether in terms of reinforcing current management, establishing asthma policies in their practice, or for teaching. Those who did not report any personal impact were significantly more likely to disagree with the specific sections reported above. At district level GPs were much less certain about the impact: 36% thought they had and 40% that they had not made any difference to management, the remainder believing it was too soon to judge. Many commented on poor presentation of the most relevant parts to GPs. Others stated that concise abstracts should be more widely circulated, especially to the GPs who most needed to be aware of them.

Segmental defect in lung scanning: problems of definition

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The identification of segmental and lobar defects is important in the interpretation of ventilation-perfusion scans for diagnosing pulmonary embolism. The aim of this study was to define the appearances of ventilation (and therefore perfusion) defects of known anatomical location and to compare these with predicted anatomy. Normal volunteers underwent fibreoptic bronchoscopy positioned supine over a gamma camera. Temporary occlusions were then produced by inflation of a balloon catheter, passed via the bronchoscope, in the orifices of lobar and segmental bronchi. Before and during each occlusion a krypton-81m (^{81m}Kr) ventilation scan was performed in the posterior, posterior-oblique, and lateral projections. 250 000 to 300 000 counts were collected in each position. Anterior views were included if the defect was not apparent on the other three views. The occluded segment was then ventilated independently with approximately 10% of its estimated volume by using a mixture of 100% O_2 and ^{81m}Kr in time with respiration while the subject breathed air; 25 000 counts were collected for these images. In this way negative and positive images of segmental anatomy were collected by using an isotope (^{81m}Kr) that gives similar resolution to technetium-99m used in perfusion studies. Our results show that the positive image of a segment resembles more closely its predicted appearance from anatomical drawings than the negative image, the latter appearing considerably smaller. The greatest discrepancy between the appearances of positive and negative images exists in the basal segments of the lower lobes. Possible causes of this effect, which has important implications in interpreting ventilation-perfusion lung scans for pulmonary embolism, include the influence of diaphragmatic movement, shine through of isotope in contiguous lung areas, and collateral ventilation. These possibilities are being explored.

Notification of tuberculosis: how many cases are never reported?

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In England and Wales there is a statutory requirement to notify patients diagnosed as having tuberculosis (TB). However, there is evidence that many patients are not notified and the scale of this problem is not known. We identified 608 adult patients diagnosed as having tuberculosis who presented to the London Chest Hospital, and the Royal London Group of Hospitals, in a five year period from January 1985. Cases were identified retrospectively from the following sources: microbiology records, histology records, statutory notifications, postmortem examinations, coroners' cases, hospital activity data, and death certificates. Clinical information and definitive knowledge of whether the patient was notified were available on 582 patients (96%), of whom 434 (75%) were notified. The proportion of patients notified varied according to the specialty of the clinician in charge of the case (table above). Patients with a history of tuberculosis and those who died were significantly less likely to have been notified. Age, race, and lack of microbiological or histological confirmation of diagnosis did not influence the proportion notified. Among the 85 patients with pulmonary TB who were not notified, 20 (24%) had smear positive disease. Although chest physicians reported the highest proportion of their cases (83%), undernotification by this group represented 44% of all unnotified cases. This study suggest that the true incidence of TB in our area is 34% higher than that officially reported and lack of notification may mean that contacts are not traced.

Proportion of patients notified as having TB by specialty of clinician in charge of their case

Specialty	*No notified*	*Total No*	*Percentage notified*
Chest physicians	314	379	83
General medicine	65	94	69
Surgery	25	40	63
Neurology/neurosurgery	9	18	50
Renal	2	12	17
Haematology	1	6	17
Others	18	33	55
Total	434	582	75

Preferential chemotactic activity for CD4 positive T cells in sputum from patients with bronchiectasis

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Recent data have shown that large numbers of T cells are present in the lungs of patients with bronchiectasis (Silva *et al*, *Thorax* 1989;44:668–73). Furthermore, CD8 positive T cells predominated. It is unknown whether this reflects increased recruitment of these cells to the lung or proliferation in situ. We therefore looked for lymphocyte chemotactic activity in sputum samples from patients with bronchiectasis and determined the phenotype of the T cells recruited. All samples contained chemotactic activity towards lymphocytes obtained from a healthy donor. However, five mucoid (M) secretions (diluted one in five) recruited less cells ($p < 0.01$) than five mucopurulent (MP) or five purulent (P) samples (mean (SE) values M = 18·8 (1·2); MP = 64·3 (10·4); P = 67·2 (6·2). Studies of phenotypic distribution of cells showed that four mucoid secretions recruited equal numbers of CD4 and CD8 cells (ratio 1·05 (0·07), whereas four mucopurulent and four purulent samples recruited more ($p < 0.01$) CD4 than CD8 positive cells (MP = 1·82 (0·2); P = 2·0 (0·13). In conclusion, sputum from patients with bronchiectasis contains a factor/s that are chemotactic for lymphocytes. This is greatest in MP or P samples and has a preferential effect on CD4 cells. Therefore chemotaxis alone cannot account for the predominance of CD8 T cells in lung biopsy specimens from patients with bronchiectasis.

Changes in sputum inflammatory contents in acute exacerbations in bronchiectasis

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Neutrophil mediated mechanisms are postulated to have a role in the pathogenesis of persistent airway inflammation in bronchiectasis (Cole, *Recent Advances in Infection* 1989:141). Neutrophil chemotactic activity (NCA) and elastolytic activity (EA) have been detected in the sputum produced in the stable clinical state, and decreased with antibiotic treatment (Stockley, *Clinics Chest Medicine* 1987:481). However, continuous antibiotic treatment has been largely avoided and treatment is only given for exacerbation of symptoms. We studied the changes in sputum NCA and EA in acute exacerbations treated with antibiotics. NCA was measured using a multiwell chemotaxis chamber and EA with N-succinytrialanine-p-nitroaniliade as elastase substrate. Twelve patients who chronically produced sputum were assessed in the stable state and when they developed acute exacerbations, prior to antibiotic treatment, during two weeks of antibiotic treatment, and at two and six weeks after stopping treatment. All had NCA (42·0 (23·5) cells/field and EA (15·5 (19·9) mU/100 μl) in their sputum in the stable state. At acute exacerbation there was a significant increase in NCA ($p < 0.001$) and EA ($p < 0.05$). All 12 responded clinically after one week of antibiotic treatment, and this was associated with a decrease in NCA back to and EA below ($p < 0.001$) the values in the stable state. A further week of antibiotic treatment did not result in further decline of NCA or EA. Three patients had another exacerbation clinically between two and six weeks after stopping antibiotic treatment and their NCA and EA rose again. In the nine other patients both NCA and EA at two and six weeks after treatment were similar to the preexacerbation values. Our findings suggest that short course antibiotic treatment prescribed for acute exacerbations of chronic bronchial sepsis effectively controls the upsurge in inflammatory activity, but patients return to their basal level of airway inflammation soon after stopping treatment.

Interaction of *Haemophilus influenzae* with human respiratory tract mucus in vitro

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Unencapsulated non-typable *Haemophilus influenzae* (NTHi) form part of the normal nasopharyngeal flora and commonly infect the bronchial tree. Encapsulated *H influenzae* type b (Hib) less frequently colonise the nasopharynx, rarely infect the bronchial tree, but do cause serious systemic diseases—for example, meningitis in children. Possession of capsule reduces and possession of fimbriae enhances adherence of *H influenzae* to buccal epithelial cells. The majority of *H influenzae* in infected organ cultures of human respiratory mucosa are present in the mucus layer rather than at-

tached to the epithelial surface. We used a microtitre plate assay to determine whether isogenic strains of *H influenzae* sufficient or deficient in these two virulence determinants (capsule, fimbriae) differ in their interaction with human respiratory tract mucus. Two F+ strains of NTHi were more adherent to mucus than their respective F− partners ($p < 0{\cdot}02$, $n = 12$; $p < 0{\cdot}05$, $n = 17$; Wilcoxon rank). In contrast, the adherence of F+/F− pairs of two Hib strains to mucus were similar ($n = 9$, $n = 14$). The adherence to mucus of a cap+/cap− pair of Hib ($n = 14$) was similar. Although fimbriae enhance adherence of NTHi to mucus, they do not influence interactions of capsulate organisms with mucus. These findings suggest that interactions with mucus probably do not explain the different pathogenicity of Hib and NTHi, but fimbriae may influence NTHi pathogenicity.

Effect of *Streptococcus pneumoniae* on oxidative response of polymorphnuclear leucocytes

FE PERRY, CJ NELSON, JR CATTERALL *Department of Pathology and Microbiology, Bristol University, and Respiratory Department, Bristol Royal Infirmary, Bristol* Polymorphnuclear leucocytes (PMNL) are thought to have an important role in the host's defence against *Streptococcus pneumoniae*, but the mechanisms by which they kill pneumococci are unknown. Previous studies of microbial killing by phagocytes have stressed the importance of reactive oxygen species (ROS). We have therefore attempted to establish whether ROS are important in killing *S pneumoniae*. PMNL were incubated with *S pneumoniae* type 1 in suspension and superoxide (O_2^-) production was measured by reduction of ferricytochrome C. No significant increase in O_2^- production was detected with *S pneumoniae* alone or in the presence of 0·625–20% of normal human serum. Addition of *S pneumoniae* to PMNL actually abrogated spontaneous production (PMNL alone 8·56, PMNL+*S pneumoniae* 0·16, PMNL+*S pneumoniae*+serum 0·00 mmoles $O_2^-/1{\cdot}2 \times 10^5$ PMNL/90 min, mean of four experiments each with eight replicates per condition), implying that *S pneumoniae* may inhibit rather than stimulate O_2^- production. This possibility was investigated by comparing O_2^- production stimulated by phorbol myristate acetate (PMA) with O_2^- production stimulated by a combination of PMA and *S pneumoniae*. The powerful respiratory burst stimulated by PMA was inhibited by the concomitant addition of *S pneumoniae* (PMNL+PMA 34·1, PMNL+PMA+*S pneumoniae* 0·0 mmols). This phenomenon was dose dependent and observed at bacterial concentrations greater than $1{\cdot}5 \times 10^7$/ml. These results suggest that *S pneumoniae* can scavenge O_2^- or prevent its formation, or can interfere with the assay, by reoxidising cytochrome C. Whichever of these explanations is correct, the results imply that *S pneumoniae* can interfere with oxidation-reduction processes. The ability of *S pneumoniae* to interfere with oxidation-reduction processes may help explain its pathogenicity.

Detection of subclinical *Pneumocystis carinii* infection with the polymerase chain reaction in asymptomatic renal and heart-lung transplant recipients receiving no prophylaxis against *Pneumocystis carinii*

TR LEIGH, AE WAKEFIELD, SE PETERS, JM HOPKIN, MH YACOUB, WR CATTELL, JV COLLINS *Department of Chest Medicine, Westminster Hospital, London; Institute of Molecular Medicine, John Radcliffe Hospital, Oxford; Department of Cardiac Surgery, Harefield Hospital, Middlesex; and Renal Unit, St Bartholomew's Hospital, London* *Pneumocystis carinii* (PC) is thought to be a normal commensal in normal subjects, but frequently causes life threatening pneumonitis (PCP) in those severely immunocompromised. Using sputum induction (SI), a sensitive and specific technique for the diagnosis of PCP (Leigh *et al*, *Lancet* 1989;ii:205), and a highly sensitive immunofluorescence stain (IF), we previously found evidence of PC infection in a renal transplant recipient but not in normal subjects (Leigh *et al*, *American Thoracic Society*, May 1991). We set out to detect PC infection in transplant recipients taking cyclosporin, and combinations of prednisolone, and azathioprine using a recently described technique using DNA amplification by the polymerase chain reaction (PCR) (Wakefield *et al*, *Molec Biochem Parasitol* 1990;**43**:69). Thirty asymptomatic subjects were studied, 10 normal controls (mean age 28 years), 10 renal transplant recipients (mean age 48 years, mean time from transplantation 11 months), and 10 heart-lung transplant recipients (mean age 35 years, mean time from transplantation 32 months), none of whom were receiving prophylaxis against PC. All subjects underwent SI with nebulised 3% hypertonic saline; all specimens were stained by IF as well as being processed for PCR. PCR was performed with positive and negative controls using the oligonucleotide primers pAZ102-E and pAZ102-H as previously described. The PCR products underwent electrophoresis on a 1·5% agarose gel in the presence of ethidium bromide and Southern transfer and hybridisation with a human PC specific oligonucleotide probe labelled with phosphorus-32. The procedure was repeated on all specimens to ensure reproducibility. All control specimens were consistently negative to PC on IF and PCR. All 20 of the transplant recipients were negative for PC on IF; three out of 10 renal transplant recipients and two heart-lung patients were repeatedly positive for PC on PCR. Of these, one renal and one heart-lung transplant recipient were positive on both gel and hybridisation and two renal transplant recipients and one heart-lung patient were positive on hybridisation alone. These results show an increased sensitivity of PCR over IF, question the hypothesis that PC is a commensal in normal subjects, and show the presence of subclinical PC infection in asymptomatic immunosuppressed transplant recipients. PCR may become useful in diagnosing PCP and in determining both the need and efficacy of PCP chemoprophylaxis.

Use of polymerase chain reaction and DNA probes in detecting mycobacterial DNA in patients with sarcoidosis and tuberculosis

SA SABOOR, NMcI JOHNSON, J McFADDDEN *School of Biological Sciences, University of Surrey, Guildford; and University College and Middlesex School of Medicine, London* The polymerase chain reaction (PCR) was used to amplify a 626 base pair fragment of the 65 k antigen, a heat shock protein common to all mycobacteria, to detect mycobacterial DNA in bronchoalveolar lavage (BAL) samples. Patients with suspected tuberculosis (TB), sarcoidosis, and other illnesses requiring a bronchoscopy were included in the study. A total of 59 patients were studied, of whom eight had histologically proved sarcoidosis, five had TB, 24 had a likely diagnosis of TB, and 22 acted as negative controls in whom TB was thought unlikely. BAL was performed on all patients and samples taken for bacteriological examination were also examined by PCR. PCR product was detected by gel electrophoresis and by DNA probing. All culture positive TB samples were positive by direct PCR. Two out of eight samples from patients with sarcoidosis were similarly positive. Of the 24 samples from patients with a possible diagnosis of TB but negative culture results, 16 gave a positive result. However, nine samples out of 22 from the patients thought unlikely to have TB also gave a positive result. The results indicate that a significant proportion of patients without TB, including those with sarcoidosis, harbour small numbers of mycobacteria in their lungs that may be detected by PCR. The specific identity of these mycobacteria requires further investigation.

Systolic blood pressure profiles in sleep and breathing disorders

KB VARDI-VISY, RJO DAVIES, JR STRADLING *Osler Chest Unit, Churchill Hospital, Oxford* The vigorous inspiratory efforts of obstructive sleep apnoea (OSA) and heavy snoring produce falls in systolic blood pressure (SBP) in time with each effort. A rise in SBP occurs concurrently with arousal and termination of apnoea. Thus the beat to beat SBP includes information relating to both respiratory effort and sleep disturbance. We report the fluctuations in sleep SBP seen in nine snorers, 11 patients with untreated OSA, and seven normal controls. An electroencephalogram, electro-oculogram ×2, a chin electromyogram, respiration, arterial pulse oximetry, and beat to beat non-invasive blood pressure (Finapres, Ohmeda) were recorded in all subjects. Two hundred and forty five 10 minute periods of stable body position, slow wave sleep stage, and respiratory state were identified. During these periods all falls in SBP occurring over 1·5–7·5 s were measured; all rises in SBP > 18 mm Hg occurring over 4·0–15·0 seconds were counted and expressed as number per hour of sleep (table below). Sleep and breathing disorders were associated with abnormalities in the pattern of SBP over time that reveal information about both respiratory effort and sleep disruption. Thus analysis of these profiles may provide a simple screening test for nocturnal upper airway dysfunction and any related arousals.

	SBP falls (mm Hg) (respiratory effort)	*SBP rises (per h) ("arousals")*
Normal sleep	6·9 (2·6)	12·9 (15·8)
Snoring	10·8 (4·2)	32·5 (42·2)
OSA	12·8 (4·8)	54·2 (23·0)

Effects of minor arousal stimulation on blood pressure in normal sleeping humans

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During obstructive sleep apnoea (OSA) transient arousal at the resumption of breathing and normoxia is coincident with a substantial but poorly understood rise in blood pressure (BP). To assess the haemodynamic effect of the arousal element alone we studied arousal stimuli in sleep deprived normal subjects (five men, four women, aged 18–29). An electroencephalogram, electro-oculogram × 2, chin electromyogram, and beat to beat blood pressure (Finapres, Ohmeda) were recorded in all subjects. A total of 170 transient arousal stimuli were administered from a vibrating box beneath the pillow. Stimulus length was varied to produce a range of cortical EEG arousals, which were graded: 0 = no rise in high frequency EEG or EMG; 1 = increased high frequency EEG or EMG or both, for < 10 s; 2 = increased high frequency EEG or EMG, or both, for > 10 s. Overall, compared with control, there was a rise in mean systolic (slow wave sleep 10·7 (SD 7·2), rapid eye movement 4·8 (6·8) mm Hg) and diastolic (SWS 6·7 (4·6), REM 3·4 (3·0) mm Hg) pressure during the 10 seconds after the stimulus (paired *t* test, SWS pp < 0·0001, REM p < 0·02). There was a correlation between this rise and arousal grade in SWS but not REM (analysis of variance) (table below). Arousal in SWS consistently provoked a rise in blood pressure, which could explain almost all the blood pressure increase that we have seen during OSA. In REM the response is less predictable. During SWS arousal stimuli provoke rises in blood pressure even without any EEG change. Thus autonomic features may be a more sensitive marker of arousing stimuli than the cortical EEG.

Mean (SD) rise in systolic and diastolic pressures and arousal during slow wave sleep

	Arousal grade			
	0	*1*	*2*	*p Value*
Systolic (mm Hg)	7·7 (5·3)	10·3 (7·3)	15·6 (8·1)	< 0·0001
Diastolic (mm Hg)	3·4 (2·9)	7·1 (4·3)	10·4 (4·9)	< 0·0001

Breathing during wakefulness and sleep in anxious patients with chronic obstructive airways disease: effect of buspirone anxiolysis

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Twelve patients with chronic obstructive airways disease (COAD; FEV_1 18–160 predicted; pH 7·39–7·54, $PaCO_2$ 28·2–43·7 mm g; age 48–77 years) who were also anxious (Hamilton scale 13–28) were studied in a double blind study of an anxiolytic drug, buspirone, against placebo to assess the effect of anxiety on respiration during wakefulness and sleep. All patients received placebo for four weeks; after randomisation seven subjects received buspirone 30 mg/day for four more weeks (group A) and five continued to receive placebo (group B). Sleep staging was performed by electroencephalography, electro-oculography, and submental electromyography with standard criteria. Ventilation (calibrated respiratory inductance plethysmography), percentage oxygen saturation (Sao_2%, by ear oximetry), transcutaneous P_{CO_2} ($P_{tc}CO_2$), and nasal end tidal P_{CO_2} ($P_{et}CO_2$) were recorded throughout the night breath by breath. Hamilton anxiety scales were reduced in group A (mean 18·6 pretreatment, 15·9 post-treatment; p = 0·02) but unchanged in group B (p = 0·81) (table below). The results show that at an anxiolytic dose, one month's buspirone treatment did not produce any significant change in breathing during relaxed wakefulness or sleep.

Effect of posture on genioglossal electromyographic activity in normal subjects and in patients with the sleep apnoea hyponoea syndrome

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Having found that many patients with untreated sleep apnoea/hypopnoea syndrome (SAHS) sleep better sitting than lying, we were surprised to observe (Yildirim *et al. Am Rev Respir Dis*, in press) that the retroglossal airway widens on lying down both in normal subjects and in patients with SAHS. To investigate the mechanism behind this we investigated the effect of posture on genioglossal electromyographic (EMG) activity in 10 normal subjects and 10 age matched patients with SAHS during quiet oral and quiet nasal breathing. EMG was recorded with peroral, intramuscular wire electrodes and surface local anaesthesia. In each subject EMG activity was normalised with respect to the maximal EMG obtained during forced tongue protrusion or swallowing. Statistics were performed with Wilcoxon rank test with Bonferonni correction. When subjects breathed through the nose peak inspiratory genioglossal EMG was higher on lying than sitting both in the normal subjects (geometric mean 4·5; 1·3%; p = 0·01) and patients with SAHS (11·8; 2·0%; p = 0·01) but there was no significance difference in expiratory activity with nasal breathing between the two postures (p = 0·15). Similarly, when subjects breathed through the mouth genioglossal EMG activity during inspiration was higher lying than sitting for both normal subjects (5·2; 2·7%; p = 0·04) and patients with SAHS (5·9; 2·9%; p = 0·02). There was no significant difference in expiratory EMG with oral breathing between the two postures in the patients with SAHS (p = 0·35) but it was higher lying than sitting in the normal subjects (4·2; 1·6%; p = 0·02). This study shows that genioglossal EMG activity is increased on lying down, in keeping with our observation of widening of the retroglossal airway.

Mean (SD) values in the two groups with probability for null hypothesis between fourth and eighth week for each group

Treatment group		*VT (ml)*		*Respiratory rate*		*Min SaO_2 deep sleep*
		Wakefulness	*Deep sleep*	*Wakefulness*	*Deep sleep*	
A	4th week	535 (228)	438 (118)	20·4 (7·5)	20·6 (3·8)	88 (2)
	8th week	523 (195)	407 (114)	22·3 (7·0)	21·6 (3·7)	90 (2)
	p Value	0·87	0·15	0·6	0·12	0·014
B	4th week	387 (115)	472 (205)	19·2 (4·5)	19·7 (5·0)	88 (4)
	8th week	517 (176)	504 (199)	22·0 (4·8)	20·5 (1·1)	87 (9)
	p Value	0·26	0·47	0·38	0·77	0·71

Prevalence of sleep disordered breathing in 4–5 year old children and its relation to daytime symptoms

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The parents of 997 children aged 4–5 years identified consecutively from the Oxford birth register were surveyed with a questionnaire designed to identify those with sleep disordered breathing (SDB). In all, 782 questionnaires were returned (79%). We studied with home video and oximetry 66 children who were "most likely" to have SDB from the results of the questionnaire and 66 who were "least likely". We identified eight children with SDB and another four children who had been studied previously in this department but who had had tonsillectomy in the interim and were now free of symptoms. Thus our estimate of the prevalence of SDB in the community is 12/997—that is, 1·2% (95% confidence interval 0·6 to 2·1). The results of the questionnaire showed that 8·7% of the children were reported to snore often and another 30% to snore "sometimes even without a cold." In all, 14·4% were restless sleepers and 3·4% "often fell alseep when reading or watching TV." Children who were reported to snore by their parents were more likely to fall asleep when not busy (relative risk 1·56, 95% confidence interval 1·2 to 2·06), suggesting that snoring may disrupt sleep sufficiently to cause daytime symptoms. Snoring was highly significantly associated with restless sleep (relative risk 1·33, 95% confidence interval 1·2 to 1·6), implying that snoring causes sleep disruption. Parents of snoring children regarded them as "hyperactive" and difficult to manage (relative risk 1·75, 95% confidence interval 1·37 to 2·19). Maternal but not paternal smoking was strongly associated with snoring in children. Thus the prevalence of demonstrable SDB in 4–5 year old children is about 1%, but the associations between daytime symptoms and snoring were identified in a larger number.

Sleep related desaturation during infective exacerbations of cystic fibrosis

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Sleep related hypoxaemia is recognised in adults and older children with clinically stable cystic fibrosis (*Am J Dis Child* 1980;**134**:734). There are no published studies examining nocturnal oxygen saturation in young children with cystic

fibrosis (CF) either when the disease is stable or during infective exacerbations. We performed overnight oximetry and spirometry on admission in 45 children with CF (27 girls, mean (SD) age 8·2 (4) years) who were admitted to hospital with exacerbations. Thirty eight of the 45 children desaturated during sleep, with 17 (38% of the total) spending more than 100 minutes desaturated. When compared with the remaining 28 children, age, Schwachman score, spirometry results, and peak flow rates were not significantly different between the two groups. However, the mean awake supine saturation before sleep was lower in the hypoxaemic group (88·8% (2·1) *v* 92·9% (2·4), $p < 0·001$). Many centres do not routinely give supplemental oxygen when treating exacerbations in children with CF. Over one third of the children we studied would probably have benefited from oxygen treatment but they are difficult to identify clinically. Oximetry, either while awake or overnight, would identify the subgroup of patients with CF who may benefit from oxygen treatment during infective exacerbations.

Steroid reversibility trials: are the tablets taken?

MQF HATTON, MB ALLEN, SV VATHENEN. R STEAD, M FEELY, NJ COOKE *Department of Respiratory Medicine, Leeds General Infirmary, Leeds* Some patients with chronic airflow limitation (CAL) who improve with β agonists do not respond to a trial of oral steroids. This may be due to fixed airways disease, steroid resistance, or failure to take the drugs. We assessed tablet compliance by using a small dose of phenobarbitone as a marker. Thirty outpatients with CAL requiring a steroid trial were instructed to take eight capsules (5 mg prednisolone + 0·5 mg phenobarbitone a day) for two weeks. Response was assessed by home peak flow measurements and clinic spirometry. Plasma phenobarbitone concentrations were measured after the trial and the ratio of phenobarbitone dose (mg/kg) to plasma concentration was calculated. The ratio was compared with the reference range for fully compliant patients (*Genitourin Med* 1988; **64**:312). Four patients failed to attend for review. Of the remaining patients, 20 had plasma phenobarbitone values within the reference range and six were below. Of these six, one had very low values of phenobarbitone and none was found in a second. When the four patients who did not attend for review and whose compliance must be questionable, were excluded, 30% of patients given a steroid trial fail to take sufficient tablets. Poor compliance probably explains why a proportion of patients with CAL fail to respond to steroid trials.

Comparative effect of terbutaline on mast cell and neurally mediated bronchoconstriction in asthma

BJ O'CONNOR, SM RIDGE, PJ BARNES, RW FULLER *Department of Thoracic Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London* Inhaled β adrenoceptor agonists relax airway smooth muscle but may have additional actions in asthma. These agents stabilise mast cells and may modulate sensory nerve activity in the airways. To investigate this we compared the effects of low dose terbutaline on airway responsiveness (AR) to the direct stimulus methacholine (Mch) and the indirect stimulus adenosine 5'-monophosphate (AMP), which activates mast cells, and sodium metabisulphite (MBS), which acts on sensory nerves. In two similar randomised double blind studies 15 subjects with mild asthma inhaled a single dose of terbutaline (0·5 mg via Turbohaler) or matched placebo for 20 minutes prior to challenge with Mch and AMP in study 1 (n = 12) and with Mch and MBS in study 2 (n = 10). Doubling increments of Mch, AMP, and MBS (0·06–64, 0·78–800, and 0·6–80 mg/ml respectively) were nebulised until FEV_1 fell by 20% from baseline; $logPC_{20}$ was calculated by linear interpolation. In study 1 terbutaline reduced AR to Mch by 2·1 doubling dilutions (D.D.) but caused a significantly greater reduction in AR to AMP (3·4 D.D.). In study 2, terbutaline caused an equivalent reduction in AR to both Mch and MBS (2·5 and 2·2 D.D. respectively) (table below). Thus terbutaline reduces AR to a neural stimulus; MBS acts by inhibiting airway smooth muscle constriction but has an enhanced effect on AMP, a mast cell dependent stimulus. We conclude that a single normal therapeutic dose of an inhaled β agonist inhibits mast cell function without affecting neural activity.

Mean (SE) $logPC_{20}$ (mg/ml)

	Study 1		*Study 2*	
	Mch	*AMP*	*Mch*	*MBS*
Placebo	−0·12 (0·13)	1·00 (0·09)	−0·16 (0·11)	0·58 (0·09)
Terbutaline	0·53 (0·12)*	2·02 (0·18)**	0·61 (0·20)*	1·24 (0·08)*

*p < 0·01, **p < 0·001, ANOVA.

Single dose steroid treatment compared with three doses in treatment of acute asthma in childhood

RD CLIFFORD, P CHETCUTI, MJ DUNN, T BAILWARD, F FINLAY, SJ MORRIS, F CARSWELL *Institute of Child Health and Royal Hospital for Sick Children, Bristol* Short courses of oral steroids are of proved value in acute severe asthma in both adults and children. A single dose of oral prednisolone has been shown to dramaticaly hasten recovery from acute asthma in children, but a 3–5 day course is more common in paediatric practice and even longer courses are routine in adult practice. Seventy five children admitted for acute asthma with poor reversibility after nebulised salbutamol were randomised to a double blind trial of one versus three daily doses of oral prednisolone at 2 mg/kg to a maximum of 60 mg. Complete symptom diary cards for the first 14 days were received from 43 families: 25 in the single dose group and 18 in the three dose group with peak flow recordings in 16 children. The median time until a score of just 1 was recorded (equivalent to occasional day time cough) was 5 days for both groups. Regression analysis indicated a straight line recovery rate for the first seven days of 0·65 diary card points per day in the single dose group and 0·63 in the three dose group, the confidence interval for this difference being −0·25 to 0·21. Overall, peak flow was greater than 80% of best achievable peak flow by 10 days. The single dose peak flow recovery rate after the first 24 hours, regressed over 14 days, was equivalent to 1·9 percentage points per day and the three dose rate 1·1 percentage points per day with a confidence interval for this difference of 0·08 to −1·6. We conclude that further doses of prednisolone beyond the first dose are unlikely to confer significant further benefit to the vast majority of children with acute asthma.

Cyclosporin in chronic severe steroid dependent asthma

AG ALEXANDER, NC BARNES, AB KAY *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, and Royal Brompton National Heart and Lung Hospital, London* There is increasing evidence for a role for activated CD4+ T lymphocytes and their products in asthma. We therefore performed a double blind, placebo controlled trial of cyclosporin (initial dose 5 mg/kg/day) in severe corticosteroid dependent asthma. All patients had documented asthma, required long term maintenance oral prednisolone and had impaired lung function. After a four week run in period subjects received cyclosporin (n = 17) or placebo (n = 16) for 12 weeks. In the cyclosporin group morning peak expiratory flow rate (PEFR) rose steadily from week 2 onwards, with an increase of 27·2% at week 12 ($p = 0·0027$). In the placebo group there was a non-significant 9% increase in PEFR at week 12. Similar results were seen in evening PEFR, PEFR after bronchodilator, and the forced expiratory volume in one second. There was a trend towards less rescue courses of oral prednisolone in the cyclosporin group (cyclosporin 5/17, placebo 10/16). There was a mean 10% fall in glomerular filtration rate in the cyclosporin group. We conclude that cyclosporin is an effective treatment in severe steroid dependent asthma, causing a clinically significant improvement in lung function. This result lends support to a role for T lymphocytes and possibly other cytokine producing cells in asthma.

Methotrexate in severe chronic steroid dependent asthma: 12 week double blind crossover study of 15–30 mg per week

CJ TRIGG, RJ DAVIES *St Bartholomew's Hospital, London* Intermittent low dose (15 mg/week $^{-1}$) methotrexate (MTX) has been successfully used as a steroid sparing agent in severe chronic steroid dependent asthma, achieving a mean reduction in prednisolone dosage of around 35% (Shiner *et al*, *Lancet* 1990;**336**:137). Mullarkey *et al* (*Ann Intern Med* 1990;**112**:577) used doses of up to 50 mg/week in 25 patients, and 15 of these were able to completely discontinue steroid treatment over an 18–28 month period. We studied 18 patients (nine men, nine women, mean age 49·7 years (range 23–68)) who had required at least 10 mg prednisolone and 1500 μg beclomethasone dipropionate daily

for at least six months to control asthma. All were screened for contraindications to the use of MTX. Patients received either 12 weeks MTX (7·5 mg week, 15 mg week, then 30 mg for 10 weeks if tolerated) or placebo in a randomised cross over design. Tests included full lung function tests and chest radiography at the start and at 12 and 24 weeks; with full blood count, urea and electrolytes, liver function tests, and clinical assessment every three weeks and daily diary card recording of peak flow, respiratory symptoms, and prednisolone dose. Six patients withdrew: pneumonia at six weeks (only 15 mg/week tolerated because of nausea); headache and nausea at four weeks; pneumococcal pneumonia at seven days; depression at 12 weeks (on placebo); poor compliance (two patients). Adverse events were common: raised activities of transaminases (two patients successfully reintroduced 15 mg week); nausea (six patients); sacral shingles six weeks after stopping treatment; pneumonia (two patients); diarrhoea (one patient). Although eight of the 12 patients who completed the trial achieved large reductions in prednisolone, four required increased dosage and the difference between placebo and MTX was not significant.

In vitro pulmonary vasorelaxant effect of the phosphodiesterase inhibitor enoximone

AY BUTT, TW HIGENBOTTAM, J PEPKE-ZABA, AT DINH XUAN *Papworth Hospital, Papworth Everard, Cambridge* Enoximone is a new phosphodiesterase inhibitor that has both positive inotropic and vasorelaxant activities (*J Cardiovasc Pharmacol* 1982;**4**:721). Phosphodiesterase inhibitors have been shown to potentiate endothelium dependent relaxation of rat and rabbit aorta (*J Pharmacol Exp Ther* 1986;**237**:539), but their effect on pulmonary vasoreactivity is not well established. Endothelium derived relaxing factor (EDRF) is a potent endogenous pulmonary vasodilator (*Eur J Pharmacol* 1989;**163**:401). We studied the effect of enoximone on endothelium dependent relaxation (mediated by EDRF) as well as endothelium independent relaxation of isolated porcine pulmonary arterial (PA) rings (n = 76). Pairs of PA rings with (E+) and without endothelium (E−) were challenged by cumulative doses of enoximone (10^{-7} to 10^{-4}M). Half of the rings in one set of experiments were treated with L-NAME, an EDRF inhibitor. Endothelium dependent relaxation to ADP was also studied with and without pretreatment with enoximone. The vasorelaxant effect of enoximone was not affected by the presence of endothelium (maximum relaxation 37% (5%) and 36% (11%) in E+ and E− rings, respectively; NS). Endothelium dependent relaxations to ADP were also not modified by pretreating rings with enoximone (10^{-4}M) (maximum relaxation 65% (9%) and 55% (14%) in the enoximone treated and untreated rings, respectively; NS). Similarly, addition of L-NAME did not influence the degree of relaxation to enoximone in rings with and without endothelium (maximum relaxation 47% (8%) *v* 46% (6%) in E+ rings, and 50% (5%) *v* 52·5% (6%) in E− rings with and without L-NAME treatment, respectively; NS). We also found that endothelium independent relaxation to sodium nitroprusside was not modified by pretreatment with enoximone (maximum relaxation 99% (1%) *v* 94·5% (5%) in E+ rings and 93·67% (6·33%) *v* 77·17% (10·43%) in E− rings with and without enoximone pretreatment, respectively; NS). This indicates that enoximone is a potent pulmonary vasodilator but its action is not mediated by EDRF. This agent may have a potential role in the treatment of pulmonary hypertension, especially when there is impairment of EDRF production.

Vasoreactivity to hypoxia and *N*-monomethyl-L-arginine in isolated perfused lung during pulmonary vascular remodelling

RJD WINTER, L ZHAO, DE CRAWLEY, JMB HUGHES, TW EVANS *Department of Medicine, Respiratory Division, Royal Postgraduate Medical School, Hammersmith Hospital, and Department of Thoracic Medicine, National Heart and Lung Institute, London* *N*-monomethyl-L-arginine (L-NMMA), a false substrate for the synthesis of endothelially dervied nitric oxide, potentiates hypoxic pulmonary vasoconstriction (HPV). Because changes in endothelial cell structure are seen in developing pulmonary hypertension we have studied the effect of L-NMMA on HPV responses in chronically hypoxic rats. Male Wistar rats (weight 200–250 g) were kept in hypoxia (Fio2 10% (0·5%)) for 15 h, 2 days, and 7 days (15hCH, 2dCH, and 7dCH) with the littermate controls in air (n = 12 for all groups, except 15hCH, when n = 6). Rats were anaesthetised (diazepam 0·6 mg/kg intraperitoneally, fentanyl 0·15 mg/kg intramuscularly) and lungs perfused with normal packed cell volume at constant flow (18 ml/min) ventilated with (*a*) air + 5% CO_2 (normoxia) and (*b*) 2% O_2 + 5% CO_2, balance N_2 (hypoxia) with L-NMMA (30 μM and 300 μM) and L-arginine (1 mM and 6 mM) in separate groups. Baseline pulmonary artery pressure (Ppa) was 15·2 (SD 2·2) mm Hg in controls, 18·0 (1·3) in 15hCH ($p < 0·05$ *v* controls), 21·3 (1·4) in 2dCH ($p < 0·001$ *v* controls) and 24·8 (1·7) in 7dCH rats ($p < 0·001$ *v* controls and 2dCH). The mean increases in Ppa (ΔPpa) in hypoxia were 15·3 (5·2), 3·5 (0·8), 13·6 (5·5) mm Hg in controls, 15hCH ($p < 0·05$ *v* control and 7dCH), 2dCH ($p < 0·001$ *v* control and 7dCH), and 7dCH rats respectively. Hypoxic ΔPpa in control, 15hCH, 2dCH, and 7dCH rats were 137% (13%), 179% (19%), 196% (45%), and 166% (25%) of control respectively after 30 μM L-NMMA (all $p < 0·05$ *v* controls). Results were similar after 300 μM L-NMMA. Hypoxic ΔPpa in control, 2dCH and 7dCH rats were 96% (3%), 82% (6%) ($p < 0·01$ compared with controls and 7dCH) and 91% (10%) of control after 1 mM L-arginine and 88% (10%), 56% (4%) ($p < 0·001$ compared with control and 7dCH) and 82% (10%) of control after 6 mM L-arginine. These data are consistent with increased synthesis of endothelially derived nitric oxide during the early stages of pulmonary vascular remodelling.

Endothelial derived relaxing factor is not responsible for hypoxic pulmonary vasorelaxation in vitro

J PEPKE-ZABA, TW HIGENBOTTAM, T KEALEY, AT DINH XUAN *Papworth Hospital, Papworth Everard, Cambridge* We studied the effect of acute hypoxia on pulmonary arteries (PA) of six pigs. PA rings with intact endothelium were suspended in organ chambers containing 20 ml of 37°C Krebs-Ringer bicarbonate solution. During 90 minutes of equilibration, the baths were gassed with 95% O_2 and 5% CO_2, eliciting Po_2 of 40–50 kPa. PA rings were then precontracted with phenylephrine (10^{-5}M) and treated either with L-NMMA (10^{-4}M), a specific inhibitor of endothelium dervied relaxing factor (EDRF), or with ouabain (Oua; $5·10^{-6}$M), an inhibitor of the sodium-potassium pump. When the contraction of PA rings reached a plateau, gas mixture was changed to 5% CO_2 and 95% N_2 giving a mean Po_2 of 6·48 (SE 0·39) kPa. A reduction in tension of the rings followed the fall in Po_2. At maximum relaxation with hypoxia (about 1 hour) PA rings were rapidly frozen by clamps precooled in liquid nitrogen for measurement of cyclic GMP by radioimmunoassay (*J Biol Chem* 1972;**247**: 1106) (table below). Relaxation of porcine PA rings in response to hypoxia was inhibited by ouabain but not L-NMMA. Hypoxic relaxation of PA rings is not due to EDRF release but is more likely due to activation of Na^+/K^+ pump.

No of PA rings	*Normoxia* 5	*Hypoxia* 7	*L-NMMA + hypoxia* 6	*Ouabain + hypoxia* 6
Tension (% relaxation)	0	89 (4)	82 (8)	35 (9)
Cyclic GMP (pmol/mg wet wt)	0·09 (0·04)	0·22 (0·09)*	0·14 (0·02)	0·26 (0·08)*

*$p < 0·005$ by comparison with normoxia; mean (SE).

Vasoreactivity to neutral endopeptidase 24·11 inhibition in isolated and blood perfused rat lung

RJD WINTER, L ZHAO, JMB HUGHES *Department of Medicine, Respiratory Division, Royal Postgraduate Medical School, Hammersmith Hospital, London* Neutral endopeptidase 24·11 (NE 24·11) is widely distributed in lung tissue. Immunolabelling shows NE 24·11 to be primarily associated with airway epithelium but there is also labelling associated with the vascular endothelium. We studied the effect of a specific inhibitor of NE 24·11 (NEI, UK 73,967, candoxatrilat, Pfizer) on vascular reactivity to atrial natriuretic peptide (ANP) and sodium nitroprusside (SNP) in rat lung. Male Wistar rats (weight 200–250 g) were anaesthetised with pentobarbitone (6 mg/100 g, intraperitoneally) and isolated lungs perfused with normal haematocrit at constant flow (18 ml/min) and ventilated with: air + 5% CO_2 (normoxia) and 2% O_2 + 5% CO_2, balance N_2 (hypoxia). NEI (0·07 mg and 0·2 mg) or vehicle in a volume of < 20 μl were administered during normoxic ventilation or during the stable phase of vasoconstriction during hypoxic ventilation (HPV). Synthetic ANP (300 ng, 3–28, Bachem, CA) and SNP (10^{-11}M final reservoir concentration, Sigma) were given during normoxic ventilation and during the stable phase of HPV in the absence and presence of NEI. Baseline pulmonary arterial pressure (Ppa) was 16·4 (SD 1·3) mm Hg (n = 6) and the mean increase in Ppa in hypoxia (ΔPpa) was 9·9 (2·7) mm Hg (n = 6). NEI (0·07 mg, 0·2 mg) had no effect on

either the resting tone or the stable phase of HPV. Three hundred ng ANP and 10 ^{11}M SNP had no effect on baseline Ppa. In the stable phase of HPV 300 ng of ANP produced a fall in ΔPpa of 2·9 (0·8) mm Hg (n = 6); in the presence of 0·07 mg of NEI ANP produced a greater decrease in ΔPpa of 4·8 (0·7) mm Hg ($p < 0·05$) compared with ANP 300 ng alone. Similar results were obtained in rats kept in hypoxia (FiO_2 = 10% (0·5%)) for seven days. SNP produced similar falls in ΔPpa in the absence or in the presence NEI. Inhibition of NE 24·11 increases the vasodilator effects of ANP on pulmonary vessels when tone is increased during HPV. This mechanism may partly account for the attenuation of pulmonary hypertension seen with continuous infusion of NEI in the hypoxic rat.

Measurements of ventilation, pulmonary blood flow, and right to left shunt on exercise in intrapulmonary vascular shunts

MKB WHYTE, AM PETERS, JMB HUGHES, JE JACKSON, DP MOORE, HA JONES, GJ BELLINGAN *Departments of Medicine (Respiratory Division) and Diagnostic Radiology, RPMS, Hammersmith Hospital, London* We previously observed that patients with intrapulmonary vascular shunts secondary to arteriovenous malformations (PAVMs) have remarkably well preserved exercise capacity despite profound hypoxaemia (Chilvers *et al*, *Am Rev Respir Dis* 1990;**142**:420). Eight studies were performed in six patients aged 13–63 years (mean 32) who all had proved PAVMs on pulmonary angiography. Measurements were made at rest and on exercise at a workload of 30–90 W, equal to 50% of their own maximum. Oxygen saturation (by oximetry), ventilation, and heart rate were monitored. Ventilation and gas exchange were analysed by mass spectrometry. Right to left shunt was measured by injection of albumin microspheres labelled with technetium-99m. Pulmonary capillary blood flow ($\dot{Q}_P$) (freon-22) was measured by rapid rebreathing of a gaseous mixture (0·8–1·0 litre bag containing 10% each of helium, sulphur hexafluoride, and freon-22 with 30% oxygen in argon). Total cardiac output ($\dot{Q}_T$) was calculated from the measurements of $\dot{Q}_P$ and right to left shunt. In four patients pulmonary vascular resistance (PVR) measured at angiography, was 0·25 (SE 0·06) (n = 9), NR 1·0–2·0 mm Hg 1 × min. On exercise all patients desaturated from 78% (SE 3·6%) at rest to 73% (3·4%) on exercise. Exercise produced a modest, appropriate tachycardia, heart rate rising from 93 (6) (beats/min) at rest to 133 (6) beat/min on exercise. Right to left shunt was 35% (4%) of cardiac output at rest, increasing to 41% (5%) on exercise. There was a marked ventilatory response on exercise: for a mean $\dot{V}o_2$ of 0·94 (0·10) l/min $\dot{V}_I$ was 38 (3) l/min. At the same $\dot{V}o_2$, $\dot{Q}_P$ was 10·0 (1·3) (NR 12·2 (0·9)) l/min, but $\dot{Q}_T$ was increased at 16·6 (1·7) l/min. The appropriate $\dot{Q}_P$ and high $\dot{Q}_T$ reflect excellent cardiac compensation on exercise for the pulmonary right to left shunt, made possible by a low pulmonary vascular resistance in these patients.

