Proceedings of the British Thoracic Society

The British Thoracic Society’s summer 1993 meeting was held on 30 June–2 July at Trinity College, Dublin

Age period cohort analysis of mortality due to lobar and pneumococcal pneumonia in the 20th century

G MARKS, P BURNLEY Department of Public Health Medicine, UMDS, London From 1938 to 1939 mortality due to lobar pneumonia fell by 32%. This was attributed to the commencement of widespread use of sulphonamides during 1939. However, this dramatic short-term reduction is small compared to the 100-fold reduction in mortality from this condition in young adults during the course of this century. The decline in mortality from lobar and pneumococcal pneumonia has continued well beyond the time when the use of antibiotics became widespread. We examined the role of cohort factors in this particular cohort by comparing the OPCS' historical mortality data files. Age and sex specific death rates for lobar pneumonia (ICDs 2 to 7, 1911 to 1967) and pneumococcal pneumonia (ICDs 8 and 9, 1968 to 1990) were plotted by year of death (period) and year of birth (cohort) for subjects aged 15 to 64 years. Age-period-cohort analysis using iterative reweighted least squares regression showed that there was a significant independent risk attributable to age, period and cohort effects (all p < 0.0001). The period-by-age plots showed a decreasing risk of death over time in all age groups, with higher death rates and a slower rate of decline in the older age groups. The cohort-by-age plot, however, showed that there was no apparent interaction between age and period may represent a cohort effect. Plots of mortality rate by year of birth for each age group all declined steeply and were superimposed on each other. Since age at death, period of death and cohort of birth are linearly related, analysis cannot distinguish an effect due to an age-period interaction from a simple cohort effect, however, the latter is a more parsimonious explanation. The presence of a cohort effect implies that developmental or environmental factors which influence the risk of acquiring or succumbing to lobar or pneumococcal pneumonia have played an important part in reducing mortality from this disease. [Data for this analysis were provided by OPCS.]

Reliability of the sputum Gram film

CM PARRY, C CONNELL, J CORKILL, R CUNNINGHAM, E RIDGWAY, A RIGBY, R WHITE Department of Medical Microbiology, Royal Liverpool University Hospital, Liverpool A Gram film of expectorated sputum may provide a clue to the bacterial aetiology of a lower respiratory tract infection, although contamination with upper respiratory tract material can make interpretation difficult. The criteria for evaluating specimens include estimating numbers of neutrophils (N) or squamous epithelial cells (SEC) per low power field and noting the association of a particular organism, such as Gram positive diplococci (GDPC) or Gram negative cocacobacilli (GNCB), with a purulent area of the film. To assess the reliability with which these features are recorded, Gram films were prepared from 70 routine sputum samples. The films were coded and scored by five microbiologists (experience range 6–23 years) according to numbers of N (<=25/LPF), SEC (<=10/LPF), GPDC or GNCB (<=15/HPF) and whether the Gram film suggested infection (purulence with an associated organism—INF). The films were randomly recoded and read again by each rater. Intrarater and interrater agreement was assessed by the kappa statistic with a kappa value >0.6 suggesting reasonable agreement.

Intrarater (rater no.)

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The association of purulence with a predominant organism and the scoring of significant numbers of GPDC were the most reliably recorded features of the sputum Gram film.

C-reactive protein in pneumonia

RP SMITH, BJ LIPWORTH Departments of Respiratory Medicine, King's Cross Hospital and Clinical Pharmacology, Ninewells Hospital, Dundee C-reactive protein (CRP) is an acute phase protein synthesised by the liver in response to a number of stimuli including infection and inflammation. The purpose of the present study was to evaluate whether CRP levels are a useful marker of parenchymal lung sepsis in patients with pneumonia. Serum concentrations of CRP were measured on day 1 of admission in 40 patients with uncomplicated pneumonia (age 64 (3) years) and in 20 patients with an infective exacerbation of chronic obstructive pulmonary disease (COPD) without pneumonia (69 (2) years). Pneumonia patients had a higher temperature (37.7 (0.2) v 36.6 (1.0)°C) and WBC count (13.7 (1) v 7.0 (6) x 10⁹/l). CRP concentrations were appreciably raised to above 70 mg/l in all cases of pneumonia and were above 100 mg/l in all but two cases. In COPD there were no cases with a CRP above 70 mg/l, and only seven out of 20 had had concentrations above the normal range (<10 mg/l). Mean (SEM), range, lower/upper quartiles for CRP were: (pneumonia) 217(16), 73–494, 130/275; (COPD) 18 (3), 10–61, 10/18. A CRP above 70 mg/l in pneumonia on day 1 occurred in association with a WCC <12 x 10⁹/l in 45% of cases, and with a temperature <37-0°C in 32%. Measurements of CRP were repeated after 3–7 days of antibiotic treatment in 21 cases of pneumonia: (pre) 213 (21), 104–494, 136/270, (post) 31 (5), 10–96, 17/47 (p < 0.0001); 99% CI for difference 141–221. Thus a CRP >100 mg/l will clearly separate patients with parenchymal lung infection from those with endobronchial infection. There was a pronounced fall in CRP in response to treatment of pneumonia. This suggests that CRP may be a useful adjunctive test in the management of patients with pneumonia.

The value of microbiological investigation of community-acquired pneumonia in relation to disease severity

N FRENCH, C PARRY, R WONG, CRK HIND Department of Microbiology, Royal Liverpool University Hospital, Liverpool To examine the value of routine microbiological investigations of community-acquired pneumonia (CAP) in relation to disease severity, all patients admitted to the RLHU between 1 January 1992 and 30 April 1992 with CAP were identified and their notes reviewed. The recording and presence of severity markers (respiratory rate >30, diastolic BP <90, urea >7 mmol/l, confusion, Po2 <8 kPa, extremes of white cell count, age >60, albumin <25 g/l) and microbiology investigations were related to antibiotic treatment and clinical outcome. 111 patients were identified, median age 72
Factors other than severity of pneumonia associated with increased mortality from lower respiratory tract infection

R CHAN, L HEMERYCK, J FEELY, L CLANCY Departments of Therapeutics and Respiratory Medicine, St James's Hospital, Dublin We prospectively studied patients with a clinical diagnosis of community acquired lower respiratory tract infections (LRTI) requiring hospital admission over a one year period. Patients were classified as severe and excluded if they required admission into the intensive care unit, intravenous support, respiratory stimuli, or exhibited signs of sepsis. Details of age, sex, previous exposure to antibiotics, chest radiological changes consistent with acute infection were present in 206 (42-2%) patients. Sputum and blood cultures were obtained from 303 (55-7%) and 137 (25-3%) patients, respectively. At least one pathogen was isolated in 31-2% and 8-7% of the respective samples; Haemophilus influenzae (33%), Streptococcus pneumoniae (28%), Pseudomonas aeruginosa (15% and 8%) and Fusobacterium nucleatum and Enterobacter cloacae (9%). The average duration of stay in hospital was 8-78 days (range 1 to 52) days and 34 (6-3%) patients died during their hospital stay. Factors associated with increased mortality were age >60 years ($\\chi^2 = 7-53$, p < 0-01), urea >7mmol/l ($\\chi^2 = 9-472$, p < 0-01) and chest x ray films consistent with cardiac failure ($\\chi^2 = 20-102$, p < 0-01). Acute infective changes on chest radiographs and culture positivity were not statistically significant factors. We found that the British Thoracic Society and the Public Health Laboratory Service findings (Q J Med 1987;62:195-220) on severity can identify high risk patients who may benefit from special medical attention in LRTI. [This work was supported by the Health Research Board.]

Pneumonia after stroke: a prospective study

DS RENWICK, DG SMITHARD, R ENGLAND, PA O’NEILL Departments of Medicine for the Elderly, University Hospital of South Manchester and Manchester Royal Infirmary Pneumonia is a common complication of acute stroke: a recent retrospective survey reported an incidence of 33% (Wang et al. Thorax 1992;47:874). Patients with swallowing problems secondary to stroke may be especially at risk. We report a prospective study of the incidence of lower respiratory tract infection (LRTI) and swallowing problems in patients with acute stroke. 121 consecutive patients with acute stroke were included (median age 63 (range 17-92) years, 54% men. Six or more markers of severity were recorded in 102 (92%) of patients. 15/61 (25%) patients with one to three markers of severe disease died or required ventilation compared with 1/50 (2%) who did not have those markers ($\\chi^2 = 0-01$). The number of microbiological investigations and their yield was not related to disease severity, except that pneumococcal bacteremia was commoner in those with severe disease. Antibiotic treatment in such patients was not influenced by the empirical antibiotics chosen as confirmed as appropriate in 22 (20%). Antibiotic treatment was changed as a result of the microbiological result in only one patient with a penicillin resistant Staphylococcus pneumoniae. Confirmation of the correct antibiotic choice is particularly important in severe pneumonia. Intensive microbiological investigations should concentrate on patients with markers of severe CAP.

Is penicillin the drug of choice in human immunodeficiency virus (HIV) positive patients with community acquired lobar pneumonia?

AA JEFFREY, D KESSEL, NM FOLEY, RF MILLER Department of Medicine, UCLMS, and Department of Imaging, Middlesex Hospital, London The British Thoracic Society recently updated their recommendations on the treatment of pulmonary infection (Br J Hosp Med 1993;49:346-50). It is suggested that lobar pneumonia is best treated with penicillin. We have previously questioned whether these guidelines apply to patients immunosuppressed by HIV infection. 33 HIV positive patients (all homosexual men) aged 23-58 years (21 smokers, two ex-smokers) presented with radiographic lobar pneumonia (confirmed by DK) between 1987 and 1993. Fever was present in 21 patients (>38°C in 14) and 11 had purulent sputum egression. A bacteriological diagnosis was made in 17 patients and revealed Streptococcus pneumoniae in eight (including two with capsulated organisms). Pneumocystis carinii, Mycoplasma pneumoniae, Staphylococcus aureus, one Enterobacter cloacae, and another Salmonella typhi. The results were analysed by day 7. Overall median survival was seven months. Gemcitabine was well tolerated, WHO grade 3 and 4 toxicities by patient were: anaemia 5%, thrombocytopenia 1%, leucopenia 7%, neutropenia 22% (no WHO 3 and 4 infections), transaminases 12%. Two patients developed transient WHO rises in serum creatinine. Two patients developed acute renal failure associated with microangiopathic haemolytic anaemia, four and six weeks after their last dose of gemcitabine. This was of uncertain aetiology. There was no WHO grade 4 symptomatic toxicity. WHO grade 3 toxicity was: vomiting (10% of patients), nausea (10%), pyrexia (10%), rash (10%). WHO grade 3 toxicity was: vomiting (10% of patients), nausea (10%), pyrexia (10%), rash (10%). WHO grade 3 toxicity was: vomiting (10% of patients), nausea (10%), pyrexia (10%), rash (10%). WHO grade 3 toxicity was: vomiting (10% of patients), nausea (10%), pyrexia (10%), rash (10%).
A review of the process of management of lung cancer

J Prewitt, A Wilcock, R Hubbard, J Macfarlane, J Britton
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Between 1 November 1991 and 31 October 1992, 379 cases of lung cancer were diagnosed histologically in our hospital. 176 (121 males) were referred directly by surgery. Histological cancer types included squamous (62), large cell (42), small cell (37), adenocarcinoma (25), other/unspecified (10). 84 were referred to respiratory physicians (RPs), 33 direct to thoracic surgeons (TSs), and 59 to other consultants (OCs), including 21 to gynaecologists. Bronchoscopy was performed a median of 3 days after referral to RPs, 8 days for TSs and 10 days for OCs. Other investigations performed included (% cases for RPs; TSs; OCs): fine needle aspirates (FNAs) (19%; 21%; 13%), pleural biopsy (19%; 21%; 19%), sputum cytology (13%; 0%; 29%). FNAs were arranged a median of 20 days after referral for RPs, 12 days for TSs, and 72 days for OCs. 49% and 45% of cases seen by RPs and TSs respectively were discussed with an oncologist a median of 14 days and 21 days after referral compared with 27% of those seen by OCs, a median of 50 days after referral. 13% of cases seen by both RPs and OCs were referred to TSs on a median of 22 days and 55 days after referral. We conclude that a significant proportion of lung cancer cases are seen initially by non-respiratory specialists with whom investigations and specialist referral occur more slowly.

Palliative care and lung cancer

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St Gemma's Hospice and St James' Hospital, Leeds
Lung cancer has a poor prognosis and is rarely curable. The role of symptomatic palliation is increasingly important. The study was undertaken to assess the frequency and type of symptoms, palliative treatment undertaken, and prognostic influence of symptoms on survival for 80 patients with lung cancer admitted to a hospice over a period of eight months. There were 42 male and 38 female patients with a median age of 70, range 36-89 years. Tumour type: 14 small cell lung cancer, 54 non-small cell lung cancer, and 12 unknown histology. Seven patients (9%) were alive at the end of the study. 73 patients were admitted for terminal care of whom 12 had two or more previous admissions. The overall median number of hospital stays, 21 (range 0-10) was 24 in patients. Symptoms were poor mobility 83%, fatigue 82%, dyspnoea 78%, pain 75%, and anorexia 74%. Analysis of symptoms according to performance status score, Eastern Co-operative Oncology Group (ECOG) scale showed that change were completely unable to self care and bed bound) showed no significant relation, although the median number of symptoms (10) was higher in patients (ECOG score 3 and 4) compared with seven in patients (ECOG score 2). Commonest forms of symptomatic treatment were: non-steroidal anti-inflammatory drugs (98%), benzodiazepines (76%), aperients (73%) antibiotics (64%), corticosteroids (54%), bronchodilators (44%) and antifungal compounds (43%). Oxygen was used infrequently (11%). Adjuvant pain controls were non-steroidal 26%, anticonvulsants 13%, TCNS 9%, nerve blocks 9%, and radiotherapy 5%. In the terminal phase, drugs were given by syringe driver in 47/80 patients (59%) using diamorphine in 47, midazolam in 35 (44%) and hyoscine in 26 patients (33%), respectively. Overall median survival was 17 days (range 1-72), which decreased with worsening of respiratory score (rs; MRC Lung Cancer Working Party 1979). 19 patients without dyspnoea (rs = 1-2), median survival 22 days; 20 patients (rs = 5), median survival 13 days. 14 patients died within 72 hours of whom 13 had an rs of 3-5. Symptoms are prognostically important in cancer; this study supports the requirement of accurate assessment of symptoms for treatment needs and outcome.

Audit of the work of a hospital based Macmillan nurse with an interest in lung cancer

M Campbell, A Wilcock, J Macfarlane, R Corcoran
Respiratory Medicine and Haywood House Macmillan Palliative Care Unit, City Hospital, Nottingham
In early 1992 we appointed a full time hospital based Macmillan nurse specialist (MN) with a responsibility primarily for patients with intrathoracic cancer. We review progress here over the year. 303 patients have been seen (243 lung cancer, 60 oesophageal/GI cancer); 81 as outpatients (OPs), 222 as inpatients/day cases (IPs); the numbers having nearly doubled between the first and last three month periods. During 162 lung cancer IP stays, patients were seen for psychological support (56%—including relatives), pain/symptom control (37%), and 7% for advice on discharge/services. Action taken included referral to community MNs in 63, to district nurses (DNs) in 22, hospice day care (DC) in 13, and social services (SS) in 3. Transfer was suggested/arranged for palliative radiotherapy in 11 and to two local hospices in 11. 26 deaths (16% of admission episodes) occurred in hospital. The MN took 33 teaching sessions for medical/nursing staff and frequently attended informal discussions and accompanied doctors breaking bad news. For the 81 OPs, there were 146 contacts within a special combined lung oncology clinic during 41 clinic attendances by the MN. 46% patients were referred on to community MNs, DNs, SSs and hospice DC. Following discussion, 72% of patients, 40% (37), relatives (54), or made to patients/relatives (41) and various community services (38). OPs most requested psychological/physical support, relatives also wanted further information about diagnosis/prognosis. We conclude that the first year has uncovered an enormous need and work load for an MN with an interest in thoracic cancer in a general hospital.