Effect of SCH34826 on plasma ANP concentration and pulmonary artery pressure, right ventricular hypertrophy, and pulmonary vascular remodelling induced by chronic hypoxia in the rat

AG STEWART, AH MORICE *University of Sheffield, Sheffield* ANP within the pathophysiological range vasodilates pulmonary vessels constricted by hypoxia. Chronic raised plasma concentrations of ANP may reduce the development of hypoxic pulmonary hypertension. However, ANP's half life of less than three minutes is too short for it to be regarded as a therapeutic agent. SCH34826 inhibits neutral endopeptidase and thus raises plasma ANP concentrations. We gave SCH34826 90 mg/kg subcutaneously twice a day to six Wistar rats and gave vehicle (0·4% aqueous methylcellulose) to six littermate controls. All animals were chronically exposed to a 10% oxygen environment for two weeks. We investigated whether raised ANP concentrations by inhibition of its metabolism ameliorates the pulmonary vascular changes and cardiac hypertrophy seen in this model of hypoxic pulmonary hypertension (table below). SCH 34826 raises ANP concentration, which may be responsible for lowering pulmonary artery pressure and reducing the degree of muscularisation. The proportion of vessels with double elastic laminae is an index of the degree of smooth muscle hypertrophy. This hypertrophy is responsible for the irreversible hypoxic pulmonary hypertension and the increased vascular reactivity seen in rats adapted to hypoxia. The reduction in right ventricular hypertrophy is presumably secondary to this reduction in pulmonary artery pressure. Drugs that inhibit neutral endopeptidase may prove to be useful in treating diseases characterised by raised pulmonary artery pressure and pulmonary remodelling.

Mean (SE)	*Control*	*SCH34826*
Animal weight (g)	279 (4)	276 (3)
Right ventricle (mg)	303 (7)	270 (10)*
Left ventricle + septum (mg)	569 (8)	543 (14)
Pulmonary artery pressure (mm Hg)	24·0 (1·8)	20·4 (0·4)
Vessels < 50 μm diameter with 2 elastic laminae	24	18*

*$p < 0·05$ by *t* test.

Action of carbon dioxide on hypoxia and angiotensin II induced pulmonary vasoconstriction in the isolated rat pulmonary circulation

SV BAUDOUIN, PJ BARNES, TW EVANS *Department of Thoracic Medicine, National Heart and Lung Institute, London* Carbon dioxide (CO_2) reduces hypoxic pulmonary vasoconstriction (HPV) in the isolated rat pulmonary circulation (Barer, *J Physiol* 1971;**213**:633). This action could be caused by non-specific vasodilatation, as occurs in the systemic circulation, or by a specific antagonism of HPV. We tested these hypotheses by comparing the effect of hypercapnia on the increased pulmonary vascular tone produced by either hypoxia or angiotensin II (A-II). Isolated, blood perfused heart-lung preparations from adult, male Wistar rats were used in all studies. In the first series of experiments the effect on pulmonary artery pressure (PAP) of hypoxia (3% O_2/5% CO_2) and hypoxia with hypercapnia (35% O_2/15% CO_2) was studied. In the second series repeated doses of A-II (1 μg) were added to the perfusate until two consistent readings were obtained. The lungs were then ventilated with 21% O_2/15% CO_2 for 12 minutes and a further dose of A-II (1 μg) given. Finally, the lungs were ventilated with 21% O_2/5% CO_2 and a further 1 μg A-II given to ensure reproducibility of the constrictor response (table below). CO_2 causes a similar reduction in pulmonary vasoconstriction induced by either hypoxia (21%) or A-II (18%). These results suggest that CO_2 is not a specific antagonist of HPV in the isolated rat pulmonary circulation.

	Mean (SE) PAP (mm Hg)		
	Base	*Constrictor*	*Constrictor + 15% CO_2*
Hypoxia (n = 4)	15 (1)	34 (4)a	27 (3)b
A-II (n = 8)	14 (2)	39 (5)c	32 (10)d

$p < 0·02$ a *v* b; $p < 0·001$ c *v* d.

Bronchial responses to inhaled hypertonic saline and adenosine in middle aged smokers and ex-smokers

H JOYCE, JCH YAP, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, London* Smokers and ex-smokers with mild airways obstruction often show bronchial hyperresponsiveness (BHR) to direct acting constrictor drugs, such as histamine (H). The response to H cannot distinguish between active inflammation and geometric factors because the latter might amplify a normal contractile response of airway smooth muscle (ASM). Hypertonic saline and adenosine are believed to rely on neural or cellular amplification to narrow airways and to have no direct action on ASM and no effect in normal subjects. We examined bronchial challenge with inhaled H, with ultrasonic nebulisation of 4·5% sodium chloride (NaCl), and with adenosine 5-monophosphate (AMP) in nine smokers (mean (SE) age 62 (1·3) years, pack years 48·2 (7·5), FEV_1 % pred 78 (4·2) (range 61–100) and 12 long established ex-smokers (age 59 (2·5) years, pack years 34·2 (6·7), FEV_1 % pred 84 (3·4) (range 66–107) duration of cessation of smoking 13·9 (1·7) years) with previously known BHR to H. Bronchial challenge was performed by a dosimeter method using doubling concentrations of H from 0·5 to 32 mg/ml and subsequently 4·5% NaCl challenge by ultrasonic nebulizer using doubling time from 0·5 to 8 minutes and doubling concentrations of AMP from 0·4–400 mg/ml. Responsiveness was assessed by the dose (PD_{35}) resulting in a 35% fall in specific airway conductance (sGaw). PD_{35} histamine was smaller in ex-smokers than smokers (1·35 vs 3·83 μmol). Of nine smokers, seven responded to 4·5% NaCl

(PD_{35} 9·84 ml) and eight to AMP (PD_{35} 38·6 μmol). Of 12 ex-smokers, 10 responded to 4·5% NaCl (PD_{35} 15·4 ml and eight to AMP (PD_{35} 178·6 μmol). The results indicate that a considerable proportion of long established ex-smokers continue to show increased responsiveness to supposedly indirect acting challenges. The mechanism of this response requires further investigation.

Effect of indomethacin on the protection afforded by inhaled sodium cromoglycate against exercise induced asthma

I PAVORD, A WISNIEWSKI, A KNOX, A TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* There are close similarities between the effects of inhaled frusemide and sodium cromoglycate (SCG) in asthma. There is some evidence that the effects of inhaled frusemide in asthma are mediated through production of inhibitory prostaglandins within the airway and we have shown that indomethacin attenuates the protective effect of frusemide against exercise-induced asthma (Pavord I *et al*, British Thoracic Society winter meeting 1990). We investigated whether a similar effect occurs with SCG in a double blind crossover study. Ten subjects (nine men; age 22–52) with mild asthma were studied on four days. Subjects were pretreated with indomethacin (50 mg three times daily for three days) or matched placebo before a seven minute treadmill exercise test previously shown to cause a 20–30% fall in forced expiratory volume in one second (FEV_1). They inhaled SCG (20 mg) or placebo via a Medix ultrasonic nebuliser 10 minutes before exercise. Baseline, pre-exercise FEV_1 did not differ significantly on any of the treatment days, although the mean change in FEV_1 after inhalation was significantly greater after inhaled SCG with indomethacin pretreatment (0·09 l) than the change after inhaled placebo with placebo (−0·08 l; $p < 0·05$) or indomethacin pretreatment (−0·11 l; $p < 0·02$). After placebo inhalation exercise resulted in a mean maximum fall in FEV_1 of 25% with placebo capsules and 23·1% with indomethacin. After SCG inhalation the maximum fall was significantly less with both placebo (13%) and indomethacin (13·3%) pretreatment ($p < 0·01$). Assessed over 30 minutes, SCG inhibited the airway response to exercise by a median of 65% with placebo pretreatment and 58·7% with indomethacin (NS). We conclude that the protective effect of SCG against exercise induced asthma is unlikely to be mediated via inhibitory prostaglandins. Despite the similar spectrum of action of SCG and frusemide in asthma, the mechanism of action seems to be dissimilar.

Effect of inhaled prostaglandin E_2 on bronchial reactivity to sodium metabisulphite and methacholine in subjects with asthma

I PAVORD, A WISNIEWSKI, R MATHUR, I WAHEDNA, A KNOX, A TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Inhaled frusemide confers protection against the bronchoconstrictor response to a wide variety of stimuli that cause bronchoconstriction by indirect mechanisms. One possible explanation for this protection relates to the known ability of frusemide to enhance synthesis of prostaglandin E_2 (PGE_2). Studies in vitro suggest that PGE_2 might protect against indirectly acting bronchoconstrictor challenges rather than those that act directly on airway smooth muscle, although little is known about the effects of PGE_2 in vivo. We studied the effect of inhaled PGE_2 on the bronchoconstrictor response to inhaled sodium metabisulphite (a stimulus with an indirect action) and methacholine (an airway smooth muscle spasmogen) in nine subjects with asthma. Subjects were studied on four days, inhaling PGE_2 (100 μg) or placebo in a double blind fashion followed immediately by a cumulative dose challenge with sodium metabisulphite or methacholine. The response to the constrictor stimuli was measured as the provocative dose causing a 20% fall in FEV_1 (PD_{20}). There was no significant change in FEV_1 after inhaled PGE_2 compared with placebo, nor any significant change in the response to methacholine; the geometric mean methacholine PD_{20} being 0·9 μmol after PGE_2 and 0·56 μmol after placebo (mean difference 0·7 doubling doses; 95% confidence interval −0·1 to 1·5; $p = 0·08$). However, PGE_2 conferred marked protection against sodium metabisulphite, the geometric mean sodium metabisulphite PD_{20} being 11·8 μmol after PGE_2 and 1·8 μmol after placebo (mean difference 2·5 doubling doses; 95% confidence interval 1·9 to 3·1; $p < 0·001$). PGE_2 conferred significantly greater protection against sodium metabisulphite than methacholine (mean difference 1·8 doubling doses; 95% confidence interval 0·8 to 2·8; $p < 0·005$). This suggests that PGE_2, like frusemide, has a greater inhibitory effect on pathways relevant to the bronchoconstriction induced by sodium metabisulphite than methacholine.

Effect of bronchial allergen challenge on airway responsiveness to methacholine and bradykinin

R DJUKANOVIC, R POLOSA, ST HOLGATE *Immunopharmacology Group, University of Southampton, Southampton* To investigate the effect of inhaled allergen on airway responsiveness to bradykinin (Bk) and methacholine (Mch) in asthma, nine patients with atopic asthma underwent bronchial challenge with Mch followed after recovery by Bk challenge three days (d) before and eight hours, and one, two, and three weeks (wk) after allergen inhalation. This induced an early (EAR) and a late asthmatic response 4–8 hours after inhalation (LAR). Five subjects underwent Bk challenge three days before and eight hours after methacholine challenge acted as controls. The mean (SE) percentage maximal fall in FEV_1 during the EAR after allergen (38·4% (5·1%)) was not different ($p > 0·05$) from that induced by Mch (38% (5·2%)). Allergen caused a maximal 41·6% (10·5%) fall in FEV_1 during the LAR, whereas no LAR was recorded after Mch inhalation. There was no significant difference ($p > 0·05$) in PC_{20} Bk measured three days before and that measured eight hours after Mch challenge on the control day. After allergen inhalation the mean (range) increase in PC_{20} Bk by comparison with baseline values was 41-fold (0·3–208) at eight hours ($p < 0·05$), 40-fold (9–156) at one week ($p < 0·001$), 10-fold (0–22) at two weeks ($p < 0·001$), and six-fold (0·2–15·8) at three weeks, but the increases in PC_{20} Mch at eight hours (threefold (0·2–9), one week (twofold (0·2–8)), two weeks (twofold (0·2–11)), and three weeks (twofold (0·7–5)) after allergen challenges were not significant at any timepoint, although they were seen to occur in six of the eight subjects eight hours after allergen inhalation. This study suggests that allergen challenge causes a more marked and protracted increase in airway responsiveness to Bk than to Mk and that Bk is a more sensitive indicator of allergen induced airways hyperresponsiveness than is Mch. The striking increase in Bk responsiveness could be due to allergen induced sensitisation of sensory nerve endings, the protracted course of which could result from slow epithelial repair.

Endobronchial allergen challenge of airways in mild asthma: cells and mediator values in bronchoalveolar lavage fluid

C GRATZIOU, M CARROLL, K RAJAKULASINGAM, R POLOSA, ST HOLGATE *Immunopharmacology Group, University of Southampton, Southampton* This study was undertaken to investigate the cellular and biochemical events involved in allergic asthmatic reaction. A local endobronchial allergen challenge was performed through a flexible bronchoscope in a group of 14 patients with mild atopic asthma and in a group of 10 normal subjects. The allergen solution was instilled through a fine nylon catheter in the right middle lobe (RML), and during the same bronchoscopy a control challenge with 0·9% sodium chloride was undertaken in the right upper lobe (RUL). Bronchoalveolar lavage (BAL) was performed 10 minutes after instillation of allergen solution. BAL cells were subjected to total and differential cell count and the immunological phenotype of lymphocytes was evaluated by flow cytometry (FACS). Histamine, tryptase, PGD2 and eosinophil cationic protein (ECP) values were measured in normal and asthmatic subjects in BAL samples taken from both areas. A visible bronchoconstriction was observed in all of the asthmatic subjects but in none of the normal subjects. The analysis of BAL fluid showed no differences in the volume recovered from the two different areas in both groups. The total cell number was less in allergen challenged area only in asthmatics. No statistical difference was found in the differential cell counts between the two challenged areas. FACS analysed showed no differences in T cell numbers (CD3+) or their CD4+ and CD8+ subsets between the two groups in the control challenged area. However, there was a significant rise of CD8+ cells ($p < 0·05$) and a fall in CD4+ cells ($p < 0·05$) with a consequent fall in the CD4 to CD8 ratio ($p < 0·05$) in the asthmatic subjects after allergen challenge. There were no such changes in the two challenged areas in normal subjects. In addition, no differences were found in T cell activation markers I1-2 and HLA-DR between normal and asthmatic subjects or the control and challenged site in both groups. The concentration of histamine, PGD2, and ECP and the activity of tryptase were significantly higher ($p < 0·050$) in asthmatic than in normal subjects in both allergen and control area. The individual changes in histamine, tryptase, and ECP values after allergen challenge were well correlated ($p < 0·001$) with the individual changes in CD4+ cells in asthmatic subjects. No such correlation was seen in normal subjects. In conclusion, the results of this study showed that values of histamine, tryptase, PGD2, and

ECP are present in the airways of subjects with mild asthma. After endobronchial allergen challenge of asthmatic airways there was an alteration in lymphocyte subset population which correlated with mediator levels in BAL. These results may provide further evidence to support the role of T cells in the early regulation of inflammatory processes in allergic asthmatic reaction.

Absence of seasonal variation in domestic Der pl concentrations

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House dust mite (Dermatophagoides pteronyssinus) numbers and the concentration of their main allergen, Der pl, are dependent on ambient temperature and humidity and have been reported to show a seasonal variation in homes in the US. Comparable data on changes in levels of exposure are lacking in the United Kingdom. We measured the concentration of Der pl in dust collected from mattresses and carpets in 40 houses in south Manchester. Dust was sampled using a modified Medivac vacuum cleaner on to filter paper (Whatman GFF). Samples were coded and analysed blind. Der pl was assayed by enzyme linked immunoadsorbent assay (ALK Laboratories). Twenty four hour recordings of indoor relative humidity were made in 20 houses on the sampling day and the remaining houses had spot readings taken at the time of sampling. Complete data for the four seasons were available from 37 houses. Mean concentrations from all sources rose in October paralleled by a rise in humidity (table below). However, there was no statistical correlation between Der pl concentrations and relative humidity, house type, ventilation, or double glazing. The temperature and humidity data showed that the indoor environment remained relatively constant and conducive to mite growth through the year.

Der pl (ng/g of dust)—geometric mean (with 95% confidence intervals) by month and with mean (SE) relative humidity

	Der pl (ng/g of dust)—geometric mean (95% CI)			
	Jan	*Apr*	*July*	*Oct*
Mattress	2399 (1698 to 3388)	2290 (1349 to 4677)	1412 (1096 to 2188)	4073 (2188 to 7079)
Bedroom carpet	1820 (1096 to 3020)	1659 (1023 to 3388)	1122 (832 to 1738)	2884 (1778 to 4898)
Living room carpet	2188 (1479 to 3236)	1669 (1000 to 3162)	1126 (758 to 1698)	2630 (1412 to 4898)
Relative humidity (%)	58·9 (3·3)	63·7 (1·3)	68·5 (1·1)	79·2 (3·4)

ANOVA Jan *v* Jul, Jan *v* Oct, Apr *v* Oct, Jul *v* Oct, $p < 0.05$.

House dust mite allergen (Der p1) exposure dosage determines sensitivity in atopic siblings

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Atopic sensitisation to house dust mite (HDM) allergens is a major cause of asthma in children and young adults in Britain. This study investigates the relative roles of allergen exposure and the genetic tendency to atopy leading to HDM sensitivity. Genetic linkage studies in a sample of nuclear families suggest that the tendency to atopic IgE responses is conferred by an atopy locus on chromosome 11q. From this sample exposure studies were undertaken in 36 families. Pairwise analysis of siblings from 21 familes showed that children sensitive to HDM were exposed to higher concentrations of *Der p*I allergen in their mattress ($p = 0.005$) and bedding ($p = 0.04$), but not on the bedroom floor ($p = 0.33$), than was their atopic sibling who was not sensitive to HDM antigens. There was no difference in the exposure to HDM numbers/g of dust in the mattress ($p = 0.61$) or on bedroom floors ($p = 0.09$). In contrast, pairwise analysis of siblings from 15 families showed that children sensitive to HDM were not exposed to significantly different concentrations of *Der p*I in the mattress ($p = 0.96$), in bedding ($p = 0.11$) or on the bedroom floor ($p = 0.70$) or to HDM numbers/g of dust in the mattress ($p = 0.12$) and bedroom floor ($p = 0.98$) than their non-atopic siblings. These findings were identical when absolute allergen load was compared in these pairs. These results together suggest that differences in allergen concentrations in beds among siblings with a comparable genetic tendency to atopy play a significant part in determining the development of HDM allergy.

DER pl concentrations six months after application of the acaricide Acarosan

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The house dust mite, *Dermatophagoides pteronyssinus* and its major allergen Der pl, have an important role in the pathogenesis of asthma. We evaluated the effect of Acarosan (Crawford Chemicals, Milton Keynes), a benzyl benzoate containing acaricide, on Der pl levels in 10 houses. Acarosan was applied according to the supplied instructions with powder for carpets and foam for mattresses. Dust samples were collected by vacuuming (Medivac, Taylormaid, Macclesfield) for five minutes through a 0·7 μm filter (Whatman GFF) from the mattress surface, bedroom carpet, and living room carpet. Samples were obtained before Acarosan application and twice, at three month intervals, afterwards. Samples were coded and analysed blind. Der pl was measured in dust samples by enzyme linked immunoadsorbent assay (ELISA) (ALK Laboratories) (table below). The absence of any significant decline in domestic allergen load over a six month period is consistent with the high degree of stability of Der pl. After treatment there was no significant difference from a control group of 40 untreated houses sampled concurrently. These results suggest that acaricides are unlikely to produce any quick benefit to patients sensitive to house dust mite and underscore the need for all acaricidal methods to be assessed by direct quantification of allergen rather than by mite counts or indirect assays—for example, guanine.

	Der pl (ng/g of dust)—geometric mean (95% confidence interval)			
	Before	*3 months*	*6 months*	*ANOVA*
Living room carpet	1669 (436 to 6546	1369 (724 to 2570)	1000 (339 to 2884)	NS
Bedroom carpet	1153 (457 to 2884)	1334 (616 to 2884)	1039 (389 to 2818)	NS
Mattress	2432 (1000 to 5888)	2318 (759 to 7079)	2227 (794 to 6166)	NS

Relation between airway responsiveness, respiratory function, and family history in the first year of life

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The relation between airway responsiveness (AR), respiratory function (RF), and historical factors during the first year of life is unknown. We aimed to establish these relations by studying AR and RF longitudinally in normal infants from birth to 12 months of age. Eighty three infants (38 girls, 45 boys) were studied at 1, 6, and 12 months. RF was assessed using the squeeze technique to obtain maximal flow at functional residual capacity (VmaxFRC) and tidal flow-volume curves to obtain time to maximal expiratory flow/total expiratory time ratio (Tme/Te). AR was determined as the concentration of nebulised histamine causing a 40% fall in VmaxFRC (Pc40). On the basis of history infants were divided into four groups: (1) normal (n = 17), no family history of asthma or parental smoking; (2) asthma (n = 22), family history of asthma; (3) smoke (n = 16), history of parental smoking; (4) asthma/smoke (n = 28) both histories positive. Pc40 was lower in group 2 than in group 1 (geometric means 0·88 and 2·03 g respectively, $p < 0.05$) at 1 month, but not at 6 months and was again lower at 12 months (2·46 and 4·72, $p < 0.05$). Baseline VmaxFRC was less for group 2 than group 1 at 6 months (mean percentage of predicted values 84 *v* 106, $p < 0.05$), but not at 1 and 12 months. Tme/Te was lower in group 3 *v* group 1 at 1 month (median 0·29 *v* 0·41 respectively, $p < 0.05$) but not at 6 or 12 months. These data suggest that both genetic make up and parental smoking affect AR at birth but that only genetic make up affects AR and perhaps RF at the end of the first year of life.

Effect of inhaled steroids alone on bone formation

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Medicine, Hammersmith Hospital, London, Department of Biochemistry, Royal London Hospital, London, and Section of Endocrinology, University of Auckland, New Zealand Inhaled corticosteroids are being increasingly advocated for mild asthma. Osteoporosis is a common complication of corticosteroid treatment. We previously showed that oral prednisolone in the doses used to treat asthma reduces bone formation as reflected by serum osteocalcin concentrations in both short term volunteer and long term patient studies (*Thorax* 1990;45:791). The effects on bone of long term inhaled corticosteroid treatment remain controversial. To examine the effects of inhaled steroids alone 34 outpatients with symptomatic asthma or chronic obstructive airways disease who had not used any oral prednisolone in the previous three months were studied. Some were taking inhaled beclomethasone regularly. Patients taking higher doses of inhaled beclomethasone had lower serum concentrations of osteocalcin (correlation coefficient of $-0{\cdot}39$ ($p < 0{\cdot}05$)). To examine the short term effects of oral and inhaled corticosteroids healthy male volunteers were given a seven day course of either 15 mg oral prednisolone daily ($n = 10$) or 500 μg inhaled beclomethasone twice daily ($n = 20$). After a week of oral prednisolone plasma osteocalcin concentration fell from 11·8 (SE 1·1) ng/ml to 6·9 (0·8) ng/ml ($p < 0{\cdot}001$). With inhaled beclomethasone, mean plasma osteocalcin fell from 11·6 (0·6) ng/ml to 9·6 (0·6) ng/ml ($p < 0{\cdot}001$). With short courses of both oral and inhaled corticosteroids there is inhibition of bone formation as shown by the fall in plasma osteocalcin concentration. Further studies are needed to indicate whether chronic use of inhaled steroids leads to osteoporosis.

Effects of immunotherapy for summer hayfever on the immunohistology of the cutaneous late phase reaction and serum IgE concentrations

V VARNEY. M GAGA, M JACOBSON, AJ FREW, AB KAY, SR DURHAM *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London* The effect of immunotherapy (IT) on the immunohistology of the cutaneous late phase reaction (LPR) was determined in a double blind, placebo controlled study in 40 hayfever sufferers. After IT with Alutard SQ (Timothy grass pollen, ALK, Denmark) the active group showed a 61% decrease in symptoms ($p = 0{\cdot}001$) and a 79% reduction in medication ($p = 0{\cdot}002$). LPRs were elicited with 30 biological units of grass pollen administered intradermally. Induction was inhibited by 57% in the active group ($p < 0{\cdot}001$) Skin biopsy specimens (3 mm) were taken in all subjects before and after treatment. Before IT there were no differences in the number of infiltrating cells between the groups, all reactions showing a predominant influx of T cells (CD3, CD4) and eosinophils. After treatment the group treated with Alutard SQ showed a significant reduction in CD3 ($p < 0{\cdot}05$) and CD4 ($p < 0{\cdot}02$) with a trend towards reduced eosinophils (median Alutard SQ 9 *v* placebo 33/hpf) compared with the placebo group. There were no changes in CD8, neutrophils, or macrophages, although the expression of CD25 ($p < 0{\cdot}05$) and HLA-DR ($p < 0{\cdot}05$) was significantly increased. Before treatment there were no differences in total and specific serum IgE concentrations between the groups. After eight months of IT both groups showed increases in specific and total IgE, but there were no significant differences between the groups. These results indicate that successful IT is associated with alterations in T lymphocyte responses rather than IgE production.

Pattern of suppression of hypothalamopituitary-adrenal axis in adult patients with asthma inhaling high dose beclomethasone dipropionate

PH BROWN, AP GREENING, GK CROMPTON *Respiratory Unit, Northern General Hospital, Edinburgh* The development of suppression of the hypothalamopituitary-adrenal (HPA) axis was examined in 23 adults (12 men) with chronic asthma requiring high dose inhaled steroids who completed a double blind parallel group study investigating the HPA effects of large doses (>2000 μg daily) of beclomethasone dipropionate (BDP), administered with and without a large volume spacer. An initial dose of 2000 μg daily was increased by 500 μg at monthly intervals until HPA suppression was detected or a dose of 5000 μg daily was reached. HPA function was assessed by serum cortisol concentration at 0900, a short tetracosactrin test, and 24 hour urinary free cortisol concentration. HPA suppression was defined as subnormal results in at least two of these tests (0900 cortisol < 190 nmol/l; rise in cortisol in response to tetracosactrin < 200 nmol/l or achieved cortisol < 500 nmol/l or both; urinary cortisol < 80 nmol/24 h). With increasing BDP dose two patterns of response of 0900 cortisol and urinary cortisol were seen; (*a*) a progressive fall (60%) implying gradually increasing suppression of endogenous steroid production and (*b*) a threshold effect (40%) in which HPA function remained stable until a critical dose of BDP was reached. These patterns of response occurred whether or not spacers were used. HPA suppression developed in 22 of the 23 patients. At this point 0900 cortisol and post-tetracosactrin cortisol concentrations were subnormmal in 20 (91%) and urinary cortisol subnormal in 18 (82%). In contrast, the rise in cortisol in response to tetracosactrin was low in only five (23%). Increasing doses of BDP produce suppression mainly at the hypothalamopituitary level, the capacity of the adrenal gland to respond to stimulation being preserved. The short tetracosactrin test in most patients was unnecessary for the diagnosis of subnormal HPA function.

Large volume spacers and the influence of high dose beclomethasone dipropionate on hypothalamopituitary-adrenal axis function

PH BROWN, AP GREENING, GK CROMPTON *Respiratory Unit, Northern General Hospital, Edinburgh* A randomised double blind parallel group study was performed to determine the dose of beclomethasone dipropionate (BDP) (aerosol) that induces subnormal hypothalamopituitary-adrenal (HPA) function when administered with or without a 750 ml spacer (Volumatic). Fifty adults with asthma requiring long term high dose inhaled steroids were assessed by peak flow monitoring and HPA function tests (0900 serum cortisol concentrations; short tetracosactrin test; 24 h urinary free cortisol concentration). Six had HPA suppression (two or more tests subnormal), five of whom were taking 1500 μg BDP daily. Asthma was well controlled in six others. The remainder ($n = 38$; mean age 43 years range 23–68 years, 19 men) were randomised to inhale BDP 2000 μg daily with (group V $n = 20$) or without (group MDI, $n = 18$) a Volumatic. Placebo aerosol was inhaled by the alternative route. HPA function was assessed at monthly intervals and the daily dose was increased by 500 μg if two or more tests were normal until HPA suppression was detected or a dose of 5 mg daily (20 puffs Becloforte) was reached. Twenty three patients completed the study (14 in group V, nine in group MDI). Reasons for withdrawal were non-compliance (10), patient decision (three), and exacerbation of asthma (two). Seventeen had normal HPA function while taking 2500 μg BDP daily and 13 (eight in group V; five in group MDI) taking 3000 μg daily. The median dose producing HPA suppression was 3250 μg via V and 3000 μg via MDI. One patient (V) had normal HPA function while taking 5000 μg daily. Mild dysphonia occurred in eight patients (four in group V) and clinical candidiasis in three (MDI). One patient had spontaneous bruising at a dose that caused HPA suppression. There is substantial interindividual variation in the dose of BDP that causes subnormal HPA function whether or not a large volume spacer is used. Many patients were able to tolerate BDP doses higher than the currently recommended maximum of 2000 μg daily.

Leucocyte sodium transport mechanisms in asthma

RM TRIBE, L POSTON, PGJ BURNEY *Renal Research Laboratory, Departments of Public Health Medicine and Physiology, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, St Thomas's Hospital, London* We previously showed that a high salt diet in asthmatic men leads to an increase in bronchoreactivity. The physiological mechanisms involved are unknown. Cells from asthmatic subjects may handle sodium abnormally owing to a membrane defect, or a high salt diet may release a humoral substance that alters sodium transport. Using the radioisotope sodium-22 we measured leucocyte sodium transport in 16 subjects (eight with mild asthma, eight controls). One subject was taking sodium cromoglycate (stopped one week before the study) and inhaled salbutamol, (stopped six hours before the study). All subjects had PD_{20} methacholine measured and donated venous blood for serum and leucocyte isolation. Resting sodium influx and frusemide sensitive influx (1 mM) were measured in a bicarbonate buffer. These measurements were repeated in the presence of 20% autologous serum. Intracellular electrolytes were determined by flame photometry. No difference between cases and controls was found for basal sodium influx ($p = 0{\cdot}70$) or total serum stimulated influx ($p = 0{\cdot}30$). However, the frusemide insensitive serum stimulated sodium influx was higher in cases 39·6 (SE 6·7) mmol/h/kg than in the controls 16·9 (5·8) ($p = 0{\cdot}024$). Regression of $\log_{10} PD_{20}$ against this component of influx in the cases showed a significant association ($\beta = -0{\cdot}0195$, $p < 0{\cdot}01$) between them. Serum from asthmatic subjects may contain a substance that increases cellular sodium transport by a mechanism that is insensitive to frusemide.

Regulation of sodium transport in airway epithelium: effect of intracellular calcium concentration and of C kinase stimulation

A GRAHAM, D STEEL, EWFW ALTON, DM GEDDES *Ion Transport Laborary, National Heart and Lung Institute, London* Regulation of ion transport is a major factor controlling airway fluid transport. We studied the regulation of the isolated sodium current by intracellular calcium and C kinase in sheep and human airway epithelium mounted in Ussing chambers under short circuit conditions. The sodium current consisted of amiloride sensitive (57%) and amiloride insensitive (43%) components. Mucosal application of the calcium ionophore A23187 to sheep trachea resulted in a dose related reduction in Isc which was maximal (38% (SE 6%)) at a concentration of 10 μM. Mucosal addition of phorbol dibutyrate (PDB) to stimulate C kinase in concentrations of up to 50 nM resulted in a dose related fall in Isc of up to 56% associated with a small fall in tissue conductance (G). At higher PDB concentrations large rises in G occurred. Similar results were obtained with human bronchi (n = 2). Pretreatment of tissues with 100 μM amiloride reduced the A23187 and PDB induced falls in Isc by 56% and 88% respectively. Pretreatment of tissues with PDB, both alone and followed by a combination of 1 μM forskolin (F) and 100 μM zardaverine (Z) to raise intracellular cyclic AMP, had no effect on the subsequent A23187 effect. Neither did pretreatment with A23187 followed by F and Z affect the subsequent PDB effect. We conclude that both elevation of intracellular calcium with A23187 and C kinase stimulation with PDB have significant independent inhibitory effects on airway epithelial sodium transport which seem to be independent of the A kinase pathway. The effect of PDB is mediated predominantly by the amiloride sensitive sodium current.

Effect of carbonic anhydrase inhibition on sheep and human airway ion transport

DM STEEL, A GRAHAM, EWFW ALTON, DM GEDDES *Ion Transport Laboratory, National Heart and Lung Institute, London* The carbonic anhydrase (CA) catalysed production of bicarbonate (HCO_3^-) and hydrogen (H^+) ions occurs in several transporting epithelia. Thus CA activity may influence the ion transport properties of airway epithelia and in turn the regulation of airway surface fluid pH. Therefore we investigated the role of CA in sheep and human airway epithelia mounted in Ussing chambers under short circuit conditions. Acetazolamide, a specific inhibitor of CA in doses up to 100 μM, caused a dose related reduction in Isc with a maximum effect at 100 μM of 11% (1·2%) (n = 18) and an IC50 20 μM in sheep trachea, irrespective of the side it was added. In human bronchi acetazolamide caused a similar significant reduction of 5·4% (2·4%) (n = 7). To examine the source of HCO_3^- for this reaction, Cl^-/HCO_3^- exchange was inhibited by serosal addition of SITS, which significantly reduced Isc by 6·2% (1·8) after 25 minutes. However, pretreatment with SITS did not significantly alter the acetazolamide effect, of 7·3% (1·1), compared to the unpretreated acetazolamide effect suggesting that the CA catalysed reaction may be of greater importance as a source of HCO_3^- than the SITS-inhibited pathway. To examine the effect of altering the intracellular H^+ concentration mucosal EIPA (5 μM), a specific inhibitor of Na^+ H^+ exchange, was added, significanlty reducing Isc by 24% (2·4) (n = 6). The decrease in Isc is probably due to a secondary effect of intracellular acidiosis on ion transport. Pretreatment with EIPA significantly reduced the effect of acetazolamide on Isc, suggesting a decrease CA activity secondary to an increase in cellular H^+ ions. These results suggest that CA activity is involved in the generation of the Isc across both sheep and human airway epithelia.

Endobronchial pH measurements in anaesthetised subjects

CIA JACK, J TRAN, RJ DONNELLY, CRK HIND, CC EVANS *Cardiothoracic Centre, Liverpool* With a fibrescope and topical anaesthesia the endotracheal surface in humans has been reported to have a pH of 5·71; more distal airways were apparently less acidic (*Thorax* 1990;45:315P). In this previous study the topical anaesthetic agent used included 4% lignocaine, which is acidic. To investigate whether the endobronchial pH may be influenced by the topical anaesthesia used we repeated these experiments in 10 patients undergoing rigid bronchoscopy under general anaesthesia (a mixture of intravenous suxamethonium and propofol) for suspected lung carcinoma. Via a rigid bronchoscope a monocrystan, unipolar antimony electrode was inserted down an Olympus BF3 fibrescope (to allow direct visual placement of the electrode) and a reference electrode was placed on the sternum. We found a mean tracheal pH of 7·0 (range 6·5–7·4). The mean pH of the left main bronchus was 6·7 (range 6·3–7·0) and the right 6·6 (range 6·3–7·4). The pH of peripheral airways was recorded by "wedging" the electrode: left upper lobe 6·7 (range 6·3–7·0), right upper lobe 6·4 (range 6·0–7·0), left lower lobe 6·6 (range 6·0–6·9), right lower lobe 6·6 (range 6·1–7·1). These pH values are consistently higher than those reported previously. We therefore instilled topical 2·5% cocaine (pH = 3·5) or 4% lignocaine (pH = 4·9) and repeated the pH measurements. This resulted in a significant fall in all endobronchial pH values to a similar level to those reported previously—for example, tracheal pH = 5·6—which suggests that the previous authors results were attributable to the use of topical anaesthetic agents.

Effect of inhaled loop diuretics on bronchial responsiveness to methacholine in normal subjects

K RAJAKULASINGAM, R POLOSA, C GRATZIOU, ST HOLGATE *Medicine 1, Southampton General Hospital, Southampton* Inhaled frusemide produces protection of the asthmatic airways against methacholine induced bronchoconstriction. To investigate whether inhaled loop diuretics may have a non-specific effect on baseline bronchial responsiveness a double blind, randomised, placebo controlled and crossover study was undertaken using single doses of inhaled frusemide and bumetanide to test the ability of the diuretics to displace concentration-response curves with inhaled methacholine. Fourteen normal subjects underwent concentration-response studies with methacholine on three separate occasions each after having been given premedication 10 minutes before challenge with 40 mg frusemide, 1 mg bumetanide, or matched placebo. Changes in airway calibre were monitored as maximum expiratory flow at 30% of the vital capacity (Vp30) and as forced expiratory volume in 1 sec (FEV_1) and methacholine responsiveness was expressed as PC_{40} Vp_{30} and as $PC_{15}FEV_1$. PC_{40} Vp_{30} value was obtained in all 14 subjects and $PC_{15}FEV_1$ value was obtained only in 10 subjects. Both inhaled frusemide and bumetanide reduced significantly the airways sensitivity to methacholine measured after placebo, the geometric mean $PC_{15}FEV_1$ value increasing from 58·6 to 129·0 ($p < 0·01$) mg/ml and to 104·6 ($p < 0·05$) mg/ml respectively. Similarly the geometric mean PC_{40} Vp_{30} of 14·8 mg/ml after placebo increased to 32·2 mg/ml ($p < 0·01$) after frusemide and to 24·0 mg/ml ($p < 0·05$) after bumetanide. When expressed as concentration ratios frusemide and bumetanide elicited a protection of the airways of 2·2-fold and 1·8-fold against methacholine induced bronchoconstriction respectively. The concentration ratio for frusemide was not significantly different from that of bumetanide. No side effects were reported throughout the study. The present study shows that inhaled frusemide and bumetanide reduce airway responsiveness to methacholine in normal subjects and supports the view that inhaled loop diuretics may exert a non-specific protective effect towards a wide variety of bronchoconstrictor stimuli by modulating baseline non-specific bronchial responsiveness.

Effect of frusemide on release of prostaglandin E_2 by bovine tracheal mucosa

I PAVORD, A KNOX, A COLE, A TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham, and Department of Therapeutics, Queen's Medical Centre, Nottingham* Inhaled frusemide protects subjects with asthma against the bronchoconstrictor response to a wide variety of stimuli. One possible explanation for these effects relates to the ability of frusemide to enhance synthesis of the inhibitory prostaglandin (PG) PGE_2. Frusemide has been shown to enhance production of PGE_2 from animal renal tubular epithelium in a dose related manner at concentrations between 10^{-6} and 10^{-3} M (Miyanoshita *et al, J Pharmacol Exp Ther* 1989;251:1155). We examined whether airway epithelium responds to frusemide in a similar way by studying the effect of frusemide (10^{-3} M) on the release of PGE_2 by bovine tracheal mucosa. Seven paired strips weighing approximately 200 mg were suspended in 20 ml Krebs-Henseleit solution at 37°C and continually gassed with 95% oxygen and 5% carbon dioxide. After a 1·5 hour equilibrium period the strips were washed and frusemide or vehicle (acetone) was added to the Krebs-Henseleit solution for 20 minutes. A 2 ml sample of bathing fluid was then removed for PGE_2 assay. PGE_2 was assayed by radioimmunoassay; values were expressed as pg/mg tissue and compared by a paired *t* test of log transformed values. The geometric mean PGE_2 produced was 16 pg/mg with frusemide treatment and 9·2 pg/mg with vehicle treatment ($p < 0·05$). These preliminary data suggest that airway epithelium produces PGE_2 in response to frusemide in a similar way to renal epithelium.

Effect of frusemide on cough response to low chloride solution in subjects with mild asthma

RA STONE, PJ BARNES, KF CHUNG *National Heart and Lung Institute, London*

Frusemide (F) reduces cough responses to low chloride ([Cl]) solution for up to four hours in normal volunteers. As cough is a predominant symptom of asthma we investigated the activity of F against a single low [Cl] cough challenge (nebulised 1·26% sodium bicarbonate) in a randomised, double blind, placebo controlled crossover study of 10 mildly asthmatic patients. Baseline cough responses were first obtained and subjects returned after two hours to inhale either F (40 mg) or saline (control). Cough challenge was repeated after intervals of 30 minutes, and 2, 4, and 6 hours. FEV_1 was measured before and after each challenge. Changes in the cough response from baseline were compared between the F and control limbs. Cough challenge induced minimal bronchoconstriction which was not influenced by F. Fall in FEV_1 did not correlate with cough number ($r = -0·04$ for F and $-0·25$ for control). F had no significant activity against cough responses, as shown in the table below, which represents median data at each time point. Individual data were analysed by Wilcoxon's rank test. The inactivity of F against low [Cl] solution in asthmatic subjects is in contrast to its prolonged effect in normal subjects. The explanation is unclear, but changes in airway calibre induced by the cough challenge do not seem to be responsible for masking any potential effects of F.

Baseline	*30 min*	*120 min*	*240 min*	*360 min*
P 15	11	11	10	10·5
P 14·5	11	8·5	11	12·5

Lung cancer in elderly people: a suitable case for treatment

DA STEWART, S GHOSH, GJA MACPHEE *Department of Geriatric Medicine, Southern General Hospital, Glasgow*

Lung cancer is a common condition in elderly people. The view that treatment should be merely palliative has recently been challenged particularly for small cell cancer (SCC) with the recent introduction of single agent chemotherapy (SAC). This is often well tolerated and can significantly improve survival without impairing quality of life (Carney DN, *et al, Semin Oncol* 1990;17:49). The aims of this study were to define current approaches to investigation and management of this condition in elderly patients and to assess the benefits of any treatment offered. We carried out an audit of 150 consecutive patients over the age of 65 years discharged with a diagnosis of bronchial carcinoma using standardised mortality rate data. Histological diagnosis was obtained in 50% of cases. In patients with SCC the median survival was significantly longer in patients treated with SAC compared with untreated patients (381 *v* 50·5 days ($p < 0·04$). This was despite no demonstrable difference in mean age, WHO performance and breathlessness scores, and duration of symptoms. SAC was well tolerated with no significant haematological toxicity. In patients with non-small cell cancer those treated (mainly with radiotherapy) survived longer than untreated patients (299·5 *v* 127·5 days; $p < 0·006$). Treated patients were significantly younger (71·7 *v* 77·5 years; $p < 0·001$) but were similar in performance scores and other measured characteristics. Overall, there was no correlation between age and length of survival or performance and breathlessness scores. Despite this, patients offered investigation or treatment were significantly younger (71 *v* 77 years; $p < 0·001$). Modern lung cancer treatment is well tolerated by elderly patients and may signficantly improve survival. Current practice, which favours investigation and treatment in younger patients, seems to be unjustified.