Dietary sodium intake and the risk of atopy and hyperreactivity in a general population sample

Respiratory Medicine Unit, City Hospital, Nottingham, and Harvcard Medical School, Boston, USA
We have tested the hypothesis that dietary sodium intake is a risk factor for atopy and airway hyperreactivity in a cross sectional study of a random sample of adults aged 18-70 from an administrative district of Nottingham. Of 2633 subjects who took part in a survey of diet and respiratory symptoms, we were able to estimate dietary sodium intake from a 24 hour urine collection in 1879 subjects, of whom 945 (50%) were female, 370 (20%) were current smokers and 937 (50%) were lifelong non-smokers, and 781 (42%) were defined as atopic on the grounds of at least one positive response to allergen skin prick testing with D pteronyssinus, grass pollen, or cat fur. Methacholine PDE2 was measured in 1702 subjects, of whom 222 (12%) were reactive to 12-25 µmol and less. Geometric mean 24 hour excretion of sodium was higher in men and in ex-smokers and current smokers compared with never-smokers. It also decreased significantly with age. 24 hour sodium excretion was significantly higher among subjects with at least one positive allergen skin test, by 10-8 (95% CI 4.7-17-2) mmol, and after adjustment for confounding by age, sex, smoking and 24 hour creatinine excretion in a multiple logistic regression, the odds of having a positive allergen skin test were increased independently by a ratio of 1.9-97 (95% CI 1.02-3.8, p = 0.043) per log10 unit increase in 24 hour sodium excretion. There was no difference, however, in sodium excretion between hyperreactive and non-reactive subjects, either before or after adjustment for sex, smoking, atopy, or age. Our study does not therefore support previous reports that dietary sodium intake is a risk factor for airway hyperreactivity, but does indicate that dietary sodium may be an important environmental determinant of the expression of atopy in the adult population.
Effect of factors operating in pregnancy and early childhood on the occurrence of wheezing up to age 16

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Respiratory Medicine Unit, City Hospital, Nottingham, and Social Statistics Unit, City Hospital, Nottingham

Introduction: Many studies have shown that the occurrence of asthma in early childhood, low birth weight, premature birth, low maternal age, and cessation of breast feeding have all been implicated in the aetiology of wheezing in childhood. These effects, however, have all been shown to be interrelated, and in particular to be confounded by smoking. Using data from the Southampton District Hospital Register, we estimated the relative independent importance of these effects on the occurrence of wheezing up to 16 in 15 712 subjects from a British national birth cohort of children born in one week of April 1970, and followed up at ages 5, 10, and 16. Relevant perinatal information was established by the midwife at birth, and at each contact during the first five years of a child's history and a number of family and social factors, including quantified maternal consumption of cigarettes. We found a cumulative report-ed prevalence of wheezing up to 16 of over 30%. Univariate comparisons of prevalence revealed an association with maternal smoking, both during pregnancy and in the first five years of childhood, low social index, a birth weight of less than 2000 g, low maternal age, and absence of breast feeding, and showed that social index, birth weight, maternal age, and breast feeding were all significantly associated with maternal smoking, both during and after pregnancy. In a multivariate regression, wheezing was found to be closely related to maternal smoking in pregnancy in a dose response manner (adjusted OR for 15+ cigarettes/day = 1.330; 95% CI 1.182–1.496), and independently related to low birth weight (adjusted OR for birth weight <2000 g = 1.562; 95% CI 1.001–1.853). After adjustment for maternal smoking in pregnancy and birth weight, there was no additional association with maternal and/or smoking in early childhood, indicating that the univariate associations with these variables arose from confounding by maternal smoking. These data show that maternal smoking in pregnancy and low birth weight are the major independent predictors of childhood wheezing.

Association of virus infections with hospital admissions for asthma: a time trend analysis

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University Medicine and Medical Statistics and Computing, Southampton, MRC Common Cold Unit, Salisbury, and Department of Microbiology, University of Leicester

Many asthmatic subjects on admission to hospital give a history of a cold in the days preceding the exacerbation, but attempts to prove an association between virus infections and asthma exacerbations have foundered as a result of inadequate virus identification techniques. Using the polymerase chain reaction to identify rhinovirus (RV) and coronavirus (C), we have recently shown that viruses are the major trigger of asthma-like episodes in susceptible children in the community; however, many episodes were not diagnosed as asthmatic, and none of the episodes was of sufficient severity to lead to a hospital admission. Hospital admissions are known to be the major risk factor for asthma mortality and identifying the major cause of such admissions is essential to target future preventive strategies. We have therefore carried out a time trend analysis to examine the possible association between virus infections and hospital admissions for asthma. During a prospective community based study between 1 April 1989 and 31 March 1990, in the Southampton area, 108 children (9–11 years) kept a diary card of daily symptoms, including the lower respiratory symptom scores and twice daily peak expiratory flow (PEF) recordings. On reporting an episode (identified by a fall in PEF of <50 l/s or if the child developed upper or lower respiratory symptoms) children were visited at home within 24–48 hours and samples taken for virus identification. The fortnightly virus identification rates were then compared with fortnightly hospital admission rates for asthma (ICD code 493) for the same time period, for the Southampton District Health Authority (SDHA), and the Wessex Region Health Authority (WRHA) for both paediatric and adult age groups. Regression analysis was carried out. A Durbin-Watson test failed to show any significant serial correlation of the residuals. Strong correlations were found between virus identification rates and hospital admission rates for asthma in children, r = 0.55; p = 0.003 (SDHA) and r = 0.66; p < 0.001 (WRHA) (r = 0.46; p < 0.001 (SDHA); r = 0.53; p = 0.001 (WRHA)). Material smoking during pregnancy and shows that virus infections (which in this study were 66% rhinovirus and 13% coronavirus) are strongly associated with exacerbations of asthma requiring hospital admission in all age groups, and suggests that efforts be intensified to find an effective treatment for these virus infections.

Role of virus infections in exacerbations in children with recurrent wheezing or cough

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Previous studies in exacerbations of asthma or “wheezy bronchitis” have identified virus infections in only 10–40% of episodes due to difficulties in identifying rhinovirus (RV) and coronavirus (C) infections, which are responsible for causing the most common colds. We conducted a 13 month prospective community based study with standard virological techniques and the polymerase chain reaction (PCR) to identify RV and C infections. 108 children (9–11 years), identified by questionnaire as having wheezy and/or troublesome cough, kept a diary card of daily symptoms and the lower respiratory symptom scores and twice daily peak expiratory flow (PEF) recordings. On reporting an episode (identified by a fall in PEF of >50 l/s or if the child developed upper or lower respiratory symptoms) children were visited at home within 24–48 hours. A capillary blood sample, and a nasal aspirate (NA) were taken, and a convalescent blood sample two weeks later. Viral identification methods were culture of NAs for three passes in Ohio HeLa, Hep2, C16, and MDCK cells; immunofluorescence (IMF) for respiratory syncytial (RS) virus, influenza virus (Flu) type A, parainfluenza virus types 1–3 (PF), and adeno- and coronaviruses (Ad); ELISA for RS, FlU, PF, Ad and C; and PCR identifying PV (PV = RV and entrovirus) and C RNA in NA samples. Viruses were identified in 228 of all 292 (78%) reported episodes (2.5/child/y). Data were computerised and analysed: PEF episodes were defined as two or more days in which morning PEF was below the 10th centile, preceded by one day above the 10th centile and followed by two days at or above the median. A respiratory symptom episode for cough and/or wheeze (LRT), wheeze (W) and cold (URT) symptoms were defined as two or more days with scores above the median, preceded by one day and followed by two days at or below the median. Viruses were identified in 81% of LRT, 60% of PEF, 81% of W episodes, and in 83% of URT/LRT/PEF episodes: viruses identified were 147 PV (50% of episodes), 38 C (13%), 21 Flu (7%), 21 PF (7%), 12 RS (4%), and five others (2%). Of the 147 PVs 84 were characterised as RV by further tests, it is likely that most of the remaining URT and RV rather than virus which cultures readily, thus about 66% of viruses identified are likely to be RV. PV was identified in 12% of the children when symptom free. This study suggests that viruses are the major trigger of asthma-like episodes in susceptible children.

Gastro-oesophageal reflux in patients with brittle asthma

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As part of the West Midlands Brittle Asthma Register, 40 patients with peak expiratory flow (PEF) variability (amp % max) of greater than 40% for more than three hours out of every six despite considerable medical treatment (mean inhaled steroid dose 1975 µg/day) have been identified. Age, sex, and inhaled steroid matched asthmatic controls exhibiting PEF variability of 25% or less for a similarly continuous period have subsequently been recruited. Twenty brittle asthmatic patients have undergone oesophageal manometry and 24 hour pH monitoring. Sixty 24 hour pH monitoring study controls agreed to be studied and their results were compared with all 20 brittle asthmatic patients by the z test for two sample means. All control patients used only PRN short acting bronchodilators, 12 of the 20 patients were on continuous subcutaneous infusions of terbutaline, and the other eight on salmeterol. 19/20 (95%) of the brittle group had symptoms suggestive of reflux as did all six controls; 15 of the brittle group had abnormal manometry compared with only two controls (p = 0.06). Herniation of the LOS was noted in 14 out of the 20 brittle asthmatic patients and in no controls (p < 0.02). In severe asthma LOS pressure may be lowered either by changes in transdiaphragmatic pressure or by differences in bronchodilator use causing sphincter relaxation and thus facilitating reflux. We suggest that gastro-oesophageal reflux occurs in severe asthma as a result of the disease or its treatment as opposed to acid reflux causing worsening asthma.
Comparison of bone density in asthmatic patients taking inhaled budesonide and beclometasone dipropionate

GE PACKE, O ROBB, DM REID, JG DOUGLAS Departments of Thoracic Medicine and Rheumatology, City Hospital, and Department of Radiology, Aberdeen Royal Infirmary, Aberdeen We have previously shown that vertebral bone density (VBD) is reduced in asthmatic patients taking high dose inhaled beclometasone dipropionate (BDP) and intermittent systemic corticosteroids (Thorax 1992;47:414–7). The object of the present study was to examine VBD in a group of similar asthmatic patients taking inhaled budesonide (BUD). VBD was measured by quantitative computed tomography in 20 patients with a mean (SD) age of 36 (7) years. Median dosage of BUD was 800 μg. All had taken this treatment for more than one year, and had not previously taken BDP. None were taking regular oral steroids. 13 female patients were premenopausal. VBD in the patients taking BUD was 139.5 (28.6) mg/ml. This was significantly lower (p < 0.05, unpaired t test) than the VBD of 160 (27) mg/ml in a group of mild asthmatic patients studied earlier who had never taken these drugs or systemic steroids. Our previous study showed that VBD in patients taking BDP in a median dosage of 1000 μg daily and intermittent corticosteroids was 128 (23) mg/ml. This value was lower than that seen in the patients taking BUD but not significantly so (p = 0.1). Differences between BUD and BDP in terms of bone density values have been adjusted for dose of inhaled steroid (covariate analysis). Seven patients taking BUD had not previously taken systemic steroids; VBD was 148 (35) mg/ml compared with 135 (25) mg/ml in the 13 patients who had taken intermittent steroids (p = 0.4). VBD is reduced in asthmatic patients taking BUD and BDP. These reductions in VBD is similar in magnitude to that seen in patients taking inhaled BDP.

Withdrawal of fenoterol and the end of the asthma mortality epidemic in New Zealand

J CRANE, C BURGESS, R BEASLEY, N PEARCE The Wellington Asthma Research Group, Wellington School of Medicine, Wellington, New Zealand A series of epidemiological and experimental studies have implicated the high dose preparation of fenoterol as a major factor in the second New Zealand asthma mortality epidemic. These studies led to the warning from the New Zealand Department of Health, in 1989, that fenoterol should not be used by patients with severe asthma, and then to the withdrawal of fenoterol from the drug tariff in New Zealand in 1990. These regulatory moves led to a large reduction in the sales of fenoterol from a stable 30% of the β agonist market during 1983–84 to 6% in 1990. During the same period, the mortality fell from an average of 2.3 (range 1.9–2.6) per 100 000 in the 5–34 year age group to 1.1 in the second half of 1989, and to 0.8 in 1990. The 1990 figures represent the lowest New Zealand mortality for more than 25 years. Thus the end of the New Zealand asthma mortality epidemic occurred during the period of the withdrawal of fenoterol in 1990, in a similar way as the epidemic commenced when fenoterol was introduced in 1976. By contrast, the increased use of β agonist drugs as a class occurred after the epidemic began, with sales continuing to increase during the period when mortality fell. Data on time trends should be assessed with considerable caution; nevertheless, it is useful to note that the time trends are consistent with other epidemiological and experimental evidence indicating a major role of fenoterol, but not β agonist drugs as a class, in the second mortality epidemic in New Zealand.

Therapeutic response to oxygen supplied from a complex polymer membrane

CB COOPER, JM STRAKOVA, LE WILKINSON, JR COLTHURST UCLA School of Medicine, Los Angeles, California, USA For therapeutic uses, it has been assumed that an O2 supply should be 100% (or nearly 100%) to be effective. Membrane separator technology currently produces lower concentrations of O2, but these concentrations might produce an adequate therapeutic response in some patients with chronic hypoxemia. We evaluated a prototype membrane separator made of complex polymer straws differentially permeable to O2 and N2. When fed with compressed air at 7 bar, this membrane produced 47% O2, fully humidified, up to flow rates of 10 l/min. We studied 10 subjects (three men, seven women) of mean (SD) age 58 (11) years with chronic hypoxia (breathing room air, PaO2 = 53 ± 2 (10–3) mmHg and PaCO2 = 47 ± 7 (10–3) mmHg). Night had obstructive lung disease, one restrictive lung disease, and one obesity hypventilation syndrome. All subjects had received domiciliary oxygen treatment and four had tracheostome catheters. We compared the membrane separator (SE) at flow rates of 4, 6, and 8 l/min with a PSA molecular sieve (SI) at 1, 3, and 5 l/min. Also we compared the three types of O2 delivery: standard nasal cannulae (NC), occluding nasal cannulae (OC), and tracheostome catheters (TC). Seven subjects had arterial catheters for sequential blood gas measurements. Oxygen saturation (SpO2) was measured by pulse oximetry with an ear probe. Using SE with nasal cannulae, for the whole group, mean values of PaO2 increased from 54 to 76 mm Hg and SpO2 from 82 to 92%. Using SE with tracheostomy catheters, in four subjects, PaO2 increased from 41 to 71 mm Hg and SpO2 from 69 to 93%. We found greater increases in SpO2 and PaO2 with the SI. All changes were significant (p < 0.05). The comparable peak alveolar (PaCO2) values were also significantly higher than in oxygenation in selected patients with chronic hypoxia. Membrane technology for therapeutic O2 supply has the advantages of high flow capability, humidification, bacterial filtration, and the possibility of miniaturisation.

Role of oxygen during recovery from exercise in patients with chronic obstructive pulmonary disease

JJ WILLIAMSON, CJ CLARK Department of Respiratory Medicine, Hairmyres Hospital, East Kilbride During pulmonary rehabilitation programmes, patients with chronic obstructive pulmonary disease (COPD) frequently become breathless due to exercise hyperpnoea and reduced O2 tension. Oxygen at rest can improve exercise tolerance. However, it is not clear whether the additional O2 present in the alveoli during exercise, but unable to diffuse into the capillaries, is beneficial and whether it optimizes physical function in patients with COPD.

Nasal ventilation in acute exacerbations of chronic obstructive pulmonary disease (COPD): effect of ventilator modes on arterial blood gases

DJ MEECHAM JONES, EA PAUL, C GRAHAME-CLARK, JA WEIDZICHA Department of Thoracic Medicine, The London Chest Hospital, Bonner Road, London Acute hypercapnic respiratory failure due to exacerbations of COPD is associated with a high mortality despite advances in medical treatment. Several recent studies have reported

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the successful use of nasal positive pressure ventilation in this condition. We have examined the acute effect of four different modes of nasal ventilation on arterial blood gas tensions in 12 patients (11 men; median age 69 (range 49–79) years within 16 hours of admission with acute exacerbations of COPD. At the start of the study, mean (SD) FVC 1.1 (0.5) L, FEV1 0.59 (0.13) L, PaO2 8.2 (0.74) kPa, PaCO2 7.5 (0.39) kPa, and PaO2 8.2 (0.74) kPa. Each patient underwent four one-hour periods of nasal ventilation in randomised order, three with the BiPAP ventilator: (a) pressure support (PS) 18 cm H2O (IPAP), (b) PS 18 cm H2O + PEEP 6 cm H2O (IPAP + EPAP), (c) CPAP 8 cm H2O, and one period using the volume cycled Brompton PAC ventilator (d) adjusted to deliver the maximum calculated minute volume that the patient could tolerate. There was an interval of at least one hour between treatment periods to allow blood gases to return to baseline. There was no significant change in baseline blood gas concentrations during the course of the study. Arterial blood samples were obtained from a radial arterial line immediately before each period of ventilation and at one hour. Oxygen treatment at the same flow rate was continued throughout the whole study. All modes of ventilation produced a significant improvement in PaO2, however, repeated measures analysis of variance showed no difference between modes. Mean (SD) changes in PaO2 (kPa) were: (a) IPAP +2.5 (2.27), (b) IPAP + EPAP +0.82 (2.34), (c) CPAP +1.35 (2.24), (d) Brompton PAC +2.34 (1.51). For the 12 patients, mean changes in PaCO2 were: (a) IPAP –0.29 (0.74) kPa, (b) IPAP + EPAP –0.24 (1.09), (c) CPAP +0.25 (0.67), (d) Brompton PAC +0.04 (0.83). None of these changes were statistically significant. When patients were subdivided into those starting PaCO2 above or below 8 kPa, however, there was a significant difference between the modes: those with PaCO2 <8 kPa, but rose in those with PaCO2 >8 kPa (p = 0.014). This pattern was not found in changes in PaO2. Although the PaCO2 improved in all patients, the change in PaCO2 depends on the initial degree of hypercapnia. This suggests that in patients with severe hypercapnia, nasal ventilation may not be sufficient to reduce PaCO2, but will control further rises in PaCO2 allowing safe controlled oxygen treatment. [This work is supported by The British Lung Foundation.]

Nasal intermittent positive pressure ventilation in advanced progressive chronic respiratory failure due to chronic obstructive pulmonary disease

DJ MEECHAM JONES, GM BRAID, JA WEDZICHA Department of Thoracic Medicine, The London Chest Hospital, Bonner Road, London Long term oxygen treatment (LTOT) is beneficial to patients with chronic respiratory failure due to chronic obstructive pulmonary disease (COPD). Nasal intermittent positive pressure ventilation (NIPPV) has been used increasingly to treat patients with chronic respiratory failure due to COPD, but the criteria for starting NIPPV in these patients have not been established. Also, the effects of treatment of NIPPV in COPD patients with advanced disease have not been fully evaluated. We report the effect of domiciliary nocturnal NIPPV in a group of nine patients (five men, four women, median age 60 years, range 48–68) with advanced chronic respiratory failure due to COPD and long standing peripheral oedema. All were established on domiciliary LTOT (median duration 59, range five–85 months). Eight of the nine had refractory hypoxaemia with resting PaO2 less than 8 kPa while on supplemental oxygen and all had symptomatic hypercapnia that limited further oxygen treatment. All patients had shown clinical deterioration in the three month period immediately before starting NIPPV. At initiation of NIPPV, mean (SD) FVE1 was 0.58 (0.11) L, FVC 1.6 (0.39) L, mean PaO2 (room air) 5.34 (0.73) kPa, and PaCO2 8.04 (1.17) kPa. On oxygen, the mean PaO2 was 7.37 (1.58) kPa, and PaCO2 8.63 (1.16) kPa. The patients were followed up for a period of four–19 months (median nine) and LTOT, diuretics, and all other appropriate treatments were continued. Six months follow up blood gases are available for six patients. In this group the mean PaO2 fell from 5.61 (0.76) to 4.91 (1.26) kPa, and PaCO2 rose from 8.00 (1.38) to 8.52 (2.22) kPa, five of the six patients showing a deterioration in blood gases. PaO2 returned to normal in six patients (range 4–14 months) during exacerbations of cor pulmonale. The four surviving patients were followed up for six–19 months (median 11): at six months mean PaO2 (room air) fell from 5.75 (0.94) to 5.41 (1.14) kPa and PaCO2 rose from 7.76 (0.96) to 8.37 (0.61) kPa. Symptomatic hypercapnia was still present in all patients and all required further admissions to hospital with cor pulmonale. In these patients with advanced and progressive COPD, the addition of NIPPV to LTOT and standard treatment produced no improvement in clinical condition or blood gases. In COPD, studies have shown that despite an initial fall in mortality with LTOT, mortality still rises later due to an irreversible deterioration in airflow obstruction. We suggest that to be clinically effective, NIPPV should be added to LTOT at an earlier stage in the natural history of the disease, before rapid clinical deterioration occurs. [This work is supported by The British Lung Foundation.]

Non-invasive inspiratory pressure support and exercise tolerance in patients with severe chronic airflow limitation (CAL)

SEI KEILTY, TA FLEMING, J MOXHAM Department of Thoracic Medicine, King’s College School of Medicine and Dentistry, London Patients with chronic airflow limitation (CAL) commonly present with dyspnoea limiting exercise tolerance. We have studied the effects of non-invasive inspiratory pressure support (IPS), continuous positive airways pressure (CPAP), and O2 on exercise in six patients with CAL mean (SD) FEV1 0.73 (0.21), complaining of disabling dyspnoea. Patients walked on a treadmill until their sensation of dyspnoea, scored at one minute intervals, reached level 5 (severe) on the modified Borg Scale (Borg GAV. Med Sci Sports Exercise 1982;14:377–81). Studies were performed with IPS (mean airway pressure 15 cm H2O), CPAP at 6 cm H2O (with a face mask), and O2 at 2 L/min (with an oxygen mask) in random order on three separate days. Each of these was compared with walking with a sham circuit (breathing air via an oxygen mask at 2 L/min from an unlabelled cylinder) and with no support. On cessation of exercise, distance achieved and leg fatigue score were recorded. No patients stopped walking due to leg fatigue, only stopping when their breathlessness became too severe to reach level 5. Non-invasive IPS improves median walking distance when compared with sham: median increase 97% (139, range 14 to 533 metres, p = 0.003, n = 6). Compared with no support IPS increased walking distance in five out of nine patients: median increase 42% (140, range 11 to 1342 metres, p = 0.09, n = 6). Neither CPAP nor O2 significantly improved walking distance in the six patients studied. We conclude that walking with non-invasive IPS may improve exercise tolerance in patients with CAL.

Cough reflex sensitivity decreases with successful treatment of chronic cough

F O’CONNELL, VE THOMAS, RW FULLER, NB PRIDE Departments of Clinical Pharmacology and Respiratory Medicine, Royal Postgraduate Medical School, London We have investigated the effects of specific treatment on cough severity measured by visual analogue score (VAS) and cough sensitivity to inhaled capsaicin (log concentrations required to elicit two (C2) and five (C5) coughs) in 87 consecutive unselected referrals with chronic cough. A specific cause of cough was successfully treated in 48 (55%) patients. In 11 patients with rhinitis, VAS was less (p = 0.014) after treatment with intranasal steroids and anticholinergics. Log C2 and C5 were greater after treatment but the differences were not significant. In nine patients with gastro-oesophageal reflux (GOR), VAS was less (p = 0.009) and log C2 (p = 0.02) and C5 (p = 0.015) greater after antireflux treatment. Six patients with rhinitis and GOR had lower VAS (p = 0.04) and higher log C2 (p = 0.04) and C5 (p = 0.05) after treatment. Twenty two patients with asthma (n = 9), postviral (n = 9), or ACE inhibitor cough (n = 4) also had lower VAS and higher log C2 and C5 values after treatment. All remaining 39 (45%) patients had negative histamine challenge tests. Twenty had rhinitis and/or GOR. In eight of these patients (a) the symptoms of PND/GOR cleared with appropriate treatment whereas the VAS, log C2, and log C5 showed no change. Treatment of PND/GOR failed in the other 12 patients (b) and there was no change in VAS, log C2, or log C5 (table). Nineteen patients in whom no specific cause of cough was found showed no change in VAS or capsaicin responses after empirical trials of treatment for PND and GOR. Enhanced capsaicin cough sensitivity in patients with chronic cough returns to normal with successful treatment of the cough.
Asthma

PND/GOR

sarcoidosis

recently shown

antigens,

Treatment

patients,

kD

No

National

Espitia C

lingula

choalveolar

fluid

encouraging

College

of the bronchus.

DNA in

samples.

Further doubts

tuberculosis.

other

leaving

organisms/ml.

included

subsequent sample

handling.

We

expected the presence of active, "truncated" form of a,PI, in bronchopulmonary samples from CF patients and the absence of a,PI complex in the same samples, despite the presence of active NE. In a recent study, we noted that addition of serine protease inhibitors to sputum samples after collection altered the electrophoretic protein profile of the samples, suggesting that degradation of protein may occur subsequent to sample collection. The aim of the present study was to examine the effect of postsampling proteolysis on a,PI in sputum from CF patients. Sputum samples, collected from 14 CF patients, were extracted in the presence of absence of serine protease inhibitors (PMSF and DIPF) and/or metallo-protease inhibitors (EDTA and phenanthrene). Samples were examined by electrophoresis and immunoblotted as an antibody specific for a,PI. Quantification of the a,PI positive bands was performed by laser densitometry. Results indicated that the preservation of complexed a,PI was best achieved by addition of both serine- and metalloprotease inhibitors to sputum samples on collection. Although the major form of a,PI is present in all aliquots corresponded to a "truncated" form of the protein, significantly lower amounts of this form and larger quantities of native a,PI were present in aliquots containing both serine- and metalloprotease inhibitors (p < 0.05). These results indicate that significant proteolysis of a,PI-NE complex and a,PI can occur in CF sputum following collection in the absence of added protease inhibitors. In the light of these findings, reports suggesting that a,PI is inactivated in vivo in the CF lung may have to be reassessed.

C-reactive protein and plasma cytokines in cystic fibrosis

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Circulating markers such as C-reactive protein (CRP) and tumour necrosis factor-a (TNF) may be inappropriately inflammatory response to chronic bronchial sepsis in cystic fibrosis (CF) (Thorax 1991;46:91). We measured plasma TNF and granulocyte-macrophage colony stimulating factor (GM-CSF), together with total white cells (WCC) and serum CRP in 15 adults (17 years, 10 men) with CF. CRP was measured in 21 post-sampling days of intravenous antibiotics and when patients were in a stable state. Exacerbations of bronchiectasis were defined clinically by increase in sputum volume and purulence accompanied by reduction in FEV1, and vital capacity. Samples for cytokines were taken into aprotinin-supplemented EDTA, spun at 4°C, and stored at

80°C until batch assay with in house sandwich ELISA (detection limit 15 pg/ml for both TNF and GM-CSF). After antibodies (AB) there were increases (p < 0.001; paired t tests) in mean (SE) FEV1 (156 (16) to 2-05 (201)), vital capacity (2-8 (0-26) to 3-4 (0-27)), and body weight (53-4 (2-1) to 55-3 (1-8) kg). WCC fell from 13-1 to 10-9 (p < 0.001). The table shows the results for CRP, TNF, and GM-CSF. TNF was detectable in only three patients before AB and changes in TNF and GM-CSF were not significant. Although CRP fell in CF sputum samples following C. The results of 15 patients had normal values before treatment. WCC was >11 × 10^9/1 in 11 patients and was increased after AB in three. Measurements of CRP and TNF are of limited value in exacerbations of CF bronchiectasis.
Effects of seasonal exposure to allergen on nasal cytokine immunoreactivity and its modulation by fluticasone propionate

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Immunopharmacology Group, Southampton General Hospital, Southampton

In this study, we have employed immunohistochemistry with specific antibodies to IL-4, IL-5, and IL-6. With nasal mucosal biopsy samples taken before and after exposure to allergen, we found significant changes in cytokine expression. IL-4 and IL-6 were increased in the nasal mucosa following exposure to allergen, whereas IL-5 levels remained unchanged.

There was a significant increase in the number of submucosal eosinophils in the placebo group (p = 0.003), which was prevented by treatment with FP, but no change in the number of submucosal mast cells. Most IL-4 and IL-6 immunoreactivity was localised to mast cells, whereas IL-5 was localised to both mast cells and eosinophils. With the mAb 3H4, which detected IL-4, there was a seasonal increase in +ve cells in the placebo group that did not reach statistical significance (p = 0.08) and a decrease from baseline on the FP group (p = 0.08). When these changes were compared between the two groups, there was a significant difference (p = 0.014). Cells +ve for mAb 4D9, which detects IL-6, were not altered on placebo (p = 0.68), but comparing the two groups, the difference was not significant (p = 0.07).

No significant differences were found in cells +ve for IL-5 or IL-6. These results do not show a clear seasonal variation and the number of cytokine +ve cells present in the nasal mucosa but do suggest that IL-4 expression in vivo is suppressed by topical corticosteroids.

Intrinsic variability of asthmatic airways

RICHMOND, H BOOTH, GE Pritchard, C WARD, PA CORRIS, RH WALTERS

William Leech Centre for Lung Research, Freeman Hospital, Newcastle upon Tyne, and Department of Respiratory Medicine, Alfred Hospital and Monash University, Victoria, Australia

This study examines the intrinsic variability of inflammatory cell numbers in airway biopsies with lobe examined (upper vs lower) and with time. A standard fibroptic bronchoscopy was performed on 12 patients with mild asthma (eight men and four women, median age 31.5, range 18–53 years; five receiving beclomethasone dipropionate up to 500 μg/day, and the remainder on inhaled β2 agonists as required). Endobronchial biopsies were taken from third generation carinae of both right upper and right lower lobes. The procedure was repeated one month later. There had been no change in active treatment, lung function (mean % predicted 89.6% [16.5%]), or airway responsiveness to methacholine (geometric mean 21.1 [1.4]). On each occasion the biopsies were snap frozen in liquid nitrogen at −196°C after immersion in cold isopentane. Standard 7 μm step sections were taken from each sample and stained with monoclonal antibodies against T lymphocytes (CD3), T helper cells (CD4), T suppressor cells (CD8), and the mast cell marker (CGRP). Quantitative analysis was used to obtain submucosal counts (mm²) to a depth of 150 μm. All counts were made by one observer (IR) and interobserver coefficients of variation for measurement and counting functions were <5% and <8% respectively. There was no significant difference between upper and lower lobe counts for any of the markers. Large intrasubject variations for both T lymphocytes and eosinophils were apparent, however, with time (CD3 median difference 185.0, range of differences 109.9–426.3 mm²; CD4 91.5, range 67.7–202.1 mm²; CD8 167.7, range 71.0–322.9 mm², and EG2 12.3, range 9.9–110.1 mm²). This may support the view that the asthmatic airway is in a constant state of flux with regard to inflammatory cell numbers and types, or may reflect difficulties in the sampling technique.

Nerves containing calcitonin gene related peptide are increased in bronchial epithelium of patients with chronic idiopathic cough

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With an anatomical diagnostic approach similar to that of Irwin et al (Am Rev Respir Dis 1981;123:413–7) we excluded specific causes of cough in 16 patients with persistent cough for a minimum of one year by history, physical examination, spirometry, home PEFR monitoring, histamine bronchial challenge, skin tests for common allergens, chest, and sinus x ray films, barium swallow, and oesophageal pH monitoring. In addition all patients failed to respond to empirical two month courses of topical intranasal corticosteroids and anticholinergic agents and of aggressive asthma treatment including diet, postural measures, alginates, and high dose H2 antagonists or omeprazole. We compared cough sensitivity to inhaled capsaicin and endobronchial biopsies in these 16 patients (P) with six normal healthy volunteers (H). Cough sensitivity was enhanced in P compared with H (log C2 (concentration required to elicit one cough) = 2.6 ± 0.2, P = 1.4 ± 0.1, p = 0.003 and C5 (concentration required to elicit five coughs) H = 3.5 ± 0.1, P = 1.7 ± 0.2, p = 0.001). At fibroptic bronchoscopy under local anaesthesia, endobronchial biopsies were taken from the carina between the right main bronchus and the bronchus intermedius and a subsegmental bronchus of the right lower lobe. Biopsies were fixed immediately in Zamboni’s solution. Frozen sections were stained by indirect immunofluorescence for the anatomical nerve marker PGP9-5 and for the sensory neuropeptide calcitonin gene related peptide (CGRP). Immunoreactivity of CGRP was quantified by image analysis to measure the fluorescent area as a percentage of epithelial area. The overall weighted percentage for each marker in two sections from each site was calculated for each subject and compared between patients and controls. Total nerve density (PGP9-5) was greater in P than controls (p = 0.001). Either an increased number or functional changes of sensory nerves in airway epithelium may be responsible for upregulation of cough sensitivity in patients with chronic idiopathic cough.

Increased expression of the monocyte chemotactic protein 1 in asthmatic bronchial epithelium

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This study examined the expression of the monocyte chemotactic protein 1 (MCP-1), a member of the chemokine low molecular weight cytokine family, was assessed in the bronchial wall, in vivo, on frozen bronchial biopsies from patients with idiopathic cough. Biopsies were processed for immunohistochemistry with a highly specific monocular antibody (clone F9). A mouse myeloma protein (MOPC21) without antibody specificity was used as a control immunoglobulin to ensure specificity of the staining. H&E-saturation intensity (HESI) colour image analysis was used to quantify epithelial staining of both the test and control antibodies. The epithelium of the bronchial biopsies of asthmatic subjects stained strongly with MCP-1 antibody, with 51.8% (3.7%) (mean %) of the epithelium being reactive, whereas the epithelium of normal individuals stained significantly less with only 6% (2.0%) of the epithelium being stained (p = 0.001). There was no overlap between the groups. Increased staining was also present in blood vessels and macrophages of asthmatic biopsies. There was negligible staining of the bronchial wall with the control MOPC21 antibody. A polyclonal antibody against MCP-1 gave similar positive results. These data show upregulation of MCP-1 in the asthmatic bronchus, suggesting that MCP-1 may play an important part in the immunopathogenesis of bronchial asthma.

Airway eosinophil infiltration in fatal asthma

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The diagnosis of eosinophilic infiltration of the bronchial wall was compared in 28 asthmatic patients who died of asthma with 11 mild to moderate asthmatic patients who died of unrelated causes. Lung tissue sections 4 μm thick were cut from paraffin embedded blocks taken at postmortem. The resting and activated eosinophils were
detected by monoclonal antibodies (EG1 and EG2) with the streptavidin-biotin horseradish peroxidase technique. The size of the airways was determined by measurement of basement membrane length. Eosinophils within the airway wall were counted per mm² of airway wall area. All airways regardless of their size were evaluated first. Then large airways (>2 mm) and small ones (<2 mm were studied separately. There was no overall significant difference in the degree of airway eosinophil infiltration between the group of asthmatic patients who died from asthma and those who died from unrelated causes. Cell densities in the airway wall were 52 ± 1 ± 46 cells/mm² for EG1 and 94 ± 4 ± 87-9 cells/mm² for EG2 (all NS). In the airways >2 mm, however, there was significantly higher eosinophil infiltration of the airway wall in asthma deaths. The figures were 49 ± 4 ± 0-7 cells/mm² (p = 0.01) for EG1 and 101 ± 1 ± 19-7 cells/mm² (p = 0.01) for EG2. In small airways (<2 mm) no significant differences between the two groups were found. This study suggests a role of eosinophil infiltration in large but not in peripheral airways in fatal asthma.