Study comparing use of two anti-carcinoembryonic antigen monoclonal antibodies (Mabs) in the immunoscintigraphy of small cell lung cancer

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Twenty one patients with histologically diagnosed small cell lung cancer (SCLC) underwent immunoscintigraphy with one of two radiolabelled anticarcinoembryonic antigen (anti-CEA) monoclonal antibodies (Mabs). Ten patients were studied using Mab 35 labelled with indium-111 (^{111}In-Mab 35) (Oris Industrie, France) and 11 with BW 431/26 labelled with technetium-99m (^{99m}Tc-BW 431/26) (Behringwerke, Germany). Nine patients were newly diagnosed and 12 had recurrent disease. Sites of disease were identified by clinical examination, chest radiography, and other investigations as clinically indicated. A total of 38 were identified. Serum CEA concentration was measured in 19 patients and was raised in three. Tumour was imaged in 13 patients, corresponding to 18/38 known sites of disease. Seven out of 10 patients imaged with ^{111}In-Mab 35 were positive (9/18 sites) and 6/11 with ^{99m}Tc-BW 431/26 (9/20 sites). All three patients with known raised serum CEA concentrations had abnormal uptake, but eight out of 15 without raised concentrations had so too. This study confirms that anti-CEA Mabs are capable of localising deposits of SCLC, even when serum concentrations are not raised. The use of ^{99m}Tc labelled antibody did not offer any clear advantage over ^{111}In labelling. However, these findings do not support the routine use of anti-CEA antibody in the staging or monitoring of SCLC.

Cheap system for brachytherapy with iridium-192

MR HETZEL, SGT SMITH, CM ROBERTS, VHF MAK, PJ MULVEY, AJ VINALL, CE BANKS *Departments of Thoracic Medicine and Medical Physics, University College Hospital, London*

High dose rate afterloading brachytherapy with iridium-192 achieves good palliation in bronchial carcinomas (Burt PA *et al, Thorax* 1990;45:765) but equipment is expensive. We therefore report a simple manual low dose rate afterloading techique, designed to be cheap. Initial laser bronchoscopy is used to improve the airway if possible and the tumour length is measured. A length 1 cm longer is cut from an iridium-192 wire (Amersham; initial activity 5–10 mCi/cm) and crimped into the end of an 0·85 mm catheter. At rigid bronchoscopy under general anaesthesia a mini tracheostomy tube is inserted and through this an outer 1·6 mm catheter is guided into the tumour with a fibrescope. The iridium catheter is then fed into position, through the outer catheter, with forceps. Patients are transferred to a ward sideroom with bedside lead screens. Exposures are calculated to give a nominal dose of 40 Gy at 1 cm from the centre of the wire. Twelve patients (seven men, mean age 65 years, range 50–77 years) were treated. Nine had squamous carcinomas and three adenocarcinomas. Five had main bronchus tumours, three upper lobe, one intermediate bronchus, and three lower lobe tumours. One had not had previous treatment, the others had had radiotherapy (10), laser resection (8), or chemotherapy (3). Mean exposure was 64 hours (range 36–98 hours). At review four weeks later dyspnoea was improved in eight, slightly better in three and worse in one. Haemoptysis in one patient resolved. Forced expiratory volume in one second improved in five patients and vital capacity in seven (mean improvements 45% and 21% respectively). By April 1991 five patients had died at a mean of 15 weeks after brachytherapy and seven survived (mean 19 weeks, range 6–38 weeks). The isotope cost about £80 per patient. This technique seems to be effective and safe for both patients and staff.

Symptom control in non-small cell lung cancer

MF MUERS, C ROUND (on behalf of The Thoracic Group of the Yorkshire Regional Cancer Organisation) *Respiratory Unit, Killingbeck Hospital, Leeds*

Management of most patients with non-small cells lung cancer (NSCLC) is palliative. However, apart from short term studies of individual treatment modalities, there are surprisingly little data on the adequacy of symptom relief. A total of 289 (242 with histological confirmation) patients being managed for NSCLC by four physicians and two oncologists were prospectively studied. The severity of 12 symptoms on a four point scale and a modified WHO activity score were recorded every two months from presentation. Sixty four (22%) patients had surgery, 122 (42%) palliative radiotherapy, and 103 (30%) supportive care. The table below shows the percentage of patients with major respiratory symptoms; a palliative index for all symptom grades (median duration of relief/follow up); and the mean percent fewer patients with moderate/severe symptoms at 2, 4, and 6 months. Palliation of the other less frequent symptoms was variable. Cough and breathlessness were much less successfully palliated than haemoptysis or pain, and this common clinical problem merits further study.

Symptom	*% present*	*Palliative index*	*% Fewer with moderate/severe symptoms*
Cough	79	66	46
Breathlessness	75	50	16
Chest pain	37	85	64
Haemoptysis	35	85	85

Prospective survey of continuity of care in lung cancer

SE HAYNES, S AHMEDZAI, MDI MORGAN *Department of Respiratory Medicine, Glenfield General Hospital, Leicester* Patients with lung cancer may receive several forms of treatment and therefore risk interruption in the continuity of care. We examined the route taken by consecutive patients through the medical process, from diagnosis to outcome at six months, together with an estimate of their quality of life and level of satisfaction with the service. Fifty patients (age range 45–86 years) with histologically proved carcinoma had their progress, relevant to the disease, tracked through the system. After an initial interview they received monthly estimates of quality of life (QOL: EORTC questionnaire) and after three months a consumer satisfaction assessment. At six months 34 patients (68%) had died, only 21 patients were admitted to hospital (LOS 6 days), and the majority of deaths (19 (55%)) occurred at home. Nine (18%) had surgery, 28 (56%) had radiotherapy, 10 (20%) had chemotherapy, 10 (20%) received no active treatment, 10 (20%) received hospice care, and 32 (64%) received community nursing care. In their perception of QOL patients who received surgery or chemotherapy had the lowest scores during treatment. However, patients given chemotherapy improved to pretreatment values after treatment whereas the others did not. The consumer responses highlighted failures of communication and education. The relatively short time spent in contact with the hospital services emphasised the need for improved coordination of care and increased use of community services.

The role of adhesion receptors in asthmatic epithelium

N MANOLITSAS, AJ D'ARDENNE, A MCAULAY, K JONES, RJ DAVIES *Departments of Respiratory Medicine and Histopathology, St Bartholomew's Hospital, London* Adhesion receptors have an important role in regulating cellular interactions of the immune system. Some adhesion receptors, in particular intercellular adhesion molecule-1 (ICAM-1) and the β1 Integrins (very late activation antigens (VLA 1–6)) are also expressed in other tissues. We investigated the expression of these adhesion receptors in the bronchial epithelium of mildly asthmatic subjects. In our initial study we examined bronchial biopsy specimens from 10 patients with atopic asthma (histamine concentration required to induce a 20% fall in FEV_1 (PC_{20}) <2 mg/ml with a DeVilbiss 646 nebuliser) and six normal volunteers via fibreoptic bronchoscopy. Frozen sections were examined by immunohistochemistry. VLA 2, 3 and 6 were expressed whereas VLA 1 and 4 were not in both normal and asthmatic epithelium with no significant differences between the 2 groups (VLA 5 not tested). In contrast ICAM-1 was found to be expressed in the epithelium of four out of 10 asthmatic subjects, but not in any of the six normal controls. Numbers were too small to allow statistical analysis. We subsequently studied 16 subjects with atopic asthma to look for a relation between ICAM-1 staining in the epithelium of bronchial biopsy specimens and bronchial hyperresponsiveness. Eight out of 16 subjects had positive staining in the epithelium. The mean log PC_{20} FEV_1 to histamine in the asthmatic subjects with positively staining epithelium was not significantly different from those with negative staining. Although we have not found a correlation with PC_{20} FEV_1, ICAM-1 may still have a role in the migration of inflammatory cells into asthmatic epithelium as PC_{20} FEV_1 has not consistently correlated with the presence of various cellular infiltrates.

Expression of interleukin-5 granulocyte macrophage colony stimulating factor, and granulocyte colony stimulating factor by cultured human bronchial epithelial cells

JL DEVALIA, XQ PAN, RJ SAPSFORD, RJ DAVIES *Department of Respiratory Medicine, St Bartholomew's Hospital, London* Although there seems to be a close association between eosinophil infiltration and airway epithelial cell damage, the specific mechanisms underlying attraction, activation, and maintenance of the eosinophils in the epithelium are not well understood. We cultured human bronchial epithelial cells (HBE) and tested the hypothesis that dysfunction of the epithelial cells themselves lead to the generation of specific cytokines which influence the activity of the eosinophils. HBE, cultured from surgical bronchial explants, were evaluated for their ability to express interleukin 3 (IL 3), IL 5, granulocyte macrophage colony stimulating factor (GM-CSF), and granulocyte colony stimulating factor (G-CSF), by in situ hybridisation techniques. Two to three week old cultures established on glass slides were fixed in paraformaldehyde and treated with 0·2 M hydrochloric acid and proteinase K. After a further fixation in paraformaldehyde the cultures were incubated overnight with specific oligonucleotide probes labelled with human biotin and visualised with gold labelled antibody and silver enhancement. Cultures investigated for expression of IL 3 stained only weakly and focally compared with control cultures either treated with ribonuclease or incubated in the absence of the probe. In contrast, cultures investigated for the expression of IL 5, GM-CSF, and G-CSF showed appreciable staining when compared with appropriate controls as above. These results suggest that human bronchial epithelial cells have the ability to express the cytokines which influence eosinophil activity and may therefore have an important role in the aetiology of airway disease, particularly asthma.

Identification of cells expressing messenger RNA for interleukin-5 in the nasal mucosa after allergen provocation: relation to tissue eosinophilia

SR DURHAM, Q HAMID, S YING, V VARNEY, M JACOBSON, R SUDDERICK, IS MACKAY, AB KAY *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London, and Nose Clinic, Royal Brompton National Heart and Lung Hospital, London* Two nasal provocations were performed in 16 patients sensitive to grass pollen by application of allergen and diluent solutions on 4 mm filter paper discs to the inferior turbinate. Nasal biopsy specimens (2·5 mm) were taken at 24 h. The cellular infiltrate was determined by immunostaining with a panel of monoclonal antibodies. Expression of interleukin 5 (IL 5) messenger RNA was assessed by in situ hybridisation using a riboprobe labelled with sulphur-35. Allergen induced nasal responses were indicated by immediate increases ($p < 0·001$) in sneezes, weight of secretions, blocking of the nostril, and a swollen appearance of the turbinate. Late nasal responses were equivocal and evident only as prolonged nostril blocking. Immunohistology showed significant increases in CD4+ lymphocytes ($p < 0·05$) CD25+ (interleukin 2 receptor bearing) cells ($p < 0·02$), EG2+ cells ("activated" eosinophils) ($p < 0·01$), and neutrophils ($p < 0·01$) at allergen challenged sites, compared with control sites. Positive hybridisation signals for IL 5 mRNA were increased at allergen challenged sites ($p < 0·01$). IL-5 mRNA+ cells were highly significantly correlated with EG2+ eosinophils ($r = 0·95$, $p < 0·001$). The results support the view that allergen induced rhinitis is associated with tissue eosinophilia which may be IL-5 dependent.

Expression of cytokine messenger RNA in bronchoalveolar lavage cells from patients with atopic asthma and normal controls

DS ROBINSON, Q HAMID, S YING, SR DURHAM, AB KAY *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London* Previous studies have suggested a role for T helper lymphocyte activation in asthma (Azzawi *et al*, *ARRD* 1990; 142:1407), and it has been suggested that cytokines corresponding to the murine T_{h2} pattern may contribute to eosinophil infiltration and IgE synthesis in atopic asthma (Mosmann, *Immunol Today* 1987;8:223). We used in situ hybridisation with 32P riboprobes labelled with phosphorus-32 to investigate the expression of cytokine messenger RNA in bronchoalveolar lavage cells from 10 patients with atopic asthma (mean age 25, range 22–28) and 10 normal healthy volunteers (mean age 25, 19–33). All asthmatic patients had positive skin prick or radioallergosorbent tests to aeroallergens, and median FEV_1 was 86% of predicted values (75–109) and methacholine PC_{20} 0·5 mg/ml (0·25–16). Normal volunteers had normal FEV_1 (101–113%) and $PC_{20} > 32$ mg/ml. All subjects were non-smokers. In situ hybridisation was quantified by counting dense deposits of silver grains overlying cells on autoradiographs of BAL cytospins (table below). In asthmatic patients IL 5 mRNA cell numbers correlated with eosinophils in BAL samples ($r = 0·68$, $p < 0·003$). These results are compatible with activation of a T_{h2}-like lymphocyte population in atopic asthma.

Median cells per 1000 total, 95% confidence interval

	Asthma	*Control*	*95% confidence interval*	*p Value*
IL 2	13·5	4·5	2 to 15	<0·02
IL 3	16·0	5·5	5 to 20	<0·004
IL 4	24·0	4·0	15 to 30	<0·0002
IL 5	28·5	6·5	15 to 32	<0·0002
GM-CSF	38·0	8·5	23 to 45	<0·0002
IFN-γ	1·5	0	0 to 1·0	NS

Activated T cells and eosinophils in bronchial mucosa in occupational asthma

AM BENTLEY, P MAESTRELLI, LM FABBRI, SR DURHAM, AB KAY *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London, and Institute of*

Occupational Medicine, Padua, Italy Fibreoptic bronchoscopic mucosal biopsy specimens were compared between nine patients with occupational asthma (five sensitive to toluene diisocyanate, four sensitive to methylene diisocyanate) who had not been exposed in the previous four weeks (O), seven patients with extrinsic asthma (E), and 12 normal healthy controls (N). The phenotype and activation state of leucocytes in the bronchial mucosa were examined by immunohistology (alkaline phosphatase antialkaline phosphatase method) using a panel of monoclonal antibodies. Cell counts per mm length of basement membrane were as shown in the table below. No significant differences in neutrophil counts (elastase positive cells) or macrophage counts (CD68 positive cells) were observed. These results confirm our previous findings in allergic asthma and identify comparable findings in occupational asthma. The data support the hypothesis that T cell-eosinophil interactions are important in the pathogenesis of asthma of diverse aetiology.

	O	*E*	*N*
CD45	57	79	58
CD3	35	39	37
CD4	19	25	19
CD8	6	1	0
CD25 (IL-2R)	0·5**	0·5*	0
EG2	5**	23**	0
BMK12 (MBP)	11*	20	3

*p < 0·02, **p < 0·01 (asthmatic *v* normal subjects).

Magnetic stimulation as a simple and reliable method for stimulating the phrenic nerves in the neck

R AQUILINA, S WRAGG, J MORAN, J GOLDSTONE, M GREEN, J MOXHAM *King's College and the Royal Brompton Hospitals, London* Percutaneous electrical stimulation of the phrenic nerves can be a useful technique for evaluating the function of the diaphragm and phrenic nerves. Recently a magnetic stimulator has been available that allows stimulation of the phrenic nerves in the cervical region (Similowski *et al, J Appl Physiol* 1989;67:1311), and we have used and compared this with supramaximal percutaneous electrical stimulation. We used a Magstim 200 with a 90 mm coil (Magstim Company) to apply a time varying magnetic field to the phrenic nerve roots while recording transdiaphragmatic pressure (Pdi). The coil was positioned in the midline at the level of C6/C7 with the neck flexed and the subject semirecumbent. Twitch Pdi was measured at functional residual capacity in six normal subjects. The maximum Pdi obtained magnetically equalled that produced electrically in five subjects (see table below). We conclude that magnetic stimulation does supramaximally activate the diaphragm. In addition, the technique was well tolerated and easy to perform, being less dependent on operator technique, and it may be more applicable clinically as a non volitional measurement of diaphragm strength.

Means of best three results

Case no	*1*	*2*	*3*	*4*	*5*	*6*
Electrical Pdi (cm H_2O)	36·8	24·7	40	27	46·7	28·5
Magnetic Pdi (cm H_2O)	40·3	37·2	33·5	32·7	50·3	32·3

Serial measurements of pulmonary physiology in adult respiratory distress syndrome

PD MACNAUGHTON, S BRAUDE, BF KEOGH, CJ MORGAN, TW EVANS *Adult Intensive Care Unit, Royal Brompton National Heart and Lung Hospital, London* The adult respiratory distress syndrome (ARDS) is characterised by increased pulmonary microvascular permeability, a reduction in lung volume, and impaired gas exchange. The natural history of these changes is poorly defined. We therefore performed serial measurements of the lung extravascular accumulation of transferrin labelled with iridium-113m and lung function in five patients with ARDS (age range 19–66). A protein accumulation index (PAI, normal range < 1·0) was derived by using a standard dual isotope technique (*Nuc Med Comm* 1990;11:879). Rebreathing measurements of helium dilution functional residual capacity (FRC, litres), carbon monoxide gas transfer (TLCO, mmol/kPa/min) and gas transfer coefficient (KCO, mmol/kPa/min/l) were undertaken by a standard technique adapted for patients being ventilated. The arterial: alveolar oxygen partial pressure ratio (a/A) was also assessed. Mean values (SE) on three different occasions are shown in the table below. In all patients PAI values and lung function parameters remained significantly abnormal while patients were ventilator dependent, although in survivors they tended to improve. The abnormalities of pulmonary microvascular permeability and lung function persist during the course of ARDS and their serial assessment may be useful in assessing clinical progress. This work is supported by the Medical Research Council and the Dunhill Medical Trust.

	PAI	*FRC*	*TLCO*	*KCO*	*a/A*
1	2·34 (0·4)	1·10 (0·12)	0·76 (0·13)	0·38 (0·09)	0·21 (0·02)
2	2·83 (0·4)	1·04 (0·08)	0·81 (0·19)	0·36 (0·07)	0·26 (0·06)
3	2·29 (1·0)	1·15 (0·16)	1·32 (0·53)	0·57 (0·19)	0·33 (0·12)

Respiratory symptoms and lung function in survivors of Wilms' tumours treated in childhood

M JENNEY, PH MORRIS JONES, N CLAYTON, D JACKSON, B FARAGHER, A WOODCOCK *North West Lung Centre, Wythenshawe Hospital, Manchester, and Pendlebury Children's Hospital, Manchester* We studied 45 patients (6–30 years) who had been treated for Wilms' tumour in childhood (mean 12 years previously) with chemotherapy alone (n = 12) or chemotherapy plus radiation to the flank (n = 15), whole abdomen (n = 12), or thorax (n = 6). Treatment started at a mean age of 3·7 years. Predictive equations were calculated from 84 age, height, and sex matched control subjects. Patients completed a questionnaire (cough, wheeze, breathlessness, exercise intolerance) and were examined. Lung volume, airways resistance, gas transfer, and maximal inspiratory and expiratory mouth pressures were measured.

Seventeen (38%) of the Wilms' group graded their subjective exercise tolerance as impaired; all these patients were in the irradiated groups. Thoracic hypoplasia was observed in three (50%) patients who had received thoracic irradiation, and hypoplasia of the lower thoracic cage was present in 12 (44%) patients who had received flank or abdominal radiotherapy. A restrictive defect of pulmonary function was present in all groups that had received radiotherapy. The table at the foot of the page shows the mean percentage of predicted values. Transfer coefficient and mouth pressures were normal. There is significant impairment in lung function in patients who received irradiation at a young age and sequential follow up is recommended. This work was supported by the British Lung Foundation.

	Control (n = 82)	*Chemotherapy (n = 12)*	*Flank (n = 15)*	*Abdomen (n = 12)*	*Thoracic (n = 6)*	*Irradiated v control*
FEV_1	100·5	106·2	86·2	71·4	56·1	p < 0·001
FVC	100·6	108·9	84·0	67·1	56·3	p < 0·001
TLC	100·7	104·4	84·8	74·1	67·3	p < 0·001
TLCO	100·1	102·0	93·4	80·7	69·0	p < 0·001

Thermic effect of carbohydrate in chronic obstructive pulmonary disease

JH GREEN, PN BRAMLEY, MF MUERS *Department of Medicine, St James's University Hospital, Leeds* We measured diet induced thermogenesis (DIT) after a carbohydrate (CHO) rich meal in patients with the emphysematous type of chronic obstructive lung disease (E-COPD) ($Paco_2$ < 5 kPa); nine patients with smoking related COPD (B-COPD) ($Paco_2$ > 6 kPa); eight patients with chronic asthma (A); and six control subjects (C). DIT was measured for four hours after a meal (87% CHO, 11% protein, and 2% fat as energy) with a total energy content of 40% of basal metabolic rate. Energy and substrate balances were derived by indirect calorimetry (Datex Deltatra Monitor) and urinary nitrogen excretion (Kjeldahl method). DIT was similar in all groups. In only the B-COPD group was DIT as a percentage of energy intake significantly higher than C (50·0% (SE 0·7) *v* 46·4% (0·6), p < 0·05). The postprandial non-protein respiratory quotients (as a measure of the ratio of metabolism of carbohydrate and fat) were similar between groups: 0·96 (0·01) (E-COPD), 0·94 (0·01) (B-COPD), 0·93 (0·01) (A), and 0·92 (0·01) (C). The postprandial protein oxidation rates were also similar between groups: 0·59 (0·07) (E-COPD), 0·68 (0·15) (B-COPD), 0·71 (0·15) (A), and 0·63 (0·07) kJ/h/kg (C). This normal metabolism contrasts with the enhanced postprandial oxidation of protein we have reported in E-COPD patients after a meal comprising 45% CHO, 19% protein, and 36% fat as energy (Green and Muers. *Eur Respir J*, in press). This may have implications for dietary recommendations in COPD.

Double blind controlled study of inspiratory muscle training

K McCONNOCHIE, K CHATHAM *Departments of Respiratory Medicine and Physiotherapy, Llandough Hospital, Penarth, South Glamorgan* The aim of this study was to ascertain whether inspiratory muscle training (IMT) in a group of selected patients with chronic lung disease resulted in subjective or objective improvement, or both. Maximum inspiratory pressure (MIP) was measured in outpatients who agreed to take part in the study. Men with MIP (-55 cm H_2O) and women with MIP (-40 cm H_2O) were randomly allocated to real inspiratory muscle training (RT), sham training (ST), or diaphragmatic breathing exercises (DB). At the same time a questionnaire was completed regarding breathlessness and activities of daily living. In all, 550 patients were assessed, of whom 162 were eligible for the study. Comparable numbers of men and women were entered into each study group. Measurements were made at the beginning of the study and at two, four, and six months. Compliance with DB and ST was 65% and 55% respectively, but for RT was only 40%. Mean MIP at start for DB ($n = 32$) was -33 cm H_2O and at six months -41 cm H_2O ($p < 0{\cdot}01$). Mean MIP at start for ST ($n = 29$) was -35 cm H_2O and at six months -43 cm H_2O ($p < 0{\cdot}05$). Mean MIP at start for RT ($n = 23$) was -37 cm H_2O and at six months -48 cm H_2O ($p < 0{\cdot}001$). MIP entry criteria were exceeded by 47% of RT compared with 23% of DB and 28% of ST. Those who recorded subjective improvement also significantly improved MIP in both DB and RT groups. In conclusion, we found that IMT offered to outpatients with low MIP can lead to subjective and objective improvement but compliance was low, especially in women. We also found that diaphragmatic breathing benefits a subgroup of patients, most of whom had asthma.

Effect of chest wall restriction on bronchial responsiveness in asthmatic patients

DPS SPENCE, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* The ability of airway smooth muscle to contract is influenced by airway-parenchymal interdependence and may be enhanced when chest wall movement is restricted. Observations in normal subjects suggest that this is possible (Ding *et al, J Appl Physiol* 1987:1324) but took no account of normal compensatory mechanisms during bronchoconstriction, nor were the symptoms experienced recorded. We studied eight patients with mild asthma (mean age (SE) 48 (6) years) during an extended methacholine challenge protocol (by the method of Cockcroft) in a constant volume body plethysmograph on two occasions in random order with and without chest wall strapping. We recorded functional residual capacity (FRC), airways resistance (R_{aw}), and forced expiratory volume in one second (FEV_1) and also "chest tightness" on a Borg scale. The mean FEV_1 (SE) fell from 82 (8)% of predicted values to 40 (6)% without chest strapping and from 52 (7)% to 26 (3)% when strapped. There were no significant changes in either PC_{20} (geometric mean 0·98 mg/ml) or the slope of the dose-response curve (16%/doubling concentration) with chest strapping; PC_{20} was unrelated to this slope. No patient showed a plateau response in either FEV_1 or R_{aw}. During the challenges FRC was relatively constant ($\pm$ 10% of baseline) in four patients until the last 2–3 doubling concentrations; it did not rise in two and increased progressively in two others. Despite chest wall restriction FRC rose in a similar fashion from 136 (6)% of predicted values to 172 (11)% unstrapped and from 110 (10)% to 155 (15)% strapped during the challenge. Strapping increased baseline chest tightness but relatively slightly given the fall in resting FEV_1. Symptom scoring increased in a linear fashion with increasing methacholine concentrations. The slope of the symptom/dose-response relation was increased from 0·9 (0·1) units/DC unstrapped to 1·2 (0·2) strapped ($p < 0{\cdot}05$). These data suggest that chest wall restriction does not of itself enhance bronchial reactivity. Changes in end expiratory position during challenge are relatively late in onset and occur after symptoms have developed. Pulmonary hyperinflation is not the principle cause of dyspnoea in these asthmatic patients with induced bronchospasm.

Is the QTc interval a predictor of death in chronic obstructive pulmonary disease?

AG STEWART, JC WATERHOUSE, P HOWARD *Department of Medicine and Pharmacology, University of Sheffield, Sheffield* Patients with chronic obstructive pulmonary disease (COPD) have a subclinical cardiac parasympathetic autonomic neuropathy (*Thorax* 1989;**44**:899), the severity of which correlates with the degree of arterial hypoxaemia. In the congenital long QT syndrome and in diabetics with autonomic neuropathy sympathetic imbalance prolongs the QTc interval, which predisposes these individuals to sudden arrhythmias and death. The QTc interval is the time in ms between the q wave and the beginning of the t wave on the ECG trace, corrected for heart rate. A year ago we measured the QTc interval at rest and at the peak of a Valsalva response in 34 consecutive patients with COPD (but without ischaemic heart disease) assessed for cardiovascular autonomic dysfunction by the method of Ewing and Clarke (*BMJ* 1982;**285**:916). Seventeen of these patients had a subclinical autonomic neuropathy (group A) and were compared with the remainder (group C). The two groups were similar in age, $Paco_2$ (6·4 (SE 0·3) in A and 5·9 (0·4) in C), FEV_1 (0·94 (0·10) in A and 1·48 (0·23)). As expected, the group A had a lower Pao_2 (7·3 (0·3) compared with 9·2 (1·8) kPa in C) ($p < 0{\cdot}05$ by Mann-Whitney U test) and much lower results in parasympathetic tests, but similar values between tests for the sympathetic system. Group A had a significantly longer QTc (0·43 (0·01) compared with 0·40 (0·01)) ($p < 0{\cdot}01$). However, in only five patients (all in group A) was the QTc > 440 ms (three of whom died). At peak Valsalva QTc tended to be further prolonged 0·44 (0·01) in A compared with 0·41 (0·01) in C ($p < 0{\cdot}005$). In eight of group A QTc was > 440 ms (five deaths) and in five (two deaths) of group C. Only one other patient died; he had a definite cardiac autonomic dysfunction but a normal QTc. Three deaths were sudden, the remainder occurring during infective exacerbations of the disease. QTc prolongation occurs in COPD, particularly if there is autonomic dysfunction. This seems to have prognostic implications.

Comparison of nasal intermittent positive pressure ventilation and pressure support ventilation in patients with nocturnal hypoventilation

NC FOX, LJ RESTRICK, G BRAID, EM WARD, JA WEDZICHA *Department of Thoracic Medicine, London Chest Hospital, London* Nasal intermittent positive pressure ventilation (NIPPV) has been shown to be an effective method of ventilatory support in patients with nocturnal hypoventilation. Nasal pressure support ventilation (NPSV) in response to patient triggering may also be effective, simpler, and cheaper but has not been evaluated. We compared the effects of these two forms of ventilation in 12 patients requiring domiciliary ventilatory support (seven patients with chest wall/muscular disease mean (SD) Pao_2 8·1 (1·3) kPa; $Paco_2$ 6·9 (0·9) kPa; FEV_1 0·7 (0·2) litres; FVC 1·3 (0·3) litres) and five patients with chronic airflow limitation (CAO) (Pao_2 7·1 (1·1) kPa; $Paco_2$ 7·6 (1·3) kPa; FEV_1 0·6 (0·2) litres). The patients were studied on three consecutive nights in random order—a control night without ventilation and then with the two forms of ventilatory support with the BIPAP ventilator (Respironics). NIPPV was delivered on the spontaneous/timed (S/T) mode, minimum respiratory rate 12/minute, and NPSV on the spontaneous (S) mode, with the patient triggering each breath (mean inspiratory pressure 16 cm H_2O for both modes). NIPPV and NPSV significantly increased mean Sao_2 compared with the control night (NIPPV mean increase 4·1%; 95% confidence interval 2·2 to 6·1; NPSV 4·4%; 2·1 to 6·6) and there was no significant difference between the modes of ventilation (NIPPV 91·5%; NPSV 91·7%; (mean difference 0·2; $-0{\cdot}5$ to 1·0). The percentage of the study night spent below 90% Sao_2 was similar on both ventilator nights (median difference 2%; $-1{\cdot}5$ to 6·5) and was significantly better than the control night for both NIPPV and NPSV (median reduction in percentage of time below 90% Sao_2 with NIPPV 30%; 10 to 54; with NPSV 27%; 9 to 53). There was also no difference in the time spent below Sao_2 of 85% and 80% with NIPPV and NPSV, with similar overnight $Paco_2$ pressures on both nights. NPSV was equally effective in patients with CAO and with chest wall/muscular disease. Patient acceptability of the two systems was similar and visual analogue scales of symptom scores showed no significant differences. NPSV is adequate for ventilatory support in most patients with nocturnal hypoventilation and NIPPV should be reserved for patients with documented apnoea. The widespread use of NPSV will have considerable economic advantages.

Effect of domiciliary nasal intermittent positive pressure ventilation on exercise capacity in chronic obstructive pulmonary disease

MW ELLIOTT, MA BRANTHWAITE *Royal Brompton and National Heart Hospital, London* Improved exercise capacity has been reported in patients with chronic obstructive pulmonary disease (COPD) after negative pressure ventilation in hospital (Guttierez *et al, Am Rev Respir Dis* 1988; **138**:617). We studied the effect of six months' nocturnal domiciliary nasal intermittent positive pressure ventilation (NIPPV) on exercise capacity in eight patients with severe

COPD (median (range) FEV_1 543 ml (290–880), FEV_1/FVC 30% (19–38), Pao_2 6·7 kPa (5·6–7), $Paco_2$ 7·9 kPa (6·3–9·9)). Exercise capacity was determined by six minute walks and maximal incremental treadmill tests (using the modified Bruce protocol, with measurement of oxygen consumption ($\dot{V}o_2$), carbon dioxide production, and minute ventilation (MV)) before staring NIPPV and after six months. Six minute walking distance increased by a median of 24 m (−47–113) (NS). Exercise was terminated by breathlessness and exhaustion in seven out of eight patients during the treadmill test. Exercise duration in these seven patients increased by a median of 85 s (60–140 s) ($p < 0·05$). This was associated with an increase in ventilation at peak exercise of 3·1 l/min (19%) (−1·7–6·2 l/min (−8–50%) ($p < 0·05$)) but no difference in maximal $\dot{V}o_2$ (111 ml/min (−183–269), $p = 0·15$). Alveolar ventilation as a percentage of MV was unchanged at rest (median −2% (−7–3%), $p = 0·55$) but decreased by a median of 16% (−4–−30%, $p = 0·04$) at peak exercise. Exercise capacity as measured by six minute walk was not increased and the improvement during the treadmill test may reflect greater motivation.

Use of nasal intermittent positive pressure ventilation in weaning intubated patients from assisted intermittent positive pressure ventilation

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Nasal intermittent positive pressure ventilation (NIPPV) has been used for domiciliary ventilatory support in patients with chest wall/muscle disease and chronic airflow limitation (CAL). However, its role in weaning patients from ventilatory support in intensive care has not yet been defined. We reviewed 12 episodes in 11 patients (eight women, three men; mean age 52 (range 21–68) years). NIPPV (ventilators: Bromptonpac (8), Monnal D (3), Ventimate (1)) was used to aid weaning from assisted ventilation, conventional methods having been unsuccessful. The median number of days the patients were intubated was 17 (range 1–229); four patients later had a tracheostomy performed, three being removed before starting NIPPV. Emergency ventilation was instituted in nine episodes (four CAL, four chest wall disease, one haemopneumothorax) with a mean (SD) Pao_2 before ventilation of 5·9 (1·7) kPa and mean $Paco_2$ of 10·9 (3·1) kPa, and three patients received elective postoperative ventilation after thoracoabdominal surgery (two had underlying chest disease). NIPPV was established in all patients, successful weaning occurring in 11 out of 12 episodes. One patient with CAL required reintubation but was later weaned by using NIPPV during a second episode. Hypoxia was corrected by NIPPV in all cases; the mean Pao_2 achieved was 11·9 (3·8) kPa, the mean $Paco_2$ 7·7 (2·1) kPa; supplemental oxygen was required in seven of the 12 episodes. NIPPV was used for a median of seven days (range 1–60) and the median duration of hospital stay from extubation to discharge was 17 days (range 8–46). At discharge the mean (SD) FEV_1 was 0·8 (0·3) litres, FVC 1·2 (0·4) litres, Pao_2 8·6 (1·2) kPa, $Paco_2$ 6·7 (1·0) kPa; four patients continued to use NIPPV long term, and all had chest wall or muscle disease. Four of the patients in the study died; one patient with CAL died during the admission despite successful weaning, while three patients died at a later date (two from their underlying chest disease, one from unrelated problems). NIPPV is a useful adjunct to weaning in intensive care as it corrects hypoxia and is well tolerated. It is effective when weaning from assisted ventilation is difficult, as often found in patients with CAL. Most patients in whom NIPPV was used for weaning did not require long term ventilatory support.

Effect of nasal intermittent positive pressure ventilation on acute exacerbations of chronic obstructive pulmonary disease

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Nasal intermittent positive pressure ventilation (NIPPV) has been used successfully to treat acute to chronic respiratory failure in patients with musculoskeletal disease. We are conducting a randomised controlled trial on the effects of NIPPV versus conventional treatment in patients with acute exacerbations of chronic obstructive pulmonary disease ($Paco_2$ >6 kPa, Pao_2 <7·5 kPa). Measurements of arterial blood gas tensions, from spirometry, of maximum walking distance, and of treatment tolerance are made in both groups. To date, 40 patients have completed the study, 23 (10 female) in the NIPPV group and 25 (nine female) in the control group. Mean baseline measurements for the NIPPV group are: age 66·3 years, FEV_1 0·64 l, $Paco_2$ 8·64 kPa, Pao_2 5·24 kPa, pH 7·34. For the controls they are: age 64·4 years, FEV_1 0·59 l, $Paco_2$ 8·64 kPa, Pao_2 5·27 kPa, pH 7·31. Three patients refused NIPPV: two were confused, and one of these patients died. Four patients in the control group required ventilation, one of whom died, and eight further patients died ($p < 0·05$). Between admission and stabilisation by treatment (about one hour) $Paco_2$ fell by 1·52 (SD 1·19) kPa in the NIPPV group and by 0·54 (1·08) kPa in the control group ($p < 0·025$); the change in pH was 0·04 in the NIPPV group and −0·02 in the controls. Between admission and day 7 $Paco_2$ fell by 2·00 (1·51) kPa in the NIPPV group and by 1·12 (2·47) kPa in controls while Pao_2 rose by 2·42 (1·74) kPa and 1·30 (1·18) kPa respectively. These preliminary data show a more rapid improvement in $Paco_2$ and pH and an increase in survival in patients with an acute exacerbation of chronic obstructive pulmonary disease treated with NIPPV. This study is supported by the British Lung Foundation.

T cell phenotype and activation state in bronchoalveolar lavage samples from patients with atopic asthma and from normal controls

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We examined the relation between T cell activation and eosinophils in bronchoalveolar lavage samples (BAL) and bronchial hyperresponsiveness and symptoms in atopic asthma. Samples were obtained from 15 patients with atopic asthma and from 13 normal volunteers. The patients all had positive skin prick tests or radioallergosorbent tests to allergens. Nine patients (age 22–27) had perennial asthma with current symptoms (median FEV_1 85% of predicted values, range 74–100%, methacholine PC_{20} 0·4, 0·2–0·9), and six had seasonal symptoms only and were studied out of season (FEV_1 103%, 86–119, PC_{20} 8·7, 2·2–19·9). Normal subjects were non-atopic, with normal FEV_1 and a $PC_{20} > 32$ mg/ml. No subjects were smokers and none had received corticosteroid treatment. Flow cytometry showed increased expression of T cell activation marker CD25 on bronchoalveolar lavage samples CD4+ lymphocytes in asthmatic patients compared with control subjects (median 13·2% positive compared with 8·7%, 95% confidence interval 1·7 to 7·4; $p < 0·005$, Mann-Whitney U test). Peripheral blood lymphocytes (PBL) showed 12·0% CD4+CD25+ in asthmatic subjects and 8·0% in controls (0·5 to 6·2; $p < 0·02$). In both asthmatic and control subjects BAL CD4+ cells were of memory phenotype (CD4+CD45RO+, 93·9% patients with asthma, 96·8% controls) in contrast to a mixed population in PBL (39·4% *v* 38·4%). BAL eosinophil numbers were increased in asthmatic compared with control subjects (2·0% *v* 0·2%, 0·4 to 5·0; $p < 0·001$). Within asthmatic subjects there was a negative correlation between log PC_{20} and percentage of CD4+CD25+ BAL cells (Spearman's $r = -0·656$, $p < 0·01$) and between percentage of CD4+CD25+ BAL cells and BAL eosinophils ($r = 0·792$, $p < 0·0001$). Symptomatic asthmatic patients showed a greater degree of T cell activation (CD4+CD25+ 16·9% *v* 11·5% 1·9 to 8·7; $p < 0·01$) and more BAL eosinophils (5·4% *v* 0·5%, 1·0 to 8·8; $p < 0·01$) than did asymptomatic patients. These results suggest that activation of CD4+ memory T cells is a feature of atopic asthma.

Cells infiltrating the human tuberculin induced delayed type skin reaction have a T helper cell 1-like cytokine profile

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Our previous study on the profile of cytokine messenger RNA (mRNA) expression in the inflammatory infiltrate associated allergen induced late phase reaction (LPR) in atopic subjects has shown a predominance of the interleukin 4 (IL 4) gene cluster family but not interferon (IFN-γ) or IL 2 (Kay *et al, J Exp Med* 1991;173:775). In this study we examined the profile of these same cytokines in tuberculin induced delayed type hypersensitivity (DTH). Skin biopsy specimens were taken from seven non-atopic subjects and the mRNA expression for a number of inflammatory cytokines was assessed by hybridisation with riboprobes in situ labelled with sulphur-35. Positive hybridisation with mRNA for IL 2 and IFN-γ was detected in all seven subjects while only two out of seven expressed mRNA for granulocyte-macrophage colony stimulating factor and one out of seven for IL 3 and IL 5. None expressed mRNA for IL 4. There were very weak positive signals in sites injected with diluent but those observed in sites injected with tuberculin were stronger and numerous ($p < 0·05$ for both IL 2 and IFN-γ). A significant correlation was observed between mRNA positive cells for IL 2 and IFN-γ ($r = 0·86$, $p < 0·05$). The results indicate that the infiltrat-

ing cells at tuberculin induced DTH (at 24 h) transcribe mRNA mainly for IL 2 and IFN-γ. Our data provide evidence for the possible existence of a dichotomy of cytokine profiles between DTH and LPR, with the former expressing a T helper cell 1-like profile while LPR seems to be characterised by a T helper cell 2-like pattern.

Cell adhesion molecules during lung rejection after heart and lung transplantation

JFJ MORRISON, C DENNIS, TW HIGENBOTTAM *Medical Research Council Molecular Genetics Unit, Cambridge, and Papworth Hospital, Cambridge* Adhesion molecules of the immune system are important regulators of inflammatory responses. They are involved in the induction, enhancement, and regulation of the immune response; in effector cell function; and in migration of cells from the blood to sites of inflammation. A pilot study has found differences in the transcription of the messenger RNA (mRNA) coding for LFA 2 and 3, ICAM 1 and 2, VLA 2 and 4, and also interleukin (IL) 1 and 6 in endobronchial biopsy specimens from normal subjects and patients undergoing lung rejection after heart-lung transplantation (HLT). In this study we examine this further in 13 control patients who were having a bronchoscopy as a diagnostic procedure (six haemoptysis, normal bronchoscopic results; six carcinoma of the lung; and one pulmonary fibrosis) and in 12 patients during acute lung rejection after HLT. Total RNA was extracted from endobronchial biopsy specimens by a method adapted from Chomzynski and Sacchi. After extraction the RNA was dissolved in 50 μl water. To convert the mRNA in cDNa for PCR, 5 μl of the RNA mix was reverse transcribed in a total volume of 20 μl according to standard protocols. The RT mix (1 μl) was used for PCR in a total volume of 30 μl, containing 3 μl each of forward and reverse primers (10 μlM), 3 μl 10 × buffer (100 mM Tris HCl, pH 8·3 at 20°C, 50 mM KCl, 15 mM $MgCl_2$, 0·1% gelatin), 3 μl dNTPs (10 mM) (17·7 water μl, and 0·3 μl Cetus Taq polymerase. After denaturation for three minutes at 95°C 35 cycles at 95°C for 0·5 minutes, 55°C for 0·5 minutes, and 72°C for one minute was performed. The DNA was separated using a 2° agarose gel. The results demonstrate decreased expression of the mRNA in HLT recipients coding for LFA 2 and 3, ICAM 2, VLA 2 and 4. IL 1 expression was increased after HLT. Expression was similar for both control and HLT recipients for ICAM 1 and IL 6. Therefore different expression was seen in adhesion molecules between control and HLT recipients. The reason is likely in part to be due to the immunological process of rejection and in part to immunosuppressive drugs and requires further study. JFJM is an MRC training fellow.

Pulmonary β receptor imaging in vivo using positron tomography and active enantiomer of CGP 12177 labelled with carbon-11

CG RHODES, JMB HUGHES, LI ARAUJO, R DE SILVA, Y YAMAMOTO, F BRADY, SK LUTHRA, H TOUCHON-DANGUY, C STEEL, HA JONES, PW IND, T JONES *Medical Research Council Cyclotron Unit, Hammersmith Hospital, and Department of Medicine, Royal Postgraduate Medical School, London* The active enantiomer (S) of the high affinity (K_D 0·8 nM) non-selective hydrophilic β antagonist CGP 12177 was synthesised, labelled with carbon-11 (t½ 20 min), and injected intravenously (2·1–6·0 μg) at time zero into four dogs (anaesthetised with dinitrous oxide and halothane (0·5%)) and one human volunteer (two studies). Continuous positron emission tomography was started (spatial resolution 7–8 mm) and blood samples were drawn from the pulmonary artery (dog) or from a peripheral vein (human). At −60 or +65 minutes pindolol (dogs) or propranolol (+40 min) (human volunteer) (5 mg intravenously in each case) was given to displace or block S-CGP 12177 labelled with carbon-1 ^{11}C S-CGP. No significant concentrations of metabolites were found in plasma in the dog or human studies. From an ^{11}CO scan and blood sampling pulmonary vascular ^{11}C-CGP 12177 was estimated and lung extravascular tissue concentrations measured. In dogs tissue to plasma ratios varied from 100 to 250 at 35 minutes falling to 12–15 at 75 minutes after intravenous pindolol. Lung uptake (μCi/g of lung per mCi injected/g body weight) varied from 12 to 23 but was only 2·7 if pindolol was given before intravenous ^{11}C CGP 12177. In the human being lung uptake was 9·8 and tissue to plasma ratio 50–60 at +35 minutes and 26 at 20 minutes after propranolol. In the decubitus dog lung uptake of S-CGP 12177 per gram was similar in the upper and lower lung, implying independence from pulmonary blood flow. Preliminary calculations of Bmax for S-CGP 12177 in the dog (29 nmol/kg tissue) are in good agreement with in vitro measurements. With further refinement of tracer kinetic modelling, β receptor density in the lung and its distribution will be measured in vivo and its regulation monitored in serial studies. ^{11}C S-CGP 12177 seems to be a suitable ligand for in vivo assessment of adrenergic β receptor density in the lung.