Regular inhaled salbutamol may exacerbate bronchial inflammation in patients with mild asthma

R J DAVIES, C J TRIGG, J H WANG, N MANOLITAS, A MACAULAY, N J HALLI, S HAMILTON, Department of Respiratory Medicine, St Bartholomew's Hospital, London β₁ agonist use may worsen asthma control when administered regularly or in high dose. In this study, regular salbutamol (200 μg four times a day) was compared double blind with nedocromil sodium (4 mg four times a day) and placebo. All subjects received intermittent inhaled salbutamol as required. Histamine bronchial provocation, bronchial biopsies, and bronchoalveolar lavage (BAL) were performed before and after four months of treatment in 38 non-smoking patients with mild asthma aged 18-45 years who had received only intermittent inhaled β₂ agonist in the preceding six months. There was a non-significant trend towards improvement in bronchial responsiveness in the nedocromil treated group but no clinical deterioration in the placebo and regular salbutamol groups. Mast cell numbers were not affected by treatment but activated (EG2) eosinophils increased significantly on regular salbutamol compared with a reduction on nedocromil sodium. ECP and tryptase levels in BAL were not significantly affected. These data suggest a deleterious effect of regular inhaled β₂ agonists on bronchial inflammation in mild asthma. Similar trends have been found in comparison of intermittent and regular β₂ agonists with inhaled steroids (our experience; also Laitinen et al. J Allergy Clin Immunol 1992;90:32-42).

<table>
<thead>
<tr>
<th>Treatment</th>
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<th>Post</th>
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<tr>
<td>Nedocromil sodium</td>
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<td>143-8</td>
</tr>
<tr>
<td>Regular salbutamol</td>
<td>(n = 11)</td>
<td>127-5</td>
</tr>
<tr>
<td>Placebo</td>
<td>(n = 12)</td>
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*p < 0.05, Wilcoxon test; n = number of viable biopsies.

Placebo controlled trial of long term inhaled beclometasone dipropionate (BDP) in asthma: effect on bronchial mucosal inflammation

C J TRIGG, J H WANG, N MANOLITAS, M A CALDERON, A MACAULAY, M H HERDMAN, J DUDDLE, R J DAVIES Department of Respiratory Medicine, St Bartholomew's Hospital, London The effect of long term inhaled BDP on bronchial inflammation has not previously been studied in a placebo controlled double blind trial. 25 non-smoking patients with mild asthma received either beclometasone dipropionate (BDP) (500μg twice daily) or placebo double blind for four months. None of the subjects received antiasthma treatment other than intermittent inhaled β₂ agonist in the preceding six months. Histamine bronchial provocation, fibreoptic bronchoscopy with biopsy, and bronchoalveolar lavage (BAL) were performed before and after treatment. There was a non-significant trend towards improvement in lung function and bronchial responsiveness. Tissue mast cells, total (EG1), and activated (EG2) eosinophils were all significantly reduced in the BDP group. There was also a trend towards reduced BAL eosinophils and ECP level. No change in CD4 or CD25 T lymphocytes was seen. The results compare well with the response to six weeks BDP and three months budesonide.

<table>
<thead>
<tr>
<th>Time</th>
<th>EG1 (n = 8)</th>
<th>EG2 (n = 8)</th>
<th>Mast (n = 7)</th>
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<tr>
<td>Before</td>
<td>136-7</td>
<td>120-4</td>
<td>42-0</td>
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<tr>
<td>After</td>
<td>197-2</td>
<td>156-0</td>
<td>48-2</td>
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* p < 0.05; ** p < 0.01; values are geometric mean cells/mm².

Symptomatic asthma unresponsive to corticosteroids

AE REDINGTON, J MADDEN, R DJUKANOVIĆ, J WILSON, ST HOLGATE, PH HOWARTH Immunopharmacology Group, University of Southampton Although corticosteroids are an effective form of treatment in most cases of asthma some patients remain unresponsive to their effects. We have studied the endobronchial biopsy and bronchoalveolar lavage (BAL) findings in 16 patients (five male, 17 female; mean age 41 ± 15-9 years) who, despite high dose inhaled (n = 13) and/or oral (n = 11) corticosteroids, have persistent symptoms, peak flow variability (period maximal diurnal variation median 37 ± 7%) and airflow obstruction (mean FEV₁, 74 ± 22-4% predicted) (SU group) and compared these findings with 10 asthmatic patients (five male, five female, mean age 25 ± 5-4 years) who were well controlled on inhaled corticosteroids (SR group) as indicated by their symptoms, peak flow variability (median 14 ± 0-9%) and airflow obstruction (mean FEV₁, 80-4 ± 31-6% predicted). Immunostaining was performed on biopsies by means of specific monoclonal antibodies against mast cells (AA1), eosinophils (EG2), and T lymphocytes (CD3, CD4 and CD8). BAL fluid was analysed for T lymphocyte subsets (CD4, CD8) and activations status (CD25 and HLA-DR). The a standard ABC technique did not differ significantly between the SU and SR groups with respect to submucosal mast cells (median cell/mm² 21 ± 1 ± 28-5), eosinophils (5 ± 7 ± 3-5), or T lymphocytes (52 ± 6 ± 45-5). Similarly, there were no significant differences between the two groups in the proportion of CD4+ cells (median 54-9% CD3 ± 57-9) or CD8+ (33 ± 24-4), nor in the activation markers CD25 (2-2 ± 3-0) and HLA-DR (4-8 ± 3-4). These findings suggest that either non-inflammatory mechanisms contribute to disease expression in corticosteroid unresponsive asthma or, alternatively, that proximal airway biopsies may not reflect events either in the distal airways or deeper within the airway wall.

Bronchial mucosal inflammation in patients with corticosteroid sensitive (CS) and corticosteroid resistant (CR) chronic asthma

SP MATUSEWICZ, PH BROWN, WAH WALLACE, E RAMAGE, SEM HOWIE, OK CROMPTON, AP GREENING Respiratory Unit, Western General Hospital and University Department of Pathology, Edinburgh Bronchoscopic procedures have increased our understanding of asthma immunopathology, but most studies have looked at patients with mild asthma. Such studies have tended to show increased numbers or activation of lymphocytes and eosinophils (Eos). Our aim was to examine, with immunohistochemical staining, bronchial mucosal biopsies from severe chronic asthmatic patients. We have bronchoscoped a group of non-smoking, clinically stable patients with severe asthma and chronic daily symptoms despite high dose inhaled (800–3200 μg/day) steroids ± systemic steroids (mean age 51 years; histamine PC₂₀ < 1 mg/ml; FEV₁, 62% predicted). Asthmatic patients were defined as relatively corticosteroid resistant (CR) by a failure of PEF, or mean FEV₁ compared to predicted. We used a panel of monoclonal antibodies for a panel of cell surface markers. Positive cells were counted by eye with light microscopy and an image analysis system (HOME) and quantified as number of +ve cells/mm² submucosa (group mean data (SE)). No differences were seen between the

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre</th>
<th>Post</th>
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<tr>
<td>CR</td>
<td></td>
<td></td>
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<tr>
<td>CS</td>
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</table>
groups for leucocytes (CD45), cells (CD33), or type II MHC anti- gens. Corticosteroid resistant asthma was associated with reduced submucosal CD4 counts compared with CS asthma and increased NK cells compared with normal controls.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Control (n = 7)</th>
<th>CS asthma (n = 9)</th>
<th>CR asthma (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>28 (8)</td>
<td>±43 (6)</td>
<td>±16(5)*</td>
</tr>
<tr>
<td>CD8</td>
<td>35 (9)</td>
<td>41 (8)</td>
<td>71(22)</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>7 (2)</td>
<td>28 (8)</td>
<td>14(6)</td>
</tr>
<tr>
<td>NK cell</td>
<td>14 (2)</td>
<td>10 (4)</td>
<td>±26(7)*</td>
</tr>
</tbody>
</table>

*p < 0.05 (ANOVA); p < 0.05 (t test)

Airborne inhalable dust and fungi in homes of asthmatic patients and matched controls

A MACLEAN, I HOGG, E CORNER, G MORRIS, K ANDERSON Department of Respiratory Medicine, Western Infirmary and Department of Environmental Health, University of Strathclyde, Glasgow

Indoor air is the major source of inhalable material in winter, the constitution of which is determined by heating, ventilation, and predominant use of a particular room. We studied the indoor environment of 49 homes under varying circumstances to establish a local range of measurements for airborne dusts and fungi. Our homes contained 12 subjects with asthma who lived in nine different houses and nine similar houses for comparison. The other houses were selected for study under circumstances that we considered would be the dustiest conditions possible during occupation—in homes undergoing renovation, and in moderately dusty circumstances during a house removal. The asthmatic patients were volunteers who attended the chest clinic in the hospital and did not perform any specific dust lowering manoeuvres. Airborne samples were taken with low volume cyclone samplers for dust and SAS samplers for fungi. The highest dust and fungal counts were in the houses undergoing renovation where fungal counts normally do not have a specific pattern recorded in 6/15 (>5600 colony forming units/m3) and higher during than after renovation in all the other homes. Respirable dust was also significantly lower (mean 0·6 (0·37) v 0·11 (0·07) mg/m3). A similar, less pronounced pattern was found during and after house moving.

Sump bay fever: a new inhalational fever associated with a Pseudomonas laden water aerosol

A SARTAINSON, J C JAYES, G MCGILL, C MCHARRY Department of Respiratory Medicine, Western Infirmary, and Environmental Health, University of Strathclyde, Glasgow

A cross sectional survey was performed in an industrial complex after several employees complained of feverish, flu-like symptoms which seemed to be work related. These symptoms appeared as episodes, and were attributed to the generation of aerosol spray from a covered 130 000 gallon pool (surface 15 × 4 metres) by pumps that recirculated the water flow from test rigs. All staff within the complex of buildings (n = 83) completed a screening questionnaire for symptoms, and attended for interview and clinical examination.

Prevalence of respiratory symptoms among workers in the Irish mushroom industry

D MOLONEY, J HAYES, G KELLY, O DOYLE, M FITZGERALD National Agricultural and Veterinary Biotechnology Centre and Departments of Medicine, and Statistics, University College, Dublin, Ireland

Mushroom workers are exposed to a variety of fungi, bacteria and chemicals that may induce respiratory disease. We assessed the prevalence of respiratory symptoms in an interview administered questionnaire (modified MRC) among 254 (77%) workers in the mushroom industry from nine rural based compost yards and mushroom growing units. Of those questioned 117 (46%) were women. There were 132 (52%) current smokers and seven (3%) ex-smokers, mean age 30 (4·1) (range 15-61) years. Workers were categorised according to their job description. The overall number of workers with at least one symptom was 28%. Prevalence of symptoms that improved when away from the workplace included dry cough (16%), cough with phlegm (15%), a wheeze or whistle in breathing (8%), difficulty with breathing (8%), tightness of chest (13%), fever/general aches and pains following work (24%), and flu-like symptoms in association with work (13%). A positive response to two asthma questions (sleep disturbance and early morning symptoms) was found in 6-7% of the population. Similarly a positive response to two of three symptoms of allergic rhinitis (difficulty breathing, flu-like symptoms and fever/general aches and pains) was found in 5-1% of the population. Using stepwise regression analysis there was a significant association of exercise induced cough among mushroom pickers and flu-like symptoms among compost workers (p < 0·05). There was no relation with age, smoking and cigarette smoking or duration of exposure. Thermophilic actinomycetes, Aspergillus and Penicillium species were the most common microorganisms identified (Burkard spore trap analysis).

Method of quantifying dampness in homes

1 WILLIAMSON, G MCQUEEN, C MARTIN, R MTON, A FENNERTY Department of Respiratory Medicine, Southern General Hospital, Glasgow and Healthy Homes Ltd, Glasgow

Dampness in homes has been associated with an increased risk of respiratory symptoms, but methodological differences make an objective measurement of dampness in homes difficult. Previous methods include identifying dampness and mould growth by questionnaire or detecting dampness with an electronic meter. Neither are reliable for quantification purposes. We describe a quick, semiquantitative method of assessing dampness in homes. The important measure of dampness is the excess free moisture within a material that is available to support mould growth. By trapping a small volume of air exposed to the surface of a material, water vapour evaporating from the material will raise the relative humidity (RH) of the air until both are in equilibrium. We measured RH after equilibration times of one and five minutes with a digital hygrometer probe sealed within a rubber hemisphere at the surfaces of wood and plaster board that had acclimatised to humidity values of 66, 79, 88, and 100%, ranges normally found in indoor homes in the United Kingdom. The free moisture content of the wood samples (WM) at each humidity could be predicted from standard theoretical sorption isotherms. We checked this by weighing the sample before and after drying at 110°C. WM as assessed by drying gave values similar to those predicted from the sorption isotherms. The RH values after one minute of equilibration were about 10% below, and the five minute values fell within the predicted RH range. To minimise survey times, a compromise two minute period of equilibration is recommended. By adding a constant 10% to this RH value all readings were within 5% of predicted. There were no significant differences in the RH values obtained from wood or plaster exposed to similar levels of humidity. We suggest that RH can be used in medical surveys to quantify dampness in homes, giving information on its severity and hence likelihood of mould growth, both of which may have an impact on health.
and PIVC) was normal in 77/81. Transfer factor was normal in all those with the fever symptoms. Chest examination was normal in 80/81. Chest radiology was normal in five subjects who were the highest exposed and most symptomatic including the only man who was ill enough to stop work. These findings superficially resemble humidifier fever, which also has a water based cause, but in this case the illness occurred in the absence of air conditioning, in a building designed around 750 metres of pipe of varying calibre and the sumptuous bay that seemed to have been the cause.

Quality of self recorded peak expiratory flow

PGF GANNON, S DICKINSON, D HITCHINGS, PS BURGE ON BEHALF OF THE OCCUPATIONAL ASTHMA SYSTEM GROUP Occupational Lung Disease Unit, Hartlands Hospital, Birmingham and Electronic Engineering, Staffordshire University, Stafford 1 Little information exists on the quality of self recorded peak expiratory flows (PEF). Twelve workers with a suspected diagnosis of occupational asthma recorded PEF at and away from work with a self recording electronic PEF meter (Midland Thoracic Society). This dates and times each reading and records up to five readings per test session. A manual record was also kept including date and time of PEF to the nearest hour. On return six sets of records were technically unsuitable for analysis (for example, corrupted electronic memory). The remaining records (mean duration:19 days, mean number of readings per day: 7) were analysed. 99.2% of test sessions contained at least three PEF readings and 95.1% of sessions had a 5% reproducibility between the two highest PEF readings per session. In 92.6% of sessions the electronic memory confirmed that a reading had actually been taken as manually recorded, 7.4% of manual readings per session were therefore probably falsified. The manually timed recording was out by one hour on 17.8% occasions (two hours in 2.1%). These results suggest that workers can carry out PEF readings to the recommended standard without supervision. Occasional falsification of readings and errors of manual timing of up to two hours are unlikely to affect diagnosis of occupational asthma. More accurate timing is required for some forms of analysis such as spectral analysis. [PGF Gannon is supported by the Health and Safety Executive, UK.]

Computer assisted diagnosis of occupational asthma (OA)

PGF GANNON, DT NEWTON, J BELCHER, CPA PANTIN, PS BURGE Occupational Lung Disease Unit, Hartlands Hospital, Birmingham and ICHRC, North Staffordshire Hospital Centre, Stoke A computer assisted diagnostic aid, OASYS, for identifying work-related effects in serial peak expiratory flow (PEF) measurements, based on expert practice is under development. 86 PEF records from workers under investigation for possible OA were scored by an experienced observer. Each work or rest period was scored for changes consistent with OA. Scores ranged from 1-4 (1 = 0% chance of OA, 2 = 1-49%, 3 = 50-99%, 4 = 100%). 50 measurements of PEF change comparing each work or rest period with the surrounding periods were reduced by discriminate analysis to the most predictive measurements for the score for these periods. The analysis gave two formulae with which OASYS scored each period in a manner similar to the expert. The score for the whole PEF record was obtained by adding the period scores, with a weight for scores 1 and 4. The OASYS scores were compared with the experienced observer scores on 40 new records. The results are encouraging, the score produced by the observer being closely matched by OASYS. [PGF Gannon is supported by the Health and Safety Executive, UK.]

Tuberculosis in a cohort of gold miners

RL COWIE Department of Medicine, Ernest Oppenheimer Hospital, Welkom, South Africa A cohort of 1153 southern African gold miners including 818 men and 335 men with chronic simple silicosis were followed up for seven years by routine radiological surveillance and with a central tuberculosis diagnostic service and registry. Tuberculosis was diagnosed in 23 (1% per annum) of the men without silicosis and in 155 (2.7% per annum (pa)) of the men with silicosis. The relative risk for tuberculosis was 2.8 (95% CI 1.9-4.1) for the men with silicosis compared with the similar aged men without silicosis. The risk of developing pulmonary tuberculosis increased with the extent of silicosis: 2.2% pa for category 1 nodule profusion, 2.9% pa for category 2 and 6.3% pa for category 3 (x2 = 9.8, df 2, p = 0.007). Extrapulmonary tuberculosis developed in 30 men and there was no significant difference in the proportion of extrapulmonary to pulmonary tuberculosis between the men with and those without silicosis. In a separate study which included 73 men with silicosis from the cohort, 240 miners with silicosis with category 2 or greater nodule profusion had Mantoux tests with 5 TU. The tests were positive (>9 mm induration) in 238 men: a prevalence of 99% tuberculin positivity in this population. It appears that these men with silicosis were highly susceptible to infection with Mycobacterium tuberculosis and had a roughly three-fold increase in risk of developing pulmonary tuberculosis.

Long term efficacy of short course chemotherapy for pulmonary tuberculosis in men with silicosis

RL COWIE Department of Medicine, Ernest Oppenheimer Hospital, Welkom, South Africa There has been concern about the long term risk of relapse following short course chemotherapy for pulmonary tuberculosis in subjects with silicosis. In this study of gold miners, 549 consecutive cases of pulmonary tuberculosis assessed for the presence of silicosis were followed up since completion of treatment for tuberculosis. The men received streptomycin 1 g IM, rifampicin 600 mg, pyrazinamide 2 g and isoniazid 300 mg given daily on weekdays for 5 months. The last man included in the study completed treatment 5 years before 20 December 1992. A total of 167 of the 549 men had evidence of silicosis on their initial chest radiograph. All of the men were followed up to the time of their departure from mine service, relapse, or 20 December 1992 by the routine mine radiological surveillance for tuberculosis and by a central tuberculosis registry. A total of 29 of the 167 men with silicosis had died or moved away leaving 796 person-years and 43 of the 382 men without silicosis followed up for 1826 person-years suffered a relapse of their tuberculosis. The incidence density ratio for relapse of tuberculosis in men with silicosis was 1.55 (95% CI 0.97-2.48) that for the men without silicosis. There was no difference in the pattern of relapse over time between the two groups: the mean period to relapse in the men with silicosis was 2.6 (SD 1.89) years and for the men without was 3.1 (SD 2.23) years (p = 0.6). It seems that silicosis causes a small increase in the risk of relapse of tuberculosis that might justify an extension of the treatment period in such cases.

Lung function of workers seeking compensation for "welder's lung"

M MOHAN, SC STENTON, EH WALTERS, DJ HENDRICK Regional Unit for Occupational Lung Disease, Newcastle General Hospital, University of Newcastle upon Tyne After a recent court settlement, a large number of welders have been encouraged to seek compensation for "welder's lung". The aim was to see how many welders with a history of exposure to welding fume, rather than siderosis. We have analysed the lung function of 82 such claimants (two women, median age 55 (range 28-78) years) referred for assessment by local solicitors. They had selected themselves because of a belief that welding fume had adversely affected their health. Their median exposure time to welding fume was 25 years (range 0-49) years. 55 had spent more than 30% of their time working in confined spaces. 24 were never smokers and 58 were current or ex-smokers. 64 complained of breathlessness. NYHA grade >3 (within the time of diagnosis of tuberculous lung disease caused by exposure to welding fume, rather than siderosis). FEV1, TLC and KCO measurements were significantly lower in smokers than non-smokers (<0.01) but were unaltered by the degree of exposure to welding fume or work in confined spaces. 33 workers were thought by the assessing physician to have asthma or possible asthma. 18 had >15% reversibility of FEV1, and 10 had reversibility in the range 10-15%. This might represent a high asthma prevalence among welders, or a selection bias making asthmatic welders more likely to
Hospital admissions for asthma in relation to a sugar beet factory in Kidderminster

S WALTERS, J JACKSON, J AYRES, C BELLINGHAM Institute of Public and Environmental Health, University of Birmingham Medical School, Chest Research Institute, Birmingham Heartlands Hospital, and West Midlands RHA Information Department, Birmingham. The standardised hospitalisation ratio for asthma was noted to be high in Kidderminster DHA during routine study. We investigated a reported association with a sugar beet factory. Processing takes place between the months of October and February. This was studied using Korner inpatient data for 1988-91 for the residents of Kidderminster DHA. There was a peak of asthma admissions between October and February among children <15 living in Kidderminster that was not seen in the rest of the West Midlands, nor for other diagnoses in Kidderminster residents. There were 7-9% (95% CI 3-4%-12-4%) more asthma admissions between October and February in Kidderminster than in the rest of the Region. Four groups were studied by computer mapping of postcodes: group A (n = 433), children <15 admitted to hospital for asthma; group B (n = 177), children <15 admitted to hospital for other acute respiratory conditions; group C (n = 909), random sample of acute non-respiratory hospital admissions in children <15 (hospital controls); group D (n = 461), random sample of children <15 from the FHSA register (1992) (community controls). The proportion of asthma admissions living <1 km and >1 km from the factory were quite similar to the same proportions in each control group. The odds ratio (OR) for asthma (group A) against community controls was 1.52 (95% CI 1.02-2.52, p < 0.05), and for asthma against hospital controls was 1.46 (1.05-2.04, p < 0.05). The OR was not significantly raised for a similar analysis for other respiratory admissions (group B). When potential confounding effects of other factories to the north were removed by inclusion of only residents living within 2.5 km of the factory, the ORs were even higher, 2.36 (1.49-3.75, p < 0.05) and 1.71 (1.14-2.56, p < 0.05), respectively. The raised ORs and unusual seasonality of admissions suggest that emissions from the sugar beet factory may be affecting the health of children with asthma in this area of Kidderminster.

Effect of an air pollution episode on respiratory function of patients with asthma

S WALTERS, J MILES, J AYRES, G ARCHER Institute of Public and Environmental Health, University of Birmingham Medical School, and Chest Research Institute, Birmingham Heartlands Hospital An unusual pollution episode occurred in Birmingham between 17 and 27 December 1993. Levels of ozone (up to 0.3 ppm), particulates (PM 10), and NO2 were high, peaking in the area. Residential and hospital asthma admissions increased. We studied 92 patients with asthma living within 5 km of the enhanced urban air quality monitoring station in Birmingham to determine the effect of the pollution episode. The level of change (mean difference ± standard error) was 1.6 ± 1.2% for FEV1, 5 ± 2.5% for FEV/FVC, and 15.6 ± 20.5% for PC20 histamine. The effect was most marked in children. The peak value of PC20 was 207% (95% CI 162-252). These changes are likely to be due to the pollution episode.
Peak flow variability and asthma severity

JP JAMISON, RK MCKINLEY School of Biomedical Science, Medical Biology Centre, Queen's University of Belfast, Belfast Asthmatic subjects (n = 123), aged 10–70 years, recorded their peak expiratory flow (PEF) three times daily for 12 days. Several indices of PEF and its variability were correlated with a severity score which was the sum of four symptoms and four limitations of lifestyle due to asthma, each graded 0–5 (Soc Sci Med 1987:25:1033–8). Significant negative linear correlations with the severity score were obtained for the minimum and maximum PEF on the day of greatest variability, the overall mean PEF for the 12 days, and the FEV1 (r < 0.3, p < 0.0003). There were significant positive linear correlations with the severity score for PEF amplitude variability as a percentage of minimum, maximum, or mean PEF (r > 0.2, p < 0.02). Wheeze was best correlated with PEF variability and exercise limitation was best correlated with the FEV1. Variability of PEF amplitude, if uncorrected for baseline PEF, was not linearly dependent on the severity score (r = +0.07, p = 0.43), increasing with severity at low scores and decreasing again at high scores (quadratic coefficient = −0.17, p = 0.01). Similar curvilinear dependency on the severity score was obtained for PEF amplitude variability as a percentage of predicted PEF. These data suggest that PEF variability is a suitable index of asthma severity when the PEF variability is expressed as a percentage of some measure of the subject's actual baseline PEF.

Regression coefficients (95% CI); Y = a + b (severity score)

\[
\begin{align*}
\text{FEV1, } (\% \text{ predicted}) & = 92 - 1.11 \text{ (−1.69 to −0.52)} \\
\text{Minimum PEF (} \% \text{ predicted)} & = 86 - 1.14 \text{ (−1.69 to −0.59)} \\
\text{Maximum PEF (} \% \text{ predicted)} & = 109 - 1.10 \text{ (−1.66 to −0.54)} \\
\text{Mean PEF (} \% \text{ predicted)} & = 105 - 1.13 \text{ (−1.70 to −0.56)} \\
\text{PEF amplitude/minimum PEF (} \% \text{)} & = 96 - 0.47 \text{ (−0.69 to +1.63)} \\
\text{PEF amplitude/mean PEF (} \% \text{)} & = 27 + 1.00 \text{ (+0.25 to +1.75)} \\
\text{PEF amplitude/mean PEF (} \% \text{)} & = 24 + 0.49 \text{ (+0.08 to +0.90)} \\
\text{PEF amplitude/predicted PEF (} \% \text{)} & = 24 + 0.04 \text{ (−0.23 to +0.32)}
\end{align*}
\]

What do general practitioners carry for the assessment and treatment of asthma?

SA EVANS, JN STONE, CG HARDY Unit M6, Manchester Royal Infirmary, Oxford Road, Manchester and Petholow Medical Centre, Middleton The British Thoracic Society (BTS) guidelines on asthma management (BMJ 1990;30:651–3 and 797–800) were issued in response to the unacceptably high morbidity and mortality associated with asthma in the United Kingdom. They suggest how acute severe asthma should be assessed and treated. To determine if the equipment and drugs routinely carried by general practitioners (GPs) are appropriate for this, a brief questionnaire was sent to the 102 GPs on the medical list of the Rochdale Family Health Services Authority. 64 GPs responded. 55% carry peak expiratory flow meters (PEFM) 38% carry drugs, 33% nebulizers, and 50% either a spacing device or a nebulizer. The % of respondents carrying each drug was β agonists: metered dose inhaler (MDI) 84%, nebulises 20%, and inhaled preparation (iv) 60%; anticholinergic drugs: MDI 21%, nebulises 5%; steroids: oral 70%, iv 66%, 88% carrying steroids in some form; theophylline: oral 28%, iv 38%; adrenaline: 73%. 56% of respondents said they would never consider using adrenaline for the treatment of acute asthma. The BTS guidelines suggest PEF as a useful criteria for assessing asthma and making treatment decisions, but little more than half the respondents carried a PEFM. Whereas the high % of respondents carrying steroids is encouraging, the fact that half carried neither a spacer nor a nebulizer suggests probable excessive reliance on the intravenous route for the administration of bronchodilator treatment.

Management of acute asthma in the accident and emergency department: how practical are the guidelines?

JM MEIGHAN, VHF MAK, DJ WILLIAMS, NT BATMAN Department of Thoracic Medicine and Accident and Emergency, St Thomas' Hospital, London The British Thoracic Society (BTS) guidelines for the management of acute asthma in the accident and emergency (A and E) department involve (i) recognition of severity, (ii) use of objective measurements, and (iii) careful assessment of response to treatment. To evaluate how practical and successful these guidelines are in a busy A and E department, we carried out a study over a four month period of patients presenting with acute asthma.

The A and E case notes of 67 consecutive adult patients were analysed retrospectively to determine how far the BTS guidelines were being followed. The BTS guidelines suggest using percent predicted or percent of previous best PEF values as an objective indicator of severity. In the 66 cases where PEF on arrival was recorded there was no indication of how this value compared with predicted or best, despite tables for predicted PEF being readily available. If the patient improved after nebulised bronchodilators, none had a further repeat assessment of the PEF after one hour as recommended. Of the 54 patients who were discharged, there was no record of whether inhaler technique was checked in 45 (83%). Eighteen patients (33%) were discharged without oral corticosteroids, only four of whom had an estimated percent predicted PEF of more than 75%. Two of these 18 patients did not receive any form of anti-inflammatory treatment (one of whom did not have bad asthma on arrival), three had inhaled steroid treatment introduced, three were told to take previously prescribed inhalers, and four had their inhaler steroid dose increased. Twelve patients were given oral corticosteroids without addition of inhaled steroid treatment. All but one patient were given a letter for their general practitioner. In conclusion, asthmatic patients discharged from the A and E department are not assessed for maintenance improvement after nebuliser treatment. Very few have their inhaler technique checked as a cause of treatment failure, and some were discharged without appropriate anti-inflammatory treatment. This could be due to the time constraints faced upon the casualty officers and nurses in a busy A and E department.

Primary care treatment for acute asthma in the accident and emergency department: are the British Thoracic Society guidelines being followed?

JN MEIGHAN, VHF MAK, NT BATMAN Department of Thoracic Medicine, St Thomas' Hospital, London If a patient attends the accident and emergency (A and E) department with acute asthma, this may imply failure of prior treatment. These patients should be identified as requiring more careful monitoring and reappraisal of their treatment. The British Thoracic Society (BTS) guidelines for the management of asthma suggest a stepping up or down of treatment according to a monitored response. To investigate whether the BTS guidelines are being followed in primary care for this at risk group, we undertook a retrospective study of patients registered to local GPs who attended our A and E department for acute asthma over a four month study period. The GP records of these patients were analysed three weeks after their A and E visit to assess if there was adequate monitoring of the patient's asthma, and if there were appropriate changes to treatment in response to the clinical state. The study was performed with the full cooperation of the GPs, and the retrospective nature meant that we did not influence the management of the patients in the study. We managed to follow up 41/54 patients who were discharged from A and E. All patients were given letters for their GP and told to visit them within one week; 32/41 of these were received. Of these 41 patients, only one reattended the A and E department within three weeks. Sixteen patients were monitored taking peaks before the A and E visit, six patients were prescribed home peak flow meters on discharge from A and E, and all of these continued to use them. Four patients were using self management plans before the A and E visit, two patients were given one on discharge, and a further two by their GPs after their A and E visit. The nine patients whose asthma had improved significantly were discharged from the A and E department. It was not clear whether all patients had stopped taking inhaled corticosteroids (ICS), two were not taking any prophylactic treatment, and the other six remained on their current dose of ICS. Of 32 patients who were stable or improving, six were not taking any form of prophylactic treatment, seven actually stopped taking ICS, 13 remained on the same dose, two had a dose increase, and two had a reduction in their ICS dose. In conclusion, despite the existence of BTS guidelines for over two years, their recommendations are still not being acted upon, even in an at risk group.
In acute severe asthma is arterial blood gas analysis always essential or can measurement of arterial oxygen saturation be used to determine which patients require blood gas measurement?

DM Curruthers, BDW Harrison Department of Respiratory Medicine, West Norwood Hospital, Bosthorpe Road, Norwood. We aimed to determine whether arterial oxygen saturation (So2) as recorded by pulse oximeter in patients admitted with acute severe asthma was a safe and reliable method of predicting those in respiratory failure and therefore in need of more aggressive management. We defined to be the So2 below which arterial gases should be taken as safe asthma management. Arterial blood gases and So2 by pulse oximeter were measured in seventy five patients admitted consecutively with acute severe asthma to our respiratory medical ward. Measurements were made either on or off oxygen at the initial assessment, along with other indices of asthma severity.

Results showed that 62 out of 75 patients had a So2 >92%. Only two of these had a PaO2 <8 kPa and one other had a PaO2 >6 kPa. None of the others had arterial blood gases indicating respiratory failure. When an So2 >90% is considered (70 out of the 75 patients) then six had blood gases indicating respiratory failure. It seems that in the initial assessment of acute asthma an So2 >92%, as measured by pulse oximeter, indicates that respiratory failure is unlikely and therefore measurement of arterial blood gas is unnecessary. We recommend that blood should be taken in patients who have an So2 <92% and in other patients whose condition deteriorates as assessed by other standard criteria no matter what the initial So2.

Effect of inhaled corticosteroids on blood spot cortisol concentrations in asthmatic children

JM Doull, SJ Donovan, PJ Wood, ST Holgate University Medicine and Regional Endocrine Laboratory, Southampton General Hospital, Southampton. Conventional dynamic testing of the hypothalamic-pituitary-adrenal axis shows little measurable effect in asthmatic patients on normal doses of inhaled steroids. We have developed a new method of measuring cortisol by fingerprint on to blotting paper. This is acceptable to children and has excellent correlation with conventional plasma cortisol assays (r = 0.965). We used it to assess the effect of inhaled steroids on daytime cortisol. 20 mild to moderate asthmatic children aged 7 to 9 years were randomised to receive double blind either placebo or beclomethasone dipropionate (200 μg twice daily). Blood was taken by fingerprint immediately on waking in the morning (T1), and treatment was given. Blood was then taken at one hour after treatment (T2), at lunchtime (T3), and in the evening (T4). Area under the curve (AUC) for the four time-points was calculated as a composite index of daytime cortisol. Blood spot cortisols fell progressively during the day at each time from a mean of 226±8 nmol/l at T1 to 56±4 nmol/l at T4. Mean cortisol in the steroid treated group was lower at times T1, T2, and T3 but reached significance only at T2 (111±5 vs 203±9 nmol/l, p < 0.04). Mean AUC for the steroid treated group was significantly decreased (487±333, p < 0.03). Thus blood cortisol is significantly decreased immediately after inhalation of steroid and, furthermore, composite daytime cortisol is significantly decreased.