Modulation of multidrug resistance in a human tumour xenograft using the tiapamil analogue RO-112933

S BICKNELL, J PLUMB, G WISHART, S BANHAM *Department of Respiratory Medicine, Glasgow Royal Infirmary, and Department of Medical Oncology, University of Glasgow, Glasgow* The multidrug resistance phenotype has been implicated as a cause of treatment failure in a number of malignancies, including lung cancer. The membrane bound efflux pump P170 which underlies this resistance mechanism can be blocked in vitro by a variety of drugs known as modulators. There is, however, little evidence that resistance modulation is possible in vivo. Verapamil is the best characterised modulator in vitro but clinical use as a modulator is limited by cardiovascular effects. We previously suggested that the tiapamil analogue RO-112933 has greater clinical potential by virtue of its low calcium ion activity and high affinity for the P170 pump. We have now studied the effects of these two drugs in an animal model. The human carcinoma cell line 2780AD was grown as a subcutaneous xenograft in MF1 nunu mice. This cell line expresses high levels of P170 and is highly resistant to anthracyclines in vitro. Mice were randomised to receive no treatment, epirubicin alone, epirubicin and verapamil 50 mg/kg, and epirubicin and RO-112933 30 mg/kg. Tumour volumes were assessed from calliper measurements taken on days 0, 2, 5, and 7. Tumour growth in each group was assessed by pairwise group comparison using Bonferoni p values. Epirubicin alone did not significantly change tumour growth. Verapamil and epirubicin also failed to alter growth and, in addition, this combination caused deaths consistent with cardiovascular collapse. The combination of RO-112933 and epirubicin did produce a significant growth delay ($p < 0·001$) and did not produce toxicity. Thus RO-112933 may have clinical potential as a resistance modulator.

Inhibition of neutrophil chemotaxis by active site mutants of α_1 antitrypsin

DA LOMAS, RW CARRELL, RA STOCKLEY *Department of Haematology, University of Cambridge, Medical Research Council Centre, Cambridge, and Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* Neutrophil chemotaxis (PMN) has an important role in the pathogenesis of chronic lung disease. Studies with monospecific antibodies and chloromethylketones have indicated that inhibitors of cathepsin G are able to attenuate PMN migration in vitro. To investigate this further four active site mutants of the inhibitor α_1 antitrypsin were prepared and purified to homogeneity. The effects of the engineered proteins (in which the P1 methionine residue was mutated to leucine, arginine, valine, and lysine) on PMN chemotaxis were then assessed and the association rate constants of the new proteins with neutrophil elastase, cathepsin G, and bovine chymotrypsin determined. Leucine (P1) antitrypsin produced a dose related inhibition of PMN chemotaxis ($n = 6$) to the peptide FMLP (10^{-8}M) after preincubation for 30 minutes. The protein reduced the control value of 40·8 (SE 6·8) cells per field (cpf) to 31·2 (4·9) cpf at 0·25 μg/ml active site ($p < 0·025$), to 25·4 (4·8) cpf at 0·5 μg/ml ($p < 0·025$), and to 18·8 (4·2) cpf at 0·8 μg/ml ($p < 0·025$). The protein was not itself a chemoattractant and the effect was not abrogated by polymyxin B (a sequester of endotoxin). An FMLP dose-response curve showed pansuppression (rather than a shift of the curve), with the peak response still occurring at 10^{-8}M. The valine, arginine, lysine, and methionine variants had no effect on PMN chemotaxis at active site concentrations of up to 20 μg/ml. Leucine (P1) antitrypsin had the fastest association rate constant with cathepsin G (8·9 (SD 3·4) × 10^6/M/s) compared with 2·2 (0·2) × 10^5 for methionine (P1) antitrypsin, 2·1 (0·3) × 10^4 for lysine (P1) antitrypsin, 8·0 (0·1) × 10^2 for arginine (P1) antitrypsin, and 5·6 (0·1) × 10 for valine (P1) antitrypsin. Methionine (P1) antitrypsin had the fastest association rate with both elastase (2·8 (1·5) × 10^6/M/s) and bovine chymotrypsin (3·4 (0·4) × 10^6). Thus leucine (P1) antitrypsin is an effective inhibitor of PMN chemotaxis in vitro and also the most efficient inhibitor of cathepsin G. These data suggest that inhibition of cathepsin G may have an important role in the modulation of PMN migration.

Effect of glucocorticoids on granulocyte-macrophage colony stimulating factor and interleukin 5 enhanced in vitro survival of eosinophils

MP HALLSWORTH, TH LEE *Department of Allergy and Allied Respiratory Disorders,*

Guy's Hospital, London Glucocorticosteroids are known to inhibit allergic inflammatory reactions and eosinophilia. We investigated the effects of three corticosteroids—namely, hydrocortisone, dexamethasone, and methylprednisolone—on eosinophil survival enhanced by recombinant human granulocyte-macrophage colony stimulating factor (rhGM-CSF) and recombinant murine interleukin 5 (rmIL 5) over a period of seven days. Eosinophils, purified from atopic individuals by metrizamide density gradient centrifugation (purity $\leqslant 90\%$), were incubated at a concentration of 5×10^5 cells/ml in the presence of different concentrations of the three steroids, with either rhGM-CSF (1 ng/ml) or rmIL 5 (50 U/ml). The eosinophils were cultured in the presence of the same concentrations of rhGM-CSF or rmIL 5 alone as a positive control and buffer alone as a negative control. Viability was assessed by trypan blue exclusion. All three steroids inhibited rhGM-CSF enhanced eosinophil survival from a positive control of 75% (7%) viability in a dose dependent manner; hydrocortisone from 10^{-10}M (72% (8%) viability) to 10^{-4}M (54% (12%) viability); dexamethasone from 10^{-10}M (62% (14%) viability) to 10^{-4}M (34% (8%) viability); methylprednisolone from 10^{-10}M (67% (13%) viability) to 10^{-4}M (23% (4%) viability) (n = 6). Both dexamethasone and methylprednisolone inhibited rmIL 5 enhanced eosinophil survival from a positive control of 68% viability in a dose dependent manner: dexamethasone from 10^{-10}M (72% viability) to 10^{-4}M (31% viability); methylprednisolone from 10^{-10}M (66% viability) to 10^{-4}M (15% viability). Hydrocortisone did not inhibit eosinophil survival induced by rmIL 5. When eosinophils were cultured with rhGM-CSF (1 ng/ml) in the presence of β-oestradiol and testosterone for a period of seven days neither of these steroids inhibited rhGM-CSF induced eosinophil survival over the concentration range of 1×10^{-10}M to 1×10^{-4}M (n = 3). These results, suggesting that glucocorticoids inhibit cytokine enhanced eosinophil survival, may show one mechanism for their efficacy against eosinophil related disorders.

Geographical and social class effects on asthma mortality in England and Wales

BG HIGGINS, AE TATTERSFIELD, JR BRITTON *Wythenshawe Hospital, Manchester, and City Hospital, Nottingham* The rise in asthma mortality affecting the United Kingdom and other Western countries and the geographical variations in mortality between and within countries are largely unexplained. Potential causes include changes in prevalence or severity, effects of treatment, and changes in diagnostic labelling. We have studied the geographical, social and temporal trends in mortality from asthma in England and Wales from 1979 to 1987. Mortality was analysed in both sexes in four age bands (0–4, 5–34, 35–64, and >64 years) and compared between the 15 regional health authority areas. The effect of occupational social class was assessed in subjects aged 5–34 and 35–64 by comparing non-manual and manual occupational groups. Mortality increased over the study period in both sexes and in all age groups above 4 years by between 13–36%. There was significant ($p < 0.001$) geographical heterogeneity in mortality between regions (odds ratio between highest and lowest = 1·32) but the differences were age dependent; mortality was generally higher in the south of the country for ages 5–34, but higher in the north for ages 35–64. Mortality also increased over the study period in both non-manual and manual occupational groups, and tended to be higher in men in manual occupations. Thus the increase in asthma mortality has affected all age groups except the youngest, and both sexes and both social class groups. The age-area interaction suggests that the geographical variation has a multifactorial aetiology.

Self recorded peak flows: how accurate are they?

PFG GANNON, J BELCHER, JN NOBBS, CFA PANTIN, PS BURGE (on behalf of the Occupational Asthma System Project Group) *Occupational Lung Disease Unit, East Birmingham Hospital, Birmingham; Department of Mathematics, University of Keele, Keele; Department of Respiratory Medicine, City General Hospital, Stoke-on-Trent* Self recorded peak flow records form an integral part of the management of asthma. Few studies have been performed to assess the accuracy of these measurements. Seventeen patients of working age were randomly selected at a general chest clinic. They included normal subjects and patients with reversible and non-reversible airways disease. Patients were trained in the correct use of a peak flow meter by PFGG and their technique was checked by a pulmonary function technician (JNN) before leaving the clinic. Following a two week period of self recorded peak flows they returned to the clinic, where they were asked to perform peak flow measurements—first unobserved (while waiting to be seen), then observed (but not encouraged) and encouraged (and unobserved). A second unobserved measurement was then taken. Each patient used the same meter for all readings. These readings were assessed for agreement (Bland and Altman. *Lancet* 1986;**30**:7–10). Means and confidence intervals of the differences in peak flow reading are shown in the table below. Thus the first unobserved peak flow taken after two weeks' self recording may be 48 l/min below or 13 l/min above the encouraged level (*$p < 0.05$). After retraining the second unobserved blows are not significantly different from the encouraged, but are significantly higher than the first unobserved.

Visit 1 (l/min)	*Mean (2 SD)*
PFGG *v* JNN	2·4 (29·8)
Visit 2	
Encouraged *v* 1st unobserved	17·7 (30·4)*
Encouraged *v* observed	4·7 (34·6)
Encouraged *v* 2nd unobserved	1·2 (29·5)
1st *v* 2nd unobserved	16·5 (36·6)*

Role of the hospital based asthma education nurse

MJ WARD, D REYNOLDS, C WARD *Asthma Education Centre, King's Mill Hospital, Sutton-in-Ashfield, Notts* In the treatment of chronic illnesses it is well noted that to improve compliance the following are required: nurse contact, a personalised self management treatment plan, simple educational material, and a reward or system of self reinforcement to encourage continued compliance. We set up an asthma education centre to bring all of these components together. We investigated 45 consecutive patients aged 14–60 years attending the centre. The education programme was given by an asthma education nurse, not a doctor. Assessments were made with a questionnaire and diary and with peak flow monitoring before and three months after education. After education the patients showed improved knowledge about their asthma and its treatment. More importantly, they were also more likely to increase their inhaled corticosteroid or start oral prednisolone and seek help early in an attack ($p < 0.05$). Before education the mean peak flow was 238·5 l/min and after it was 285·7 l/min ($p < 0.05$). The patients found the nurse contact very helpful. They were often worried about their disease, and levels of anxiety fell after education ($p < 0.05$).

Comparison of quality of life, psychological morbidity, and personality in asthmatic and non-athmatic subjects

FH QUIRK, PW JONES *Division of Physiological Medicine, St George's Hospital Medical School, London* Yellowlees *et al* reported raised anxiety in mild and severe asthmatic patients and suggested that asthma may cause anxiety (*Chest* 1990;**37**:628). We measured psychological morbidity in 13 (seven female) non-asthmatic subjects and 13 sex and age matched asthmatic patients whose illness was judged to be well controlled by spirometric criteria. The asthmatic patients' mean FEV_1 as a percentage of predicted values was 76% (22%) and that of the normal subjects 86% (13%). Both groups completed a quality of life measure—the St George's respiratory questionnaire (SGRQ)—together with the hospital anxiety and depression scale and the Eysenck personality inventory. SGRQ scores, anxiety (A), depression (D), extraversion (E), neuroticism (N), and social conformity (L) were derived from the appropriate questionnaires. A two group unpaired *t* test was performed for each of the variables. Means and p values are presented in the table below. The scoring range for the SGRQ is 0–100. The SGRQ scores of the asthmatic patients indicated moderate impairment of quality of life (table below). Anxiety levels in the asthmatic patients were low, and these patients did not show any increased psychological morbidity or personality differences compared with normal subjects. SGRQ was positively correlated with anxiety ($r^2 = 0.49$, $p = 0.017$) in the asthmatic patients but not in the normal subjects ($r^2 = 0.28$, $p = 0.06$). It seems that, although asthmatic patients' perception of their quality of life was related to their level of anxiety, the degree of anxiety and psychological morbidity was not raised compared with a non-asthmatic age and sex matched population.

Comparison of SGRQ, psychological, and personality scores in asthmatic and normal subjects

	SGRQ	*A*	*D*	*N*	*E*	*L*
Asthmatic	29	5	2	10	14	3
Normal	4	7	2	10	12	2
p Value	<0·01	0·8	0·5	0·9	0·2	0·5

Symptoms and quality of life in asthma: one year placebo controlled trial with nedocromil sodium

PW JONES for the Nedocromil Sodium Study Group *St George's Hospital Medical School, London* This double blind, placebo (PLAC) controlled study was designed to measure the effect of nedocromil sodium (Tilade) (NED) on asthma symptoms and quality of life. In all, 719 patients (mean age 44 years and mean FEV_1 68% predicted values) were recruited in 14 countries. A total of 574 patients completed the study. After a four week baseline period patients were randomised to 48 weeks' treatment. Patients taking bronchodilators alone received NED 4 mg twice daily. Patients taking inhaled steroids received NED 4 mg four times daily. Patients recorded asthma symptoms daily by using dairy cards. At baseline and at six and 12 months they completed the St George's respiratory questionnaire (SGRQ)—a standardised and validated quality of life measure for airways disease. This has three components: Symptoms (SYM), Activity (ACT), and Impacts (IMP) on daily life. The IMP score correlates most closely with measures of general health. The scoring range for SGRQ is 0 (no effect of disease) to 100. Results at 12 months are reported. Significant improvements in night time asthma, clinic assessment of asthma severity, and daytime inhaled bronchodilator use were found with NED compared with PLAC ($p \leqslant 0{\cdot}01$). Patient and physician assessments of efficacy both favoured NED compared with PLAC ($p \leqslant 0{\cdot}005$). Both PLAC and NED groups showed moderate to large reductions in all SGRQ scores—that is, better quality of life ($p < 0{\cdot}0001$ in all cases; table below). NED was more effective than PLAC in reducing asthma symptoms. Patients and physicians showed significant preferences for NED. NED produced an improvement in quality of life that was additional to marked PLAC effects resulting from recruitment to the trial. These are the first quality of life measures from a long term trial of asthma prophylaxis.

Baseline and changes in SGRQ scores (means (SD). p Values are for comparison between changes with NED and PLAC

	SYM	*ACT*	*IMP*
Baseline	55 (16)	38 (21)	33 (17)
NED	−7·7 (17·6)	−7·4 (17·3)	−8·1 (15·0)
PLAC	−6·4 (18·6)	−5·3 (17·1)	−5·5 (15·9)
p Value	>0·05	>0·05	<0·05

Patient self treatment in asthma

M LEVY, R JEREMY, J BRADLEY *Edgware Chest Clinic, Middlesex* A hospital based uncontrolled study has shown improved asthma self treatment measured by a new questionnaire. Asthmatic patients were referred by medical registrars and general practitioners. After an initial questionnaire followed by a 20 minute education session (Levy, Asthma folder, Royal College of General Pracitioners, 1987), provision of a peak flow meter and a booklet, and an invitation to join the National Asthma Campaign (NAC); patients were followed up for one year (five interviews, three by telephone). Only completed sets of data were analysed (n = 29) with McNemar's test for dichotomous data and the Wilcoxon matched-pairs signed-ranks test for continuous data. Pre-education behaviour was compared with each of the five subsequent interviews spread over one year. Patients failed to attend 35% of appointments (new and follow up) during the 21 months. Thirteen (45%) joined the NAC. There was quite strong evidence for improvement in symptom scores ($p < 0{\cdot}05$) and for perceived improvement by patients ($p < 0{\cdot}05$ at second and third interviews). There was very strong evidence for a reduction in hospital admissions ($p < 0{\cdot}0052$) and for successful self treatment during the 12 months after education ($p < 0{\cdot}05$ at fifth interview and $p = 0{\cdot}0078$ for the same relative three month period one year previously). We conclude firstly, that patients self treatment of asthma can be improved by education, and secondly, that attendance at outpatient clinics could possibly be circumvented by providing inpatient or community education; and we also present a new instrument for auditing self treatment of acute asthma.

Catastrophic asthma and life events

C COYLE, E NEVILLE *Chest Clinic, St Mary's Hospital, Portsmouth* Twelve patients with severe asthma were studied. All of these patients had had multiple (3–25) admissions to hospital with acute severe asthma. They had also all been admitted on at least one occasion with preadmission symptoms lasting less than 24 hours. Six had had attacks with symptoms for less than six hours and three for less than one hour. All patients were followed up for more than five years (range 5–10); one patient died, two were lost to follow up but are thought to be alive, three continued to have frequent admissions for acute severe asthma, and six remained well with no admissions in the past 18 months or longer. Six of the patients were ventilated on at least one occasion (range 1–3). Ten of the 12 patients were female and eight of them initially presented with asthma before the age of 10. Asthma was diagnosed in three others in their teenage years and in one at the age of 23. The first acute severe attack occurred in the teenage years in six patients, in the 20s in three patients, in the 30s in two, and at the age of 50 in one. It is this oldest patient who has died. Nine of the 12 patients had significant life events around the time of their first acute severe asthmatic attack, ranging from leaving home to becoming divorced and being sacked. Of the six that are currently known to be well, two stopped getting acute severe attacks shortly after becoming single mothers, two left home and either got married or established a stable relationship, and one moved into more satisfactory accommodation. In conclusion, catastrophic asthma may be precipitated by significant adverse life events, and control of asthma may improve dramatically after more favourable life events in the same individual.

Asthma policy in schools in the county of Avon

EC SMITH, AH KENDRICK *Respiratory Department, Bristol Royal Infirmary, Bristol* Asthma in children may not be adequately controlled at school, and important precautions may be omitted. Furthermore, some schools are unwilling to permit the use of asthma medication (Nocon and Booth, *The Social Impact of Asthma*, University of Sheffield, 1989). This may reflect a lack of knowledge and understanding of management of asthma. A questionnaire was sent to all the head teachers of all the state schools in the county of Avon to determine their policy and potential deficiencies. In all, 302 schools replied: 11 nursery (N), 69 infants (I), 49 junior (J), 135 primary (P), and 38 secondary (S). The responses from each category are presented in the form (N:I:J:P:S). A total of 176 (60%) schools had no formal register of their asthmatic pupils (8:35:32:87:14). The designated person responsible if a child became ill with asthma was the head teacher in 32% and the pupils' class teacher in 30%. Eight schools left it to the parent, and in many no individual was designated. Only 32 (11%) schools had arranged any form of training (0:6:2:13:11). Seventy nine (26%) schools (0:2:11:33:33) allowed some pupils to carry their own medication, principally on the basis of age. In most schools the medication was located in a central location (3:53:32:72:1) and generally pupils were allowed access as required (1:38:28:57:2). In all, 148 (49%) schools had a procedure to deal with an asthma attack (2:36:19:58:32). Most (93%) schools wanted more information and 76% (10:53:40:96:30) wanted a member of staff to attend a short course. We conclude that in Avon, and possibly elsewhere, much more needs to be done to provide guidelines for teachers in the care of asthmatic children.

Prospective study of holidaymakers and daytrippers admitted to Victoria Hospital, Blackpool, with acute severe asthma, having previously been diagnosed as having asthma

P SISSONS, MS HENDY *Chest Clinic, Victoria Hospital, Blackpool* During the six months starting 1 May 1990, 483 holidaymakers (HM) and daytrippers (DT) were admitted to the general medical wards, of whom 27 (24 HM, three DTs) were diagnosed as having acute severe asthma. Their ages ranged from 15–80 years (mean 50) and 19 were female. All had previously been diagnosed as having asthma and 14 (52%) had required hospital admission during the previous 12 months. Ten patients (37%) did not know there was a hospital in Blackpool, ten holidayed alone, and 19 (70%) did not own a peak flow meter. Only one patient forgot to bring any medication. Nineteen (70%) had evidence of instability of their disease in the preceding week; 14 had consulted their family doctors and five others had increasing symptoms of wheeze, cough, and bad nights. Nineteen patients used both quick relieving and preventive inhalers, of whom eight did not appreciate the difference. The average duration of stay in hospital for these 27 patients was significantly less when compared with a local group matched for consultant, age, and sex (2·9 days compared with 6·5 days; $p < 0{\cdot}01$). From these data we conclude that the majority had unstable asthma before departure and that a significant number did not

make contingency plans should their condition deteriorate. In addition, the stay in hospital for holidaymakers was significantly shorter, suggesting that they may be at further risk on returning home. We have been prompted to design an "asthma holiday checklist" card.

Perception of asthma: effects of age

AH KENDRICK, G LASZLO *Respiratory Department, Bristol Royal Infirmary, Bristol*
Perception of asthma may be studied by relating changes in the 100 mm visual analogue scale (VAS) to changes in peak expiratory flow (PEF) using a coded meter (Higgs *et al, Thorax* 1986;41:671). To determine whether age influences the ability of asthmatic patients to perceive changes in airway function we studied 255 such patients (138 men, age 17–76 years) recruited from family practice. Recordings of VAS and coded PEF were made up to four times daily for 14 consecutive days. Linear regression analysis and analysis of variance as applied to regression determined the significance of the relation of VAS to $\log_e$ (percentage predicted PEF), and the slope, intercept, and correlation were obtained. A significant negative correlation of VAS to PEF indicates good perception of airway function. Age was normally distributed within each sex. Mean age was 44·2 (17–76 years) for men and 42·6 (17–70) for women. There was no significant difference in age between the men and women. In the group (n = 255) there was no significant relation of intercept (r = 0·09, F = 1·94) or slope (r = − 0·05, F = 0·57) to age. When separated by sex, similar results were obtained for intercept (male r = 0·02, F = 0·07; female r = 0·17, F = 3·55) or slope (male r = 0·02, F = 0·07; female r = − 0·148, F = 2·59). Division of each sex into good and poor perceivers showed no significant relations of intercept (good perceivers: n = 62, r = 0·13, F = 1·09; n = 46, r = 0·17, F = 1·30; poor perceivers n = 76, r = 0·04, F = 0·13; n = 71, r = 0·21, F = 3·13) or slope (good perceivers: n = 62, r = 0·13, F = 0·98; n = 46, r = 0·19, F = 1·58; poor perceivers: n = 76, r = 0·05, F = 0·16; n = 71, r = 0·20. F = 2·88) to age. We conclude that, within the age range of 17–69, the perceptive threshold (intercept) and the ability of asthmatic patients to discriminate (slope) changes in their airway function is not influenced by age. Whether alterations in either index occur above the age of 70, where few subjects were studied (n = 4), needs further investigation.

Perception of asthma in general practice

AH KENDRICK, CMB HIGGS, G LASZLO *Respiratory Department, Bristol Royal Infirmary, Bristol*
Perception of diurnal variation of bronchial calibre may be studied in asthmatic patients by relating changes in the 100 mm visual analogue self assessment scale (VAS) to changes in peak expiratory flow (PEF) using a coded meter (Higgs *et al, Thorax* 1986;41:671). Previous studies have suggested that between 10% and 20% of asthmatic patients are unable to sense moderate changes in their airway calibre during induced bronchoconstriction (Rubinfeld and Pain, *Am Rev Respir Dis* 1977: 381). We studied 255 asthmatic patients (138 men; age 17–76 years) randomly recruited from general practice. Recordings of VAS and coded PEF were made up to four times daily for 14 consecutive days. Linear regression analysis determined the significance of the relation of VAS to $\log_e$ (percentage predicted PEF), and the slope, intercept, and correlation were obtained. A significant negative correlation (p < 0·05) indicated good perception. The results are given as means (range) in the form of poor: good perceiver. In all, 152 asthmatics (60%) showed no significant correlation. The intercept was significantly lower (22·4 (−85·5 to 207):86·70 (4·5 to 317); p < 0·001) and the slope significantly flatter (−2·4 (−44·4 to 23·3: −18·0 (−80·3 to −0·90); p < 0·001) in the poor perceivers (Mann-Whitney test). We conclude that the majority of asthmatic patients in general practice are poor perceivers, having lower perceptive thresholds (intercept) and poorer discrimination (slope). The differences between this and previous studies may reflect differences between hospital and family practice based populations of asthmatic patients.

Bronchial hyperreactivity and perception of asthma

AH KENDRICK, G LASZLO *Respiratory Department, Bristol Royal Infirmary, Bristol*
Perception of asthma may be studied by relating changes in the 100 mm visual analogue scale (VAS) to changes in peak expiratory flow (PEF) using a coded meter (Higgs *et al, Thorax* 1986;41:671). To determine whether a relation exists between indices of perception and the degree of bronchial hyperreactivity we studied 25 asthmatics (10 men, age 19–63 years) recruited from family practice. Recordings of VAS and coded PEF were made up to four times daily for 14 days. Linear regression analysis and analysis of variance as applied to regression determined the significance of the relation of VAS to $\log_e$ (percentage predicted PEF). The slope, intercept, and correlation were obtained. A significant negative correlation indicates good perception. Bronchial hyperreactivity to histamine was assessed (Yan *et al, Thorax* 1983;38:760), and the provocation dose to elicit a 20% fall in FEV_1 (PD_{20} (μmol)) was obtained by linear interpolation. Mean PD_{20} was 0·78 (0·015 to 3·87) for the group. Bronchial hyperreactivity was reassessed in 15 out of 25 after 14 days. Mean PD_{20} was 1·05 (0·021 to 3·875). There was no significant difference between the two assessments. Mean PD_{20} in men (0·84 (0·018 to 3·4)) was not significantly different to that in women (0·74 (0·015 to 3·87)). There was no significant relation (n = 25) of PD_{20} to intercept (r = 0·21, F = 1·01) or slope (r = 0·21, F = 1·11). When separated by sex, there were also no significant relation of slope (male, r = 0·15, F = 0·18; female, r = 0·28, F = 1·12) or intercept (male, r = 0·03, F = 0·01; female, r = 0·34, F = 1·69) to PD_{20}. Division of each sex into good and poor perceivers gave a significant relation (p < 0·05) for intercept in female good perceivers (n = 7, r = 0·75, F = 6·51) only. No significant relations were obtained for slope to PD_{20} in good and poor perceivers. We conclude that the perceptive threshold (intercept) and the ability of asthmatics to discriminate (slope) changes in airway function are not predicted by the degree of bronchial hyperreactivity.

Cough responses to low chloride solutions and capsaicin in patients with chronic cough

RA STONE, PJ BARNES, RW FULLER *National Heart and Lung Institute, London*
Low chloride ([Cl^-]) solutions may induce cough via different neural pathways from capsaicin (C). We have developed a challenge in which low [Cl^-] solutions (150 mM controls and 75, 37·5, and 0 mM) are nebulised before doubling concentrations (10^{-6} to 5×10^{-4}M) of C are dispensed as single breaths. Cough number is counted for each low [Cl^-] inhalation and sensitivity to C is taken as the log concentration that first induces two and five coughs (C2 and C5). We report median data from 57 normal subjects and 30 patients with chronic, dry cough (table below). Patients showed increased responses to both challenges when compared with normal subjects (p < 0·01). Normal women responded more than men to the low [Cl^-] solutions (p < 0·05). No sex difference existed within the patient group, the majority of whom were female. Our C data confirm the work of others, but the low [Cl^-] data suggest neural pathways stimulated by this challenge are also sensitised in patients with chronic cough. The heightened response of normal women to low [Cl^-] challenge is intriguing and merits further study.

Low [Cl^-]	*150 mM*	*75 mM*	*37·5 mM*	*0 mM*
Normal males (n=36)	0	0	5	9·5
Coughing males (n=7)	0	1	4	13
Normal females (n=21)	0	1	7	18
Coughing females (n=23)	2	6	13	21

Capsaicin	*log C2*	*log C5*
Normal males	−1·08	−0·27
Coughing males	−1·21	−0·88
Normal females	−0·99	−0·22
Coughing females	−1·62	−1·4

Group comparison by multiple ANOVA.

Capsaicin aerosol stimulates lung irritant receptors independently of reflex bronchoconstriction in anaesthetised cats

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Capsaicin aerosol causes stimulation of lung irritant receptors (rapidly adapting stretch receptors) in anaesthetised cats (SP Mohammed *et al, J Physiol* 1990;432: 38P). In this study we investigated the effect of capsaicin aerosol on lung irritant receptors in the absence of reflex bronchoconstriction (RB). Male cats were anaesthetised (chloralose 60–80 mg/kg intravenously), paralysed with dimethyl tubocurarine, and artificially ventilated. Impulse discharges were recorded in vagal fibres arising from lung irritant receptors from the respiratory tract with conventional electrophysiological techniques. Aerosols were administered to the lower airways by an ultrasonic nebuliser. Inhalation of capsaicin vehicle (six breaths)

had no significant effect on irritant receptor discharge (n = 7) and pulmonary mechanics in bilaterally vagotomised animals. In animals that had been either vagotomised or treated with atropine (0·1 mg/kg intravenously) no RB occurred after inhalation of capsaicin (six breaths, 0·1 and 1·0 mg/ml). In these vagotomised or atropine treated animals capsaicin aerosol stimulated four out of the 11 irritant receptors examined. We conclude that (*a*) capsaicin aerosol can stimulate lung irritant receptors independently of reflex bronchoconstriction; (*b*) stimulation of irritant receptors may contribute to the RB induced by capsaicin; (*c*) cough evoked by inhalation of capsaicin is also due to stimulation of lung irritant receptors.

Nedocromil sodium and citric acid induced cough in normal subjects and in asthmatic and bronchitic patients

PJ REES, MJ BARROS *United Medical and Dental Schools of Guy's and St Thomas's Hospitals, Guy's Hospital, London*
Nedocromil sodium has been shown to have an effect on some forms of induced cough. We studied the effect of one week's treatment with nedocromil sodium, 4 mg four times daily by metered dose inhaler, on citric acid induced cough in 29 subjects (10 non-smoking normal volunteers, nine asthmatic patients and 10 bronchitic patients). The study was a double blind, placebo controlled crossover design with a one week washout period between treatments. Citric acid was administered as three inhalations at each concentration from 0·25%. Doubling concentrations were given until all three produced a cough at one concentration. Cough number and cough latency were measured by an inductance test. Citric acid challenges were performed 30 minutes after the first and last dose of the week's course. Geometric mean final citric acid concentration (cough threshold) for all three groups of subjects increased during one week's treatment with nedocromil sodium and not with placebo but these changes were not significant. At the end of one week's treatment initial concentrations of citric acid produced less coughs after nedocromil sodium than placebo ($p < 0·05$). The cough latency (time to first cough) increased after nedocromil sodium and the cough index (number of coughs/latency) was significantly different after one week's treatment with nedocromil sodium ($p < 0·05$). A weighted cough count was produced from coughs at each concentration divided by the concentration. There was a greater reduction overall after nedocromil sodium, significant only in normal subjects ($p = < 0·01$). We conclude that nedocromil sodium given for one week in a dose of 4 mg four times a day reduces citric acid induced cough in comparison with placebo and with a single dose of 4 mg nedocromil sodium.

Changes in plasma and urinary histamine concentrations after allergen inhalation in asthmatic subjects

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The biogenic amine histamine was among the first mediators proposed to have a role in the pathogenesis of asthma. An increase in plasma and urinary concentrations during the early bronchoconstrictor response to inhaled allergen is well documented, but changes during the late bronchoconstrictor response are less well established. We performed a study to reassess the changes to define more clearly the role of the mediator in asthma. Ten subjects with atopic asthma participated in the study (mean age 35 (14) years). All had seasonal asthma controlled by inhaled β agonists only, and their mean FEV_1 was 3·33 (0·79) l. Subjects attended for allergen challenge outside the pollen season and withheld their inhaled bronchodilator treatment for at least eight hours. After baseline FEV_1 measurements and collection of plasma and urine samples subjects inhaled increasing concentrations of allergen until a $\geqslant 20\%$ fall in FEV_1 from baseline had been achieved. Measurements of FEV_1 and collection of plasma and urine samples were then made at regular intervals up to eight hours. Plasma and urine samples were stored at −20°C until plasma histamine and urinary N-methylhistamine concentrations were determined by radioimmunoassay. Inhalation of allergen caused an immediate fall in FEV_1, reaching a mean maximum 39% from baseline at 15 minutes. After spontaneous improvement all subjects also had a late fall in FEV_1, reaching a mean maximum 29% at eight hours. The immediate bronchoconstrictor response was associated with a significant increase in plasma histamine concentrations over the initial 15 minutes from a mean baseline 0·22 mg/ml to a mean maximum 0·64 mg/ml at 10 minutes. By 30 minutes plasma histamine concentrations had returned to baseline concentrations and no subsequent changes were seen. The mean urinary *N*-methylhistamine to creatinine ratio showed a small increase during the study but these differences were not significant. We found an increase in plasma histamine concentrations during the early but not the late bronchoconstrictor response to inhaled allergen, without any associated changes in urinary *N*-methylhistamine concentrations. These findings suggest that, though histamine may be involved in the early response to inhaled allergen in asthmatic subjects, there is no evidence to support its involvement in the late bronchoconstrictor response.

Repeatability of prostaglandin D_2 and leukotriene D_4 inhalation challenges in asthmatic subjects

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Antagonists to histamine (H), prostaglandin D_2 (PGD_2), and leukotriene D_4 (LTD_4) have been used to explore the contributions of individual mediators to the bronchoconstrictor effect of inhaled allergen and as therapeutic agents in asthma. The actions of specific drug antagonists are often assessed by their effect on inhalation challenge with the appropriate mediator. This technique is dependent on the repeatability of the challenge, which is well established for histamine but less so for other mediators. We performed a study to assess the repeatability of PGD_2 and LTD_4 inhalation challenges in asthmatic subjects compared with H inhalation challenge. Ten asthmatics participated in each mediator group; 88% of the subjects were atopic and all were taking inhaled β_2 agonists and inhaled corticosteroids. Subjects attended twice seven days apart; after baseline FEV_1 measurements were taken they inhaled doubling concentrations of histamine until a $\geqslant 20\%$ fall in the FEV_1 had been achieved. When the FEV_1 had returned to within 5% of baseline they underwent a second challenge with doubling concentrations of PGD_2 or LTD_4. The second visit followed the same protocol. For each inhalation challenge the $PD_{20}FEV_1$ was derived from the linear portion of the dose-response curve by interpolation. $PD_{20}FEV_1$ values were log (base 2) transformed and the visits compared with paired *t* tests. The repeatability of the inhalation challenges was assessed with the method of Bland and Altman. The geometric mean (SD) PD_{20} FEV_1 values (nM) and the coefficient of repeatability in doubling dilutions (CR) are shown in the table below. In conclusion, we found inhalation challenge with LTD_4 to be very repeatable and comparable with that of histamine. In comparison, PGD_2 inhalation challenge was less repeatable, which may in part be explained by a significant reduction in bronchial reactivity to histamine.

	Visit 1	*Visit 2*	*t test*	*CR*
LTD_4	380·9 (3·4)	355·2 (3·4)	NS	1·12
H	169·0 (2·3)	176·3 (2·5)	NS	1·42
PGD_2	23·1 (3·6)	31·4 (2·7)	NS	2·10
H	194·8 (2·3)	312·7 (2·7)	p = 0·025	2·06

Histamine reactivity and skin weal diameter as predictors of the early asthmatic response to antigen challenge

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Cockcroft *et al* reported that the amount of antigen required to produce an early asthmatic reaction in antigen challenge could be predicted from the product of histamine reacticity and skin reactivity to the appropriate antigen. To test this hypothesis 16 patients who entered an antigen challenge trial as medical volunteers underwent skin testing with a standard solution of *Dermatophagoides pteronyssinus* and histamine challenge with the Yan technique. All 16 were skin prick test positive, with skin weal diameters varying from 4 to 10 mm. Fifteen achieved a PD_{20} value with a maximum dose of histamine of 6·46 mmol, the last having only an 18% fall at this dose. All 16 underwent antigen challenge with *D pteronyssinus* in increasing concentrations in order to achieve a 20% fall in FEV_1 from pre-challenge baseline values. The total dose was calculated from knowledge of the nebuliser output. Fourteen out of 16 achieved an early asthmatic reaction. The dose required varied from 176 units to 2456 units. The two non-reactors had no significant fall with an excess of 2500 units. With a regression model histamine reactivity (PD_{20} value) predicted the amount of antigen required to produce a 20% fall in FEV_1 at antigen challenge ($R^2 = 0·66$), but skin weal diameter did not ($R^2 = 0·09$). Addition of skin weal diameter did not add

significantly to the R^2 value achieved with PD_{20}. Histamine reactivity but not skin weal diameter may help to predict the amount of antigen required during antigen challenge.

Effect of RG 12525 on bronchoconstrictor response to inhaled leukotriene D_4 in subjects with mild asthma

I WAHEDNA, AFZ WISNIEWSKI, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Leukotriene D_4 is a potent bronchoconstrictor and a putative mediator in bronchial asthma. We studied the effect of RG 12525, a leukotriene D_4 antagonist, on leukotriene D_4 induced bronchoconstriction in subjects with mild asthma. Eight male subjects aged 20–48 years with mild asthma (baseline FEV_1 >80% of predicted values) and a reproducible leukotriene D_4 challenge were recruited. Each subject received 800 mg RG 12525 or placebo orally in a double blind fashion. Two hours later doubling doses of leukotriene D_4 were inhaled via a nebuliser at 15 minute intervals. FEV_1 and flow at 30% of vital capacity from a partial flow volume curve ($\dot{V}_{30}P$) were measured as the best of three efforts 10 minutes after each dose of leukotriene D_4. FEV_1 and $\dot{V}_{30}P$ increased in the two hours after administration of RG 12525 and placebo but the difference in the increases on the two days was not significant. RG 12525 caused a shift of the dose response curve for leukotriene D_4 to the right. The geometric mean PC_{20} FEV_1 was 0·99 nmol after placebo and 7·34 nmol after RG 12525. The mean (95% confidence interval) difference in log PC_{20} FEV_1 on the day subjects received RG 12525 was 2·88 (1·61 to 4·17) doubling doses of leukotriene D_4 ($p < 0·01$) compared with placebo (a 7·5-fold change); the mean (95% confidence interval) difference in log $PC_{40}\dot{V}_{30}P$ was 2·88 (1·22 to 4·54) doubling doses of leukotriene D_4 ($p < 0·01$) compared with placebo. We conclude that RG 12525 when administered orally antagonises the bronchoconstrictor effect of leukotriene D_4 in subjects with mild asthma.

Effect of oxitropium bromide on bronchial reactivity in chronic obstructive pulmonary disease

DPS SPENCE, MG PEARSON, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Patients with chronic obstructive pulmonary disease (COPD) and asthma both exhibit bronchial reactivity (expressed as PC_{20}) but for different reasons. Salbutamol reduces bronchial reactivity in both asthma and COPD but increases the slope of the dose-response curve (Bel *et al, Thorax* 1991; **46**:9). No data are available on the bronchial reactivity of patients who are known to be irreversible to oral steroids or whether the drug effects are specific to β agonists. We studied the effects of oxitropium bromide, an anticholinergic bronchodilator, on histamine reactivity in a group of 10 patients with COPD (age (SE) 59 (2·8) years, FEV_1 (SE) 1·09 (0·07) l) whose condition was known to be irreversible to oral steroid, and we related reactivity to bronchodilator status. Histamine PC_{20} was measured by the method of Cockcroft after either placebo or oxitropium bromide administered in double blind random order. Oxitropium increasd FEV_1 in all patients to 1·29 (0·07) l. Oxitropium reduced PC_{20} by more than two doubling doses of histamine in only four cases. Group geometric mean PC_{20} was 0·88 mg/ml and was unaffected by oxitropium bromide. The mean slope of the dose response curve (9·8% doubling dose) was unaffected by oxitropium bromide. There was no relation between bronchial reactivity and bronchodilator reversibility to either oxitropium or salbutamol. This study suggests that patients with COPD irreversible to oral steroids are hyperreactive to histamine, that bronchodilator reversibility is unrelated to bronchial reactivity, and that oxitropium does not affect bronchial reactivity in these patients.

Effect of oxitropium bromide on breathlessness and lung mechanics during histamine challenge in chronic obstructive pulmonary disease

DPS SPENCE, PMA CALVERLEY, MG PEARSON *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Bronchoconstriction increases breathlessness in asthma and chronic obstructive pulmonary disease (COPD), but limited data are available on the relation between lung mechanics and breathlessness during induced bronchoconstriction in COPD. We induced contrasting changes in lung mechanics with oxitropium bromide and histamine and related these to changes in breathlessness in a group of 10 patients with COPD (age (SE) 59 (2·8)) whose condition was known to be irreversible to oral steroid. FEV_1, functional residual capacity (FRC), occlusion pressure, and breathlessness scores (Borg scale) were measured before and after placebo (P) and oxitropium bromide (O) administered in double blind random fashion, and after histamine challenge causing a 20% fall in FEV_1 (table below). Oxitropium caused significant bronchodilation ($p < 0·001$) in this group of patients and reduced post-histamine challenge FRC significantly ($p < 0·001$). Resting FRC, breathlessness, and occlusion pressure all fell after oxitropium, but these changes did not reach significance. Histamine challenge caused significant rises in FRC, breathlessness, and occlusion pressure. Resting breathlessness before any treatment correlated with percent predicted FRC ($p < 0·02$) but did not correlate after induced bronchoconstriction or bronchodilatation. These data suggest that breathlessness is related to pulmonary hyperinflation but the improvements after bronchodilators are not solely due to the reductions in lung volume at rest.

Allergy testing: comparison of skin prick test results with solid phase immunoassay for IgE

JA FAUX, PA SHARP, WOCM COOKSON, JM HOPKIN *Osler Chest Unit and Department of Clinical Immunology, Churchill Hospital, Oxford* In two sets of age and sex matched groups of 123 subjects skin prick testing was conducted using either allergen coated needles (Phazets from Pharmacia) or liquid reagents from Dome/Hollister-Stier. In both groups skin test results were compared with immunoassay of serum total IgE (PRIST, Pharmacia) and specific IgEs (RAST, Pharmacia) for *Dermatophagoides pteronyssinus* and clusters of mixed grass pollens, mixed moulds, and mixed animal danders. Correlation coefficients, relating weal size on skin testing to radioallergosorbent test (RAST) titres (graded 0–4), showed similar and significant associations for the Pharmacia (P) and Dome (D) reagents (*D pteronyssinus* 0·70 (P), 0·78 (D); grass pollens 0·56 (P), 0·76 (D); cat dander 0·33 (P), 0·40 (D); *Alternaria* 0·60 (P), 0·51 (D)). The differences in the correlation coefficients for grass pollens is probably explicable by the inclusion of Timothy grass alone in the Phazet reagent but a cluster of four grasses in the Dome reagent. If a positive skin test is defined as a 2 mm weal and atopy as one or more positive skin prick tests or RASTs or a raised total IgE, then the power of the different tests to recognise atopy can be compared. With Phazet reagents four out of 123 subjects were designated atopic by skin tests alone, five by RAST alone, nine by total IgE alone, 14 by RAST and total IgE, and one by skin tests and total IgE. In the Dome group 15 out of 123 subjects were designated atopic on skin tests alone, three by RASTs alone, 16 by total IgE alone, seven by RASTs with total IgE, and four by skin tests with total IgE. The different reagents perform comparably, though the data suggest that the sensitivity of the tests can be ordered from the most sensitive as Dome skin testing reagents, RAST, and Pharmacia skin testing reagents.

Comparison of skin prick tests using reagents from Pharmacia and Dome/Hollister-Stier

PA SHARP, JA FAUX, WOCM COOKSON, JM HOPKIN *Osler Chest Unit and Department of Clinical Immunology, Churchill Hospital, Oxford* Skin prick testing for house dust mite, pollens, moulds, and animal danders was performed in 67 subjects presenting to a respiratory allergy clinic, with concurrent use of purified antigen extracts presented as liquid reagents (Dome/Hollister-Stier, US) and allergen coated needles (Phazets from Pharmacia, Sweden). Weal responses, recorded in mm, were greater than with negative control reagents. Highly significant correlation coefficients were observed for weal size responses to various allergens with the different Pharmacia and Dome/Hollister reagents (tree pollen (0·79), grass pollen (0·75), *Dermatophagoides pteronyssinus* (0·85),

		FRC		*Breathlessness*		*Occlusion pressure*	
	FEV_1	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
p	1·05 (0·33)	5·96 (0·49)	6·44 (0·58)	2·15 (0·38)	4·2 (0·68)	3·1 (0·55)	4·5 (0·91)
O	1·34 (0·42)	5·66 (0·49)	5·88 (0·56)	1·85 (0·45)	3·5 (0·67)	2·44 (0·35)	3·72 (0·46)

Cladosporium (0·59), *Alternaria* (0·85), cat dander (0·65), dog dander (0·73)). If a positive response is judged to be a weal of 2 mm or greater, and atopy is defined as a positive response to any one or more allergens, the Dome/Hollister-Stier and Pharmacia reagents classified individuals as atopic or non-atopic similarly in 59 out of 67 subjects (88%). Of the remaining eight individuals, six were classified as atopic with the Dome/Hollister-Stier reagents, with weal responses of 3 mm and more to either grass pollen or house dust mite. In only three individuals was atopy diagnosed using reagents other than *D pteronyssinus* or grass pollen. These different reagents produce comparable results and testing confined to house dust mite and grass pollen antigens offers a useful preliminary screening test for atopy.

Survey of patients' attitudes to the chest clinic

RJ WOSTENHOLME *Royal Albert Edward Infirmary, Wigan* Good patient-doctor relationships tend to lead to improved compliance with treatment and to reduction in symptoms. The majority of patients with chronic respiratory disorders are seen only as outpatients and their attitudes to the medical and non-medical staff in the chest clinic may affect their perception of the quality of care that they receive. A survey of 3339 adult patients attending 127 chest clinics in the United Kingdom and Northern Ireland has been completed. Sixty three percent agreed strongly that it was important always to see the consultant, and 25% agreed strongly that they felt comfortable in the hands of junior doctors, whereas 8% disagreed strongly with the statement. Most (90%) said that the staff were always friendly and also helpful. Fifty eight percent said that they learnt about their diseases and 65% that they received teaching about their medicines. Thirty eight percent thought that they had to wait too long to see the doctor, although 22% disagreed strongly with this statement. Twelve percent said that the surroundings of the clinic made them feel uncomfortable, but 56% said that they felt better after attending the clinic. Of the 2323 asthmatic patients attending the clinic, 46% had received an explanation of their condition from a hospital doctor. Thirty two percent of patients using an inhaler had received instructions from a hospital doctor. In both instances the hospital doctor was the person most likely to give the patient such information. Although the patients seem to be satisfied with their reception at chest clinics, 13% want more information.

Why patients admitted to hospital for smoking related disease(s) refused to participate in a stop smoking programme

J BANKS, SM TJEDER-BURTON, IA CAMPBELL *Chest Unit, Llandough Hospital, Cardiff* Strategies for stopping smoking have produced lower rates of quitting in patients with smoking related disease(s) compared with healthy clients who attend stop-smoking clinics. This might reflect differences in motivation to quit between the two populations. In a recent study 62 (22%) out of 281 patients admitted to hospital for smoking related disease(s) declined an invitation to participate in a stop smoking programme in which they would have received either nicotine or placebo gum and repeated advice on stopping smoking given in a hospital outpatient department (OPD). Their reasons for not wishing to participate indicate that many had no motivation to quit but potentially remedial reasons were given by others who might quit if given appropriate advice. Thirty five (56·5%) wanted to quit but of these, 12 (19·5%) refused to participate because of disillusionment with nicotine gum previously prescribed by general practitioners or obtained from friends and taken without proper instructions on its use. Side effects had been a common problem. Another nine (14·5%) disliked chewing gum. Advice about gum usage, emphasising that it should be chewed slowly, or the use of an alternative nicotine preparation might prove successful in these patients. Fourteen (22·5%) patients were reluctant or unable to attend regular OPD sessions for advice. Locally based general practitioner or self help support groups might be more convenient and acceptable to these otherwise well motivated patients. Twenty seven (43·5%) patients clearly stated that they had no intention of stopping. Ten said that the pleasure derived from smoking exceeded any health concerns, and another 10 refused to accept that smoking contributed to their condition. Seven thought that stress relief gained from smoking outweighed any risks. Efforts to encourage this poorly motivated group to stop smoking are probably futile.

Combined approach to discharge in a chest outpatient clinic

JM WALES, PA BARDSLEY, PR BURTON, AJ EARL *Department of Respiratory Medicine, Glenfield General Hospital, Leicester* Follow up of outpatients is often too frequent and too prolonged. Unnecessary follow up is unpopular with both general practitioners and patients. A survey of patients attending a chest clinic suggested that as many as 70% could be discharged (Leitch *et al, Respir Med* 1989;**83**:329). We conducted a one year prospective study of all patients attending a chest/general medical clinic for follow up. The need for follow up was analysed by a consultant and an independent general practitioner reviewing the notes jointly before the outpatient appointment. A suggested plan of action was outlined in the notes, although the doctor seeing the patient was not obliged to follow the recommendations. The objective was to reduce the number of patients seen at follow up and to return their care to the referring general practitioner. After a run in period of three months, 104 consecutive clinics were analysed from April 1989 to March 1990. Over this period there was a steady and significant reduction in the number of patients seen at follow up. The rate of decline was 2·89% per month (95% confidence interval 1·58% to 4·22%, $p < 0·0001$). If maintained over a full year this rate of decline would lead to a decrease of 27·7% (17·4% to 40·4%). New patient referrals remained constant, numbers of patients failing to keep follow up appointments fell, and clinics ran better to time. There was little increase in rereferrals; ward activity of the clinical firm remained constant and no adverse comments were received. This study confirms that follow up attendances can be reduced. It had differed from previous surveys by offering joint prior assessment by a general practitioner and consultant.

Laboratory workload after introduction of guidelines for sputum submission

KM MOUSSA, D PRATT, JH WINTER *King's Cross Hospital; and Microbiology, Ninewells Hospital, Dundee* Consultant staff from our respiratory unit and microbiology laboratory agreed the following guidelines for sputum submission: severe or cavitating pneumonia, suspected legionnaires' disease, lung abscess; cystic fibrosis or bronchiectasis thought to be infected with unusual Gram negative organisms; purulent bronchitis unresponsive to first line antibiotic; respiratory infection in HIV positive or immunocompromised subjects; suspected fungal or mycobacterial infection. These guidelines were communicated to all junior medical staff and ward sisters in writing and orally. Numbers of sputum samples received by the laboratory, inpatient mortality, and average length of stay from three respiratory wards (67 beds) for six months before the introduction of these guidelines were analysed (table below). The implementation of these guidelines led to a significant fall (63%) in numbers of sputum samples received by the laboratory. A fall in mortality was observed as well as a fall in average length of stay. No change in the number of sputum samples received from another hospital served by the same laboratory occurred during the period of study.

Sputum submission (per 1000 admissions)		*Mortality (per 1000)*		*Average length of stay (days)*	
Before	*After*	*Before*	*After*	*Before*	*After*
368·6	135·2	107·189	57·8125	13·855	11·14

Audit of outpatient sputum cytology and influence of written instructions on sample quality

KWT TSANG, AM BENTLEY, JS MANN, CFA PANTIN *City General Hospital, Stoke-on-Trent; and New Cross Hospital, Wolverhampton* A prospective study was performed to audit the quality of sputum cytology samples in a district general hospital outpatient department and to determine whether the addition of written instructions would improve the quality of specimens received. A total of 224 consecutive patients whose clinician requested sputum cytology in the outpatient department were enrolled into the study and all were given verbal advice on sputum production. Of these, 110 were randomly allocated to receive additional written instructions (AWI) on sputum production. Both groups of patients returned 84·1% of requested specimens to the laboratory. Collection pots did not contain fixative, and samples were delivered by hand or post to the laboratory. The Papanicolaou method of staining was used. Specimens containing alveolar macrophages were considered satisfactory. In the group receiving verbal advice only (VAO) 23·9% of specimens were satisfactory, which was not significantly different

from the proportion in the AWI group (28·3%, $p < 0·05$). No samples from the AWI group and four (1·3%) from the VAO group contained malignant cells. Values for atypical/suspicious cells were five (1·8%) and two (0·7%) for AWI and VAO groups respectively. At annual review bronchial carcinoma had been diagnosed in 50 patients. The diagnoses was made either by bronchoscopy in 58% or from a combination of clinical features (CF) and radiographic features alone (4%), CF and sputum cytology (18%), or CF and computed tomography (20%). Only two subjects underwent surgical resection of their tumours. With methods of sample collection and processing widely used in district general hospitals this study showed that outpatient sputum cytology samples were of generally poor quality and provided a poor pick up rate for bronchial carcinoma. The addition of written instructions resulted in no significant improvement in quality of sputum samples.

Chronic airflow obstruction: differences in practice between respiratory and general physicians

RM ANGUS, S MURRAY, NC THOMSON, KR PATEL *Departments of Respiratory and Public Health Medicine, Western Infirmary; and Gartnavel General Hospital, Glasgow* One third of cases (100) with a discharge diagnosis of diseases characterised by chronic airflow obstruction—namely, chronic bronchitis, emphysema, and chronic obstructive airways disease (ICD 490–2 and 496)—were sampled at random from 279 cases admitted during 1988. Fifty cases were selected from those admitted under the care of respiratory physicians and 50 from those under general physicians; 89 were suitable for analysis. The groups were similar: mean age 69 and 73 (NS); smoking habit 86% and 79% (NS) being current or ex-smokers; sex distribution 27 male, 23 female compared with 25 and 14 respectively (NS). Arterial blood gas tensions were pO_2 = 8·1 and 5·8 kPa for oxygen and carbon dioxide, pH 7·39, compared with 8·1 and 5·9, pH 7·36 respectively (NS). The only significant difference noted was in pulse on admission, being 91 beats/min in the respiratory group compared with 102 beats/min in the general group ($p < 0·004$). Differences were noted in the use of investigations when the respiratory group was compared with the general group. Though 96% and 78% had chest radiography (NS) and 86% and 79% had arterial blood gas tensions measured respectively (NS), 96% of respiratory patients had either spirometry or peak flow compared with only 62% in the general group ($p = 0·0001$). No significant differences were noted in the use of antibiotics, bronchodilators, corticosteroids, oxygen, or respiratory stimulants. The mean length of stay was 9·9 days in the respiratory group and 9·3 days in the general (NS). Two patients in the respiratory group compared with seven in the general group died during the admission ($p = 0·01$); there were no further early deaths at one month from discharge. Follow up differed—92% of patients in the respiratory group were offered appointments compared with 62% in the general group ($p = 0·001$). Readmission rates were similar and at one year 44% in both groups had been readmitted. Respiratory physicians measure lung function more than general physicians and are more likely to review their patients. In this study significantly higher inpatient death rate was noted amongst the general group.

Effects of electricity cuts on home nebuliser users

M COX, R MACFARLANE, J MACFARLANE *Respiratory Medicine, City Hospital, Nottingham* We report a survey of 72 adults (mean age 60 years; 17 ⩾70) using home nebulisers (HN) (mean of four times a day; range 1–9 times) who had no electricity (46 for <24 hours, 26 for ⩾24 hours, 17 for ⩾48 hours) owing to power cuts during the severe weather in December 1990 in Nottingham. Thirty eight patients had to manage without their HN (12 for ⩾24 hours), 12 used their HN elsewhere—for example, friends' home, hotel, ambulance station, petrol station—eight used their HN in their car outside (in the snow), seven used a spare car battery inside, two used an oxygen cylinder as a pressure source, and one bought a generator. Only 27 had an HN that ran off a car battery. Extra medical support was needed by the majority, with 17 seeing their general practitioner, five attending hospital, 39 increasing their inhaled therapy, 26 taking antibiotics, and 17 taking extra oral steroids. Fifty two said that their chest was worse or much worse and all but eight suffered varying degrees of anxiety or worry. Although power cuts are unusual in this country, we conclude that they can be a major problem for people dependent on HNs, many of whom are elderly and infirm. Internal rechargeable batteries in HNs would help, as would dual voltage compressors supplied with leads to clip directly on to a spare battery or for using in the car cigar lighter socket. A home oxygen cylinder can act as an acceptable, if inefficient, pressure source in a crisis.

Home nebulisers: a survey of their benefits, problems, and influence on hospital admissions

C TEALE, MF MUERS *Respiratory Unit, Killingbeck Hospital, Leeds* To determine the benefits and problems of home nebuliser usage we sent a questionnaire to all adults loaned a nebuliser for airflow limitation from the Leeds Eastern Health Authority equipment pool. Out of 207 patients with nebulisers, 167 (81%) completed the questionnaire; there were 91 male and 76 female respondents (mean age 64 years (range 19–85)) and the mean duration of nebuliser usage was 31 months (range 3–120). Nebulisers were described as very helpful by 119 (71%), quite helpful by 35 (21%), and little or no help by 13 (8%). Nebulisers allowed 76 (46%) patients to perform activities not previously possible. Sixty three (38%) patients reported that their nebuliser had broken at least once. Side effects were experienced by 104 (62%), of which tremor (80 patients (48%)) and palpitations (31 (19%)) were the most common. A total of 126 patients (75%) were able to recall the number of hospital admissions for breathlessness after and in the 12 months before receiving their nebuliser (mean duration with nebuliser 30 months (range 3–120 months)). In all, 105 (83%) were admitted less often and nine (7%) more often and in 12 (9%) the frequency was unchanged or they had never been admitted. The mean number of admissions per year fell from 2·5 (range 0–12) to 0·6 (range 0–7), after prescription of a nebuliser ($p < 0·01$). In summary, this survey suggests that, although side effects of home nebulisers are common, they are thought to be very helpful by most patients and may reduce the frequency of hospital admissions.

Outcome of nebuliser trials in patients with chronic airflow obstruction and subsequent compliance with treatment

IP HALL, I CALLOW, SA EVANS, IDA JOHNSTON *Respiratory Medicine Unit, University Hospital, Nottingham* The aims of this study were to audit (*a*) outcome of nebuliser trials and (*b*) compliance with subsequent prescribed nebuliser treatment in patients with chronic airflow obstruction (CAO) referred over a nine month period for consideration for home nebulised β agonist treatment. Nebulisers were prescribed to patients if they showed objective (⩾20% increase in mean peak flow) or definite subjective benefit, or both, in a formal trial of inhaled (two weeks via a Nebuhaler) versus nebulised (two weeks) β agonist treatment, or if they noted clear subjective benefit from nebulised treatment but were unable to complete a nebuliser trial. Compliance with subsequently prescribed nebulised treatment was assessed by direct questioning of patients. Of 57 patients with CAO, four (7%) referrals were considered inappropriate, and 12 (21%) patients were given a nebuliser without a formal trial. Forty one (72%) patients had a formal nebuliser trial. Seven (17%) of these patients showed neither objective nor subjective benefit, and three (5%) derived no subjective benefit despite objective improvement. Twenty two patients with positive trials and five (from nine) patients who were unable to complete adequate trials received home nebulisers in addition to those receiving nebulisers without a trial (total 39, 68% of all referrals). At 3–6 months, four (10%) patients had never used their nebuliser and a further three (8%) used it less than once a week. Twenty one (54%) patients were using their nebuliser as prescribed, seven (18%) more frequently, and four (10%) less frequently. Two patients died during follow up and two patients admitted stopping other treatment owing to benefit from nebuliser treatment. These results show that after formal assessment nebulised treatment was considered appropriate for 68% of all patients with CAO. Compliance was variable but the majority of patients given home nebulisers continued to use them.

Audit of referrals for home nebuliser treatment: role of respiratory nurse specialist

IP HALL, I CALLOW, SA EVANS, IDA JOHNSTON *Respiratory Medicine Unit, University Hospital, Nottingham* One potential role of a respiratory nurse specialist (RNS) is assessing patients undergoing trials of nebulised bronchodilators. To define referral sources and potential workload from referrals for consideration for home nebuliser treatment an audit study was performed examining retrospectively all referrals to the respiratory medicine unit over a nine months period. All referrals were initially assessed by the RNS. Before the appointment of the RNS nebuliser trials were performed without a specialist assessment. A total of 76 referrals (45 (59%) in males) were made during the study period, the mean age being 66 (range 15–94) years. Twenty eight (37%) referrals were made by the respiratory medicine department, 37 (49%) originated from other hospital physicians, and 11 (14%) originated from general practitioners. In 57 (75%) patients the primary diagnosis was chronic airflow obstruction (CAO), in 18 (24%) asthma (12 chronic), and in one bronchiectasis. Only

eight (11%) patients had never previously received nebulised bronchodilator treatment. Initial assessment of non respiratory unit referrals by the RNS identified six (13%) patients who were receiving inadequate treatment in whom a nebuliser study was deferred, and a further 12 (25%) who were considered unable to perform an adequate nebuliser trial. Of the total trials performed (41 CAO, 10 asthma), five were inadequate owing to inability to complete the protocol (two weeks' β agonist via a Nebuhaler followed by two weeks via a nebuliser with daily peak flow monitoring). This study shows that initial assessment of non-respiratory unit referrals by the RNS reduced the number of nebuliser trials performed by the department by 38%. However, the assessment and running of nebuliser trials involved a considerable input of specialist time and raises the question of how cost effective such activity is for the RNS.

Investigation and management of pulmonary infiltrates after bone marrow transplantation: eight year review

JH CAMPBELL, N BLESING, A BURNETT, RD STEVENSON *Departments of Respiratory Medicine and Haematology, Glasgow Royal Infirmary, Glasgow* Pulmonary complications remain a major determinant of outcome in bone marrow transplantation (BMT), adding significantly to the morbidity and mortality of recipients. We reviewed our experience in investigating pulmonary infiltrates in bone marrow recipients over the past eight years. Particular emphasis was placed on the effects of invasive investigations on patient management and survival. From 1982 to 1990, 204 patients underwent BMT (110 allogeneic, 94 autograft); of these, 27 (13%) developed pulmonary infiltrates that failed to respond to broad spectrum antibiotics and required specialised respiratory investigations. Bronchoscopy and bronchoalveolar lavage was performed in all patients and transbronchial lung biopsy in four. A specific diagnosis was made in 20 (74%): infectious aetiology (16), non-infectious (four). Five patients died without a diagnosis of their respiratory problem; necropsy showed non-specific interstitial pneumonitis (two), disseminated candidiasis (one), non-respiratory death (one). In 17 (63%) episodes these investigations led directly to a positive change in treatment. However, in only five did the changes in treatment result in the patients surviving beyond a month. Bronchoscopy and bronchoalveolar lavage proved effective in establishing a diagnosis and were well tolerated but the impact on overall survival was disappointing.

Sedation for fibreoptic bronchoscopy?

MQF HATTON, SV VATHENEN, MB ALLEN, EJ MELLOR, NJ COOKE *Department of Respiratory Medicine, Leeds General Infirmary, Leeds* Sedation is often given before fibreoptic bronchoscopy (FOB) (*Thorax* 1986;**41**: 311), although this may not be necessary (*BMJ* 1980;**281**:779). To evaluate formally the need for sedation we compared in a double blind, randomised study the combination of intravenous phenoperidine (0·5–2 mg) and droperidol (2·5–10 mg) given immediately before FOB with matched placebo; all received atropine. Of 103 consecutive patients undergoing routine FOB but not transbronchial biopsy, 101 agreed to take part. The assisting nurse (n), bronchoscopist (b), and patient (p) completed a 100 mm visual analogue scale relating to comfort, ease of procedure, and willingness to have the test repeated if clinically indicated; higher scores represent a less favourable view. Fifty patients received active sedation (A), 51 placebo (PL). Results were expressed as medians, compared with the Mann-Whitney U test, the 95% confidence intervals are shown in the table below. Both assisting nurse and bronchoscopist thought sedation made FOB easier and more comfortable for the patient. Patients found no difference between active and placebo treatment for comfort, while those receiving active sedation were less willing to have the procedure repeated. The sedation used in this study makes bronchoscopy less acceptable for patients and perhaps should not be used.

	Median		*Difference between medians*	*95% confidence interval*	*p Value*
	(A)	*(PL)*			
P comfort (N)	12	30	16	7 to 25	<0·001
P comfort (B)	11	20	7	2 to 13	0·01
Test ease (B)	11	22	11	5 to 19	<0·001
Comfort (P)	45	45	−1	−13 to 11	0·922
Repeat? (P)	46	24	−18	−34 to −3	0·008

Sedation for fibreoptic bronchoscopy

JH GREIG, SM COOPER, HJN KASIMBAZI, RDH MONIE, AG FENNERTY *Chest Clinic, Southern General Hospital, Glasgow* Most current sedative regimens for fibreoptic bronchoscopy use an opoid, a benzodiazepine, or a combination of the two. A total of 103 patients were randomised to receive either intravenous midazolam (M), dose according to weight, intravenous alfentanil (A) 0·5 mg, or both drugs together (M+A) in a double blind placebo controlled study. Active drug was titrated to achieve further sedation if necessary, M alone being used when M+A were given. All patients received transcricoid lignocaine and bolus doses of lignocaine via the bronchoscope if required. Patients given A had fewer coughs per minute than those given M (mean (SD) 1·4 (1·7) *v* 2·4 (1·4); $p < 0·01$), and with a visual analogue scale the bronchoscopist assessed the level of discomfort as significantly less (80% (20%) *v* 64% (31%); $p < 0·05$; 100% = no discomfort). Patients receiving M, however, scored the procedure as more comfortable than those given A (88% (14%) *v* 72% (33%); $p < 0·02$). Patients given M+A had a lower cough count than patients given M alone (1·7 (1·3) *v* 2·4 (1·4); $p < 0·05$) and had less discomfort than with A alone (88% (22%) *v* 72% (33%); $p < 0·05$). M+A achieved a lower mean oxygen saturation during the procedure (82% (9%)) than when M (88% (6%)) or A (87% (6%)) were used separately ($p < 0·02$). During bronchoscopy intravenous A prevents cough more effectively than M. The addition of M has a useful amnesic effect but may increase respiratory depression.

Lung function abnormalities in heart transplant recipients

J EGAN, S KALRA, N YONAN, N BROOKS, A WOODCOCK *Wythenshawe Hospital, Manchester* Unexplained breathlessness is a frequent problem in heart allograft recipients. We compared lung function—FEV_1, vital capacity (VC), total lung capacity (TLC), $Vmax_{50}$, carbon monoxide transfer factor (TLCO), KCO, and maximal inspiratory and expiratory mouth pressures—before and after heart transplant (Tx) in 22 (21 cytomegalovirus (CMV) matched) patients. We also examined the effect of non-pulmonary factors on these measurements by correlating them with indices of cardiac state (pulmonary artery and capillary wedge pressures (PA and PCW) before and after transplantation, histological evidence of rejection), drugs (cyclosporin concentration), differences between donor and recipient body weight, and CMV status (table below). A subgroup of 13 patients who had serial post Tx lung function measurements showed a significant improvement in KCO with time ($p = 0·033$). Abnormal gas transfer with normal spirometric measurement is suggestive of a defect in pulmonary perfusion. As there was a trend towards gradual improvement with time it may be the result of some early, possibly perioperative, event.

Age (year)	49·8 (range 17–60)
Lung function (pre) to Tx (months)	6·7 (range 1–26)
Tx to lung function (post) (months)	15·0 (range 0–42)

	Before	*After*	*p Value*
FEV_1 (l)	2·68 (0·14)	2·77 (0·14)	NS
VC (l)	3·43 (0·17)	3·47 (0·16)	NS
TLC (l)	5·35 (0·22)	5·32 (0·18)	NS
$Vmax_{50}$ (l/s)	4·0 (0·27)	4·2 (0·33)	NS
TLCO (mmol/min/kPa)	7·8 (0·38)	5·6 (0·32)	<0·0001
KCO (mmol/mim/kPa/l)	1·6 (0·03)	1·1 (0·02)	<0·0001
Max inspiratory pressure (cm H_2O)	−60·0 (5·5)	−66·0 (4·7)	NS
Max expiratory pressure (cm H_2O)	101·0 (5·9)	112·0 (7·0)	NS
PCW pressure (mm Hg)	22·5 (2·2)	9·2 (1·2)	<0·0001
PA pressure (mm Hg)	32·9 (2·7)	18·4 (1·3)	<0·0001

Values are means (SE).

Pulmonary function tests in congestive cardiac failure

DP MOORE, AR WESTON, C MORDIN, M HIGHAM, JGF CLELAND, JMB HUGHES *Department of Medicine (Divisions of Clinical Cardiology and Respiratory Medicine), Royal Postgraduate Medical School, Hammersmith Hospital, London* Obstructive and restrictive ventilatory dysfunction is well recognised in patients with congestive cardiac failure: (Light *et al, Arch Intern Med* 1983;143:429), but TLCO is frequently reported as normal, a finding attributed to the increased pulmonary capillary volume and transit time. We performed pulmonary function tests on 60 patients with congestive cardiac failure, New York Heart Association (NYHA) classes I–IV, due to dilated cardiomyopathy (26), ischaemic heart disease (26), or valvar heart failure (8). Mean age was 55 years (19–77). Spirometry was carried out by standard methods, and carbon monoxide transfer factor (TLCO), alveolar volume ($\dot{V}A$), and KCO (TLCO/$\dot{V}A$) were measured using a single breath technique and expressed as percentage of predicted values. FEV_1 and forced vital capacity (FVC) were reduced to 70·1% (21%) and 75·2% (18·8%) of predicted values respectively. FEV_1:vital capacity (VC) ratio was, however, preserved (74·4% (12·2%)). Diffusion impairment was present in 61·7% of patients (TLCO = 70·8% (16·6%) of predicted values), and obstructive ventilatory defects were found in 22%; combined defects were present in 15·5%. Mean KCO was within the normal range (100·8% (23·8%)), but $\dot{V}A$ was reduced (77·9% (66·4%)). TLCO impairment was significantly associated with severity of heart failure; TLCO was 88·1% of predicted values in NYHA class I compared with 71·8%, 63·9%, and 61·0% respectively in classes II, III, and IV ($p = 0.015$). TLCO impairment was also significantly associated with reduction in $\dot{V}A$ and VC ($p = 0.016$), but not with age, smoking history, or drug treatment. Our results confirm observations of obstructive and restrictive defects in heart failure and indicate that carbon monoxide diffusing capacity is substantially reduced, a finding which we suggest is largely attributable to a reduction in number of communicating lung units ($\dot{V}A$) rather than a reduction in alveolar efficiency (KCO).

Relation between expiratory airflow obstruction and ventilatory requirements, breathing pattern and subjective responses during exercise in normal subjects using an external (non-starling) resistance

D MEEK, LM COCHRANE, RJ MILLS, CJ CLARK *Hairmyres Hospital, East Kilbride, Glasgow* Six normal subjects underwent incremental exercise using a cycle ergometer with three external resistances in the expiratory port only. These comprised perspex rods producing reductions in FEV_1 of 10% (R1), 30% (R2), and 40% (R3) on flow volume analysis. At an oxygen consumption ($\dot{V}O_2$) of 1 l.min tidal volume (l) rose from 1·33 (0·12) unloaded to 1·54 (0·22) R1, 1·94 (0·46) R2 (p 0·02), and 2·2 (0·75) R3 (p 0·05). There was no further change in tidal volume at $\dot{V}O_2$ of 2 l/min or at $\dot{V}O_2$max. Breathing frequency fell at each workload with increasing resistance. Minute ventilation (VE) (l.min) was unchanged at $\dot{V}O_2$ of 1 l but at 2 l and $\dot{V}O_2$max was significantly lower with each resistance—for example, at $\dot{V}O_2$max VE was 89 (10·6) unloaded, 75 (5·5) R1 (p 0·02), 57 (13·9) R2 (p 0·01), and 53 (6·11) R3 (p 0·002). There was an increase in Borg rating with increasing resistance at $\dot{V}O_2$ 2 l/min and at $\dot{V}O_2$max—for example, 5·6 (1·28) unloaded, 8·2 (1·33) R1 (p 0·05), 9·3 (0·52) R2 (p 0·002), 9·3 (1·2) R3 (p 0·002). Maximum voluntary ventilation (MVV) measured directly was reduced with increasing resistance but VEmax/MVV remained unchanged. There was no consistent pattern of arterial blood gas changes with increasing resistance. In summary, during exercise in the presence of expiratory airflow obstruction breathing pattern changes. As work increases there is a progressive inability to achieve optimal ventilation (reduced ventilatory equivalents for oxygen and carbon dioxide), with increasing breathlessness and reduced maximal exercise capacity ($\dot{V}O_2$max). As resistance increases these changes become more pronounced. Aspects of this model mimic clinical airways obstruction. Once breathing patterns are maximally adapted during exercise, failure to meet ventilatory requirements may contribute to breathlessness independent of exercise hyperpnoea—that is, via mechanisms analogous to those operating during breath holding at rest.

Nasal resistance, sleep apnoea, and snoring

M ATKINS, P STONE, N CLAYTON, D JACKSON, A WOODCOCK *Department of Respiratory Physiology, Wythenshawe Hospital, Manchester* Nasal obstruction has been implicated in the pathogenesis of sleep apnoea syndrome (SAS) by increasing the negative intrapharyngeal pressure that occurs during inspiration. To ascertain the clinical value of routine measurements of nasal resistance (NR) we performed anterior rhinomanometry (right (R), left (L), and calculated combined (C); cm H_2O/l/s; Jaeger body test pressure/flow transducer) on 141 consecutive patients undergoing polysomnography for symptoms suggestive of SAS. Only six patients had CNR > 3 cm H_2O/l/s. We defined patients with SAS as those with an apnoea/hypopnoea index (A/H index) > 15/h (table below). There was no correlation between CNR and A/H index ($r = 0.09$). These results indicate that there is little clinical value in NR measurements in routine evaluation of SAS and that NR is not important in the pathogenesis of SAS.

	n	*A/H index (mean (SE))*	*CNR*	*Highest NR*	*CNR > 3 cm H_2O/l/s*
SAS	71	46 (2·66)	1·50 0·14	5·50 0·86	n = 4
Snorers	70	5 (0·52)	1·58 0·17	5·25 0·59	n = 2

Prospective survey of pulmonary function in non-smoking patients with rheumatoid disease

S WATKIN, D PORTER, R CARTER, H CAPELL, R STEVENSON *Glasgow Royal Informary, Glasgow* Previous studies on pulmonary complications of rheumatoid disease confirm a significant incidence of pulmonary fibrosis, but there have also been suggestions of airflow obstruction (AFO) (other than proved obliterative bronchiolitis) which is only partly explained by smoking (Collins, *Arthr Rheum* 1976;19:623). We studied 38 lifelong non-smokers with seropositive RA attending a "second-line" treatment clinic. Patients were assessed by spirometry, by body plethysmography, and from single breath TLCO. Criteria for an abnormal test included airways resistance (Raw) and airways conductance (sGaw) worse than 0·2 kPa/l/s and 1·1 kPa/s respectively, and FEV_1, residual volume (RV), TLCO, and KCO outside our laboratory normal range (mean (2 SD)). Thirteen patients (34%) had one or more measurable abnormalities of pulmonary function, including a group of seven with AFO and high RV (n = 3), AFO alone (n = 2), or high RV alone (n = 2). Patients with AFO had SGaw 0·82 (0·17) (mean (SD)), although one had asthma. Patients with air trapping had RV of 184% (41%) of predicted values. Three patients showed a restrictive defect (total lung capacity (TLC) 68% (8%)) and normal TLCO and KCO. One patient showed combined AFO and restrictive defect; one patient showed AFO with air trapping and reduced KCO (51% of predicted values). The remaining patient (with lung volumes in the normal range) showed bronchial lability after bronchodilator (FEV_1 3·16 to 3·73). This study has shown abnormalities of pulmonary function in 34% of a rheumatoid population, including airflow obstruction or air trapping, or both, which were not explained by smoking or a history of asthma.

Effects of postoperative physiotherapy on pulmonary complications and lung function after upper abdominal surgery

JEA BOURN, JH CONWAY, ST HOLGATE *Southampton General Hospital, Southampton* Pulmonary complications are a major cause of postoperative morbidity after upper abdominal surgery. Chest physiotherapy (CP) is commonly used in the prevention of these complications. Controversy exists about the routine use of CP in the postoperative period in patients at low risk. Using a double blind, randomised design we compared a regimen of preoperative CP alone with one of preoperative and postoperative CP. Forty eight patients with an FEV_1 of at least 50% of predicted values and who were undergoing cholecystectomy were allocated to one of two groups. Group A received preoperative instruction alone in breathing exercises, forced expiration technique (FET), and supported coughing. Group B additionally received postoperative CP, consisting principally of localised breathing exercises and FET. Radiographic changes, observerd 48 hours after surgery, were comparable in the two groups (group A 79%, group B 75%; NS). Chest infection was defined as the development of three or more of the following signs: temperature > 37·5°C, cough, purulent sputum, tachypnoea. This occurred in one patient in group A, and three in group B (NS). Lung function tests were performed preoperatively and on the third postoperative day. Arterial saturation (SaO_2) was measured preoperatively and for the first three postoperative days by pulse oximetry. No difference was seen between the two groups at any time in either lung function or SaO_2. However, in patients who developed a chest infection there was a marked and persistent drop in SaO_2 particularly on the first day ($p = 0.005$). Certain patient subgroups were found to be at increased risk of developing pulmonary complications—that is, smokers

and those who were obese ($p=0.01$). We conclude that patients at low risk who undergo cholecystectomy and who receive preoperative instruction in breathing exercises, FET, and coughing do not benefit from the addition of routine postoperative physiotherapy.

Effect of 100% oxygen on ventilation and exercise tolerance in patients with severe hypoxaemia from pulmonary intravascular shunts

GJ BELLINGAN, DP MOORE, JMB HUGHES, AR WESTON *Department of Medicine (Respiratory Division), Royal Postgraduate Medical School, Hammersmith Hospital, London* The exercise capacity of patients with pulmonary arteriovenous malformations (PAVMs) is very well preserved despite their degree of hypoxaemia (Chilvers, *et al. Am Rev Respir Dis* 1990;**142**:420). We found a marked ventilatory response in such patients on exercise, with a near doubling of the expected ventilatory equivalent. The effect of 100% oxygen on the ventilatory response during progressive exercise was investigated in seven patients with PAVMs proved on angiography. On two separate exercise tests patients were randomised to receive either air or 100% oxygen from a Douglas bag in a single blind fashion. The average duration of exercise was 334 (54) s (mean (SD)) with air and this increased to 365 (68) s with 100% oxygen, accompanied by an increase in mean workload from 91 (34) W to 103 (39) W (NS). Comparisons were made at the highest workload achieved with both tests; the results are expressed in each case for air versus 100% oxygen. Oxygen saturation was substantially higher with 100% oxygen (73% (7% *v* 84% (7%); $p < 0.01$) and minute ventilation was significantly lower with 100% oxygen (46 (11) l/min *v* 38 (13) l/min) ($p < 0.05$). Tidal volume (1·44 (0·42) l *v* 1·27 (0·44) l), respiratory rate (34 (9) per min *v* 32 (5) per min), and heart rate (151 (21) *v* 141 (16)) were not, however, significantly lower with 100% oxygen. The visual analogue scale at 50% maximal workload was 4·9 (2·5) with air and 3·3 (1·0) with 100% oxygen on a scale of 0–10. The calculated $\dot{V}/\dot{V}o_2$ with air was 66·6 (normal range 22–31). A fall in both respiratory rate and tidal volume contributed to the reduction in minute ventilation with 100% oxygen, but the ventilatory response was still increased. Despite the improved oxygenation, patients did not exercise significantly longer. These results suggest that hypoxia is not the sole regulating factor in ventilatory control in these patients. We suppose that part of their hyperventilation on exercise is related to the right to left shunting of carbon dioxide, which we have measured separately.

Effect of L-NMMA on the response of the rat pulmonary circulation to hypoxia, hypercapnia and hypoxia with hypercapnia

SV BAUDOUIN, PJ BARNES, TW EVANS *Department of Thoracic Medicine, National Heart and Lung Institute, London* Hypercapnia has been reported to act as both a pulmonary vasodilator and constrictor (Barer, *J Physiol* 1971;**213**:633). These findings could be explained by direct smooth muscle constriction being antagonised by indirect dilatation mediated by endothelium derived relaxing factor (EDRF). We investigated this hypothesis by studying the action of a blocker of EDRF synthesis, *N*-monomethyl-L-arginine (L-NMMA), on the response of the isolated rat pulmonary circulation to hypoxia and hypercapnia. Isolated, blood perfused heart-lung preparations from adult, male Wistar rats were used. Three separate series of experiments compared the effect on pulmonary artery pressure (PAP) of injections of either saline control or 10^{-4} M L-NMMA (table below). After ventilation with 21% oxygen(O_2)/5% carbon dioxide (CO_2), the following challenges were performed: group 1 hypoxia (3% O_2/5% CO_2); group 2 hypercapnia (21% O_2/15% CO_2); group 3 hypoxia (3% O_2/5% CO_2), and hypoxia/hypercapnia (3% O_2/15% CO_2). Hypoxia increased PAP to 32 (2) mm Hg and hypoxia/hypercapnia to 27 (2) ($p < 0.01$ hypoxia *v* hypoxia/hypercapnia). In the isolated rat lung L-NMMA augmented hypoxic pulmonary vasoconstriction (HPV). Hypercapnia alone caused a small rise in PAP which was not altered by L-NMMA. Hypercapnia significantly reduced HPV and L-NMMA partially blocked this response. However, this can be explained solely on the basis of the augmentation of HPV produced by L-NMMA. EDRF is therefore unlikely to mediate the dilator action of CO_2 on the pulmonary circulation.

		PAP (mean (SEM)) (mm Hg)		
	n	*Base*	*Saline*	*L-NMMA*
Hypoxia	3	15 (2)	31 (5)a	40 (5)b
Hypercapnia	4	14 (2)	15 (2)	15 (2)
Hypoxia/hypercapnia	8	17 (2)	27 (2)c	29 (2)d

$p < 0.01$ a *v* b; $p < 0.01$ c *v* d.

Endothelial derived relaxant factor, nitric oxide (NO), in the lung: causes of release

CJ EMERY, GR BARER, D BEE, P HOWARD *Department of Medicine and Pharmacology, Royal Hallamshire Hospital, Sheffield* In contrast to the systemic circulation the normal pulmonary circulation has little or no tone; this state could be actively or passively maintained. Systemic pressure may be attenuated by continuous release of NO, synthesised from L-arginine in endothelial cells. Blockade of this synthesis by arginine analogues (L-NMMA and L-NAME) caused little or no rise in pulmonary artery pressure (Ppa) in lungs, which makes it unlikely that NO sustains the low tone (Barer *et al. J Physiol* 1990;**430**:43P; *J Physiol* 1991;**434**: 42P). However, both analogues raised Ppa in chronically hypoxic rats which have high Ppa, narrowed muscular arterioles, and raised vascular tone; thus NO may reduce hypoxic pulmonary hypertension. We investigated whether NO release in these rats is triggered by active vasoconstriction or high intravascular pressure. Robertson *et al. (J Physiol* 1990;**130**:44P) found that Ppa was unstable in normal rats after L-NMMA at high flow rates. We perfused isolated normal rat lungs with 10 ml blood (pH 7·35–7·45; 38°C) at constant flow (20 ml/min) and ventilated with air and 5% carbon dioxide (CO_2). We compared the effect of L-NAME (L-nitro-L-arginine methyl ester, 100 μg) during (*a*) passive rises in Ppa due to lung inflation (from 5–15 mm Hg tracheal pressure) or raising flow rate up to 400% and (*b*) active increases in Ppa due to vasoconstriction by hypoxia (7, 5, 3, and 2% oxygen (O_2) all with 5% CO_2), almitrine 5 μg, or endothelin 1 200–250 ng. In four rats the 10 mm Hg rise in inflation pressure raised Ppa by 8·4 (SE 1) mm Hg before and 8·3 (1·1) after L-NAME. In six rats pressure-flow lines were measured over a wide range; after L-NAME the lines were unchanged or trivially shifted; no instability was seen in the range studied. However, during vasoconstriction L-NAME caused a rise in Ppa; hypoxia +6·4 (0·8) mm Hg, not varying with severity (n=17); almitrine (rise in 6/7 rats) +3·2 (1) mm Hg; endothelin +10·6 (0·8) mm Hg (n=4). Thus the stimulus for NO release may be smooth muscle activity rather than raised intravascular pressure.

Atrial natriuretic peptide's effect on hypoxic pulmonary vasoconstriction is independent of endothelium derived relaxing factor, particulate guanylate cyclase, and potassium channels

AG STEWART, AH MORICE *Department of Medicine and Pharmacology, University of Sheffield, Sheffield* Atrial natriuretic peptide (ANP) within the pathophysiological range inhibits hypoxic pulmonary vasoconstriction (HPV). To understand further its mode of action 100 ng doses of ANP were injected during HPV before and after various potential antagonists in our isolated perfused rat lung model. Six control juvenile Wistar rats (C) were compared with six littermates adapted to 10% oxygen over three weeks (CH). ANP had significantly greater effect on HPV in CH ($p < 0.01$). The following results are given as percent reduction in HPV. The effect of ANP was reproducible in both groups with a combined coefficient of repeatability of 4% with means (SE) of 63% (6%) in C and 85% (2%) in CH. Endothelium derived relaxing factor (EDRF) inhibition with 100 μg L-NAME (N-nitro-L-arginine methyl ester) caused a 7·4 (1·6) mm Hg increase in pulmonary artery pressure (Ppa) in CH and only 2·2 (0·7) in C ($p < 0.001$); the subsequent HPV was similar (23·6 mm Hg in C and 25·4 mm Hg in CH) and significantly greater than HPV before L-NAME of 12·5 and 13·6 respectively ($p < 0.001$). In CH ANP lowered Ppa below the pre HPV level (119% effect $p < 0.01$); however, as a percent of total constriction measured from the Ppa before L-NAME the result was similar (86%). Methylene blue at concentrations sufficient to inhibit particulate guanylate cyclase had no effect on HPV or ANP vasodilatation. Reservoir concentration of 1 mM tolbutamide (potassium channel blocker) lowered Ppa by 3·5 mm Hg in CH with no effect in C. Tolbutamide had no effect on HPV or subsequent ANP action. Likewise, glibenclamide 10 μg in ethanol produced a stable increase in Ppa of 23 mm Hg in CH; this was lowered by 73% by 100 ng ANP ($p < 0.05$). ANP is independent

of EDRF and particulate guanylate cyclase and is not mediated by the opening of potassium channels.

Normoxic basal vascular resistance is increased by specific inhibitors of nitric oxide synthase in isolated lungs of sheep and humans

G CREMONA, T HIGENBOTTAM, AT DINH XUAN *Papworth Hospital, Cambridge* We have shown in isolated perfused lungs of sheep and humans that infusion of methylene blue (MB), an inhibitor of the effects of nitric oxide (NO), causes an increase in basal pulmonary vascular resistance (PVR) in conditions of normoxia (*Am Rev Respir Dis* 1991, in press). Although MB acts directly on NO and its precursor enzyme nitric oxide synthase (NOS), it also inhibits the second messenger guanylate cyclase. To elucidate better the role of basal release of NO on PVR, we studied the effects of infusion of a specific inhibitor of NOS in isolated perfused lungs from sheep (n=5) and humans (n=3), the latter from explants at heart-lung transplantation. Lungs were obtained immediately after excision, ventilated with 20% oxygen and 5% carbon dioxide, and perfused in a recirculating system at a constant flow of 1 l/min with buffered Krebs-Henseleit solution containing 3·5% dextran as perfusate (37°C, pH 7·33–7·45) and 10^{-5}M indomethacin. After stabilisation the NOS inhibitor Nω-nitroarginine methyl ester (L-NAME) (4×10^{-5} M) was infused and the pulmonary artery pressure (PAP) monitored. In these conditions changes in perfusion pressure reflect changes in PVR. After a plateau was reached L-arginine (4×10^{-4} M), the precursor of NO, was infused. Mean PAP (SD) (mm Hg) are shown in the table below. In both sheep and humans infusion of L-NAME provoked a slow increase in PAP (28–100% of baseline values) which was reversed by infusion of L-arginine. These results confirm our previous findings and indicate the presence of basal release of NO which regulates PVR in normoxic conditions.