Serum magnesium in elderly inpatients with acute asthma

DS Renwick, MJ Connolly Robert Barnes Unit, Manchester Royal Infirmary. Serum magnesium (Mg) supplementation can cause bronchodilatation in hypomagnesaemic asthmatic patients. Magnesium deficiency may be common in the elderly. We have assessed serum Mg in acute elderly asthmatic inpatients >65 years with acute asthma (suggestive history plus 15% peak flow (PEF) variability). Those with smoking history >10 pack years, renal failure, or recent change of diuretic were excluded. On admission serum electrolytes including Mg, evidence of chest infection (pyrexia, high white cell count, chest x ray film changes), and PEF response to nebulised bronchodilators were measured. 29 subjects were included (21±75 years), mean age 78±9 (range 69-92) years. Mean serum Mg was 0.82, range 0.59-1.01 (normal 0.6-1.0) μmol/l. Mean Mg of a group of elderly controls (mean age 79) was 0.75±5 μmol/l (NS). Serum Mg was not lower in subjects on diuretics and was not related to PEF response. 20 subjects had evidence of chronic obstructive airways disease (COPD), nine subjects did not (group B). Serum Mg and potassium (K) concentrations were significantly higher in group A than group B (see table). Serum Mg was higher in group A than in controls (p < 0.008). Acute asthma in the elderly is not associated with hypomagnesaemia. Patients with chest infection have higher serum Mg than non-infected patients and controls; this may reflect electrolyte changes associated with infection. Measurement of serum Mg does not contribute to the management of elderly patients with acute asthma.

Effect of inhaled corticosteroids on blood spot cortisol concentrations in asthmatic children

JF Miles, G Garden, JG Ayres Chest Research Institute, Birmingham. Psychological morbidity in severe asthma has been well documented but there have been few interventional studies undertaken in adult asthma. We studied eight patients (six women), mean age 44 (range 19-68) years, with well characterised severe asthma who attended weekly group sessions for six months in the presence of a facilitator. Each patient completed three questionnaires covering various psychological variables (GHQ6, Living with Asthma Questionnaire, Asthma Symptom Checklist) and were interviewed about their coping skills with asthma (Sibbald, Thorax 1989), at the beginning and the end of the six month period covering the months of May to October 1992. Eight age/sex and treatment matched patients with severe asthma who did not attend the group also completed the above assessments. Objective measures of lung function were measured at their routine outpatient visits over the study period. No significant changes in coping strategies during attacks occurred over the six month period. Patients’ knowledge of what they should do during attacks differed greatly from what they actually did. At a point when oral steroids should have been started, 13 out of the 16 patients delayed, although recognising that use of steroids was appropriate. All 16 patients delayed seeking medical attention because they knew that the consequence of so doing would be admission to hospital. Reported use of oral steroids was comparable in the two groups over the six months before the intervention (mean dose per month 249±247 mg) but fell significantly to a mean of 141 mg/month in those attending the group and rose to a mean of 379 mg/month in the non-attenders. At the end of the six month period there was a significant improvement in the GHQ score in the active group (31±6 to 14±7, p < 0.003) compared with the controls (19±5 to 18±2, p = 0.84). No consistent difference was seen in the other two questionnaires. No changes in mean group FEV1% could be shown (active 65±6 to 63±7, p > 0.87; passive 68±4 to 64±2, p > 0.76).

Choosing an alternative to the metered dose inhaler: the patient’s preference

D Dockrell, MJ Rooney, P Kelly, L Clancy Peamount Hospital, Newcastle, Co Dublin, Ireland 43 patients with chronic obstructive airways disease/asthma and 20 normal controls were instructed in the use of all inhaler devices. Questionnaires were administered to determine preference in learning, inhaler technique, and overall preferred device. 63 people took part in the study and the results are shown in the table. 35 of the 43 preferred the Turbohaler inpatients. They are easier to learn and more acceptable to use. Patient compliance will be improved by prescribing devices that they would prefer.

<table>
<thead>
<tr>
<th>Most preferred device</th>
<th>Easiest device to learn to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autohaler</td>
<td>Autohaler</td>
</tr>
<tr>
<td>Turbolahler</td>
<td>Turbolahler</td>
</tr>
<tr>
<td>MDI</td>
<td>MDI</td>
</tr>
<tr>
<td>Rotahaler</td>
<td>Rotahaler</td>
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<td>Volumatic</td>
<td>Volumatic</td>
</tr>
<tr>
<td>Spinhaler</td>
<td>Spinhaler</td>
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<tr>
<td>Dischaler</td>
<td>Dischaler</td>
</tr>
</tbody>
</table>

Adaptable inhalation technique

<table>
<thead>
<tr>
<th>Adequate inhalation technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autohaler</td>
</tr>
<tr>
<td>Turbolahler</td>
</tr>
<tr>
<td>MDI</td>
</tr>
<tr>
<td>Rotahaler</td>
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<tr>
<td>Volumatic</td>
</tr>
</tbody>
</table>

Thors: first published as 10.1136/thx.48.10.1052 on 1 October 1993. Downloaded from http://thorax.bmj.com/ on September 15, 2023 by guest. Protected by copyright.
β₂ agonist dose reduction: strategy and early results

MJ PEETERS, DH YATES, KF CHUNG, PJ BARNES
Department of Thoracic Medicine, National Heart & Lung Institute, Dovehouse St, London

The use of high doses of inhaled β₂ agonists has been associated with an increased risk of death from asthma, accelerated decline in lung function and increased asthma morbidity. The excess risk of death seen with the more potent β₂ agonist, fenoterol, in comparison with salbutamol, was greatest with nebulised treatment. The use of 50 puffs of salbutamol per week has been associated with a doubling in the risk of asthma death, yet an equivalent amount of nebulised salbutamol is used at one or two doses. By inference, reduced β₂ agonist consumption may improve asthma control but rapid reduction from high doses arouses reasonable concern in both physician and patient. We have used a five stage outpatient strategy to evaluate, in an open study, the effects of β₂ agonist dose reduction. Phase 1: Long acting and oral β₂ agonists are tapered or ceased; phase 2: 2 mg salbutamol doses are changed to 2-5 mg, at most four/day; phase 3: 2-5 mg doses are sequentially replaced with four puffs from an MDI; phase 4: the number of MDI puffs per dose is halved to two; phase 5: salbutamol is used as required only. Intervals between reductions are at least three weeks. At entry, inhaled steroids are increased to at least 1500 μg BDP (subject 5 only—from 1000 μg) or else not changed. Anticholinergics and theophylline are not changed. Oral steroids may be reduced in parallel. Eight patients have been recruited of whom five have been followed up for over three months. Data at baseline and latest follow up are shown. To this time, no complication has occurred. No patient has been kept in hospital with asthma. With this protocol, reduction in β₂ agonist use may be achieved without hospital but the frequent outpatient visits are time consuming for all involved. The rate of reduction seems to be safe and has proved acceptable to patients. In this group, it has been associated with reduction in oral steroid requirement and/or improvement in lung function but coincidental change and/or placebo effect cannot be excluded in this open study. Although not a primary aim, there is an associated cost saving for pharmaceuticals of £1230 (410) per patient. Caution-ous attempt reduction in β₂ agonist use should be further evaluated as a cheap, non-toxic alternative to methotrexate or cyclosporine.

Baseline Follow up

<table>
<thead>
<tr>
<th>Age Sex</th>
<th>Year(s)</th>
<th>Salt/Long Pred (mg/day)</th>
<th>FEV₁ (litres)</th>
<th>Duration Salt/Long Pred (mg/day)</th>
<th>FEV₁ (litres)</th>
<th>% Pred (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58/M</td>
<td>7</td>
<td>6-6</td>
<td>37.5</td>
<td>34</td>
<td>16</td>
<td>0-4</td>
</tr>
<tr>
<td>60/P</td>
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<td>31</td>
<td>20</td>
<td>19</td>
<td>12</td>
<td>0-2</td>
</tr>
<tr>
<td>45/P</td>
<td>5</td>
<td>28</td>
<td>15</td>
<td>29</td>
<td>9</td>
<td>3-5</td>
</tr>
<tr>
<td>65/P</td>
<td>3</td>
<td>13</td>
<td>5</td>
<td>13</td>
<td>5</td>
<td>4-6</td>
</tr>
<tr>
<td>58/P</td>
<td>6</td>
<td>20</td>
<td>25</td>
<td>50°*</td>
<td>4</td>
<td>0-8</td>
</tr>
</tbody>
</table>

*Predicted PEF: this patient cannot perform spirometry.

[MJP is an Allen and Hanbury/Thoracic Society of Australia and New Zealand Travelling Fellow.]

Retrospective review of the use of budesonide nebuliser solution (Pulmicort Respules) in the treatment of chronic severe asthma

S BUTTERFIELD, G BOOTH, S MARGOL, ST ATHERTON, DR GRAHAM WHITSON Hospital, Prescot, Merseyside

There are few published data available on the efficacy and side effects of budesonide nebuliser solution (Pulmicort Respules, Astra). This study on 37 asthmatic patients (13 males, 24 females) examined our experience with this new preparation. Patients received the drug for a mean of 18-5 (range three-46) weeks. A questionnaire was used to compare symptoms before and after treatment with budesonide. Objective measurements included FVC, FEV₁, PEF. Concurrent treatment before and after budesonide treatment was also examined. Symptom scores improved in 17 patients, 15 were unchanged, and five became worse. Mean FVC before treatment was 2-66 (0-81) l compared with 2-82 (0-8) l while on budesonide. FEV₁ improved from 0-82 (0-72) l to 1-02 (0-72) l. Peak expiratory flow rate was more variable, however, and there was an overall impression of improvement (before 266(118) and 397(97) l/min after). Thirty three patients were on oral steroids. There was a fall in the daily mean dose of prednisolone before treatment from 24-9 (13-3) mg to 13-2 (8-6) mg on nebulised budesonide (p < 0-001). There was a high incidence of side effects, which occurred in 26 out of the 37 patients, they reported nose bleeds, sore throat, and headache. Side effects were severe enough to stop treatment in 14 patients (two due to pregnancy). Nebulised budesonide seems to be effective, providing improved control of chronic severe asthma with decreased oral prednisolone. This effect may be due directly to inhaled steroid deposition in the lung or could be due to increased systemic absorption from the stomach. Further prospective evaluation of this expensive preparation is required before it becomes part of accepted practice in the treatment of asthma.

Trial of a "credit card" asthma self management plan in adult asthma

W D'SOUZA, C BURGESS, C CULLING, M ATSON, N PEARCE, J CRANE, R BEASLY
Department of Medicine, Whelton School of Medicine, Wellington, New Zealand

The aim of this study was to assess the efficacy of a credit card asthma self management plan in a high risk group of asthmatic patients. In an open prospective trial adult asthmatic patients treated and discharged for acute asthma in the emergency department of Wellington Hospital were invited to attend a series of hospital outpatient clinics at which the "credit card" asthma self management plan was introduced. The "credit card" plan uses guidelines for the self management of asthma based on patient self assessment of PEF recordings and symptoms, printed on to two sides of a plastic "credit card". Questionnaires were used to compare markers of asthma morbidity and use of medical care six months before and six months after intervention with the "credit card" plan. Of the 30 eligible patients who attended the first outpatient clinic, 26 (21 female) completed the programme. Among these 26 participants the proportion walking with asthma more than once a week decreased from 65% to 23% (p = 0-005), the proportion reporting a day "out of action" decreased from 58% to 19% (p = 0-01), and the proportion visiting the emergency department with acute asthma decreased from 58% to 15% (p = 0-04). Other markers of medical care utilisation also improved. Our findings suggest that the "credit card" asthma self management plan can be an effective and acceptable system for self managing asthma, when used as part of an asthma educational programme.

Assessment of peak flow monitoring on respiratory wards

MB ALLEN, J PRASAD, RL PAGE, SP PEARSON, MF MUERS
Department of Respiratory Medicine, Whittington Hospital, Whittington, London

Peak flow (PF) measurements are important in monitoring the response to treatment in patients with airflow obstruction admitted to hospital. Such measurements are usually made by the patient under nurse supervision. We have attempted to determine the accuracy of this monitoring. Fifty eight patients performing PF measurements on three chest wards in two hospitals were examined. The highest and mean of three previously recorded routine nurse supervised flows were compared with three doctor supervised flows by the same study doctor (CP), with the patient's own Mini Wright (MW) meter. The comparisons were made within 30 minutes of each other and always more than four hours after inhaled bronchodilators. The nurses were unaware of the study objectives. Also, three blows with the standard Wright (SW) meter were obtained by the doctor. Mean (SD) results were calculated for the 58 patients and compared by means of the paired t test and Bland and Altman plots. The mean difference between the nurse and doctor supervision was 11-1 l/min for the highest blow and 15-5 l/min for the mean of three blows. These results confirm that the MW overestimates PF in the range of our subjects. "Routine" PF measurements were significantly lower than those obtained by the study doctor, although the differences for both the highest and mean values are probably too small to be of clinical significance.

Reference equations for spirometric indices in native Nigerian men

GE EHRABO
Respiratory Department, Bristol Royal Infirmary, Bristol

Presently there are few reference equations available for spirometric indices in native Nigerian men. Measurements of peak expiratory flow (PEF, l/min), forced expiratory volume in one second (FEV₁, l...
livers) and forced vital capacity (FVC, litres) were obtained in 241 male subjects who had a normal clinical examination, chest x ray film, and no history of cardiopulmonary disease. PEF was measured on a Wright meter, and FEV1, and FVC were measured on a wedge-bellows spirometer. The age range was from 19 to 60 (mean 29.9 years and standing height from 1.54 to 1.93 (1.71) m. Dynamic lung volumes were determined by the body plethysmograph, with increasing age and significantly increased with increasing height. Regression analysis of each index against Ht and age gave the equations:

\[
\begin{align*}
\text{PEF} & = 350 \text{Ht} - 1.28 \text{Age} - 33.9 & \text{RSD} = 53.7 \text{r}^2 = 0.228 \\
\text{FEV1} & = 3.85 \text{Ht} - 0.28 \text{Age} - 2.50 & \text{RSD} = 50.9 \text{r}^2 = 0.393 \\
\text{FVC} & = 4.62 \text{Ht} - 0.24 \text{Age} - 3.42 & \text{RSD} = 56.2 \text{r}^2 = 0.368 \\
\text{FEV1} & = -0.21 \text{Age} + 92.8 & \text{RSD} = 5.39 \text{r}^2 = 0.111
\end{align*}
\]

where RSD is the residual standard deviation and FEV1% is the FEV1/FVC. These relations were not improved by the inclusion of body mass and various transformations and interactions of age, standard height and body mass. Comparison of these equations with the European survey equations showed that, although the decline in dynamic lung volumes with age was similar, the FEV1, and FVC were about 20% lower in Nigerian men. For PEF, there was a smaller decrease with age in Nigerian men than in European men, with PEF values being 6% lower at age 20 and 3.5% higher at age 60. [G. E. Ethabor is a British Thoracic Society Overseas Fellow.]

**Inspiratory muscle strength assessed by occlusion of mouth pressure switches induced by magnetic stimulation of cervical nerve roots**

PF DE BRUIN, A WATSON, NB BRIDE. Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London Cervical magnetic stimulation (CMS) has been shown to induce maximum activation of the diaphragm [Similowski et al. J Appl Physiol 1989;67:1311-8]. We have examined the reliability of mouth pressure switches elicited by CMS in the assessment of inspiratory muscle strength by obtaining simultaneous measurements of transdiaphragmatic, oesophageal, and mouth pressure switches (Pdi, Poes, Pm) in five normal men (mean age 32-2(1) 8 years). Subjects were studied on two separate days, seated, with the neck flexed 60° from the vertical and breathing through a mouthpiece. CMS was produced by a magnetic stimulator connected to a 90 mm diameter coil (Magnet 200, Magstim Comp, UK). Single supra maximal stimuli were delivered at FRC during relaxation and while performing graded voluntary isometric inspiratory efforts against a closed airway. As voluntary effort transdiaphragmatic pressure (Pdi) increased, Pm decreased linearly (lowest r = 0.87). The relationship between voluntary oesophageal pressure (Poes) and Pm was similar (lowest r = 0.89). Pm during relaxation was unreliable due to poor transmission of intrathoracic pressure, but during all voluntary efforts the relation between voluntary mouth pressure (Poes) and Pm was also linear (lowest r = 0.84) and very close to Poes = Pm (table). On average, our subjects voluntarily generated 99, 101, and 101% of the maximum Pdi, Poes, and Pm estimated by extrapolating the equations above to the axis. These studies confirm that CMS induces maximum activation of the inspiratory muscles. Twitch pressures induced by CMS can be used at the mouth in normal subjects, providing a simple and non-invasive technique for estimating true maximum strength of the inspiratory muscles.