Species	*Baseline*	*L-NAME*	*L-arginine*
Man (n=3)	22 (21·6)	34 (22)	23 (20)
Sheep (n=5)	6 (2·7)	13 (7·6)	9 (7)

Effect of topical beclomethasone on nasal resistance and protein output in rhinitis

F O'CONNELL, J STUDHAM, V THOMAS, J HENDERSON, RW FULLER, J BARANIUK *Royal Postgraduate Medical School and National Heart and Lung Institute, Brompton Hospital, London* The pathophysiology of rhinitis includes nasal obstruction due to filling of venous sinusoids and rhinorrhoea of protein rich secretions from vascular and glandular sources. Mediators from inflammatory cells and neural reflexes regulate these processes. Topical steroids may reduce the symptoms of rhinitis by suppressing inflammation or by altering vascular or glandular responses to mediators such as histamine. We investigated the effect of topical beclomethasone (BDP) on histamine (H) induced increase in nasal resistance (RN) and total protein content of nasal secretions (TP) in eight subjects with rhinitis. Nasal challenge with H (1 mg and 10 mg) was carried out after three weeks treatment with BDP 100 μg twice daily bilaterally or placebo (Pl) (saline) in a randomised double blind fashion (table below). BDP reduced basal and H induced increases in RN. Basal and H induced protein concentrations were not altered. Topical steroid treatment may affect vascular dilatation but not secretory processes in nasal inflammation.

	RN (cm H_2O/l/s)		*TP (g/l)*	
	BDP	*Pl*	*BDP*	*Pl*
Baseline	3·96 (0·39)*	6·75 (1·76)	202 (94)	89 (23)
H 1 mg	5·67 (1·3)*	9·73 (2·2)	238 (79)	275 (72)
H 10 mg	9·05 (2·54)*	13·14 (2·2)	430 (177)	385 (71)

Figures expressed as mean (SE). *p < 0·05 compared with placebo.

Role of non-adrenergic, non-cholinergic nervous system in the overnight variation of airways calibre in normal subjects

TW MACKAY, MF FITZPATRICK, NJ DOUGLAS *Respiratory Medicine Unit, Department of Medicine, University of Edinburgh, Edinburgh* Airway calibre decreases overnight in both asthmatic and normal subjects. The magnitude of overnight change in peak flow rate is linearly related to the degree of bronchial reactivity to histamine in both groups (Ryan *et al, Thorax* 1982;**37**:423). Similar factors may therefore contribute to the overnight changes in airways calibre in normal and asthmatic subjects. Blockade of parasympathetic efferent activity by atropine diminishes but does not abolish nocturnal airways narrowing in asthmatic subjects (Catterall *et al, Thorax* 1988;**43**:720; Morrison *et al, BMJ* 1988;**296**:1427). We therefore examined whether non-adrenergic, non-cholinergic (NANC) function varies overnight. As NANC function is best assessed in the presence of β blockade, we tested NANC function in normal subjects and compared the change in oscillatory resistance (Ros) resulting from inhalation of capsaicin ($2{\cdot}2 \times 10^{-6}$ mol) at 06.00 and 18.00 in 10 normal subjects after intravenous atropine (0·03 mg/kg) and intravenous propanolol (0·25 mg/kg). Bronchodilatation after atropine and propranolol was greater at 06.00 than at 18.00 (22% (SE 5%), 9% (5%); p=0·02). Greater bronchodilatation occurred two minutes after capsaicin inhalation at 18.00 than at 06.00 (14% (4%), −2% (3%); p=0·004). These results indicate that autonomic tone is important in causing nocturnal airway narrowing in normal subjects and suggests that inhibition of NANC function in the early morning may contribute to overnight bronchoconstriction.

Effect of high dose inhaled beclomethasone dipropionate and oral prednisolone over three weeks in patients with chronic airflow obstruction

DC WEIR, P SHERWOOD BURGE *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* We studied the effect of treatment with inhaled beclomethasone dipropionate (BDP) and oral prednisolone in 105 patients (mean (SE) age 65·8 (0·6) years) with non-asthmatic chronic airflow obstruction (CAO), (mean FEV_1 1·05 (0·05) or 40·6 (1·5) percent of predicted values, mean FEV_1 to forced vital capacity (FVC) ratio 40% (1·3)%), on lung function and quality of life in a single blind placebo controlled trial. After three weeks of receiving placebo patients were treated with 1500 μg or 3000 μg BDP per day for three weeks. Two thirds of the patients then received oral prednisolone 40 mg per day for three weeks, the other third continuing to take BDP alone. Assessments took place at the end of each treatment period, and peak expiratory flow (PEF) was measured four hourly each day. No effect of BDP dose was seen, therefore the results for both doses combined are presented here. The mean (SE) FEV_1 rose significantly from 1·04 (0·05) l with placebo to 1·11 (0·05) after three weeks of treatment with BDP. Mean FVC improved from 2·68 (0·08) l with placebo to 2·79 (0·08) with BDP, and mean PEF improved to 246 (10·1) l/min from a placebo value of 235 (9·6). The addition of oral prednisolone had no significant extra effect. A response in individual patients (defined as an increase >20% over baseline in either FEV_1, FVC, or mean PEF over the final seven days of treatment) was more common after BDP (31%) than after placebo (14%) (p < 0·02). Both doses of BDP were equally effective in individual patients, and these patients who received oral prednisolone showed no increase in the response rate when compared with those who continued to take BDP for six weeks.

Steroid sparing effect of nedocromil sodium in asthmatic patients taking high doses of inhaled steroids

CS WONG, S COOPER, JR BRITTON, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Nedocromil sodium is a non-steroidal agent that may offer an alternative to inhaled steroids in asthma prophylaxis. We assessed the steroid sparing potential of nedocromil sodium 4 mg four times daily in a randomised, double blind, placebo controlled study in 69 asthmatic subjects, aged 19 to 55 years, maintained on inhaled beclomethasone dipropionate (BDP) in the dose range 1000–2000 μg daily. After a four week run in period subjects added nedocromil (n=34) or placebo (n=35) by metered dose inhaler to their usual drug treatment for a further four weeks. Subjects maintained diary records on twice daily peak flows (PEF), daily drug usage, and asthma symptom scores. At two weekly intervals thereafter the daily dose of BDP was reduced, by 250 μg increments for doses above 1000 μg, by 200 μg increments from 1000 μg to 200 μg, and then by 100 μg to 0. Subjects were withdrawn if bronchodilator use increased by >6 puffs/day, if PEF measurements decreased by $\geq$15% from the run in period, or if asthma symptoms increased. At the end of the add on phase patient preference based on opinion scores favoured nedocromil (p < 0·01), but there was no significant difference

between nedocromil and placebo in the change in symptom scores, bronchodilator use, or PEF. Sixty patients (30 nedocromil, 30 placebo) entered the steroid reduction phase, of whom 24 (14 nedocromil, 10 placebo) discontinued taking inhaled steroids completely. The reduction in inhaled steroid dose achieved while maintaining control of asthma varied substantially in both groups with median (range) percentage decreases of 80% (16·7 to 100%) with nedocromil compared with 65% (0 to 100%) with placebo ($p = 0·34$). Nedocromil was well tolerated; the most common side effect was unpleasant taste (18/34 nedocromil, 9/35 placebo). This study suggests that nedocromil sodium may have a minor steroid sparing effect in patients with asthma controlled by high doses of inhaled steroids.

Effect of intermittent pamidronate infusions on bone metabolism in corticosteroid dependent asthma

K ANDERSON, SJ GALLACHER, JAK FENNER, A JENKINS, SW BANHAM, IT BOYLE *Department of Respiratory Medicine and University Department of Medicine, Glasgow Royal Infirmary, Glasgow* Osteoporosis is a major side effect of long term corticosteroid use and recent evidence suggests that oral pamidronate may have a significant role in treatment (Reid *et al, Lancet* 1988;i:143). We studied the effect of 30 mg pamidronate given intravenously every three months for one year in 19 patients (13 female) with steroid dependent asthma. Twelve of these patients had previously sustained at least one vertebral compression fracture. The mean steroid dose and treatment duration for this fracture group was 77 mg prednisolone/week for 13·1 years, and for the non-fracture group was 97 mg for 9·6 years (NS). The mean L2–L4 density, measured by dual energy x ray absorptiometry was significantly lower in the fracture group (0·797 g/cm^2 v 1·143 g/cm^2, $p < 0·0001$). The mean neck of femur density was also significantly lower in the fracture group (0·718 g/cm^2 v 0·901 g/cm^2, $p < 0·005$). Bone resorption after treatment, measured by fasting urinary hydroxyproline to creatinine ratio, fell significantly in the fracture group from 0·042 to 0·019 ($p < 0·005$), while a non-significant fall was found in the non-fracture group (0·022 v 0·015). Serum alkaline phosphatase fell significantly in both groups (fracture group, 212 v 167, $p < 0·05$; non-fracture group, 215 v 151, $p < 0·01$). A non-significant rise in both measures of bone density was found in the fracture group. These results show that intermittent intravenous pamidronate significantly suppressed bone turnover in these patients, though no major change in measured bone density was apparent after one year of treatment.

Inhaled corticosteroids, dysphonia, and throat problems

J WILLIAMS, S COOPER, I WAHEDNA, JT MACFARLANE *City Hospital, Nottingham* We investigated the occurrence of dysphonia and throat problems in 374 patients from our respiratory outpatient clinics and from the asthma register who were using inhalers for respiratory problems. We did this by means of a questionnaire asking for details about patients' inhaler treatment (including 302 taking inhaled steroids) and about any voice or throat problems that they had noticed since using their inhalers. Of the total, 214 patients (57·5%) admitted to problems with their voice or throat, or both. Of these, 195 (64·6%) were taking inhaled corticosteroid ($p < 0·0001$). Of the 72 patients who did not use any inhaled corticosteroids, 19 (26·4%) reported changes in their voice or throat, or both. Ninety four out of 131 (72%) receiving Becloforte reported voice or throat problems, or both, compared with 66 out of 118 (56%) receiving Becotide and 24 out of 42 (57%) receiving Pulmicort. Of the patients who had noticed changes in their voice, 94 reported their voice to be husky, croaky, or hoarse, and 63 reported that their voice was weak, quiet, and whispery; 35 patients said that the changes in their voice interfered with work, home, or social life. Voice and throat problems are common with inhaled treatment, are related to inhaled steroids, and can interfere with a patient's life style and work.

Frequency of voice problems and cough in patients using aerosol steroid preparations

I WILLIAMSON, S MATUSIEWICZ, P BROWN, G CROMPTON, AP GREENING *Respiratory Unit, Northern General Hospital, Edinburgh* All patients using a steroid inhaler who attended the clinic during a six week period in 1990 were questioned about the dose frequency, voice, and throat symptoms, and inhaler induced cough. A total of 269 patients were surveyed (163 female; mean age 54 years (range 11–90)), but 14 using dry powder devices were excluded from further analysis. The same questionnaire was completed for a control group of 72 patients (33 female; mean age 58 years (range 21–83)) who attended a diabetic outpatient clinic, and who did not use inhalers. In all 59% (n = 151) of patients using a steroid aerosol (MDI) had symptoms including huskiness, loss of voice power, throat irritation, and throat clearing, compared with 17% (n = 12) of the control group (χ^2 test, $p < 0·001$). More women had symptoms (χ^2 test, $p < 0·01$) but there was no correlation with age or smoking habit. Huskiness was the most common voice problem in those using a steroid MDI (n = 89) and tended to occur more often with high doses (table below). Cough related to steroid inhalation was as common as huskiness (n = 87), with 40 patients having both symptoms. Voice symptoms, throat irritation, and inhaler induced cough occur in the majority of patients treated with aerosol steroid preparations.

	Dose (μg)				
	≤400	*401–800*	*801–1500*	*>1500*	*Control*
No	60 (23)	58 (23)	64 (25)	73 (29)	72
Spacer	15 (25)	58 (23)	43 (67)	63 (86)	n/a
Cough	15 (25)	22 (38)	18 (28)	32 (44)	n/a
Huskiness	20 (33)	17 (29)	19 (30)	33 (45)	8 (11)

Values are numbers (percentages).

Budesonide Turbohaler once daily in mild asthma

PS LEE, LM CAMPBELL, DG WATSON, T VENABLES, KS PARRY-BILLINGS, MD TAYLOR, PDI RICHARDSON on behalf of the Maestro Research Group *General practice, Leeds, Glasgow, Great Yarmouth, and Nottingham, and Astra Pharmaceuticals* In a double blind multicentre study 141 patients (age 12–79 years) with mild symptomatic asthma were randomised to receive either budesonide (Pulmicort) 400 μg once daily in the evening (B, n = 65) or placebo (P, n = 76) inhaled via a Turbohaler for four weeks. Patients aged ≥12 years with reversible airways obstruction were eligible if they used an inhaled bronchodilator at least once a day or had symptoms despite current treatment, or both. Excluded were those patients taking inhaled or oral steroids in the previous month. Both morning and evening peak expiratory flow rates (PEFR) were increased with budesonide but not placebo (l/min (SD). Morning: B by 24 (5) from 368 (118), $p < 0·001$; P by 1 (4) from 349 (95), NS; $p < 0·001$ between groups. Evening: B by 18 (4) from 390 (119), $p < 0·001$; P by 3 (4) from 364 (103), NS; $p < 0·01$ between groups). After four weeks significantly more patients taking budesonide once daily compared with those taking placebo were improved with regard to wheeze at rest, difficulty in breathing, cough, limitation of activity, and interference with routine ($p < 0·05$, all symptoms). Concomitant β_2 agonist inhaler use did not differ between groups, although compared with baseline, bronchodilator use fell significantly with budesonide (−0·44 (SE 0·13) times/day, $p < 0·01$) but not with placebo (−0·23 (0·14) times/day, NS). Patient tolerance of budesonide 400 μg once daily and placebo was similar and good. Overall, 97% of patients preferred once daily treatment; more (74%) patients favoured budesonide than placebo ($p < 0·01$) and all (100%) patients found the Turbohaler easy to use. In this study budesonide 400 μg once daily from a Turbohaler was a suitable starting dose for inhaled steroid treatment of asthma.

Effect of inhaled sodium cromoglycate when delivered via a Nebuhaler in treatment of childhood asthma

J KUZEMKO, H FLEET, CBS WOOD *Peterborough District Hospital, Peterborough, Wycombe General Hospital, High Wycombe, Buckinghamshire, and Queen Elizabeth Hospital for Children, London* Sodium cromoglycate (SCG) can be administered by a number of devices, including a metered dose inhaler (MDI). Holding chambers can be used to facilitate delivery of drug to patients, particularly younger patients, who find difficulty coordinating activation of the MDI with inspiration. The efficacy of inhaled sodium cromoglycate (10 mg four times a day) administered via a Nebuhaler (Astra Pharmaceuticals) was assessed compared with placebo in a double blind crossover study in 48 children with asthma (age range two to six years). After a two week baseline assessment of entry criteria patients were randomly allocated to receive sodium cromoglycate or placebo for six weeks, with crossover to the alternative treatment for the subsequent six weeks. Treatment efficacy was assessed by diary card symptom scores and measurement

of peak flow (PEFR) according to five point (0–4) scales. The severity of asthma was assessed on a four point scale (0–3, with 3 being severe). The amount of bronchodilator used was also measured. Significant differences in favour of sodium cromoglycate were seen for asthma severity ($p < 0.05$), total symptom score (median score: SCG 1·67, placebo 2·96; $p < 0.05$), daytime cough (median score: SCG 0·67, placebo 0·96; $p < 0.05$), night time cough (median score: SCG 0·46, placebo 1·00; $p < 0.05$), and investigator opinions of efficacy ($p < 0.005$). Insufficient data on PEFR were obtained to draw any conclusions about peak flow. This study shows that sodium cromoglycate is an effective treatment for childhood asthma when delivered by a metered dose inhaler via the Nebuhaler.

Effect of formoterol compared with beclomethasone and placebo on allergen induced airway responses

BJO WONG, DH KAMADA, EH RAMSDALE, P O'BYRNE, JA DENBURG, J DOLOVICH, FE HARGREAVE *Asthma Research Group, St Joseph's Hospital and McMaster University, Hamilton, Canada* The allergen induced late asthmatic response and increase in responsiveness to histamine (expressed as PC_{20}) are considered to be due to airway inflammation. To investigate possible anti-inflammatory effects formoterol (24 μg) was compared with beclomethasone (200 μg) and placebo in a double blind, randomised, crossover study in six patients with stable asthma. In separate sequential periods placebo then formoterol were given prior to control inhalation of diluent for the allergen, and PC_{20} was measured at 24 hours. Then allergen inhalation tests were performed at intervals of two to three weeks preceded by the test drugs. Formoterol caused bronchodilatation, which lasted for at least seven hours ($p < 0.001$). On the placebo day allergen inhalation caused a mean maximum fall in FEV_1 of 17·8% during the first hour, 20·2% between three and seven hours, and a geometric mean (SD) fall in PC_{20} of 2·44-fold (0·32) at 24 hours. In comparison with placebo, formoterol and beclomethasone protected against the allergen induced late asthmatic response (LAR) ($p < 0.01$) and formoterol protected against the early asthmatic response ($p < 0.001$) and the fall in PC_{20} ($p = 0.004$). Further analyses using the control tests to correct for the effects of functional antagonism showed that formoterol did not prevent the development of a LAR beginning at two hours after allergen inhalation and reaching significance at seven hours ($p = 0.04$); formoterol increased PC_{20} (2·24 (0·18) ($p = 0.003$)) at 24 hours and formoterol followed by allergen eliminated the formoterol induced increase in PC_{20} ($p = 0.014$). The magnitude of the allergen induced fall in PC_{20} with formoterol present (formoterol/diluent minus formoterol/allergen) (1·93 (0·19)) was not significantly different from the allergen induced fall in PC_{20} without formoterol present (placebo/diluent minus placebo/allergen) (3·5 (0·29) ($p = 0.12$)). These results suggest that the effect of formoterol on allergen induced changes in PC_{20} are due to functional antagonism rather than to any anti-inflammatory effects.

Airway effects of regular broxaterol and salbutamol treatment in asthmatic subjects

I WAHEDNA, A WISNIEWSKI, C WONG, I PAVORD, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We looked at the time course of the increase in bronchial reactivity that occurs after regular β_2 agonist treatment and compared the changes after salbutamol with those following a new β_2 agonist broxaterol in a double blind, placebo controlled, crossover trial. Eleven non-smoking subjects aged 18 to 50 years with mild asthma (baseline $FEV_1 > 70\%$ of predicted values) taking inhaled β_2 agonist only and with a PD_{20} (dose of histamine causing a 20% fall in FEV_1) of < 2 μmol were studied. Subjects inhaled broxaterol (400 μg), salbutamol (200 μg), and placebo via a spacing device three times a day for three weeks with a two week run in/washout period between treatments. Subjects took only inhaled ipratropium bromide for symptomatic relief throughout the study. Histamine challenge tests were carried out before treatment and 12, 35, and 59 hours after cessation of treatment. There was a significant fall in FEV_1 12 hours after cessation of treatment with both salbutamol and broxaterol compared with placebo (mean difference 12·9%, 95% confidence interval 4·3 to 21·5 ($p < 0.01$) and 9·8%, 1·2 to 18·4 ($p < 0.02$) respectively). When compared with placebo there was a progressive increase in bronchial reactivity after cessation of salbutamol, with the greatest mean difference in PD_{20} (1·65 doubling doses, 0·4 to 2·9; $p < 0.02$) occurring 59 hours after cessation of treatment. The fall in PD_{20} after broxaterol was not significant, however (greatest mean difference 0·79 doubling doses, 0·47 to 2·05). Thus salbutamol treatment was associated with a fall in FEV_1 and an increase in bronchial reactivity that continued for at least two and a half days after cessation of treatment; the greater effect of salbutamol on PD_{20} may be due to differences in dose equivalence as broxaterol 400 μg seems to have less β_2 activity than salbutamol 200 μg.

Effect of 443c81, an inhaled μ opioid receptor agonist in asthma

I PAVORD, I HALL, I WAHEDNA, S COOPER, A TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Stimulation of exposed C fibre afferent nerve endings by inflammatory mediators may contribute to the airway inflammation and bronchoconstriction seen in asthma through the release of neuropeptides from collateral nerve endings. The polar opioid peptide 443c81 is a μ opioid receptor agonist that inhibits C fibre activation and non-cholinergic neurally mediated bronchoconstriction in animal models. We compared the effect of 443c81 (4 mg/ml nebulised for five minutes via a Medix ultrasonic nebuliser, output 1 ml/minute) four times daily for seven days with placebo on the control of asthma in a double blind parallel group study of 40 subjects. Twenty subjects (12 male, mean FEV_1 83% of predicted values) received placebo and 20 (15 male, mean FEV_1 91% predicted values) 443c81 after a one week run in. Efficacy was assessed by comparing changes from baseline values in FEV_1, the provocative dose of histamine causing a 20% fall in FEV_1 (PD_{20}), symptom scores, bronchodilator use, and home peak flow readings. 443c81 had no acute effect on FEV_1, and the mean changes in FEV_1 after one week's treatment were not significantly different (placebo 0·9%; 443c81 3·8%). One hour after the first dose of 443c81 PD_{20} increased from a geometric mean of 0·88 to 1·48 μmol (mean change 0·76 doubling doses; 95% confidence interval 0·23 to 1·29), although this did not differ significantly from the change with placebo (mean difference between 443c81 and placebo 0·63 doubling doses; −0·2 to 1·5; $p = 0.095$). After one week's treatment PD_{20} was similar to baseline values with 443c81 (0·78 μmol) and placebo (baseline 0·71, post-treatment 0·93 μmol). Symptom scores (including cough scores), bronchodilator use, and peak flow recordings did not change significantly during or after treatment with 443c81 compared with placebo. There were no important adverse effects. The lack of effect of 443c81 in our study argues against a role for activation of C fibres in asthma.

Effect of oral and inhaled cetirizine, a potent H_1 antagonist, on resting bronchomotor tone in patients with moderately severe asthma

M ILYAS, SK GHOSH, KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow* Patients with asthma show increased airway responsiveness to histamine. Histamine acts on the bronchial smooth muscle by interacting with at least two distinct histamine receptors, H_1 and H_2 receptors, and probably through stimulation of the irritant vagal receptors as well. H_1 antagonists produce bronchodilatation in patients with asthma, suggesting that airway tone is due to locally released histamine. We recently showed that cetirizine, a potent H_1 antagonist, is able to displace the histamine dose-response curve by 74-fold to the right after a single 15 mg dose. We have now compared the effect of a single dose of nebulised (1 ml, 10 mg/ml) and oral (15 mg) cetirizine with a matched placebo in a double blind double dummy crossover study in 10 patients with atopic asthma and moderate airflow obstruction (mean (SE) age 52 (5·22) years, mean predicted FEV_1 59·8% (3·9%))—table below. There was no significant difference in the baseline FEV_1 on three study days. The maximum mean percentage increases FEV_1 after placebo and nebulised and oral cetirizine were 11·7 (2·8), 11·3 (5·5), and 21·8 (3·7) respectively. Similarly the mean areas under the curve (FEV_1/time course effect) after placebo and nebulised and oral cetirizine

Mean (SE) maximum percentage bronchodilatation after cetirizine compared with placebo

	Baseline FEV_1	*Increase percentage*			
		60 min	*120 min*	*180 min*	*240 min*
Placebo	1·94 (0·3)	10·4 (2·3)	9·0 (2·5)	9·0 (3·9)	11·7 (2·9)
Cetirizine:					
Oral	1·93 (0·3)	21·8 (3·8)	20·3 (4·1)	16·7 (5·0)	13·2 (3·9)
Inhaled	1·93 (0·3)	11·3 (5·5)	10·9 (4·5)	9·5 (4·3)	7·7 (4·0)

were 2139 (501), 1993 (5·5), and 4265 (961) respectively. Significant bronchodilatation was observed at 60 ($p < 0·02$), 120 ($p < 0·02$), and 180 minutes ($p < 0·05$) after oral cetirizine compared with placebo. Four patients developed transient bronchoconstriction after inhaled cetirizine. These results suggest the presence of local histamine tone in the airways. The lack of bronchodilatation after nebulised cetirizine is probably related to the local irritant effect as this has been shown with other H_1 antagonists such as inhaled clemastine.

Diagnosis of suspected pneumonia in intensive care: accuracy and effect on survival

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Pulmonary infiltrates develop frequently in patients undergoing mechanical ventilation and represent a formidable diagnostic challenge. In many cases antibiotics are prescribed empirically, although the cause is often not infection. The clinical significance of bacteria cultured in tracheal aspirate is always uncertain, and several recent studies have suggested that culture of material obtained by bronchoalveolar lavage (BAL) and by using the protected specimen brush (PSB) is more reliable both in the diagnosis of pneumonia and as a guide to treatment. Whether this affects survival has not been established. We investigated 20 consecutive patients undergoing mechanical ventilation for reasons other than a primary (community acquired) pneumonia to see whether these techniques resulted in a change of treatment. All patients had developed new pulmonary shadowing while being ventilated, and were categorised as having possible (9) and probable (11) pneumonia according to previously described criteria. Fourteen patients were receiving antibiotic treatment. A PSB sample and two BAL samples were obtained from the affected area. All samples were cultured by standard techniques. A diagnosis of pneumonia was made if culture of the PSB sample yielded $> 10^3$ colony forming units (cfu) per brush or the BAL specimen yielded $> 10^5$ cfu per ml of BAL fluid. Pneumonia was diagnosed in 12 (60%) patients, six of whom were receiving antibiotics, and this led to a change in treatment in eight patients. All eight patients recovered from the pneumonia, and seven were successfully weaned from the ventilator. The remaining four all died within 24 hours of the procedure. The eight patients in whom pneumonia was not diagnosed were all receiving antibiotics and it is possible that pneumonia was masked in some of these patients. In the absence of an alternative diagnosis antibiotic treatment was continued in seven. Culture of PSB and BAL samples obtained at bronchoscopy led to a change in treatment and may have contributed to survival in seven of 20 (35%) patients undergoing mechanical ventilation.

Radiographic features of staphylococcal pneumonia

H DOUGHTY, JT MACFARLANE, DH ROSE *Respiratory Medicine and Radiology Department, City Hospital, Nottingham*
The chest radiographs of 34 patients (eight children) with proved staphylococcal pneumonia were assessed by two experienced observers. The median age (range) of the adults was 49 years (24–76) and of the children 1 year (1 month–8 years). Sixteen were male and 18 female. Nine died. On presentation consolidation was principally homogeneous in 20, patchy in 11, and mixed in three. Initially one lobe was involved in 14, two lobes in seven, and more than two in 13. Air bronchograms were present in 20 (four children). Swollen lobes displaced fissures in five. In 31 patients sequential *x* ray film were available. Twenty showed deterioration after admission, either by extension within the same lung (14) or by spread to the opposite lung (six). Associated radiographic features for all patients (numbers of children in parentheses) included pleural effusions or empyema in 11 (four), segmental or lobar collapse in six (one), pneumothorax in seven (four), pulmonary cavitation in nine (two), which was multiple in six and pneumatoceles in seven (three). Compared with other causes of bacterial community pneumonia, bilateral patchy shadowing was commoner, as was cavitation, pneumatoceles, and spontaneous pneumothorax, but most cases did not show these classic features.

Bacterial pneumonia in homosexual patients positive for HIV

AA JEFFREY, RF MILLER *Department of Medicine, University College and Middlesex School of Medicine, Middlesex Hospital, London*
Though bacterial pneumonia is increasingly recognised in HIV positive drug misusers, little is known about its clinical features and risk factors in HIV positive homosexual men. We therefore undertook this study of a cohort of such patients, all with clinical and laboratory evidence of bacterial pneumonia. Over a four year period there were 293 episodes of *Pneumocystis carinii* pneumonia (PCP) and only 36 episodes of bacterial pneumonia, of which six were associated with concomitant opportunist infections (four PCP, two *Mycobacterium avium intracellulare*); four had insufficient recorded data. Data from 26 episodes were analysed. Patients were divided into two groups: group 1 were neutropenic ($\leq 3·0 \times 10^9$) and group 2 non-neutropenic. Data were compared by χ^2 with Yates's correction ($p < 0·05$ = significant) (table below). The organisms cultured in group 1 were *Staphylococcus aureus* in three, *Pseudomonas aeruginosa* in one, and *Streptococcus pneumoniae* in one. In group 2 *Strep pneumoniae* occurred in seven, *Haemophilus influenzae* in one, *Pseudomonas fluorescens* in one, and *Fusobacterium* spp in one. Overall, sputum culture was positive in seven, blood in five, bronchoalveolar lavage samples in two, transbronchial biopsy specimen in one. Induced sputum was positive only in two patients (both had positive spontaneously expectorated sputum cultures). Five patients were taking prophylactic co-trimoxazole at the time of the episode (two with positive sputum, one with a positive blood culture). Patients in group 1 were more likely to be taking zidovudine ($p < 0·01$) and to have had previous lung disease ($p < 0·05$) or an AIDS defining diagnosis ($p < 0·05$ when skin Kaposi's sarcoma is excluded). In contrast to the findings in HIV positive intravenous drug misusers, bacterial pneumonia was rare in this cohort. In the non-smokers bacterial pneumonia was infrequently caused by *Strep pneumoniae* and was found in late HIV disease and in association with existing lung damage. In cigarette smokers the pattern was similar to that found in subjects negative for HIV.

	Group 1 (n=12)	*Group 2 (n=14)*
Fever (>37·5°C)	6	8
Smoker	3	10
Organism identified	5	10
Zidovudine	8	1
Previous lung disease (PCP)	11 (8)	6 (2)
Previous AIDS diagnosis	10	7

Gram positive bacteria in humidifier fever?

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Humidifier fever represents a syndrome that varies from a mild flu-like illness with fever to an acute illness with dry cough, shortness of breath, and arterial hypoxaemia. It is known to be due to exposure to airborn products from contaminated humidifiers. Postulated causes include airborne endotoxin, *Bacillus subtilis*, and amoebic species. Airborne micro-organisms were measured in a manmade fibre spinning mill with an outbreak of humidifier fever occurring in one workroom. This sampling showed a 20-fold increase above the count expected for Gram positive bacteria in the affected room (from a mean of 130 colony forming units (CFU)/m^3 to 2732 cfu/m^3), with no increase in fungal, thermophilic, or Gram negative counts. Sampling was repeated before and after the humidification was turned off for more than eight hours. A 70% drop in the Gram positive count (from 2776 CFU/m^3 to 848 CFU/m^3) occurred with no effect on the other organism levels. Airborne endotoxin was measured at the same time and showed low personal exposure levels (mean 16·5 ng/m^3) compared with mean levels throughout the mill (18·5 ng/m^3) and in an unaffected mill (17·0 ng/m^3). Skin testing showed no significant differences between the subjects with symptoms and a control group to common antigens and extracts from the humidifier. Serum samples were tested for specific antibodies against both water and sludge from the humidifiers by the gel filtration method. This confirmed previous work that the specific antibodies are not predictive of sufferers of the syndrome but merely indicate exposure. The aetiological agent in this outbreak is likely to have been a Gram positive organism.

Audit of use of erythromycin in the treatment of community acquired lower respiratory tract infections

A JOLLEY, A DAVIES, DT McLEOD *Departments of Microbiology and Respiratory Medicine, Sandwell District General Hospital, Sandwell, West Midlands*
The British Thoracic Society recommendations for treating community acquired pneumonia state that in moderately ill patients treatment should be started to cover *Streptococcus pneumoniae*. When mycoplasma infection is suspected, or in the case of severe pneumonia, erythromycin or tetracycline should be added. Over a three month winter period in a district general hospital a prospective study was undertaken to determine whether erythro-

mycin was being overprescribed in the treatment of community acquired chest infections requiring hospital admission. All adults prescribed erythromycin on admission were included in the study. Sixty two patients were entered (37 male, 25 female). The mean age was 63 years (range 19–94). Thirty patients had pneumonia. *S pneumoniae* was isolated from seven (five from blood cultures) and *Haemophilus influenzae* from three; legionella serology was positive in one. In 15 cases no pathogens were isolated. Serology was positive in five cases (respiratory syncytial virus (RSV) one, influenza B virus in four. There were seven deaths. Acute bronchitis was diagnosed in 32 patients. Pathogens isolated were *H influenzae* (four), *S pneumoniae* (two), *B catarrhalis* (two), *M tuberculosis* (one), and "coliforms" (four). In 19 no bacterial pathogens were isolated. Serology was positive in two (RSV one, influenza B one). There were four deaths. Erythromycin alone was given to seven patients, two of whom had a documented allergy to penicillin. Forty five patients received ampicillin in combination with erythromycin. Other β lactam antibiotics were used in 10 patients. Erythromycin was needed in five patients—two with penicillin allergy, two with *M catarrhalis* infection, and one with legionella infection—and was probably not necessary in 57. The society's recommendations for the use of erythromycin in community acquired lower respiratory tract infections are being misinterpreted, resulting in the drug being over prescribed.

Five year prospective study of hospital staff after legionella infection

RS LLOYD, D GUEST, SA DEMPSEY, JP ATKINS, AJ FAIRFAX *Department of Thoracic Medicine, Stafford, and Department of Statistics, West Midlands Health Authority* Twenty five staff were surveyed five years after infection by *Legionella pneumophila*. All had early IFAT titres ≥ 128 and 88% had experienced initial influenzae-like symptoms. They were matched 1:2 for age, sex, and employment with a control group of staff who were seronegative in 1985. Both groups completed questionnaires on general health and respiratory and mental symptoms. Perceived breathlessness was graded on a 1–5 severity scale. After five years 41% of staff retested still had positive serology for legionella with IFAT titres of 1/32 or greater. The seropositive staff described being less active ($p < 0{\cdot}03$); lacked energy ($p < 0{\cdot}001$); and had difficulty concentrating ($p < 0{\cdot}02$) compared with the controls. They also had exertional breathlessness ($p < 0{\cdot}01$). There were no differences in other respiratory symptoms such as cough, sputum production, early waking, or bronchial hyperreactivity.

Glutaraldehyde and formaldehyde exposure and symptoms in health care workers

RB DOUGLAS, A COCKCROFT *Occupational Health Unit, Royal Free Hampstead, London* Glutaraldehyde and formaldehyde are recognised to produce irritant and allergic symptoms. It is not clear how great a problem this is in practice. In our hospital we identified 210 people likely to be exposed to glutaraldehyde at work. We sent them a questionnaire enquiring into exposure to glutaraldehyde and formaldehyde and about irritant (running eyes and nose and nose/throat irritation) and allergic (dermatitis and wheeze) symptoms. A total of 124 people returned completed questionnaires. Fifty nine were exposed to both aldehydes, but 23 were exposed only to glutaraldehyde, 25 only to formaldehyde, and 17 to neither. Irritant symptoms were common and allergic symptoms comparatively rare (table below). Both irritant and allergic symptoms were more common in those with more frequent exposure (daily *v* less often) but were not related to length of exposure. Dermatitis related to either aldehyde was more common in those with previous skin problems or allergies; there were no such associations for wheeze. Women reported running eyes and nose and nose/throat irritation with glutaraldehyde more often than did men; this was not explained by their more frequent exposure. Environmental levels of glutaraldehyde were well below the OES of 0·7 mg/m^3. We are now investigating those with dermatitis and wheeze for sensitisation to glutaraldehyde or formaldehyde, or both. Further studies of this sort are needed to confirm the extent of sensitisation to glutaraldehyde and formaldehyde among health care workers.

Numbers (percentages) with symptoms attributed to exposure

Symptoms	*Glutaraldehyde (total exp = 83)*	*Formaldehyde (total exp = 84)*
Running eyes and nose	23 (28)	37 (44)
Nose/throat irritation	24 (29)	31 (37)
Dermatitis	9 (11)	7 (8)
Wheeze	5 (6)	6 (7)

exp = exposed.

Lung function in textile workers

D FISHWICK, AM FLETCHER, RM NIVEN, CAC PICKERING *Department of Thoracic Medicine, Wythenshawe Hospital, Manchester* Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured in 700 cotton workers (mean age (SD) 39 (11·3) years) and 344 manmade fibre workers (mean age (SD) 37·1 (13·3) years) in the setting of a cross sectional analysis of respiratory symptoms and lung function in textile workers. Percentage of predicted FEV_1 ($PPFEV_1$) and FVC (PPFVC) were calculated with regression equations (Quanjer P, ed. *Bull Eur Physiopathol Respir* 1983;**19**(suppl 5):45). Mean $PPFEV_1$ did not differ significantly between fibre groups. Mean PPFVC was significantly greater in current cotton workers (97·8 (16·4)) than manmade fibre workers (95·3 (14·6)), ($p < 0{\cdot}02$). Mean $PPFEV_1$ was significantly lower in current smokers (n = 548, 89·3 (17·8)) compared with current non-smokers (n = 496, 93·1 (16·8)) ($p < 0{\cdot}001$). Logistic regression analysis was performed to identify which predictor variables were associated with lowering of $PPFEV_1$ and PPFVC. Lower $PPFEV_1$ was associated with increased pack years of smoking, increasing age, increasing total time worked in the waste room (a traditionally dusty area), male sex, and working currently with cotton. Lower PPFVC was associated with the same factors, but working with manmade fibre lowered PPFVC more significantly that did working with cotton. These data, although drawn from a cross sectional study, support the hypothesis that loss of lung function in textile workers may be related both to smoking and dust exposure. The lower PPFVC in manmade fibre workers is as yet unexplained, although this may reflect operatives with impaired lung function related to cotton moving to a better tolerated workplace with exposure to manmade fibres.

Incidence of occupational asthma by class of industry in West Midlands region

PFG GANNON, PS BURGE, on behalf of the Midland Thoracic Society Research Group *Occupational Lung Disease Unit, East Birmingham Hospital, Birmingham* The Midland Thoracic Society rare respiratory disease registry surveillance scheme of occupational asthma in the West Midlands region has now been running for over two years. Previous analysis by occupational order showed incidences for broad categories of occupation—for example, bakers were grouped with carpenters. Analysis by industrial class provides more specific and readily interpretable categories (table below). The incidence of recognised occupational asthma in the general working population is similar for 1989 and 1990. The industries with a high incidence of recognised occupational asthma reflect those using recognised causative agents. Analysis by industry class provides a useful list of high risk industries.

Incidence of occupational asthma by industry class (per million working population)

	1989	*1990*	*Mean*
General incidence	35	33	34
Processing rubber and plastic	352	251	302
Timber and wooded furniture industry	292	233	263
Research and development	194	194	194
Food/drink/tobacco manufacturing	197	90	143
Other manufacturing industries	92	183	137
Sanitary services		218	114
Electrical and electronic engineering	95	119	107
Manufacture of leather and leather goods		213	107
Chemical industry	134	67	101
Agriculture and horticulture	48	48	48
Manufacture of metal goods not specified	54	39	47
Manufacture of non-metallic mineral products	18	72	45
Manufacture of motor vehicles and parts thereof	30	12	21
Metal manufacturing	32	49	41
Mechanical engineering	39	39	39
Textile industry	73		37
Medical and other health services	9	47	28

SWORD: past, present, and future

VM TAYLOR, SK MEREDITH, JC McDONALD *Epidemiological Research Unit, National Heart and Lung Institute, London Chest Hospital, London* The success of the SWORD project, launched in January 1989 in collaboration with the British Thoracic Society and the Society of Occupational Medicine, has been widely recognised. Some 80% of chest physicians and a similar number of occupational physicians now submit regular reports of new cases of work related lung disease. In 1989, 2101 cases were reported and in 1990, 2119. A notable feature of the second year was the growing contribution of occupational physicians, particularly with regard to inhalation accidents, few of which reach chest physicians. From analysis of the 4220 cases now recorded some consistent patterns emerge. Annual incidences per million working population in descending order were: asthma 21, pneumoconioses 13, mesothelioma 12, non-malignant pleural disease 11, building related illness 4, allergic alveolitis 3, infectious disease 3, lung cancer 2, byssinosis <1, and all other 10. Disease incidence overall was highest in the north west and lowest in the south east; detailed analyses suggest that much of the regional difference was due to variation in reporting. This implies that the true incidence of work related illness is considerably greater than has been documented. The importance of occupational asthma and the large number of agents responsible is evident. Many new causes have come to light, and better data have been obtained on the occupational distribution of cases from recognised causes. Despite these achievements and evidence that both participants and colleagues in the Employment Medical Advisory Service value the information derived from SWORD, the project's future requires serious thought. Voluntary effort by busy professionals is not maintained unless everything possible is done to minimise the task and maximise interest in the results. Ideas for achieving both these objectives will be presented in poster form to facilitate discussion with society members.

Aetiological factors in chronic sputum production

P CULLINAN *Department of Clinical Epidemiology, National Heart and Lung Institute, London* Aetiological factors in chronic sputum production have been assessed in a matched case-referent inquiry; subjects for study were identified after a survey (response rate 92%) of over 10 000 people living in south east England. A total of 240 people aged 5–54 years who reported sputum production on at least half of the days of the year (cases) were matched on age, sex, and town of residence with an equal number of randomly selected people who reported that they never produced sputum (referents). Subjects were interviewed by two trained nurses who were not informed of their case or referent state; 93% of subjects (89% of matched pairs) were interviewed. Three a priori hypotheses designed to assess the aetiological roles of early respiratory disease, cigarette smoking, and occupational exposure to respiratory irritants were tested in this way. Serious childhood respiratory illnesses were reported more frequently by cases than by referents (odds ratio = 2·8, 95% confidence interval 1·6 to 5·7); further analysis suggested that much, though not all, of this excess was attributable to persistent asthma. Comparison of subjects' reports with their general practice records showed no evidence of important recall bias. The relation between cigarette smoking and sputum production was affirmed (odds ratio = 4·2, 2·5 to 7·5 in those who had smoked) and a linear dose-response relation was shown for pack years of smoking. On matched pair analysis occupational exposure to respirable dusts, fumes, or gases, as assessed by a panel of three occupational hygienists, was not significantly associated with sputum production, though an exposure-response relation was apparent.

Short term morbidity after inhalation of chlorine gas

N WALKER, JG WILLIAMS *Associated Octel, Ellesmere Port, and Halton General Hospital, Runcorn* A prospective study was performed on 38 cases of accidental inhalation of chlorine gas reported to the Octel Medical Centre, Ellesmere Port, between April 1987 and March 1989. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were performed at initial presentation. All cases were reassessed 24 hours after the initial incident and daily thereafter until FEV_1 returned to 95% of the employee's most recent preincident value. Treatment was based on the severity of cough and dyspnoea at initial presentation according to the occupational sisters' assessment. Trivial cases were given symptomatic relief only (group 1). Mild cases were treated with oxygen only (group 2). Moderate and severe cases were treated with oxygen and nebulised salbutamol (group 3). No patients required admission to hospital. There was no significant difference in mean ages between the groups. Five people had pre-existing chronic bronchitis or asthma (table below). There was a significant difference in the mean FEV_1 at initial presentation, expressed as a percentage of the pre-incident level, between the three groups (group 1 *v* group 2, $p < 0.01$; group 2 *v* group 3, $p < 0.01$). A significantly greater number of current and ex-smokers (15 out of 16 subjects) in groups 2 and 3 took more than 24 hours to recover their preincident FEV_1 compared with non-smokers (three out of seven subjects), despite there being no difference in the smoking habits between the two groups ($p < 0.001$). Only four of the 38 subjects took seven days or more to fully recover their FEV_1. Three of these subjects had pre-existing lung disease. The findings suggest that current and ex-smokers as well as those with pre-existing lung disease are more likely to have respiratory illness persisting for 24 hours after inhalation of chlorine.

	Group 1	*Group 2*	*Group 3*
No	15	6	17
Mean age (years) (SD)	41·7 (13·2)	35·6 (13·1)	40·2 (10·1)
Current or ex-smoker	8	4	12
Non-smokers	7	2	5
Mean FEV_1 (% previous) (SD)	99·1 (2·66)	79·0 (9·5)	67·2 (15·4)

Symptoms and low airborne endotoxin in pigeon lofts

K ANDERSON, G MORRIS, C McSHARRY, R RYLANDER, G BOYD *Department of Respiratory Medicine, Glasgow Royal Infirmary, Glasgow, and Department of Environmental Hygiene, University of Gothenburg, Gothenburg, Sweden* In addition to more classic delayed symptoms, pigeon breeders often develop acute eye or nasal irritation and cough. These are sometimes severe enough to cause the breeders to leave the loft during dustier spells or provoke them to use a respirator. To investigate this problem further we studied the nature of the airborne material within the loft by using free standing and lapel mounted personal samplers with low volume pumps in 10 lofts during the breeding and non-breeding (moulting) seasons. Airborne antigen was estimated by enzyme immunoassay of filter eluted solution. Similar total inhalable dust concentrations were found in the undisturbed loft for each season, but the antigenic component rose significantly during the moult (medians 0·3 μg *v* 35 μg, $p < 0.001$). Dust levels were higher during cleaning in both seasons, especially during the moult (medians 0·35 mg/m^3 *v* 28·1 mg/m^3). Airborne endotoxin was present in comparatively low amounts, rising only marginally during the dustiest period (median 0·25 ng/m^3 *v* 0·33 ng/m^3, NS). These results suggest that the development of acute or delayed symptoms is unlikely to be caused by exposure to airborne endotoxin and may be more dependent on the quantity of airborne dust and the antigenic component. Both airborne dust and antigen concentration are increased during the non-breeding season, when the quantity of feather derived material is highest; this is perhaps the predominant source of the antigenic particulate.

Adult respiratory distress syndrome after cardiopulmonary bypass

M MESSENT, PD MACNAUGHTON, BF KEOGH, CJ MORGAN, TW EVANS *Adult Intensive Care Unit, Royal Brompton National Heart and Lung Hospital, London* The adult respiratory distress syndrome (ARDS) may be precipitated by a wide variety of direct and indirect insults to the lung, but the underlying mechanisms remain unknown. However, only a small percentage of patients at risk from ARDS develop the full blown syndrome. Predicting those patients likely to develop ARDS therefore assumes considerable clinical significance, enabling supportive treatments to be started without delay and the investigation of possible precipitating factors. Consequently, a retrospective, case controlled study was designed to assess the incidence of ARDS after cardiopulmonary bypass (CPB) and the extent to which this was associated with preoperative and perioperative predictive factors. Eleven patients who developed ARDS by the criteria of Murray (*Am Rev Respir Dis* 1988;**138**:720) from a total of 840 undergoing CPB (incidence 1·31%) were compared with 53 controls matched for age, sex, operation, and surgeon. The death rate was 53%. Factors predicting the development of ARDS were an intraoperative and postoperative problem score ($p < 0.05$), total volume of blood pumped during bypass (>300 l, $p < 0.05$) and age (>60 years, $p < 0.05$). In the 10 years

since the last (very much smaller) study (*Ann Intern Med* 1983;98:593) the incidence and outcome of ARDS complicating CPB remains unchanged. A high intraoperative and postoperative problem score, age over 60 years, and high pumped blood volume should alert the clinician to the possible risk of postoperative lung disease. PDM is a Medical Research Council training fellow in intensive care.

Takayasu disease with predominant pulmonary involvement

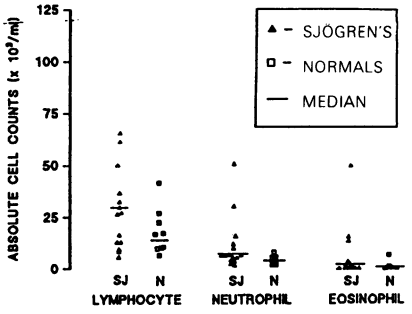
S ELSASSER, M SOLÈR, C BOLLIGER, P STULZ, K JÄGER, R FRIDRICH, U STEIGER, AP PERRUCHOUD *Divisions of Pulmonary Diseases, Thoracic Surgery, Angiology, and Nuclear Medicine, and Departments of Internal Medicine, Surgery, and Radiology, University Hospital Basle, Basle, Switzerland* Pulmonary vascular involvement in Takayasu disease is reported in 50–70% of cases. However, there are only a few reports published, in which changes in the pulmonary circulation were predominant. We report the case of a white woman who developed arterial hypertension at the age of 16 years, followed by anaemia, exertional dyspnoea, headache, and haemoptysis. The recurrent symptoms increased over three years, when pulmonary cavitations in the right upper lobe were diagnosed. Compared with previous radiography, the right pulmonary artery had considerably diminished in size. Complete obliteration of the right pulmonary artery was documented by perfusion scintigraphy and angiography. Duplex sonography of the great aortic vessels showed changes typical of Takayasu arteritis with involvement of the left and right carotid and subclavian arteries in spite of high dose steroid treatment. Erythrocyte sedimentation rate remained raised and the patient complained of recurrent haemoptysis. Radiologically, the cavities in the right lung progressively increased in size. An infectious process in the right lung was suspected and a pneumonectomy performed. Histologically there was invasive aspergillosis. The postoperative course was uneventful; the exertional dyspnoea and signs of inflammation diminished. As judged by scintigraphy and duplex sonography, the disease process stabilised six months postoperatively and cyclophosphamide treatment was discontinued and steroids reduced to 10 mg prednisone daily. This case shows that a functionally unperfused lung can be removed without adverse effects. If such a lung becomes infected it should be removed to prevent spread of the infection to the healthy lung and to achieve proper monitoring of the systemic disease process without interference from infections.

Clinicopathological features of MacLeod's/Swyer James syndrome

SK OHRI, G RUTTY, SW FOUNTAIN *Harefield and Mount Vernon Hospitals, Middlesex* We describe three cases of MacLeod's syndrome in which surgical resections were required for distressing symptoms. This provided a rare opportunity to examine the pathological features of a condition that is usually diagnosed on its radiological features and whose aetiology remains unestablished. Three patients (two women and one man aged 20, 23, and 24 years) were referred from respiratory physicians because of unilateral hyperlucent lungs and associated symptoms. Two patients had dyspnoea on exertion, but one of these patients had also had asthma since childhood. Two patients had pain on the same side as the hyperlucent lung, and in one patient the pain was precipitated by flying at high altitude. The duration of the symptoms was nine months and three and five years; none of the patients had a history of recurrent infections. All three patients had unilateral hyperlucent lungs, but only one patient had demonstrable mediastinal shift on expiratory and inspiratory chest computed tomogram. Computed tomography (CT) confirmed the plain findings, and with standard settings, it could not differentiate between patients with MacLeod's syndrome and those with bullous lung disease. A ventilation/perfusion scan was taken in one patient and confirmed the abnormality to be unilateral, with the hyperlucent area having poor perfusion and ventilation. Respiratory function tests in all the patients showed reduced lung volumes, without significant airways obstruction. The forced vital capacity (FVC) was 88%, 81%, and 82% of predicted values; FEV_1/FVC ratios were 0·79, 0·78, and 0·76 respectively. At operation all three patients had segmental involvement of one (n=2) or two lobes (n=1). Segmentectomies were performed (n=4) in all the patients without perioperative morbidity or mortality. Patients were followed up between four months and one year and remained asymptomatic with a return to normal lifestyle. Histological examination of the specimens found inflammation of the bronchus in all three cases, but only two specimens showed evidence of bronchiolar inflammation. In only one case was there a reduction in bronchiole number. All three cases showed presence of panacinar emphysema. Both alveoli and pulmonary vasculature were normal in number. These cases are notable for the segmental distribution of their disease. Pathological examination lends support to the theory that previous respiratory tract infection may have a role in the pathogenesis of this condition as all our cases had evidence of either bronchial or bronchiolar inflammation, although no reduction was found in numbers of alveolar or pulmonary vessels. These findings may help to delineate MacLeod's syndrome from congenital lobar emphysema, which is not segmental in distribution and may be associated with polyalveolar lung.

Bronchoalveolar lavage and transbronchial biopsy in dyspnoeic patients with primary Sjögren's syndrome

PV GARDINER, CA KELLY, C WARD, A ALLISON, DJ HENDRICK, EH WALTERS *Chest Unit, Newcastle upon Tyne, Newcastle* The pathological basis for pulmonary function abnormalities in Sjogren's syndrome (1°SS) is widely disputed. We studied 16 patients (15 female, two smokers) with definite or probable 1°SS (Fox's criteria) who complained of dyspnoea. At bronchoscopy bronchoalveolar lavage (BAL) samples (3 × 60 ml) were taken from the middle lobe, followed by transbronchial biopsy of the right lower lobe. Pulmonary function was reduced in 15 of 16 subjects with a restrictive pattern on spirometry and reduced gas transfer factor (TLCO) in 15 patients. BAL samples showed lymphocytosis or neutrophilia with eosinophilia, or both, in seven patients (figure below). These findings were broadly in agreement with histological results. Peribronchial lymphocytic infiltration was present in five patients and fibrosis in three. Pulmonary symptoms in 1°SS may be associated with cytological abnormality and histological evidence of peribronchial lymphocytic infiltration or interstitial fibrosis.



Assessment of lung crackles by computerised lung sound analysis: a comparison with auscultation

N AL JARAD, G BOTHAMLEY, SH LOCK, C SHELDON, R LOGAN-SINCLAIR, RM RUDD *London Chest Hospital, London* Agreement on the presence, timing during the respiratory cycle, and nature of crackles was assessed between four independent examiners on two lung zones of 30 patients (14 with asbestosis, eight asbestos workers without asbestosis who smoked, three with left ventricular failure, four with chronic bronchitis, and one with cryptogenic fibrosing alveolitis) and 13 healthy subjects (10 current smokers and three ex-smokers). A total of 86 zones were assessed by the examiners and by a time expanded wave (TEW) obtained by a computerised lung sound analysis system. In patients expiratory crackles were more frequently detected by TEW than by any of the examiners ($p < 0{\cdot}00001$, $p < 0{\cdot}003$, $p < 0{\cdot}03$, $p < 0{\cdot}009$ compared with the four examiners. Compared with TEW inspiratory crackles were overestimated by three examiners possibly because they interpreted the expiratory crackles as inspiratory crackles. The disagreement between pairs of examiners on the presence and absence of lung crackles ranged between 29–45%. The disagreement between pairs of examiners on the timing of crackles in the respiratory cycle ranged between 45–65% and on the nature of crackles (coarse, medium, fine) ranged between 35–64%. In normal subjects crackles were detected by TEW in six healthy smokers. These were identified only on one patient by one examiner. We conclude that auscultation underestimated the presence of expiratory crackles and gave rise to considerable interexaminer disagreement on the presence, timing, and nature of lung crackles.

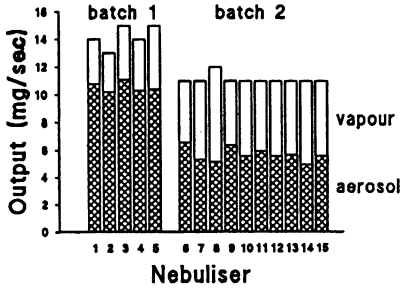
High resolution computed tomographic assessment of asbestosis and cryptogenic fibrosing alveolitis: comparative study

N AL JARAD, B STRICKLAND, RM RUDD *London Chest Hospital and Royal Brompton and National Heart Hospital, London* By using high resolution computed tomography (HRCT) the distribution and configuration of opacities in 18 patients with cryptogenic fibrosing alveolitis (CFA) and 24 patients with asbestosis were investigated. Patient groups did not differ significantly with respect to age, pack/year smoking, and spirometric results. CT technique and window settings were

similar in both groups. Shadowing suggesting fibrosis in the upper thirds of the lungs occurred in 10 (56%) patients with cryptogenic fibrosing alveolitis and six (25%) patients with asbestosis ($p < 0.05$) and in the middle thirds in all patients with CFA and in 19 (74%) patients with asbestosis ($p < 0.04$). Lung fibrosis occurred in the lower zones in all patients with CFA and asbestosis. Emphysema and bullae occurred in the upper third in 13 (72%) patients with CFA and in 11 (48%) patients with asbestosis ($p = 0.07$). Confluent ground-glass (alveolar) shadowing of moderate degrees was noted in 13 (72%) patients with CFA and in three (13%) patients with asbestosis ($p < 0.0001$). In 11 (61%) patients with CFA fibrosis was posterior in lower CT sections, lateral in middle sections, and anterior in the upper sections. This distribution was present in only four (17%) patients with asbestosis ($p < 0.001$). Fibrosis and emphysema were more distorting to lung architecture in patients with CFA than in those with asbestosis. Emphysema and severe destructive fibrosis did not occur in patients with CFA who were non-smokers or those with asbestosis. We conclude that by HRCT CFA appears more widespread than asbestosis, with more frequent involvement of the upper lobes; often a characteristic distribution from base to apex; and more frequent occurrence of a ground glass or alveolar pattern.

Calibration of the Mefar inhalation dosimeter

JH DENNIS, AJ AVERY, SC STENTON, JR BEACH, EH WALTERS, DJ HENDRICK *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne, Newcastle* It is proposed that the 50 or so participants of the forthcoming European Community study of the prevalence of asthma should all use the Mefar MB3 dosimeter to help standardise doses of nebulised methacholine in the measurement of airway responsiveness. The manufacturer provides calibrated output data (mg/s) for every nebuliser so that a standard output may be achieved by varying nebulisation time. Output, however, is measured by weight loss (WL), which overestimates true aerosol output (AO) because of concomitant evaporation (WL = AO + water vapour (*Thorax* 1990;45:728). We used a chemical (fluoride) tracer method to measure AO from two batches of Mefar nebulisers (n = 5, n = 10) and compared results with the manufacturer's calibration data. We also examined the effect of reservoir temperature on Mefar nebuliser output by simultaneously measuring WL and AO at different temperatures. We found little within batch variation in AO or QL (mg/s) but clear differences between batches (figure). The aerosol fractions (AO/WL) differed considerably also—medians of 75% and 51% respectively. Temperature influenced WL strongly (44% increase) and AO weakly (14% increase) over a 10–35°C range, implying that AO/WL is temperature dependent. If WL was used to standardise delivery of a 100 μg target dose of nebulised methacholine from the median nebulisers of batches 1, and 2, the actual aerosol doses delivered would be 75 μg and 51 μg respectively. We consequently recommend direct calibration of AO if standardised measurements of airway responsiveness are to be achieved with the Mefar inhalation dosimeter.



New electronic spirometer

SH KHOO, JS MILLEDGE, P GOHILL, HM MOSZORO, BM WRIGHT *Northwick Park Hospital, Harrow, Middlesex* The Ventilometer (Clement Clarke, United Kingdom) is a new electronic spirometer developed from the Wright mini peak flow meter. It weighs 420 g, and measures forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) as well as peak expiratory flow. We compared the accuracy of the ventilometer with that of a dry wedge spirometer in the measurement of FVC and FEV_1 and the degree of correlation between mechanical and electronic measurements of peak flow. Reproducibility of blowing between the two devices was also assessed. We found that the Ventilometer underread values for FVC by a mean of 0·09 l ($p < 0.001$) and FEV_1 by 0·11 l ($p < 0.02$, paired t test); this did not vary throughout the range of lung function tested. However, FVC was less reproducible with the Ventilometer; this is possibly due to a lack of any indication for either subject or operator of when vital capacity has been reached. This is a problem common to all electronic spirometers. The Ventilometer measures FVC, FEV_1, and peak flow with an acceptable degree of accuracy. This might be improved by an adjustment of calibration for FVC and FEV_1 and the incorporation of an audible signal to indicate the presence of airflow—that is, that full expiration has not yet been achieved.

Pharmacokinetics of ciprofloxacin in pleural effusion: comparison of oral versus intravenous administration

J JOSEPH, GS BASRAN, AMA ABBAS, C HUGHES, GS TILLOTSON, D FELMINGHAM, M HITCHEN *Respiratory Unit, District General Hospital, Rotherham, South Yorkshire* Ciprofloxacin has been shown to have good penetration into the bronchial tree. We used pleural effusion as a model to investigate the ability of ciprofloxacin to penetrate into the extravascular compartments of the body. All the patients included in the study required prophylactic administration of ciprofloxacin and a pleural catheter insertion as a part of pleural effusion kinetic study using radioisotopes. Seven patients received 200 mg ciprofloxacin intravenously and eight patients received 750 mg orally. Blood and effusion samples were taken at 15 minute intervals for four hours. Ciprofloxacin was measured by using high pressure liquid chromatography. Ciprofloxacin achieved a plateau concentration in the pleural fluid at three hours with oral or intravenous routes of administration. The table below shows the ciprofloxacin concentration in pleural fluid at three hours. Thus, significantly higher fluid concentrations were observed at the recommended oral dose of 750 mg compared with 200 mg iv ($p = 0.002$), further showing the penetrative quality of ciprofloxacin.

Dosage	*No*	*Mean (SE) ciprofloxacin (μg/ml)*
200 mg (intravenously)	7	0·7 (0·1)
750 mg (orally)	8	1·5 (0·2)

Water content of bronchial biopsy specimens and its relation to distribution of β lactam antimicrobials in bronchial tissue

DR BALDWIN, R WISE, JM ANDREWS, D HONEYBOURNE *Departments of Thoracic Medicine and Medical Microbiology, Dudley Road Hospital, Birmingham* The concentration of β lactam antibiotics in bronchial biopsy specimens is remarkably consistent at 40–50% of the simultaneous serum concentration. However, the distribution of these agents within bronchial biopsy specimens is unknown. In vitro studies have shown that β lactams do not readily penetrate cell membranes and therefore these agents are probably only present in the interstitial fluid. If interstitial fluid concentrations of β lactams equal serum concentrations, the percentage of serum antimicrobial concentration detected in biopsy samples should correspond to the percentage of extracellular water in such samples. The water distribution within bronchial biopsy samples was therefore investigated. Bronchial specimens were taken from the macroscopically normal subcarinae of five patients undergoing fibreoptic bronchoscopy for diagnostic purposes. Samples were placed in culture medium at 37°C immediately and incubated with either triatiated water (marker of total water) or inulin or polyethylene glycol (PEG) labelled with carbon-14 (markers of extracellular water). The specimens were weighed and homogenised by ultrasonication after the addition of 200 μl water. The samples were then counted in aqueous scintillant and the water distribution calculated. The results are shown in the table below. The extracellular water content corresponded to the distribution of β lactams in bronchial biopsy specimens suggesting that β lactam concentrations in the interstitium are equivalent to serum concentrations.

	Water content (vol/wt)		
	Extracellular (%)		
	Inulin	*PEG*	*Total (%)*
Mean (n = 10)	46	36	71
SE	3	2	13
Range	36–59	29–53	65–78

Occult alveolar haemorrhage in bronchopulmonary Kaposi's sarcoma

RF MILLER, L HUGHES-DAVIES, MF SPITTLE, G KOCJAN *Departments of Medicine and Histopathology, University College and Middlesex School of Medicine, and Myerstein Institute of Clinical Oncology, Middlesex Hospital, London* Bronchopulmonary Kaposi's sarcoma (KS) is often diagnosed at necropsy rather than by bronchial or transbronchial

biopsy. Occult alveolar haemorrhage (AH) has frequently been reported in open lung biopsy and necropsy specimens from patients with KS and the presence of haemosiderin laden macrophages (HLM) in bronchoalveolar lavage fluid is thought to be diagnostic of AH caused by KS. We sought evidence of AH in lavage fluid from patients with KS and other diagnoses to evaluate whether the presence of HLM increased the diagnostic yield of bronchoscopy for KS and helped discriminate between KS and other diagnoses. We studied 47 HIV positive patients, mean age 39 years, who had presented with respiratory symptoms. Twenty two patients (group 1) had KS; lesions were seen at bronchoscopy in 19, and in three with normal bronchoscopic appearances the diagnosis was made at necropsy. Twenty five patients (group 2) had alternative diagnoses: *Pneumocystis carinii* in 16; bacterial pneumonia in six, *Mycobacterium tuberculosis* in two, and lymphoma in one. In all patients blood urea concentration was <12 mmol/l and the international normalised ratio was <1·5. Aliquots of lavage fluid were centrifuged and smears were made from the cell pellets and stained with Perl's stain. The average number of HLM in 10 high power fields (×400 magnification) were counted (table below). Three patients from group 1 and two patients from group 2 had platelet counts $< 70 \times 10^9$/l but all had negative HLM scores. Of the three patients with KS and negative bronchoscopic results, two had HLM in bronchoalveolar lavage fluid. The presence of HLM did not discriminate between KS and other diagnoses $\chi^2 = 1{\cdot}21$, of 1° NS). Although AH is a non-specific finding, the presence of HLM in bronchoalveolar lavage fluid should prompt a search for KS once infective causes are excluded, even if the tracheobronchial tree is normal at bronchoscopy.

	No of HLM			
	Negative	*<10*	*10–1000*	*>100*
Group 1	7	4	7	4
Group 2	13	4	4	4

Audit of deaths from pneumonia in younger adults

CR TANG, JT MACFARLANE *Respiratory Medicine, City Hospital, Nottingham* Between April 1987 and March 1990, 600 adults <65 years old were admitted to the Nottingham hospitals with community acquired pneumonia and 64 died (10·8%). Available records on 55 of these showed that 41 suffered from significant pre-existing disease. Fourteen (mean age 54; range 33–64) had been previously well and were studied in greater detail. Five had seen their general practitioner more than once before admission, four receiving appropriate antibiotics. The correct diagnosis was made in hospital in all cases, but only five were recorded as having severe infection. The mean delay between admission and starting antibiotic treatment was 260 minutes. A mean of 2·6 doctors saw the patient before treatment was started. Antibiotics compatible with previous guidelines of the British Thoracic Society were given to 10, added oxygen therapy to 13, and intravenous fluids to 11. Arterial blood gas tensions were not checked in two patients. Eleven patients were transferred to the intensive therapy unit after a mean of 5·6 doctor contacts and one day after admission (range 1–3). Three deaths occurred on the general wards, in one after a decision not to ventilate. An aetiology was obtained in only five (pneumococcal three, staphylococcal two) after blood culture in 10, sputum culture in eight, and serology in only three. Only six fulfilled British Thoracic Society criteria for severe disease (two or three of tachypnoea >30, diastolic hypotension, urea >7), inadequate documentation being present in four. We conclude that the majority of younger adults that die of community acquired pneumonia have pre-existing disease. For previously well patients assessment and management was not ideal.

Audit of community acquired pneumonias: effect of a simple assessment protocol

S REYNOLDS, A PHILLIPS, R RICHARDS *Department of Thoracic Medicine, Llandough Hospital, Wales* We report an audit of patients admitted to the respiratory unit with a diagnosis of community acquired pneumonia over two periods of three months. The first was from December 1989 to February 1990, and the second from December 1990 to February 1991. During the first period a total of 40 patients (age 58 (SD 20) years, 17 men) were admitted. The initial assessment of eight risk factors (Harrison *et al, J R Coll Physicians Lond* 1987;21:267) were judged to be complete in six (15%) of the patients (14 (35%) recorded 7/8). The causative organism could be identified in 16 (45%). Fourteen (35%) received oral antibiotics. Of the 26 (65%) who received intravenous treatment, eight (20%) had no identifiable risk factors. There were six deaths; all had multiple risk factors (at least 3, 4, 3, 5, 2, 6). After analysis of the first period a simple protocol for the assessment and treatment of community acquired pneumonias was produced and circulated among junior doctors. The aims were (*a*) to improve the awareness of severity of community acquired pneumonia, (*b*) to increase the diagnostic yield, and (*c*) to rationalise the antibiotic treatment. In the second period 32 patients 54 (21) years, 16 women) were assessed. Initial assessments of severity were complete in 21 (65%) cases (29 (90%) recorded 7/8). Causative organisms were identified in 14 (44%). Intravenous treatment was started in 18 (56%) patients, 16 of whom had one or more risk factors. Oral antibiotics were used in 14 (44%) patients, four having one and two having two risk factors. There were four deaths, three directly attributable to pneumonia (risk factors 4, 4, and 4). We found that the introduction of these guidelines has increased the awareness of the risk factors associated with community acquired pneumonia and has led to more appropriate treatment. The audit is ongoing and we hope to refine the guidelines as more information is acquired.

Audit of long term outcome of near fatal asthma

HH MATITI, CD ERAUT, AG DAVIDSON *Southend Hospital, Essex* There are little data, except in children, on the long term outcome in patients who have had a near fatal asthma attack. We studied 50 patients (31 female) ventilated for asthma between 1976 and 1989. All were ventilated because death was thought to be imminent. Twenty percent had had a respiratory arrest and 80% were exhausted. Their ages ranged from 21 months to 80 years, 40 being over 18 years of age. Five (10%) died from asthma six weeks to three years after ventilation, and two died from non-asthmatic causes. Ten were ventilated more than once, one seven times, two three times, and seven twice. Five patients were ventilated twice during a year. The mean number of admissions for asthma after ventilation was 4·5 (7·3). Nine patients averaged over one admission a year, but 27% had no further admissions after ventilation. In 1990 86% were taking anti-inflammatory agents, 76% inhaled steroids, 5% sodium cromoglycate, 5% oral steroids; 5% were taking bronchodilators alone, 8% were not taking drugs for asthma. In all 32% were followed by chest physicians, 14% by paediatricians, 14% by general physicians, and 14% by general practitioners; the rest either died or were lost to follow up. Home peak flow recordings during 1990 in 24 patients showed the maximal diurnal variation in any one day ranged from 5% to 55%, mean 23% (13%). In the patients with greater than one admission a year for asthma, the mean maximal diurnal variation was 23% (18%). Asthmatic patients who have one episode of near death continue to have severe asthma and are at risk of dying from asthma and of having another near fatal attack. They have frequent hospital admissions. Peak flow recordings indicate that many continue to have poorly controlled asthma.

Audit of management of asthma in several outpatient clinics: pulmonary function

CK CONNOLLY, RJ PRESCOTT, SM ALCOCK, T HARDING *Memorial Hospital, Darlington, and University of Edinburgh, Edinburgh* An outpatient audit in 16 centres throughout England during four periods of two weeks in 1990 included 766 subjects. Pulmonary function was recorded as peak flow rate in nine centres and by spirometry in 13. Actual function at attendance was compared with best function. Acceptable best function had to be recorded twice daily with charting of peak flow rate while taking regular prophylaxis if below 80% of predicted values and while taking oral steroids if below 70%. Best function was recorded satisfactorily for peak expiratory flow rate (PEFR) in 71% of subjects (clinic range 42–89) and forced expiratory volume in one second (FEV_1) in 77% (range 47–92). To test the criteria of best function, actual/best function was compared where the above criteria had and had not been satisfied. This ratio was lower only in those who did satisfy the criteria when actual peak flow rate was below 70%, but not at any value of FEV_1. This suggests that a special trial of steroids may not be necessary to show best function with FEV_1 but that more stringent conditions are required to show best PEFR in patients with poor pulmonary function. The mean actual PEFR was 75% and mean actual FEV_1 71% of predicted values. The mean best PEFR was 86% and best FEV_1 88% of predicted values. Clinic ranges of actual peak flow rate were 61–81% of predicted values and for FEV_1 56–76%. The range for actual/best function was 83–90% for PEFR and 75–90% for FEV_1. Actual function deteriorated from low dose inhaled steroids, through high dose to the oral steroid step (PEFR 81–73%, FEV_1 78–72%). This was largely due to poorer best rather than actual/best function, particularly

with PEFR. Actual function in patients without a stable regimen was similar to that in those taking oral steroids. Pulmonary function was also corrected for social variables, which improved the performance of some districts. The audit shows that despite geographical and subject variations, these clinics achieved an actual/best of 80%, with little difference with intensity of regimen, suggesting appropriate adjustment of treatment.

Audit of management of asthma in several outpatient clinics: treatment

CK CONNOLLY, RJ PRESCOTT, SM ALCOCK, T HARDING *Memorial Hospital, Darlington, and University of Edinburgh, Edinburgh* The management of asthmatic patients who had been followed up for a year was audited in 16 centres throughout England in four fortnights at irregular intervals in 1990. In all, 766 subjects were entered, 194 at the authors' centre and 568 (range 9–130) at the other 15. Therapeutic regimen was regarded as stable if it had been unchanged for three months (except for planned booster doses of corticosteroids) and doctor and patient agreed that control was satisfactory. The study was started before the guidelines of the British Thoracic Society were published, and the stepwise approach included a step for cromoglycate nedocromil before low dose inhaled steroids. The regimen was recorded as unstable in 5·9% of subjects (centre range 0·0–11·1). The authors' centre had the second highest proportion, 10·8%, which compares with published figures of 5·1% in 1980 and 4·3% in 1983. Nevertheless, it is likely that centres reporting the lowest incidence of unstable patients were underestimating the problem. Of those with a satisfactory regimen, 25% were taking oral steroids (centre range 10·0–46·7), 28% high dose inhaled steroids (1·6–58·3), and 41·5% low dose inhaled steroids (19·2–71·3). There was an inverse relation between the proportion taking high dose inhaled steroids and oral steroids. In addition, 74% taking low dose and 93% taking high dose inhaled steroids were also taking regular bronchodilators; 8% taking low dose and 10% high dose inhaled steroids used cromoglycate or nedocromil. The proportion taking regular bronchodilators at both the low and high dose inhaled steroid steps suggests that regular bronchodilators are introduced at an earlier stage than recommended by the existing guidelines.

Audit of management of acute asthma

W CLAGUE HOWELL *Bishop Auckland, County Durham* Emergency admissions for acute adult asthma to a district general hospital (DGH) were audited over a 12 month period to determine the standard of initial assessment, early treatment, subsequent course in hospital, and outcome on discharge. Eighty one out of 84 admission episodes (76 referrals by general practitioners) relating to 60 patients were audited. Twenty one male, and 39 female patients had an age range of 18–84 years; 13 were current smokers. Six patients accounted for 21 readmissions (10 for one patient, two for two, three for three). At presentation formal clinical grading of severity was underused (nine of 81) (Jones ES *Proc Roy Soc Med* 1971;**64**:1151), as was the recording of pulsus paradoxus (15) and immediate peak expiratory flow (PEF) (21). A record of respiratory rate (51) and admission blood gas tensions (44) were more frequent, although many of the gas tensions were normal. Immediate treatment included inhaled β agonists in all cases (68 by nebulisation), with simultaneous ipratropium bromide in 44. Few had intravenous aminophylline (4) or an antibiotic (4), and although intravenous hydrocortisone was given in 29, immediate oral prednisolone was underused. All patients were subsequently given oral prednisolone. Subsequent supervision included peak flow monitoring in most (73 of 81) but in 13 PEF was suboptimal at discharge. Spirometry, instruction in inhaler technique, and explanation of treatment was recorded in few cases. On discharge a reducing course of oral steroid (67 of 81) often meant that inhaled steroids were underprescribed (45 of 61) and in less than half was the dose increased. All but two were referred to the respiratory clinic for review at between two and six weeks. Audit shows evidence of underrecording of clinical information relevant to immediate assessment and patient education. The lack of inhaled prophylactic therapy on discharge is disturbing and audit findings have been used to implement guidelines on asthma management.

Reaudit of management of asthma in hospital

CE BUCKNALL, C ROBERTSON, F MORAN, RD STEVENSON *Medical Audit and Respiratory Medicine, Royal Infirmary, Glasgow, and Department of Statistics, Strathclyde University, Strathclyde* Data from three consecutive audits of asthma management were compared to assess (*a*) whether the management of asthma has altered, and (*b*) whether the process of audit has had any demonstrable effect. We compared 101 cases of acute asthma admitted in 1983, 133 cases admitted in 1989, and 85 cases from the 1985–6 survey (*BMJ* 1988;**296**:1637) whose final discharge diagnosis was coded as asthma. These three groups were of similar age and smoking habit, stayed in hospital for similar periods, and, as an objective guide to the severity of the attack, had similar initial pulse rates. Major improvements in most aspects of management were observed; by 1989, 66 (50%) had peak flow measured as part of initial assessment, 119 (90%) were treated with oral corticosteroids, and 109 (82%) were treated with oxygen. In all 114 (86%) had regular recorded peak flow measurement and 103 (86%) were discharged taking oral corticosteroids. Significantly fewer patients had their regular inhaled treatment increased on discharge in 1989—26 (22%) compared with earlier years; this is the only observed change significantly away from the British Thoracic Society guidelines, and possible reasons for this are discussed. This reaudit shows that the management of asthma has significantly improved and analysis of trends within the data provides some but not unequivocal evidence that the process of audit has contributed to this improvement.

Audit of treatment of patients with small cell lung carcinoma in North West Thames Regional Health Authority

F MOSS, M RUDOLF, J SPIBY, M McNICOL on behalf of North West Thames Thoracic Society *North West Thames Regional Health Authority, London, Central Middlesex Hospital, Ealing Hospital, London* Medical audit done from a regional rather than a district perspective allows a wider forum for specialist debate and comparison of a larger number of cases. The possibility of differences in approaches to treatment of small cell lung carcinoma (SCLC) stimulated this regional audit. The aims were (*a*) to estimate the proportion of bronchial carcinomas with SCLC histology, (*b*) to determine how many patients with SCLC received chemotherapy, and (*c*) to identify factors associated with the decision to give chemotherapy. Thoracic physicians were asked to identify all bronchial carcinomas diagnosed from June 1988 to July 1989 and for those with SCLC to state (*a*) age and sex, (*b*) duration of symptoms, (*c*) comorbidities, (*d*) retrospective assessment of performance status, (*e*) whether referred to radiotherapist or oncologist, or both, (*f*) staging investigations, (*g*) date and method of diagnosis, (*h*) date of death. Eleven out of 16 physicians responded. Eight completed forms and three were unable to obtain data. A total of 577 cases of bronchial carcinoma were identified, of which 78 (14%) were SCLC. Further details were available for 76. The median age was 62 years (range 41–85); the median survival four months. The decision to give chemotherapy was related to age (given to 69% of those <70 years and to 17% of those >70 years), retrospective assessment of performance status, and eventual survival. This retrospective analysis of treatment of SCLC showed that 44% of patients did not receive chemotherapy. This result provokes concern. Either patients are being denied treatment likely to improve both cancer specific symptoms and survival, with ages and performance status seen as barriers to treatment; or there are some patients genuinely not suitable for chemotherapy who have not been identified by large randomised trials. We are investigating these questions as a concurrent audit.

Further audit of long term oxygen therapy prescription in Liverpool district: have we now "closed the loop"?

MJ WALSHAW, CC EVANS, CRK HIND *Cardiothoracic Centre, Liverpool* Our audit of oxygen concentrator use in this district in 1987 showed that the majority of patients receiving long term oxygen therapy (LTOT) were either not having it prescribed or not using the 15 hours a day of therapy recommended by the Department of Social Security guidelines (*BMJ* 1988;**297**:1030). These results were presented to the local family practitioner committee (FPC), with the suggestion that each local general practitioner receive both a copy of the audit and also regular details of their own patients' oxygen use as measured by the daily average concentrator meter readings. To assess what effect these measures might have had on local LTOT prescription and consumption since 1988, we repeated the audit. We found a large increase in the numbers taking LTOT in 1989 (120 patients) compared with 1987 (61) and 1988 (68); this was sustained in 1990 (125) and 1991 (131), suggesting increased local awareness of this form of treatment. In terms of prescribing habits, though only 30 out of 61 and 36 out of 68 patients had been prescribed at least 15 hours a day in 1987 and 1988, this proportion had significantly improved by 1990 (92/125) and 1991 (96/131) ($\chi^2 = 9{\cdot}7$, $p < 0{\cdot}002$). In terms of oxygen usage, though only 28 out of 61 and 31 out of 68 patients used at least 15 hours a day in 1987 and 1988, this proportion had also increased

significantly by 1991 (85/118 patients for whom data were available) ($\chi^2 = 10{\cdot}7$, $p < 0{\cdot}001$). These results suggest that both LTOT prescribing habits and patient compliance were improved by the educational measures taken by the FPC in 1988 as a result of our audit in 1987.

Results of a standard tuberculosis contact procedure in South Glamorgan, 1987–9

SF HUSSAIN, R WATURA, IA CAMPBELL, B CASHMAN, M EVANS *Departments of Chest Medicine, Public Health Medicine, and Applied Public Health, South Glamorgan Health Authority* The value of contact tracing for tuberculosis beyond six months has been questioned (Selby *et al. Thorax* 1988;**43**:834P). We reviewed the results of the contact procedure in South Glamorgan for the period 1987 to 1989. The procedure was modelled on the 1983 recommendations of the British Thoracic Society (Joint Tuberculosis Committee, *BMJ* 1983;**287**:1118). A total of 101 index cases and 611 contacts were identified. Seventy one index cases were pulmonary and 30 non-pulmonary. In 22 cases patients were of Indian subcontinent origin (ISC) and in 79 they were non-ISC. Five (23%) of the ISC group were smear positive and 10 (46%) culture negative. Corresponding figures for non-ISC patients were 31 (40%) and 51 (65%) respectively. The ISC group had 133 contacts, 82 (62%) close and 51 (38%) casual. The non-ISC group had 478 contacts, 88 (18%) close and 390 (82%) casual. There was a significantly higher ratio of close to casual contacts in ISC group. In all, 597 (98%) contacts underwent initial screening. Tuberculosis was diagnosed in six (1%) contacts, three ISC and three non-ISC. All were below 26 years of age and four under 10 years of age. None were known to have been inoculated. All were close or family contacts. In five of these the index case was smear positive tuberculosis, and in one smear negative, culture positive pulmonary tuberculosis. No contact of non-pulmonary or opportunist mycobacterial infection developed disease. Follow up appointments were given to 28 (22%) ISC and 42 (9%) non-ISC contacts. Attendances at six, 12 and 24 months were 83%, 36%, and 30% respectively. No new case of tuberculosis was diagnosed at these follow ups. To date no new case has been notified in those who defaulted. Our results support those of Selby *et al* and also question the value of follow up after the initial screening.

Screening of immigrants for tuberculosis at airports: is this of value?

DCS HUTCHINSON, M HIGGON *Department of Thoracic Medicine, King's College Hospital, London* A proportion of immigrants are referred by the Immigration Service to the airport medical inspector, who forwards a port health notification form (PHNF) to the appropriate medical officer for environmental health. We surveyed 64 PHNF received over a period of three months to assess their effectiveness in detecting and preventing tuberculosis. Thirty one PHNF were of type 101 (no evidence of infectious disorder) and 33 of type 102 (examination inconclusive). All 64 subjects were invited to attend for interview and tuberculin testing; 40 (62%) of the 64 subjects (29 were children aged 15 years or less) attended as requested. Twenty eight (70%) of the 40 attenders returned for tuberculin test reading, which was positive (grade 1 or 2) in 26; the two subjects who had not received BCG had a negative tuberculin test and BCG was given. Twenty nine of the 40 initial attenders had received BCG (scar identified) and in nine BCG status was not known. None were considered to need chemoprophylaxis. No cases of active tuberculosis were identified. Fifty four subjects were invited to attend for six month follow up but only 14 (26%) did so. Sixty to 80 cases of TB are identified a year in this health district, virtually none through the PHNF system. Additional TB screening should be done through the family practitioner service.

Tuberculosis may raise serum calcium concentrations

TYK CHAN, CSD WILLIAMS, P POON, R SWAMINATHAN, HS CHAN, M NISAR, PDO DAVIES *Tuberculosis Research Unit, Sefton General Hospital, Liverpool, and Chinese University, Hong Kong* Changes in the calcium-vitamin D axis including relative hypercalcaemia and deficiency of 25-hydroxy-vitamin D have been reported in patients with tuberculosis (TB). To define these changes further we studied 48 Hong Kong Chinese patients. Twenty four had culture positive pulmonary TB (age 56 (13) years, 15 males) and 24 were hospital controls (age 51 (14) years, 14 males) with no TB. Chronic ill health in the TB group was reflected by a lower serum albumin concentration (35·6 (6·7) *v* 42·5 (4·1) g/l, $p < 0{\cdot}01$) and lower body weight (48·9 (6·0) *v* 60·7 (9·3) kg, $p < 0{\cdot}01$). Relative hypercalcaemia in the patients was confirmed on comparison of serum albumin corrected calcium (2·33 (0·08) *v* 2·19 (0·09) mmol/l, $p < 0{\cdot}001$) despite a lower daily calcium intake (426 (208) *v* 564 (335) mg/day, $p < 0{\cdot}05$). Urinary calcium excretion and serum creatinine concentration were comparable in the two groups. However, marginal renal impairment in the TB group compared with controls was indicated by lower urinary creatinine excretion per day (8·0 (2·7) *v* 10·4 (4·2) mmol/day, $p < 0{\cdot}05$). Parathyroid hormone (PTH) release is normally inhibited by raised serum concentrations of calcium. In the TB group mean PTH concentrations (20·9 (8·5) pg/ml) was less than in the controls (38·2 (14·5) pg/ml, $p < 0{\cdot}001$). Serum concentrations of the storage (25-hydroxy) and active (1,25-dihydroxy) forms of vitamin D were also measured. Although not significant, the concentrations of both 25 hydroxy vitamin D and 1,25-dihydroxy vitamin D were lower in the TB group than in controls (19·7 (8·9) *v* 23·1 (12·3) ng/ml and 45·5 (14·9) *v* 48·1 (11·9) pg/ml respectively. These data suggest that active TB is associated with raised serum calcium concentrations but hypercalcaemia is prevented by down regulation of PTH release. The mechanism is unclear but may involve increased sensitivity and increased hyroxylation to the active form of vitamin D (1,25-dihydroxy vitamin D).

Tuberculin skin testing in HIV infected patients: risk of developing mycobacterial infections in those with negative test results

DJ LYONS, J KEATING, F MULCAHY, L CLANCY *St James's Hospital, Dublin 8, Republic of Ireland* We studied tuberculin skin responses as predictors for the development of myobacterial infections in patients infected with HIV. A skin test score was derived for each patient with the Multitest system, which records responses to tuberculin and to six other recall antigens. On entry into the study patients were staged according to the Centers for Disease Control (CDC) criteria. Fifteen patients were classified as stage II; seven patients were CDC III and 16 CDC IV. The mean follow up period was 22 months (range 6–34). Nine patients died of their HIV infection and one died of drug induced marrow aplasia. Three patients were lost to follow up. Twenty six patients were alive. Eleven patients were tuberculin positive, of whom one developed pulmonary infection with atypical mycobacteria. Twenty seven patients were tuberculin negative; two developed pulmonary tuberculosis and one had disseminated mycobacterial infection. Differences in the incidence of mycobacterial infection between tuberculin positive and tuberculin negative patients were not significant. Fourteen patients were tuberculin negative but gave positive responses to other antigen(s); two were tuberculin positive with negative responses to other antigens. There was a strong negative correlation between Multitest score and advanced disease ($R = -0{\cdot}7$, $p < 0{\cdot}001$). Patients with stage II and III disease had significantly higher skin test scores than those in stage IV ($p < 0{\cdot}001$). We conclude that the risk of mycobacterial infection is at least as high in tuberculin negative as in tuberculin positive patients with HIV infection. This is probably as a result of more advanced disease in the former group.