**Effect of anterior spinal surgery via a thoracotomy incision on lung volumes in idiopathic scoliosis**

WJM KINNAR, L WATSON, JK WEB, IJA JOHNSTON. Harlow Wood Orthopaedic Hospital, Mansfield and University Hospital, Nottingham. In patients with idiopathic thoracic scoliosis, correction of the spinal curvature by posterior instrumentation leads to a small increase in vital capacity (VC). We have investigated whether this is also true when the spine is approached anteriorly through a thoracotomy incision. We studied 10 patients (nine women) median (range) age 30 (23 to 39) years and pre-op Cobb angle of 60 (38 to 110) degrees. All were over 18 years of age at the time of operation. Lung volumes were measured with a wedge spirometer (Vitallograph) for VC and helium dilution (PK Morgan) for residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC). Preoperative VC was 76 (39 to 100%) predicted. Nine patients had a Zielke procedure and one an anterior release. Four subsequently also underwent posterior instrumentation. Lung volume measurements were repeated, with the same equipment, at least one year after surgery. Comparative changes in VC, residual volume (RV), and total lung capacity (TLC). TLC and FRC were not significantly different. Anterior spinal surgery leads to a fall in TLC. This seems to be related to an increase in RV, the reasons for which are unclear, as correction of ribcage deformity should increase chest wall compliance and lead to a fall in RV.

**Excursion-volume relation of the diaphragm measured by ultrasonography with a fixed transducer: normal values**

E COHEN, PH HEWGOOD, KMURPHY, J BOULTREE, A GUZ. Departments of Medicine and Radiology, Charing Cross and Westminster Medical School, London. We have used a new technique to assess the relation between diaphragmatic excursion (Poes Tol, Pdi Tol, Pm Tol) and transdiaphragmatic and lung volumes (Vl) using simultaneous M-mode ultrasonography and pneumotachography. A specially designed frame was built to hold the transducer in a fixed position. All studies were carried out in the supine position. Fifteen normal subjects were tested (ages 22 to 73 years, seven women). In 10 subjects, excursion of the right and left posterior hemidiaphragms was measured in a coronal plane with Vl varied up to 1.2 above functional residual capacity (FRC). At a larger Vl, the diaphragmatic view was obscured. Measurements in the longitudinal plane subcostally were carried out in 10 subjects on the right side only, as the view of the left hemidiaphragm is obscured by air in the stomach. In this position Vl varied up to 3 1 above FRC. Results are summarised in the table. Measurements in the coronal plane were larger (p < 0.05) than in the longitudinal plane due to an angle between the M-mode line and the cephalo-caudal movement of the diaphragm. Confirming the results of Houston et al, British Thoracic Society winter meeting, 1992, we conclude that the relation between the excursion of the hemidiaphragm and Vl is linear over the range studied. Ultrasonography of DE is a simple quantitative technique that could be applied in the clinical investigation of patients with suspected abnormalities of diaphragmatic movement.

| Y = DE (cm); X = Vl (%) |
| Slope (X/Vl) cm/l (SD) | Intercept (Y) cm (SD) |
| Right coronal | 0.949-0.997 | 3.24 (1.26) | 0.03 (0.39) |
| Left coronal | 0.942-0.999 | 3.78 (1.72) | 0.15 (0.64) |
| Right longitudinal | 0.968-0.996 | 1.86 (0.53) | 0.85 (0.34) |

**Diaphragmatic movement in hemiplegic patients measured by ultrasonography**

E COHEN, PH HEWGOOD, KMURPHY, J BOULTREE, A GUZ. Departments of Medicine and Radiology, Charing Cross and Westminster Medical School, London. Automatic breathing is controlled by centres in the lower brain stem, whereas voluntary breathing is controlled by cerebral cortical centres. In hemiplegic patients due to a lesion above the brain stem, there is confusion whether excursion of the hemidiaphragm is affected on the paralysed side. We planned to compare right and left diaphragmatic excursion in both voluntary and automatic breathing. Because a normal difference exists between the sides, it was necessary to compare both types of breathing on each side separately at a range of tidal volumes. Six normal subjects (three men) average age 65 (SD 8) range 54-73, and seven hemiplegic patients (two men) average age 61 (8) range 51-75, were studied. Four patients had a right hemiplegia and three had a left hemiplegia, all with a unilateral suprabrainstem lesion shown by CT. None suffered from respiratory disease. The subjects' inspired volume and diaphragmatic excursions were measured simultaneously in the supine position with pneumotachography and M-mode

**Effect of anterior spinal surgery via a thoracotomy incision on lung volumes in idiopathic scoliosis**

WJM KINNAR, L WATSON, JK WEB, IJA JOHNSTON. Harlow Wood Orthopaedic Hospital, Mansfield and University Hospital, Nottingham. In patients with idiopathic thoracic scoliosis, correction of the spinal curvature by posterior instrumentation leads to a small increase in
ultrasoundography in the coronal plane. In the normal subjects, the difference of excursions at a V 2 of 600 ml between voluntary and automatic breathing was 0-04(0-08) cm and 0-17(0-21) cm for the right and left sides respectively. The diaphragmatic excursions in the stroke patients are summarised in the table. We conclude that on the paralysed side in some hemiplegic patients there is an impairment of diaphragmatic movement during volitional compared with automatic breathing.

<table>
<thead>
<tr>
<th>Phlegic side</th>
<th>Right diaphragm</th>
<th>Left diaphragm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluntary</td>
<td>Automatic</td>
<td>Voluntary</td>
</tr>
<tr>
<td>Right</td>
<td>0-95 cm</td>
<td>1-90 cm</td>
</tr>
<tr>
<td>Right</td>
<td>1-27 cm</td>
<td>1-43 cm</td>
</tr>
<tr>
<td>Right</td>
<td>1-77 cm</td>
<td>2-80 cm</td>
</tr>
<tr>
<td>Right</td>
<td>2-00 cm</td>
<td>1-70 cm</td>
</tr>
<tr>
<td>Left</td>
<td>1-07 cm</td>
<td>1-27 cm</td>
</tr>
<tr>
<td>Left</td>
<td>0-20 cm</td>
<td>2-15 cm</td>
</tr>
<tr>
<td>Left</td>
<td>2-22 cm</td>
<td>2-51 cm</td>
</tr>
</tbody>
</table>

Effect of probe tissue separation on laser Doppler measurements of nasal and forearm blood flow

SC TOYNTON, AR ROBSON, RC SCHROTER, NB PRIDE Department of Medicine, RFMS Hammersmith Hospital and Centre for Biological and Medical Systems, Imperial College, London Many of the problems experienced when using laser Doppler flowmetry (LDF) to assess nasal mucosal blood flow are due to technical difficulties with probe positioning. Probe mucosal separation is required as even minimal physical stimulation of the inferior turbinate induces reflex congestion and rhinorrhea, especially in rhinitic patients. The effect on raw flux (Fn), normalised flux (Fn), and surface laser power (dc) of increasing the probe-surface distance was investigated with the inferior nasal turbinate, forearm skin, and a 0-5% (v/v) suspension of 500 nm diameter latex microspheres to simulate tissue with random, homogenous flow. Separation distances were measured with a probe holder mounted on a vernier scale. A laser Doppler flowmeter (Moor Instruments MBF2D) was used supplying a 1 mW power output of 810±10 nm laser light with an angular spread of about 40°. Settings were: time constant = 1 s, sampling rate = 10 Hz, filter bandwidth = 14-9 kHz with probe fibre separation distance of 0-5 mm. Mean values from data collection times of one minute were used. Fn values are normalised for power fluctuations at the photodetector by dividing by the square of the dc. Concentration readings become inaccurate at high flow rates and so are unreliable for nasal use. No significant changes in Fn, as compared with the touching values, were found for the turbine (Fn at 3 mm p = 0-09; n = 12). No clear decrease in dc was seen until 2-5 mm (p < 0-02) although there was a trend towards an increase in Fs as Fn went up to 1-5 mm. Similarly, no significant changes were seen using forearm skin (at 4 mm Fn p = 0-20; dc p > 0-10) although again there was a trend towards an increase in dc at 1-5 mm. Therefore, for nasal mucosal and skin, probe-mucosal separation, within normal working limits of up to 3 mm, does not significantly alter Fn values. By contrast, a mean decrease in Fn of 42-5% (SE 2-2%; p < 0-03) and an increase in dc of 119% (SE 19%; p < 0-03) were seen for the latex suspension, both being maximal at 1-5 mm. This study highlights the dependence of laser Doppler instruments on algorithmic assumptions and confirms the suggestion that probe-mucosal separation up to 3 mm is unimportant in the nose (Olsson, Bende and Ohlin 1985). The weighting factor used for generating the flux value is valid for nasal mucosa. The microsphere suspension, however, has different surface and deep optical properties hence the failure of the normalisation procedure to maintain linearity of the Fn signal. These findings are probably relevant when making LDF measurements elsewhere in the respiratory tract.

Arterial earlobe blood gas analysis: an underused technique

AD PITKIN, CM ROBERTS, JA WEDZICHA Department of Thoracic Medicine, London Chest Hospital, Bonner Road, London Measurement of arterial blood gas tensions is a routine part of the assessment of patients with respiratory and other disorders producing abnormalities of gas exchange. Direct arterial puncture is routinely used in clinical practice but it must be performed by qualified medical staff, is time-consuming, and may result in significant discomfort and morbidity for the patient. Techniques for sampling of arterialised capillary blood from the finger pulp and the earlobe were first described over two decades ago and although close agreement between arterial and earlobe samples has been reported in normal subjects (Br J Dis Chest 1976;70:263) the technique is not in common use. We tested the accuracy of earlobe blood gas sampling in 40 unselected patients attending for lung function testing with a wide range of values of Pao2 and Paco2 by measuring blood gas in simultaneously earlobe and arterial samples. We also conducted a survey of other hospitals to find out how commonly the technique is used elsewhere, and the reasons, if any, for not adopting this method. We found a close concordance between earlobe and arterial blood gas tensions over a wide range of values of Pao2 (95% confidence intervals −0-1 to +0-72 kPa) and Paco2 (95% confidence intervals −0-25 to +0-68 kPa). A particularly good correlation between samples was observed at Pao2 values lower than 8 kPa. Above this level the earlobe Paco2 tended to be slightly lower than the arterial Paco2. Nearly all values however lie within 0-5 kPa or less and underestimation of true Paco2 at higher levels of oxygenation is unlikely to be of clinical significance. Fifty United Kingdom hospitals with a respiratory department were surveyed by telephone. Of these, nine used the earlobe arterial technique and two had plans to introduce it. In 32 centres the main reason for not using earlobe blood gases was that the laboratory staff were unaware of the technique. In three hospitals a blood gas analyser was not available in the laboratory. In two centres the main technique was considered inaccurate and in a further two there were insufficient technical staff to carry out the procedure. Our data indicate that earlobe blood gas analysis is sufficiently accurate to be reliably substituted for arterial sampling in routine clinical practice. Despite its advantages, most centres in the United Kingdom do not use the technique. The main reason for this seems to be lack of knowledge of its existence or uncertainty over its accuracy.

Oxygen saturation during methacholine challenge in a mixed population

DS RENWICK, MJ CONNOLLY Manchester Royal Infirmary It is unclear whether the fall in arterial oxygen saturation during non-specific bronchial challenge relates to degree of bronchoconstriction produced or to dose of challenge agent given (Fontana et al, Am Rev Respir Dis 1991;143:A411). We tested this in 133 subjects (80 women) aged 24 to 87 (mean 56 years) undergoing methacholine challenge by dosimeter (Connolly et al, Am Rev Respir Dis 1991;143:A411). The mean fall in arterial oxygen saturation in the large number of subjects over a wide age range is not 0-17 (1)). Seven normal subjects (80 women) aged 24 to 87 (mean 56 years) underwent methacholine challenge by dosimeter (Connolly et al, Am Rev Respir Dis 1991;143:A411). The sample included those with and without airways obstruction. These with baseline FEV1 < 60% predicted were excluded. Arterial oxygen saturation was monitored by finger oximetry. Bronchial responsiveness was expressed as methacholine dose causing 20% fall in FEV1 (PDE20), 78 subjects achieved a PDE20. Mean fall in oxygen saturation (fallSa02) was 2-4% (SE 2-2%; p < 0-001) while regression analysis showed independent positive relations between fallSa02, baseline Sa02 (p = 0-007), log of total methacholine dose (p < 0-0001) and %fall in FEV1 (p = 0-008). FallSa02 was independently negatively related to age (p = 0-015) and baseline actual FEV1 (p = 0-003). Coefficient of multiple regression (r) = 0-48. Methacholine challenge can produce appreciable desaturation in those receiving large doses of methacholine, or developing marked bronchoconstriction. Desaturation is not greater in the elderly.

Within breath changes in respiratory impedance and correlations with forced spirometry during bronchochallenge in normal and asthmatic subjects

D MACLEOD, W VAN DER PUTTEN, J FRICHARD Department of Clinical Medicine, Trinity College, St James's Hospital, Dublin, and Manitoba Cancer Treatment Research Foundation, Winnipeg, Canada Alterations in airway calibre and the airway wall are a feature of asthma and may partially explain respiratory impedance changes in this condition. We used 10 Hz monosinusoidal forced oscillation measurements gated by computer to end-inspiration and endexpiration (Van der Putten et al, Thorax 1993 (in press)) during methacholine challenge tests (European Respiratory Health Survey Protocol) to determine correlations of impedance, reactance, and resistance with FEV1, and FEF25-75%. Seven normal subjects (three men aged 23 (0-5), four women aged 21 (1)) and four asthmatic patients not taking oral steroids (two men aged 21:5 (0-5), two
women aged 22 (1)) were studied. One asthmatic and one normal subject smoked. Data acquisition was for 54 seconds (sampling rate 25 Hz) with respiratory cycle monitoring for gating. Gated impedance and resistance rose during challenge with significant negative correlations with FeV1, and FEF25-75 in all asthmatic patients (except one excluded from challenge by sensitivity to control nebulisation) and in normal patients showing a 10% or greater fall in FeV1 (r = -0.7 to -0.8, p < 0.05, df 6). Gated reactance was positively correlated with FeV1, in asthmatic patients (r = +0.78 to +0.88, p < 0.01, df 6), compatible with other studies. Asthmatic patients also had 0-4-2-5 Hz spikes in impedance with a phase angle maximal at the time of PDI=FeV1, and reversed by inhaling 200 µg salbutamol.

Pulmonary resistance is diminished by exercise in asthmatic patients

S FREEDMAN, R LANE, P BOYLE, A GUZ Department of Medicine, Charing Cross and Westminster Medical School, London. Despite the recognition of exercise as a common precipitant of asthma, there is a paucity of measurements of airway patency made during exercise rather than afterwards. We have measured total pulmonary resistance (Re) in six asthmatic patients, aged 35-51 years, who all had exercise induced symptoms. Re was calculated breath by breath from flow and oesophageal pressure with a hybrid computer (Lane et al. Clin Sci 1991;82:31). Patients abstained from all treatment for 12 hours before the test, and mean initial FeV1 was 53% predicted (range 18%-78%), and corresponding Re 5-25 (range 3-0-10-45) cm H2O/l/s. Exercise was for 10 minutes on a cycle ergometer at around two thirds of predetermined maximum in an air conditioned room maintained at around 18°C. Patients achieved maximum steady state ventilations of 45-102 l/min. In five patients Re fell within three minutes of the start of exercise by 44-58%, to reach minimum values of 1-5-5-3 cm H2O/l/s. Re was unchanged in the sixth patient, but in all there was a significant rise in Re within five minutes of the end of exercise to values equal to or greater than the pre-exercise level. From our previous work on methacholine induced bronchoconstriction in normal subjects (Freedman et al. Thorax 1988;43:631-6) we believe the fall in resistance to be due to the increased tidal volumes, which cause a disproportionate increase in hysteresis of large airways compared with lung parenchyma.

Stage changes and awakenings as indicators of sleep architecture: effect of patient group and an acclimatisation night

MARTIN ALLEN, KEITH PROWSE City General Hospital, Stoke on Trent, Staffs. The number of changes in sleep stage has been suggested as a useful measure of sleep architecture. No single laboratory has assessed the usefulness of stage changes (SCs) and awakenings (As) as an indicator of sleep architecture in either different subject groups or after an acclimatisation night. Nine normal subjects, five patients with chronic obstructive airways disease (COAD) and seven patients with obstructive sleep apnoea (OSA), underwent full polysomnography on two consecutive nights. Sleep was staged visually with 20 second epochs by one experienced scorer. The number of SCs and As were counted by the scorer from sleep onset to set time for a comparable ratio in all three subject groups. No significant differences were found between the two consecutive nights within the same group or for all three groups together. Between subject groups the only significant differences were in the number of SCs between the OSA and COAD patients on the first (p = 0.03) and second nights (p = 0.05). Although SCs and As were greater in patients with OSA, the results suggest that routine calculation of SCs and As are of little clinical use in assessing sleep architecture.