HIV related tuberculosis in England and Wales

M NISAR, IS NARULA, NJ BEECHING, PDO DAVIES *Tuberculosis Research Unit, Sefton General Hospital, Liverpool, and Infectious Disease Unit, Fazakerley Hospital, Liverpool* In December 1987 we presented data to this society (*Thorax* 1988;**43**:244P) showing that the arrest in the decline of tuberculosis between 1982 and 1986 was mainly due to a relative increase in the numbers of elderly people, particularly elderly women, presenting with the disease. Between 1987 and 1990 there was again virtually no change in the numbers of patients notified. In fact, total notifications for all age groups increased from 1987 to 1989 by 7·7%. Data from the US has shown that the halt in decline of notifications for tuberculosis (TB) since 1986 has been caused by a large increase in the numbers of young men (20–44) with disease while decline had occurred in all other groups. This seems to be related to HIV infection. It is possible that the halt in the decline in TB notifications in this country may also be HIV related. To determine whether this might be occurring, we again undertook an analysis of notifications by age and sex including the years 1982–9. Data have been extracted from the relevant Office of Population Censuses and Surveys monitors (Communicable diseases). Although notification in men aged 25–44 increased by 9% in 1987–9, notifications in other groups have increased as well; in women aged 25–44 by 10%; women aged 45–64 by 12%; men aged $\geqslant 75$ by 17%; and women aged $\geqslant 75$ by 14%. Reasons for this may include immigration, increased longevity of elderly people, high rate of infection in the group now aged $\geqslant 75$ during the second world war, and poverty. There is therefore no evidence that the group most at risk from

HIV related disease, the younger adult male population, is showing any increase in notifications over other groups. HIV infection is unlikely to be a contributory factor in the arrest in the decline of notifications at present, though it may still present a threat for the future.

Mycobacterial infection in an inner city children's hospital

HM GOODYEAR, EH PRICE, J MOORE-GILLON, VF LARCHER, MO SAVAGE, CBS WOOD *Queen Elizabeth Hospital for Children, London, and St Bartholomew's Hospital, London* Fifty seven cases of active mycobacterial infection in children (0·5–12 years) were diagnosed at Queen Elizabeth Hospital (QEH) in the decade 1981–90. Pulmonary *Mycobacterium tuberculosis* infection occurred in 36, lymph node disease in nine, and bone in three. Cervical node infection was seen with *M avium-intracellulare* (seven), *M scrofulaceum* (one), and *M chelonei* (one). The number of cases in the last three years 1988–90 (17) showed no decline from the first three years 1981–3 (eight) or indeed the last three years of the preceding decade 1978–80 (11). This was despite the institution in 1980 of a BCG vaccination policy for all neonates, new child immigrants, and 12–14 year olds. Uptake of neonatal BCG is 70–80%, but only 13 (23%) of our patients were vaccinated and only four of these (7% of total) had been vaccinated neonatally. Twenty three (47%) cases at QEH were in non-Asian children (11 white, 11 Afro-Caribbean, five non-Asian mixed race). Local trends have not followed the national decline in tuberculosis. BCG vaccination of children in areas such as ours should continue and should be given in the neonatal period; it should be offered to all children regardless of whether they seem to fall into a high risk group. In areas with such high population mobility, however, a neonatal BCG policy is not enough to protect the child population. Efforts must be directed not only at increasing the proportion of vaccinated neonates but also at the prompt identification and tuberculin testing of new child arrivals in the area.

Childhood non-tuberculous cervical lymphadenitis

A COLVILLE, MJ BAKER (this abstract is sponsored by IDA Johnstone) *Public Health Laboratory, University Hospital, Queen's Medical Centre, Nottingham* Childhood mycobacterial lymphadenitis in Britain is usually caused by non-tuberculous mycobacteria. The recommended treatment is complete excision alone. Diagnosis must be confirmed by culture as histology cannot distinguish *Mycobacterium tuberculosis* from other mycobacteria. We reviewed 21 consecutive cases of culture positive cervical lymphadenitis in children in Nottingham during 1979–90. Six cases were tuberculous from an epidemiologically distinct outbreak. The remainder were: *M avium-intracellulare*, four *M malmoense* and one *M kansasii*. None were in Asians. Mean age was 5 (range 1–14), six boys and nine girls. All patients were systemically well with normal results on investigations except for the patient with *M kansasii*, who was febrile with hilar lymphadenopathy. Differential Mantoux testing with avium-intracellulare antigen and human purified protein derivative (PPD) correctly identified *M avium-intracellulare* infection when used. Human PPD alone was not helpful. Cultures took 25 to 81 days (mean 55), at which time their non-tuberculous identity was recognised. Antituberculous drugs were used in nine non-tuberculous infections from one to 14 months. Five were formally notified and contacts examined. Repeat excision was required five times. Outcome was uniformly good irrespective of chemotherapy. In childhood mycobacterial cervical lymphadenitis in non-Asians, antituberculous chemotherapy, and notification should be delayed until microbiological results are available. If the patient is systemically well the initial treatment should be complete excision alone.

Self image in adolescents with cystic fibrosis

M BAUM, D BOLDY, G GARDEN, DE STABLEFORTH *Medical School, University of Birmingham, Birmingham, and Department of Respiratory Medicine, East Birmingham Hospital, Birmingham, and West Midlands Poisons Unit, Dudley Road Hospital, Birmingham* The outlook for patients with cystic fibrosis (CF) continues to improve. Despite this, many individuals do not reach their ideal body weight in adult life, and the long term prognosis is poor. For patients with CF awareness of disease related problems and of prognosis might exacerbate the normal psychological stresses of adolescence. For this reason we undertook a study of self image and body satisfaction in three groups of adolescents aged 16–19: 31 patients with CF (16 male; 16 female), 16 patients with insulin dependent diabetes mellitus (seven male, nine female), and 69 normal adolescents (31 male, 38 female). All subjects completed the offer self image questionnaire (OSI), comprising 130 items covering many areas of adolescent functionings (*Arch Gen Psychiatry* 1972;27:529), and the body satisfaction scale (BSS) measuring satisfaction with 16 body parts, confined general, head, and body scales (*Psychology and Health* 1990;4:213). Female adolescents with CF were significantly better adjusted than normal adolescents in the impulse control scale of the OSI ($p=0·013$) and had a higher general ($p=0·0021$) and body ($p=0·0407$) satisfaction score. There were no significant differences between female patients with CF and female patients with diabetes, or between any of the male groups. Thus despite their physical problems there is no evidence that adolescents with CF have more problems with self esteem than normal adolescents or those with insulin dependent diabetes mellitus.

Cost of caring for adults with cystic fibrosis in a specialist unit

M ROBSON, J ABBOTT, M DODD, AK WEBB *Adult Cystic Fibrosis Unit, Monsall Hospital, Manchester* This study represents an extensive cost description of a regional adult cystic fibrosis (CF) centre and a cost analysis of types of patients with CF, categorised by treatment regimen. The work fulfills the information requirements of the white paper *Working for Patients*. District health authority, family health service authority, and voluntary resources utilised between April 1989 and March 1990 were evaluated by using appropriate allocation bases and "bottom up" local information. During this time 119 patients who regularly attended the centre were studied. The total annual cost (NHS and voluntary resources) of treating these patients amounted to £980 652·60, with an average cost of £8240·78 per patient. Patients were categorised by four treatment regimens. An outpatient receiving three monthly examinations cost £2791·83 per annum; an outpatient receiving intravenous antibiotics consumed £8746·41 of resources; a patient admitted to hospital for intravenous antibiotic treatment cost £13 501·33; and a high care patient cost £19 955·89. Such detailed cost analyses have enabled the unit to acquire a separate contract and facilitates the prediction of future requirements. The work also highlights the problem of using average patient costs and the difficulties incurred because of the nature of the NHS accounting and information systems.

Compliance with nebulised colistin in adults with cystic fibrosis

J MADDISON, M DODD, AK WEBB *Adult Cystic Fibrosis Unit, Monsall Hospital, Manchester* The relation between the bronchoconstrictor response to nebulised colistin and compliance was assessed in 46 adults with cystic fibrosis. Spirometry was performed immediately and 15 and 30 minutes after administration of 2 million units of colistin nebulised in 4 ml normal saline. Each patient received a bronchodilator and chest physiotherapy before their colistin challenge. There was a positive correlation between increasing severity of airways disease (FEV_1, percentage of predicted values) and the percentage fall of FEV_1 to colistin ($r=0·42$, $p=0·01$). The mean percentage fall of FEV_1 to colistin in those with severe disease (FEV_1 <45% predicted; $n=20$) exceeded that in patients with moderate/mild disease (FEV_1 >45% predicted; $n=26$) ($p=0·02$). No significant difference in the mean percentage fall in FEV_1 to colistin could be shown between those with reversible airways disease (rise in FEV_1 >15% to bronchodilators; $n=14$) and those with irreversible airways disease ($n=31$) ($p=0·236$). Non-compliance with colistin was significantly greater in those with severe airways disease (10/20) than in those with mild/moderate disease (5/26) ($p=0·015$). The non-compliant patients with severe disease did not have a significantly greater mean percentage fall in FEV_1 to colistin than those who complied ($p=0·186$), and there was no difference in the proportion of patients with reversible or irreversible disease in the two groups. Non-compliant patients with mild/moderate airways disease had a significantly greater mean fall to colistin (18·6% FEV_1) than those who complied (4·2% FEV_1) ($p=0·025$), but there was no difference in bronchodilator response between these two groups. Failure to comply with nebulised colistin is greater in those with severe airways disease, but there is no significant difference in bronchoconstriction between compliant and non-compliant patients in this group. Non-compliant patients with mild/moderate airways disease have a greater bronchoconstrictor response to colistin than compliant patients.

Pseudomonas cepacia: pulmonary infection in patients with cystic fibrosis

RFH TAYLOR, H GAYA, ME HODSON *Royal Brompton Hospital, London* This retrospective study reviews the pattern of *Pseudomonas cepacia* pulmonary infection found in 75 out of a total of 872 mainly adult patients with cystic fibrosis (CF) registered here during the four years 1987–90; 35 (47%) were female. During this period 55 patients acquired *P*

cepacia, and the annual incidence and prevalence remained between 1·6% and 3·1% and 4·1% and 5·9% respectively. The mean age at the time of the first isolation of *P cepacia* was 23 years, ranging from 11–45 years. *P cepacia* was isolated for the first time from five patients after an interval of 10 or more days following a hospital admission and from 15 patients who had been admitted here during the previous three months. In all, 68% of the initial isolates were multiresistant (sensitive to fewer than three out of 15 antipseudomonal agents). Before acquisition of *P cepacia* 28 (50·9%) patients already had severe lung disease and only three had normal lung function. Infection was transient in 39·1% of patients. Initial multiresistance of *P cepacia* to antipseudomonal agents was significantly associated with persistent infection. Clinical outcome was unaffected by age, sex, and early intravenous antibiotic treatment but significantly adversely affected by increasing severity of lung disease at the onset of *P cepacia* infection and by initial multiresistance and persistence of the organism. Thus all patients with normal or mild lung disease at the onset of infection remained clinically stable whereas only six out of 28 patients with severe disease remained stable, three of whom were transiently infected with *P cepacia*. The prevalence of *P cepacia* at the time of death fluctuated between 12·5% and 26·9% during the study period. Twenty three of the 75 patients died from pulmonary disease associated with *P cepacia*; the mean interval between initial isolation of *P cepacia* and death was 44 weeks.

Influenza vaccination in adults with cystic fibrosis: further analysis of serological responses

E ONG, D BILTON, J ABBOTT, K WEBB, M ELLIS, R McGARTNEY, O CAUL *Department of Infectious Diseases and Adult Cystic Fibrosis Unit, Manchester, and Public Health Laboratory Service, Bristol* We previously reported the preliminary results of the effect on clinical state and antibody response of influenzae vaccination in adults with cystic fibrosis (CF) (*Thorax* 1990;45:326P), we showed that the MFV-JECT vaccine (Merieux UK) was well tolerated by patients with CF and healthy volunteers. We have since studied 52 patients with CF (28 male, 24 female, mean age 24) and 22 healthy volunteers (14 female, eight male, mean age 44) over a period of two winter seasons (October–December 1988 and 1989). Thirty patients and 22 controls studied in 1988 showed no differences in their daily symptom score of temperature, headache, nausea, cough, or pain at site of injection over 14 days. Patients showed a significant increase in their peak expiratory flow measurement during the study period ($p < 0·05$). Twenty five (83%) patients and 16 (73%) controls had a serological response in antibody titres as measured by a single radial haemolysis (SRH) test to all three vaccine strains (A/Taiwan (H_1N_1) $p < 0·001$, A/Sichuan (H_3N_2) $p < 0·001$, B/Bejing $p < 0·001$; paired t test), with patients showing a greater change in value than did controls. An increase of > 1 mm in zone diameter between two paired samples was considered to be indicative of a response to the vaccine. Only one patient and no controls had intermediate to high antibody titre to A/Sichuan (H_3N_2) before vaccination in 1988. The majority of these patients (18 (82%) to A/Mississippi (H_3N_2), seven (32%) to A/Sichuan (H_3N_2), 15 (68%) to A/Tiawan (H_1N_1)) had maintained residual intermediate to high antibody titres (SRH $> 5·5$ mm for H_3N_2, SRH $> 6·5$ mm for H_1N_1) when studied 12 months later. Twenty two new patients were vaccinated in 1989, 18 (82%) had an intermediate to high antibody response to A/Mississippi, nine (41%) and 16 (73%) patients responded similarly to A/Sichuan and A/Tiawan respectively. Patients with CF responded well to influenza vaccine producing titres of antibody associated with an increased level of protection shown previously.

Host inflammatory responses to first culture of *Pseudomonas aeruginosa* in cystic fibrosis

JS ELBORN, SM CORDON, EJ HILLER, DJ SHALE *Respiratory Medicine Unit, University of Nottingham, and Department of Paediatrics, Nottingham City Hospital, Nottingham* The host response during early pulmonary colonisation with *Pseudomonas aeruginosa* (PA) in patients with cystic fibrosis (CF) is not clearly defined. In this study we followed six patients aged 18 to 22 years, who had had CF for one to three years during which time their sputum changed from being culture negative to PA to culture positive with raised antibodies to PA detectable. A total of 89 samples were available for measurement of antibodies to PA and of two makers of the host response—C reactive protein (CRP) and neutrophil elastase α-1-antitrypsin complex (NEC). Before sputum positivity for PA, when antibodies to PA were within the normal range, CRP and NEC were 5·8 (SD 1·8) μg/ml and 0·24 (0·05) μg/ml respectively, which is within the normal range for both. At the time of first sputum culture at 4–44 weeks after the first blood sample both increased significantly (CRP 17·2 (13·0) μg/ml ($p < 0·05$) and NEC 0·57 (0·34) μg/ml ($p < 0·05$)). Antibodies to PA became positive one to 10 months after first culture of PA and at that time CRP concentration was not significantly greater compared with the first sample (8·4 (6·4) μg/ml) whereas NEC was still increased (0·37 (0·15) μg/ml) ($p < 0·05$). This study shows that at the time of first sputum culture PA causes a significant host response. NEC is raised at this time and thereafter. As this may reflect lung injury, appropriate antibiotic treatment may be of benefit from the time of the first culture of PA.

Survey of adult cystic fibrosis services in Mersey region

MJ WALSHAW, D HEAF, CC EVANS, CRK HIND *Alder Hey Children's Hospital and the Cardiothoracic Centre, Liverpool* As a result of better clinical care, survival in cystic fibrosis (CF) is improving rapidly. The Royal College of Physicians of London (RCP) has therefore recommended that each region in the United Kingdom should have at least one CF centre with responsibility and facilities for the care of adult patients (defined as those above the age of 16 years). There are estimated to be about 2000 adult patients with CF alive in 1991 in England and Wales. Based on population numbers, about 102 of these should be resident within the area served by Mersey Regional Health Authority. We surveyed what facilities are at present provided within the region for this patient group. Thirty eight patients (mean age 21 years, range 17–28, 17 male) still attend a paediatric regional CF unit at a children's hospital, where there are no adequate facilities for their inpatient care and no input from adult physicians. A further 11 patients (mean age 27 years, range 22–33, seven male) attend a local district general hospital chest clinic; two of these have shared care with the paediatric regional CF unit and one further patient with the Brompton Hospital. In all, it was possible to identify 49 adult patients with CF for whom a service was provided within the Mersey region, although in no case did this comply with the guidelines produced by the RCP. Furthermore, we found no specific facilities provided for the remaining estimated 53 adult patients with CF within the region. This survey highlights the deficiencies of the service within Mersey region provided for adult patients with CF, whose outcome as a result may be disadvantaged.

Epidemiology of *Pseudomonas aeruginosa*: use of two genetic probes in a summer camp study

DL SMITH, EG SMITH, DE STABLEFORTH, LM DALA COSTA, PN NICHOLSON *Adult Cystic Fibrosis Unit and Department of Microbiology, East Birmingham Hospital, Birmingham, and Division of Hospital Infection, Central Public Health Laboratory, London* *Pseudomonas aeruginosa* (PA) is the organism most commonly cultured from the sputum of adult patients with cystic fibrosis (CF). Despite intensive study the risks of cross infection between patients remain unclear. Recent gene probe systems have greatly increased the accuracy of strain identification. We used a novel dual probe approach in the study of 13 adult patients with CF and pseudomonas infection in a summer camp. Sputum samples were collected from 15 patients with CF at the beginning and the end of a week long activity holiday. In 13 patients PA was cultured from both samples. Isolates were typed with two genetic probe systems: rRNA *Escherichia coli* (ribotyping) and the Tox DNA probe of PA. Two pairs of patients showed the same strain before and after the holiday, the remaining nine patients showed unique strains. In three cases the PA strain changed during the one week period of study to another unique strain; in all other patients pre and post strains were individually identical. No evidence of cross infection between patients during the holiday was found, although the existence of identical strains in two pairs of patients before the study who were not related suggests either previous cross infection or acquisition from a common environmental source. Further studies of a subsequent holiday and of strain stability within individual patients are underway. (DLS is supported by the Cystic Fibrosis Research Trust.)

Once daily netilmicin in cystic fibrosis

DL SMITH, DE STABLEFORTH *Adult Cystic Fibrosis Unit, East Birmingham Hospital, Birmingham* Recent research into the mode of action of aminoglycoside antibiotics has suggested that once daily (OD) dosing regimens are as effective as, and possibly less toxic than, traditional three times daily (TDS) regimens in the treatment of a variety of infections due principally to concentration dependent killing, post antibiotic effect (PAE), and sub MIC effects. We investigated the pharmacokinetics of OD netilmicin in 10 patients with cystic fibrosis, (CF) and its efficacy in eight of these. Netilmicin was given OD in a dose of 8 mg/kg as a 30 minute infusion to eight patients with CF (six male,

mean age (SD) 21·8 (1·8) years) in combination with a β-lactam given TDS for the treatment of a pulmonary exacerbation due to *Pseudomonas aeruginosa* infection. Pharmacokinetic studies showed wide variations in drug handling. Peak values of netilmicin (end of infusion) ranged from 29·2 to 59·5 μg/ml (mean 47·3 (SD 10)). Serum half life ranged from 95 to 205 minutes (145 (37)). No drug accumulation was seen (trough levels at 24 h all <0·3 μg/ml). Three patients were withdrawn from the study, two because of transient vestibular toxicity. Five patients completed two weeks' treatment with OD netilmicin. Audiometric studies showed no changes in hearing threshold at the end of treatment or at one month follow up. Serial serum creatinine concentrations remained stable. Treatment was clinically effective in all cases; pretreatment mean FEV_1/FVC 1·2/2·5, post treatment mean 1·5/3·0 litres. Two patients subsequently received OD netilmicin as a 60 minute infusion with a consequent mean reduction in peak values of 14·2% (4·0). OD netilmicin may be useful in the treatment of *Pseudomonas aeruginosa* infection in CF but the correct dose for individual patients is difficult to assess. This work was supported by a grant from Schering-Plough. (DLS is supported by the Cystic Fibrosis Research Trust.)

Immunohistology of bronchial mucosa in intrinsic asthma

AM BENTLEY, G MENZ, C STORZ, SR DURHAM, AB KAY *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London, and Hochgebirgsklinik Davos-Wolfgang, Switzerland* We obtained fibreoptic bronchoscopic mucosal biopsy samples from 10 subjects with intrinsic asthma (I). The phenotype and activation status of leucocytes in the bronchial mucosa were compared with those of seven subjects with extrinsic asthma (E) and 12 normal healthy controls (N). Immunohistology was performed with a modified alkaline phosphatase antialkaline phosphatase method (APAAP). Cell counts in the bronchial mucosa of asthmatic subjects compared with normal subjects (Mann-Whitney U test) were as shown in the table below. In patients with intrinsic asthma there was a pronounced mononuclear cell infiltrate predominantly of lymphocytes. Comparable findings of T cell and eosinophil activation were observed in both intrinsic and extrinsic asthma. These data support the hypothesis that T cell-eosinophil interactions are important in asthma of diverse aetiology.

	Median cells/mm basement membrane		
	I	*E*	*N*
CD45	122*	79	58
CD3	78***	39	37
CD4	51*	25	19
CD8	5	1	0
CD25 (IL-2R)	2***	0·5**	0
EG2	22***	23***	0
BMK13 (MBP)	38***	20	3
Macrophages (CD68)	33*	7	11
Neutrophils (elastase)	21	13	17

*p < 0·03, **p < 0·02, ***p < 0·01.

Effect of topical fluticasone propionate on allergen induced inflammatory cell changes in the nose

JH WANG, J DUDDLE, KE THOMAS, S LOZEWICZ, JL DEVALIA, G RILEY, RJ DAVIES *Department of Respiratory Medicine and Ear, Nose, and Throat, St Bartholomew's Hospital, London* During the early phase of the nasal allergic response there is transient infiltration of the nasal mucosa by eosinophils and degranulation of mast cells. We studied the effects of topically applied fluticasone propionate (FP) on inflammatory cellular infiltration in the nasal mucous membrane during both the early and the late phase nasal allergic reaction. Forty two patients with seasonal allergic rhinitis to grass pollen were studied in a double blind placebo controlled crossover study in which patients underwent treatment for two weeks with FP 200 μg daily or placebo. There was then a washout period of one month before treatment with the alternative agent for two weeks. At the end of each treatment period patients underwent provocation of one nostril with grass pollen followed by biopsy of the nasal mucous membrane at one of several time points between 0 and 8 hours. The specimens were investigated by immunohistochemistry using monoclonal antibodies (MAb) EG1 and EG2 for eosinophil numbers and activation state respectively. During the immediate allergic response there was a transient influx of eosinophils stained by EG1 after both placebo and FP treatment; median values increased from 5·2 to 50·0 cells/mm² for placebo and from 6·7 to 42·5 cells/mm² for FP. However, FP led to a significant attenuation ($p < 0·02$) of EG2 staining cells as compared with placebo (median values of 8·8 and 36·6 cells/mm², respectively) during the early phase response. These results suggest that topical FP reduces the numbers of activated eosinophils infiltrating the nasal mucosa during the immediate allergic reaction.

Infiltration by lymphocytes in nasal mucous membrane in allergic rhinitis

M CALDERON, S JORDAN, S LOZEWICZ, AJ d'ARDENNE, RJ DAVIES *Departments of Respiratory Medicine and Immunohistochemistry, St Bartholomew's Hospital, London* T lymphocyte products may have an important role in the generation and regulation of allergic inflammation through the effects of T cell lymphokines. We used immunocytochemical techniques to study infiltration by lymphocytes in biopsy samples of the nasal mucous membrane in 14 atopic patients. Seven had perennial rhinitis (PR), and seven seasonal allergic rhinitis to grass pollen (SR). In the patients with SR, samples were taken both in and out of season. Biopsy samples were stained using the indirect immunoperoxidase technique and monoclonal antibodies to CD3 (total T cell); CD4 (helper T cell); CD8 (suppressor T cell); CD25 (activated T cell), and CD22 (total B cell). The density of cellular infiltrate in each section was graded with a semiquantitative scale as follows: 0 (no cells), 1 (< 20 cells/mm²), 2 (20–40 cells/mm²) and 3 (> 40 cells/mm²). In both PR and SR total T lymphocytes (CD3) were significantly more numerous than total B cells (CD22) ($p < 0·01$). T helper cells were significantly more numerous in specimens from patients with PR (median 1, range 1–2) than in specimens from patients with SR out of season (median 0, range 0–1) ($p < 0·05$); corresponding values for SR in season were intermediate (median 1, range 0–2). There were more CD25 positive cells in PR specimens (median 1, range 0–2) compared with SR out of season (median 0, range 0–1; $p < 0·02$). These results suggest that in allergic rhinitis patients with perennial symptoms show a greater degree of nasal infiltration by T helper cells than do patients who have only seasonal exposure to allergen.

Bronchial biopsy specimens after endobronchial allergen challenge in asthma

M CARROLL, C GRATZIOU, L SMITH, P HOWARTH, ST HOLGATE *Immunopharmacology Group, University of Southampton, Southampton* Local allergen challenge of the airways was performed via bronchoscopy in 10 patients with mild atopic asthma. The right middle lobe (RML) was challenged with allergen diluted in 20 ml of normal saline. The right upper lobe (RUL) was used as a control area and challenged with 20 ml of normal saline. For comparison the same procedure was performed in 10 normal subjects. In all asthmatic subjects a visible bronchoconstriction was seen 1–2 minutes after instillation of allergens into the RML. In contrast, no bronchial narrowing was seen in the RUL of asthmatic airways or in either area in the normal subjects. Ten minutes after instillation of allergen or normal saline a bronchial biopsy sample was taken. The samples were immunostained with monoclonal antibodies reactive with mast cells, T cells, and eosinophils. In addition, the ultrastructural appearance of mast cells and eosinophils was analysed by electron microscopy. Immunocytochemical analysis showed no significant difference in the number of epithelial mast cells, lymphocytes, or oesinophils. However, the electron microscopic appearance of mast cells were of greater degranulation in the allergen challenged area of asthmatic airways. Eosinophils showed no ultrastructural differences when the challenged area was compared with the control area. These results suggest that at 10 minutes there is no evidence to support an increase in inflammatory infiltration, but they implicate degranulation of resident mast cells in the allergen induced asthmatic reactions.

Sodium absorption and regulation of chloride secretion in murine trachea

S SMITH, EWFW ALTON, DM GEDDES *Ion Transport Laboratory, National Heart and Lung Institute, London* With the discovery of the cystic fibrosis (CF) gene, a CF transgenic mouse may soon be available. The characteristic defect in CF is an inability to secrete chloride in response to stimulation of protein kinase A or C pathways, but with a normal response to raised intracellular calcium concentrations. We therefore characterised these responses of the normal murine trachea mounted in mini-Ussing chambers. Amiloride (10 μM) pretreatment produced a mean (SE) fall in potential difference (PD) of 56·3% (2·6%) (n = 17). The tissues were then stimulated with forskolin (1 μM) and zardaverine (10 μM) to increase cAMP, phorbol dibutyrate (10 μM) to stimulate protein kinase C, or the calcium ionophore A23187 (10 μM). These interventions resulted in mean rises in PD of 493·6% (n = 5), 279%

(n = 5), and 1037% (n = 6) respectively. After these interventions further addition of bumetanide (100 μM), an inhibitor of chloride entry, produced an inhibition of 46·7% (3·5%) of the stimulated current (n = 15). We conclude that mouse trachea is principally sodium absorbing and possesses a chloride secretory response that can be stimulated by all three second messenger pathways. We are therefore now able to compare these characteristics with the projected defects in a CF mouse.

Prostaglandin D_2 induced nasal blockage is not mediated by the thromboxane receptor

SL JOHNSTON, S SMITH, W RITTER, PH HOWARTH *Immunopharmacology Group, Southampton General Hospital, Southampton, and Bayer AG, Wuppertal, Germany* There is now considerable evidence to implicate prostaglandin (PG) D_2 in the genesis of nasal blockage in allergic rhinitis: (*a*) H_1 receptor antagonists reduce rhinorrhoea and sneezing, but have no effect on nasal blockage; (*b*) the addition of fluribprofen relieves nasal blockage; (*c*) nasal insufflation of PGD_2 results in nasal blockage; and (*d*) PGD_2 is the major prostanoid released from mast cells on immunologic challenge, and mast cells migrate to the nasal mucosa during seasonal allergen exposure. PGD_2 is known to act via at least two receptors, the thromboxane (TP) and the PGD_2 (DP) receptors, with the lower airway effects being mediated chiefly by TP. BAY U 3405 is a selective competitive TP receptor antagonist that has been shown to inhibit the lower airway response to PGD_2 by 3·5 doubling dilutions. The efficacy of single oral doses of BAY U 3405 was examined in PGD_2 induced nasal blockage in a randomised, double blind placebo controlled crossover study. Seven asthmatic and three non-asthmatic subjects (nine atopic) underwent PGD_2 dose-response challenge on two occasions after fasting for four hours after having been given premedication with either 20 mg BAY U 3405 (A) or placebo (P), with objective measurement by active posterior rhinomanometry. The challenge was started 20 minutes after ingestion to ensure that the higher concentrations of agonist were being administered to coincide with peak plasma concentrations of BAY U 3405 at around 60–120 minutes. Blood was taken for measurement of serum values of BAY U 3405 one hour after ingestion. Wilcoxon's signed ranks test was used for statistical analysis. There were no significant differences in baseline nasal resistance or in the response to vehicle challenge on the two treatment days. The PD_{200} PGD_2 (the dose required to produce an increase in nasal resistance of 200% over vehicle response) median values, 20·97 nM/nostril (A) and 21·67 nM/nostril (P), were not statistically different, nor were the areas under the dose-response curves for the two treatments. The median plasma BAY U 3405 concentration at one hour after ingestion was 82 ng/ml, which is comparable with the values in the airway study at the same time point (median 92 ng/ml), bearing in mind that plasma concentrations of only 5–10 ng/ml are required to achieve full inhibition of platelet aggregation induced by stimulation of the TP receptor. We conclude that the TP receptor does not mediate the nasal effects of PGD_2.

Bronchoconstriction and leukotriene production after inhaled platelet activating factor (PAF): abolition by an oral PAF antagonist, UK,74505

BJ O'CONNOR, SM RIDGE, YM CHEN-WORSDELL, S UDEN, PJ BARNES, KF CHUNG *National Heart and Lung Institute, Royal Brompton Hospital, London, and Pfizer Clinical Research, Sandwich, Kent* Inhaled platelet activating factor (PAF) provokes bronchoconstriction and stimulates leukotriene (LT) production in humans. We examined the effects of an oral PAF antagonist UK,74505 on each of these responses to a single 30 μg dose of inhaled PAF. In a double blind randomised crossover study 12 normal male subjects inhaled PAF three and 24 hours after intake of two doses of UK,74505 25 mg and 100 mg or matched placebo (P). Airway calibre was measured as airways conductance (sGaw) before (baseline) and at 3, 5, 10, 15, 30, 45, and 60 minutes after PAF. Changes in sGaw from baseline were calculated and results measured as area under the curve (AUC). Urine was collected for two hours after the first PAF challenge and analysed for LTE_4, the stable metabolite of LTC_4 and LTD_4 and an index of endogenous LT production. Inhalation of PAF after P stimulated urinary LTE_4 excretion and induced bronchoconstriction which was maximal at five minutes but had receded at one hour. These responses to the first PAF challenge were abolished by both doses of UK,74505. In addition, the higher dose inhibited the airway effects of PAF at 24 hours (table below, showing mean (SE) values). Thus UK,74505 is a potent inhibitor of PAF induced bronchoconstriction and LT production with a duration of action of up to 24 hours at the higher dose. Generation of sulphidopeptide LTs may be implicated in the effects of inhaled PAF.

			UK,74505	
		P	25 mg	100 mg
sGaw (AUC value)	3 h	18·9 (3·1)	−2·0 (3·0)*	−2·8 (3·3)*
	24 h	12·1 (2·9)	4·1 (2·4)	0·0 (2·4)*
Urinary LTE_4 (ng/mg creatinine)		1·62 (0·50)	0·04 (0·02)*	0·12 (0·07)*

*p < 0·01.

Nedocromil sodium blocks eosinophil induced attenuation of ciliary beat frequency of human nasal epithelial cells in vitro

RJ SAPSFORD, C RUSZNAK, JL DEVALIA, RJ DAVIES *St Bartholomew's Hospital, London* Studies by Gleich and colleagues, in particular, have suggested that the eosinophil is the chief effector cell of epithelial damage and may have an important role in the pathogenesis of asthma. We cultured human nasal epithelial cells (HNE) and, firstly, studied the effect of either stimulated or unstimulated human eosinophils on the ciliary beat frequency (CBF) of these cells and, secondly, investigated the effect of 10 μM nedocromil sodium (N) treatment on the eosinophil induced changes in the CBF. Eosinophil preparations of greater than 85% purity were cocultured with 2–3 week old cultures of HNE in the absence or presence of either 0·1 μM phorbol 12-myristate 13-acetate (PMA) or 0·1 mg/ml opsonised latex beads (LB) and the absence or presence of N. The HNE were monitored for CBF at the beginning and at several times during culture; at the end of the culture period the medium and the eosinophil cell pellet were collected and analysed for eosinophil cationic protein (ECP). Although PMA, LB, and eosinophils alone did not alter the CBF, both PMA and LB stimulated eosinophils respectively attenuated the CBF significantly from 10·2 (0·4) Hz to 8·9 (0·5) Hz ($p < 0·05$) and 9·6 (0·1) to 6·5 (0·2) Hz ($p < 0·001$), after 15 hours. N abrogated the PMA stimulated eosinophil effect immediately and the LB stimulated eosinophil effect by 24 hours, of which the latter could be abroaged immediately by preincubating the HNE with N for 20 minutes. Though PMA did not induce the release of ECP above control values (5–7% of total), LB induced the release of between 40% and 50% of total ECP, which was blocked by N treatment. These data suggest that "activated" eosinophils may lead to airway epithelial cell dysfunction through different mechanisms, which may be presented by agents such as N.

Influence of salbutamol and salmeterol on ciliary beat frequency of cultured human bronchial epithelial cells

C RUSZNAK, RJ SAPSFORD, JL DEVALIA, RJ DAVIES *Department of Respiratory Medicine, St Bartholomew's Hospital, London* Several studies have suggested that adrenergic agents may significantly influence mucociliary clearance and therefore play a vital part in the maintenance of functional integrity of the airways. We cultured human bronchial epithelial cells from surgical explants and investigated the effects of salbutamol and salmeterol on the ciliary beat frequency (CBF) of these cells. Before and at several times after exposure to either salbutamol (10^{-3}M to 10^{-8}M) or salmeterol (10^{-4}M to 10^{-8}M) cultures of HBE were monitored for CBF; on the basis of data obtained from these studies, the effect of 1 μM propranolol was investigated in the presence of optimal concentrations of salbutamol and salmeterol. Although salbutamol caused a transient increase in CBF at concentrations of 10^{-4}M—10^{-6}M after two hours incubation, this was significant only at 10^{-4}M, increasing baseline values from 8·6 (0·4) Hz to 9·6 (0·5) Hz ($p < 0·05$). In contrast, salmeterol caused a significantly rapid and prolonged increase in CBF at all concentrations from 10^{-5}M to 10^{-8}M ($p < 0·05$). This agent was maximally active at a concentration of 10^{-6}M and increased the CBF from baseline values of 9·2 (0·4) Hz to 10·9 (0·6) Hz ($p < 0·02$) and to 10·3 (0·6) Hz ($p < 0·02$) by 15 minutes and 15 hours, respectively. Incubation in the presence of propranolol abrogated the salbutamol but not the salmeterol induced increases in CBF.

Prognostic value of monocyte function in patients with small cell lung cancer

HSR HOSKER, P McARDLE, PA CORRIS *Departments of Respiratory Medicine and Haematology, Freeman Hospital, Newcastle upon Tyne* A chemiluminescence (CL)

assay was used to assess blood monocyte function in 25 patients with small cell lung cancer (SCLC) at diagnosis and in 20 control subjects. Lucigenin was used as the probe and latex beads as the stimulus. Assays were repeated six weeks later in 22 patients with SCLC immediately before the third pulse of cytotoxic chemotherapy (CT) comprising cyclophosphamide, doxorubicin, etoposide, and vincristine. CL responses in the SCLC group at diagnosis were slightly higher than those in the control group. The seven patients with extensive stage SCLC had depressed monocyte CL responses compared with 18 patients with limited disease ($p < 0.02$). Monocyte function at diagnosis showed a correlation with subsequent clinical response to CT and to survival time ($n=24$; $r=0.48$; $p < 0.02$). In the SCLC group as a whole there was no difference in CL response before and during CT. However, monocyte function improved in those making a good response to CT, and fell in those making a poor response, so that function during treatment showed a stronger correlation with survival ($n=21$; $r=0.54$; $p < 0.02$). The percentage change in function ("overshoot") for individual patients showed the strongest correlation with survival ($n=18$; $r=0.57$; $p < 0.02$). These results suggest that monocyte function at diagnosis and the change in monocyte function after treatment are prognostic markers and may be important in determining outcome in patients with SCLC.

Effects of aminophylline and terbutaline on proteolysis and superoxide generation by neutrophils

C LLEWELLYN-JONES, RA STOCKLEY *Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* Neutrophils (PMN) have been widely implicated in the pathogenesis of chronic destructive lung diseases by the release of toxic substances such as superoxide ions (O_2^-) and elastase. Mature neutrophil functions such as O_2^- generation and degranulation are associated with alterations in concentrations of cyclic nucleotides. Thus therapeutic agents which raise cAMP concentrations may also alter the destructive potential of PMN. Aminophylline related compounds and β_2 agonists are regularly prescribed in these lung diseases and are associated with increased intracellular cAMP concentrations. For this reason we studied the effect of aminophylline and terbutaline across the therapeutic range on O_2^- generation, and proteolysis of ^{125}I fibronectin labelled with iodine-125 as an assessment of neutrophil degranulation. Preincubation of PMN in separate experiments with aminophylline and terbutaline increased spontaneous O_2^- production in a dose dependent manner from 2·12 nmoles/10^6 cells/h (SE 0·53) to 2·71 nmoles (0·58) ($p < 0.001$) with aminophylline (20 mg/l) and from 1·48 nmoles (0·44) to 1·76 nmoles (0·46) ($p < 0.01$) with terbutaline (4 mg/l). Similarly, both agents increased O_2^- production when PMN were stimulated with 10^{-6} M FMLP from 4·43 nmoles (1·1) to 5·23 nmoles (0·95) ($p < 0.01$) with aminophylline (20 mg/l) and from 3·12 nmoles (1·9) to 3·77 nmoles (0·9) ($p < 0.02$) with terbutaline 4 mg/l). Neutrophil proteolysis was not affected by either agent in the absence or presence of 10^{-6} M FMLP. These results suggest that β_2 agonists and aminophylline related compounds can increase O_2^- production by healthy PMN in vitro. However, as most lung damage is believed to be mediated by release of proteinases these therapeutic agents may not affect the pathogenesis of chronic destructive lung diseases adversely.

Blood neutrophil and monocyte function after treatment with cytotoxic chemotherapy in patients with small cell lung cancer

HSR HOSKER, Y SCOTT, P KESTEVEN, PA CORRIS *Departments of Respiratory Medicine and Haematology, Freeman Hospital, Newcastle upon Tyne* A latex stimulated chemiluminescence (CL) assay was used to assess blood neutrophil and monocyte function during cytotoxic chemotherapy (cyclophosphamide, doxorubicin, etoposide, and vincristine) in patients with small cell lung cancer. Six patients underwent sequential neutrophil (N) studies before treatment (day 0) and on days 1, 3, 10, 21, and 42 after chemotherapy. Eleven patients similarly underwent monocyte (M) studies. Luminol was used as the probe for the N studies and lucigenin for the M studies. Results showed a marked depression of cell function between cycles of chemotherapy that was independent of cell numbers. Maximal suppression occurred at 10 days after chemotherapy to 10–15% of pretreatment values ($p < 0.01$ for N studies, $p < 0.001$ for M studies). Cell function returned towards pretreatment values 21 days after chemotherapy, at the time of the second cycle of treatment. Function at 42 days (21 days after the second cycle) was also normal. Nitroblue tetrazolium (NBT) tests performed on neutrophils showed a minor fall in uptake from a mean of 97% (day 0) to 89% on day 10. A significant eosinophilia of 10–20% was also noted on neutrophil cytospin preparations at day 10 in five of the six patients. Monocytes, but not neutrophils, showed "rebound overshoot" of CL responses at 21 days and 42 days which was most marked in patients who subsequently had a good response to treatment. These results indicate a profound but reversible depression in N and M function after cytotoxic chemotherapy. Recovery of function occurs 21 days after chemotherapy, providing a rationale for the use of three weekly cycles of chemotherapy.

Differences between in vivo and in vitro release of antimicrobials from alveolar macrophages

DR BALDWIN, R WISE, JM ANDREWS, D HONEYBOURNE *Departments of Thoracic Medicine and Medical Microbiology, Dudley Road Hospital, Birmingham* Release of many antimicrobials from phagocytes in vitro is rapid and complete within 10 minutes. We present here evidence that release is reduced in vivo as well as a possible explanation for the contrast with in vitro work. A total of 86 patients undergoing fibreoptic bronchoscopy received either amoxycillin, azithromycin, ciprofloxacin, lomefloxacin, temafloxacin sparfloxacin, or cefpirome. Bronchoalveolar lavage (BAL) fluid was used to determine the concentrations achieved in alveolar macrophages (AM) and in BAL supernatant. In vitro studies would predict efflux of antimicrobial from AM during BAL, but to ensure adequate time for efflux the separation of cells from the supernatant was delayed for 20 minutes in 10 patients. Release of radiolabelled antimicrobials from AM was studied by using velocity gradient centrifugation through silicone oil. The effect of pulmonary surfactant (PS) on antimicrobial release was examined with paired experiments in which AM from the same patients were incubated either with a saturated solution of PS or with plain culture media. The table below shows that the AM:supernatant antibiotic concentrations in vivo were much greater than those in vitro, implying reduced efflux. Furthermore, no significant loss of antimicrobial occurred after the delay in separation in vivo. β-Lactam agents were mostly undetectable in AM in vivo. For azithromycin efflux was similar in vitro and in vivo. PS had no effect on the release of amnoxycillin or azithromycin from AM but both rate and extent of efflux were reduced for the quinolones ($p < 0.01$) and rate reduced for cefpirome ($p < 0.01$). PS may explain the discrepancy between in vivo and in vitro findings.

	Median AM:supernatant ratio	
Antimicrobial	*In vivo*	*In vitro*
Lomefloxacin	468	7·1
Ciprofloxacin	819	6·9
Sparfloxacin	264	9·4

Tryptase activity in bronchoalveolar lavage fluid of control and asthmatic subjects

C WARD, M DUDDRIDGE, A WALLS, A AVERY, DJ HENDRICK, EH WALTERS *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne, Newcastle, and Clinical Pharmacology, University of Southampton, Southampton* Descriptions of the cellular profiles in the bronchoalveolar lavage (BAL) fluid from asthmatic subjects commonly report mastocytosis. We performed a standard 180 ml BAL in eight asthmatic (median FEV_1 86%, range 37–102, three male, one smoker) and eight control subjects (median FEV_1 100%, range 75–127, six male) undergoing bronchoscopy. All subjects had PD_{20} FEV_1 assessed using a dosimeter technique and a differential cell count performed (Wright Giemsa stained cytospin) by two observers counting 500 cells. Mast cell counts were performed by two observers on an estimated 5000 cells on further cytospins fixed in Carnoy's fluid and stained with alcian blue (30 minutes and 12 hours). BAL supernatant was gassed with nitrogen, aliquoted, and stored at −20°C until subsequent radioimmunoassay of tryptase (blinded). This was repeated in the asthmatic subjects after treatment with 2000 μg beclomethasone diproprionate daily for two months in addition to their previous salbutamol as required. Comparison of results between control and asthmatic subjects (analysis of variance) are summarised in the table below. Tryptase activities were significantly higher in asthmatic subjects compared with controls ($p < 0.01$) and values were reduced after treatment without reaching significance. PD_{20} improved after treatment ($p < 0.05$). This study indicated that differences in tryptase activities can be detected in BAL fluid. Such assays may usefully complement conventional descriptive cytology in further studies of asthmatic subjects.

		Asthmatics (n=8)	
	Controls (n=8)	*BAL 1*	*BAL 2*
Tryptase ng/ml BAL	0·076	0·295*	0·213
Geometric mean PD_{20} (μg)	—	115	519*
Median % mast cell (range)	0·01 (0–0·21)	0·04 (0–0·25)	0·05 (0–0·25)

*$p < 0.05$.