<table>
<thead>
<tr>
<th></th>
<th>Stage changes</th>
<th>Awakenings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>2nd</td>
<td>1st</td>
</tr>
<tr>
<td>Normal</td>
<td>17-3 (7.1)</td>
<td>15-5 (3.7)</td>
</tr>
<tr>
<td>COAD</td>
<td>11-0 (4.1)</td>
<td>12-2 (4.7)</td>
</tr>
<tr>
<td>OSA</td>
<td>22-4 (10.1)</td>
<td>20-7 (8.3)</td>
</tr>
</tbody>
</table>

Results are means (SD).

Scoring of apnoeas during sleep

AH KENDRICK, N WILTSHIRE, JR CATTARALL Sleep Unit and Respiratory Department, Bristol Royal Infirmary, Bristol. Apnoeas are routinely scored in the assessment of patients with breathing disorders during sleep (BDS), and may be categorised as obstructive, central, or mixed. The definitions and techniques used to score apnoeas vary, however. The purpose of this study was to examine the diversity of definitions used to score apnoeas. Eighty questionnaires were sent worldwide to sleep centres with an interest in BDS. Each was asked to give their precise definition of each type of apnoea in terms of the magnitude of desaturation, the duration of the event, and the inclusion of thoracoabdominal movement (TAm) and airflow. Scoring of hypopnoeas was asked separately. 36 questionnaires were returned. One centre did not score apnoeas in these terms, but scored only arousals; six did not score mixed, and two did not score central apnoeas. 32/35 centres used complete absence of airflow with continued TAm to define obstructive apnoeas; 25/33 centres required complete absence of TAm and airflow to define central apnoeas; and 24/29 centres defined a mixed apnoea as a central followed by an obstructive apnoea. We conclude that (1) there is not complete agreement on the definitions of scoring apnoeas, and (2) until such time as universal definitions are agreed, the precise definition of each type of apnoea should be included in epidemiological and intervention studies.

Addition of sound recording to oxygen saturation in screening a snoring population for obstructive sleep apnoea

JES WHITE, AJ SMITHSON, PR CLOSE, MJ DRINNAN, AJ PRICHARD, CJ GRIFFITHS, CJ GIBSON Departments of Respiratory Medicine, Medical Physics, and Ear, Nose, and Throat Surgery, Freeman Hospital, Newcastle upon Tyne. Recording of overnight oxygen saturation (Sao2) is often used as a screening tool for possible obstructive sleep apnoea (OSA) but is unreliable in less severe cases (Cooper et al. Thorax 1991;46:586-8). We postulated that the addition of sound recording would improve the sensitivity of the method. Thirty nine full sleep studies including sound measured by calibrated sound level meter were performed on snorers who were being investigated for possible surgical treatment. Polysomnography showed an apnoea/hypopnoea index (AHI) > 20 events per hour of sleep in five subjects, > 15 in seven, and > 10 in 21. Two experienced observers independently and without knowledge of the other data scored paper records of Sao2, alone and Sao2, plus sound level. Records were classified as OSA unlikely, equivocal, or definite. The addition of sound reduced the number of equivocal results from 23 to 14. The sensitivity and specificity of the screening investigations were calculated by defining a positive test as one where both observers reported OSA definite; any other classification was taken as negative. The resulting values depend on the level of OSA used to define OSA and are shown for different criteria in the table. We conclude that (1) an appreciable number of snorers referred for possible surgical treatment have unrecognized OSA, (2) the sensitivity of oximetry with or without sound recording increases as the threshold AHI used in diagnosis of OSA increases but at the expense of decreasing specificity, and (3) in the recognition of mild OSA the addition of a sound profile increases sensitivity without impairing specificity.

<table>
<thead>
<tr>
<th>Definition of OSA</th>
<th>Sao2 alone</th>
<th>Sao2 and sound</th>
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</thead>
<tbody>
<tr>
<td>AHI &gt; 10</td>
<td>Sensitivity</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Specifcity</td>
<td>1.00</td>
</tr>
<tr>
<td>AHI &gt; 15</td>
<td>Sensitivity</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>Specifcity</td>
<td>0.94</td>
</tr>
<tr>
<td>AHI &gt; 20</td>
<td>Sensitivity</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Specifcity</td>
<td>0.94</td>
</tr>
</tbody>
</table>
Central versus reflex activation of genioglossus muscle in subjects after laryngectomy

JA INNES, MJ MORRELL, I KOBAYASHI, RD HAMILTON, A GIZ
Department of Medicine, Charing Cross Hospital, London Activation of the genioglossus (GG) muscle during inspiration may help to defend upper airway (UA) patency in humans. Such activation may occur by central respiratory drive or as a reflex response to the negative pressure present in the UA or trachea during inspiration. To differentiate between these mechanisms, we studied seven subjects who have undergone laryngectomy and breathe only via a tracheal stoma. Square wave negative pressure stimuli (−15 cm H2O for 0.5 s) were applied at functional residual capacity (a) by facemask to the isolated UA and (b) to the stoma. GG activity was recorded with intranoral bipolar surface EMG electrodes, and quantified as described previously (Horner et al. J Physiol 1991;436:15–30). As a measure of spontaneous central respiratory drive, we quantitated (by RMS integration) phasic and tonic GG activity during normal and inspiratory loaded stomal breathing. Significant activation of GG occurred with stimuli of −15 cm H2O applied to the isolated UA (mean ratio post/pre stimulus EMG 1.70, p < 0.01) but the same stimuli caused no significant activation when applied to the stoma (ratio 1.22, p = 0.06). In five of the subjects, larger stimuli (−25 cm H2O) were also applied; these again caused significant activation of GG when applied to the UA, but not when applied to the stoma. During normal breathing, four of five subjects showed phasic inspiratory GG activation; with inspiratory loading all five showed increased phasic and tonic activation. We conclude that in these subjects, inspiration activates GG via central respiratory drive; negative tracheal pressure alone does not activate GG. By contrast, despite the absence of the larynx, negative pressure in the isolated UA can reflexly activate GG without airflow or respiratory effort.

Deleterious effect of nasal continuous positive airways pressure (NCPAP) on cardiac function in chronic heart failure (CHF)

R LISTON, PC DEEGAN, C MCCREERY, R COSTELLO, B MAURER, WT MCNICHOLAS Departments of Respiratory Medicine and Cardiology and the Respiratory Sleep Laboratory, University College and St Vincent’s Hospital, Dublin 4, Ireland NCPAP has been reported to improve cardiac function acutely (over a 10 minute period) in chronic heart failure (CHF) (Am Rev Respir Dis 1992;145:377–82), and also during sleep in patients with coexisting sleep apnoea (SAS) and CHF. We assessed the effect of NCPAP on cardiac function over three hours in seven male patients aged 51–75 years with stable severe CHF (ejection fraction <30%), all of whom had atrial fibrillation. Subjects completed the protocol and all had overnight sleep studies by standard polysomnography to investigate any associated SAS. After Swan–Ganz catheter insertion, patients were commenced on NCPAP (5 cm H2O) and standard haemodynamic variables were measured at baseline, at regular intervals during NCPAP application, and then at six hours. All patients had pulmonary capillary wedge pressure (PCWP) >12 mm Hg and showed a significant deterioration in cardiac function during NCPAP (table shows means) that recovered after withdrawal. Two patients had SAS (26 and 18 apnoeas and hypopnoeas/hour of sleep). We conclude that NCPAP has a detrimental effect on cardiac function during wakefulness, even in patients with SAS.

<table>
<thead>
<tr>
<th>Time</th>
<th>CI (l/min/m²)</th>
<th>SI (ml/min)</th>
<th>SBP</th>
<th>SVR</th>
<th>RAP</th>
<th>PCWP</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>3·5</td>
<td>46·7</td>
<td>134</td>
<td>1229</td>
<td>8·2</td>
<td>19</td>
<td>82</td>
</tr>
<tr>
<td>15 min</td>
<td>3</td>
<td>41·6</td>
<td>142</td>
<td>1227</td>
<td>8·2</td>
<td>19</td>
<td>82</td>
</tr>
<tr>
<td>2 h</td>
<td>2·9</td>
<td>38·6</td>
<td>151</td>
<td>1521</td>
<td>9·3</td>
<td>22·7</td>
<td>82</td>
</tr>
<tr>
<td>3 h</td>
<td>3</td>
<td>39·3</td>
<td>152</td>
<td>1473</td>
<td>10·8</td>
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<td>82</td>
</tr>
<tr>
<td>Recovery</td>
<td>3·4</td>
<td>39·6</td>
<td>148</td>
<td>1353</td>
<td>8·8</td>
<td>21·7</td>
<td>82</td>
</tr>
<tr>
<td>p</td>
<td>0·005</td>
<td>0·002</td>
<td>0·007</td>
<td>0·002</td>
<td>0·07</td>
<td>0·27</td>
<td>0·9</td>
</tr>
</tbody>
</table>

CI—cardiac index; SI—stroke index (by thermodilution); SBP—systolic blood pressure, RAP—right atrial pressure (mm Hg); HR—heart rate; SVR—systemic vascular resistance (dynes/s/cm⁵).

Nasal biopsies in human rhinovirus 16 infection: an immunohistochemical study

D J FRAENKEL, PG BARDIN, SL JOHNSTON, G SANDERSON, ST HOLGATE, University Centre, Charing Cross Hospital, London Rhinoviruses are a common cause of viral upper respiratory tract infection and serotype 16 (RV16) has been aetologically linked with exacerbations of asthma. Little is known of the histology of the infection and the pathophysiology of associated increases in airflow obstruction. We have studied the inflammatory changes in the cell population of the nasal mucosa during RV16 infection in 14 normal adult volunteers. Nasal biopsies were taken twice before inoculation. RV16 was then inhaled on the days 2 and 3 of a one week hospital admission with appropriate isolation procedures. Nasal biopsies were taken on day 6, and then again after six weeks of convalescence. Biopsies were fixed in acetone and processed into glycol methacrylate resin for semi-thin sectioning. Immunostaining used the streptavidin-biotin peroxidase technique with appropriate monoclonals to enumerate cell types; A1–mast cell type (anti-A1 antibody); EG2–eosinophil cationic protein (CD3, CD4, CD8 T-cell markers; and neutrophil elastase. All patients developed colds confirmed by symptom scores, viral culture, and serology. Thirty two biopsies were evaluable from 13 subjects. Median cell counts for baseline, infection and recovery phases respectively were: (cells/mm²): mast cells 26,29,18; eosinophils 2·2, 1·0, 0·7; neutrophils 21, 31, 27; lymphocytes 3·2, 1·4, 1·1. No differences were found in cell types between the different phases (Wilcoxon paired test, p > 0·05). This is in keeping with previous semiquantitative studies and suggests that mediator release rather than increased cellularity may be responsible for coryzal symptoms. [This work was supported by The British Council, Schering-Plough, Australian Bicentennial Scholarship, British Lung Foundation.]

Rhinoviral infection of nasal epithelium detected by non-isotopic in situ hybridisation

PG BARDIN, SL JOHNSTON, G SANDERSON, S ROBINSON, M PICKETT, ST HOLGATE, Immunopathology, Institute of Respiratory Medicine, General Hospital, Southampton Rhinoviruses (HRVs) are the predominant cause of the common cold and HRV serotype 16 (HRV16) may increase bronchial responsiveness and late asthmatic reactions. It is not known whether HRVs infect cells other than nasal epithelium. We have examined nasal epithelium in vivo to explore localisation of HRV infection, employing non-isotopic oligonucleotide probes and in situ hybridisation (ISH). Sections (4 m) were cut from six paired nasal biopsies obtained before and during HRV16 colds in four volunteers and two wild type HRV colds. Oligonucleotide probes were 3 labelled with biotin-1-DUTP and hybridisation was performed with two antisense oligonucleotides, a sense probe and control probe. Sections were washed at high stringency and the signal detected with the streptavidin-biotin-alkaline phosphatase method. Controls included RNase digestion, a control probe and a control slide lead (2·2, 1·0, 0·7) to adeno- and influenza A virus. Specific hybridisation signals to (+) viral strand were obtained in nasal epithelium from three subjects (one HRV16 and two wild type HRV). Intracellular HRV16 replication could be confirmed by demonstration of hybrids of oligonucleotide and sense probe. All patients had pulmonary capillary wedge pressure >12 mm Hg and showed a significant deterioration in cardiac function during NCPAP (table shows means) that recovered after withdrawal. Two patients had SAS (26 and 18 apnoeas and hypopnoeas/hour of sleep). We conclude that NCPAP has a detrimental effect on cardiac function during wakefulness, even in patients with SAS.

Cytokine profile of lung tissue in lung transplant recipients

J J GOAN, S GUY, N YONAN, P HASLETON, A WOODCOCK North West Lung Centre, Cardiorthacic Surgery and Histopathology Department, Wythenshawe Hospital, Manchester, and Department of Medical Genetics, St Mary’s Hospital, Manchester Bronchoalveolar lavage (BAL) fluid provides a ready source for the study of cytokines in lung transplantation. BAL is, however, subject to various factors that may influence the quality of the sample as a source for cytokine study with reverse transcription polymerase chain reaction. We have therefore examined directly the lung tissue of lung transplant recipients to build a cytokine profile of the tissue. Prospectively, lung tissue was obtained by standard transbronchial biopsy technique from six lung transplant recipients (four heart and lung, two single lung). Six biopsies were routinely taken from each patient to assess the presence of rejection or infection and one extra biopsy (average size 1 mm²) was saved for cytokine study. Lung rejection was graded by international classification. A total of 13 biopsies were examined for IL-1, 112, IL-3, IL-4, 116, IL-8, 1110, TNF α, TGF β, and γ interferon. To confirm extraction of undegraded high molecular weight RNA
and satisfactory reverse transcription, all biopsies were examined with primers for glyceraldehyde 3 phosphate dehydrogenase, β-actin and c-abl. In five normal biopsies and one biopsy with CMV inclusion bodies (no pneumonitis) no cytokine signals were identified. Six biopsies had evidence of rejection, two A3a, one A3d, one A2d, and two A1a and one biopsy showed an inflammatory bronchitis. Positive signals for I13, I14, and I16 were found in the A3d biopsy. I16 and I13 signals were seen with the bronchitis and in one A1a biopsy. These results suggest that cytokine gene expression in lung tissue does not closely correlate with histopathological rejection.

**Bronchoalveolar lavage (BAL) macrophage, and cytokine profiles alter before respiratory disease in patients infected with HIV**

MCI LIPMAN, MA JOHNSON, DH BRAY, LW POULTER Royal Free Hospital and School of Medicine, London The degree to which the pulmonary immune system reflects the systemic immune failure of advancing HIV infection has not been well characterised. We therefore investigated interleukin 1β (IL-1β), tumour necrosis factor a (TNFα), and transforming growth factor β (TGFβ) in bronchoalveolar lavage (BAL) from HIV infected patients with and without pneumonitis and with different blood CD4 lymphocyte counts. Cell populations recovered at BAL were investigated for the presence of macrophages (MO) by using antibodies identifying antigen-presenting cells (RFD1+ D7+), effector cells (RFD7+ D1+), and suppressor cells (RFDI+ D7+). The collected supernatant was assayed for IL-1β, TNFα and TGFβ (Quantikine, R and D Systems). Results (median) are shown in the table. These data suggest that alterations in BAL cytokines and alveolar MO subsets precede HIV-related respiratory disease. Preliminary in situ hybridisation studies reveal cytokine mRNA within these MO implying that they may be responsible for the production of these cytokines in the airway.

<table>
<thead>
<tr>
<th>CD4 D4</th>
<th>HIV</th>
<th>CD4 &lt;400</th>
<th>HIV,</th>
<th></th>
<th>CD4 &gt;400</th>
<th>Normal controls</th>
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<tbody>
<tr>
<td>12.7</td>
<td>11.3</td>
<td>3.8</td>
<td>5.6</td>
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<td>7.0</td>
</tr>
<tr>
<td>27.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>68.3</td>
<td>186.9</td>
<td>75.6</td>
</tr>
</tbody>
</table>

**Eicosanoid metabolism in squamous cell carcinoma of the lung**

MARY O’SULLIVAN, FP HOGAN, D LUKE, JS PRITCHARD Department of Clinical Medicine, TCD Medical School, St James’s Hospital, Dublin Numerous studies have suggested an association between arachidonic acid metabolites (eicosanoids) and cancer. We have previously shown that normal bronchial epithelial cells metabolise arachidonic acid (15-LO) via the lipoxigenase pathway to produce 15 hydroxyeicosatetraenoic acid (15 HETE) (O’Sullivan et al Thorax 1992,47:242P). We then compared the ‘H- AA profile of normal bronchial epithelial cells with that of cells from squamous cell carcinoma of the lung. Isolated cells were prepared by enzymatic dissociation in 0.3% collagenase for 2 hours at 37°C. Cell yield and viability were determined by ethidium bromide/acridine orange staining and fluorescent microscopy. The cells were characterised by immunohistochemical staining with AE1/AE3, an anticytoketin monoclonal antibody, and with LCA, an antibody directed against leucocytes. Cell suspensions were incubated with 2 μg of ‘H- AA and calcium ionophore A23187 (2 μM) for 30 minutes at 37°C. Labelled eicosanoids released from the cells were separated by reverse phase high pressure liquid chromatography and their relative abundance was determined by β scintillation counting. The peaks were identified by coelution with authentic standards. The relative amounts of 15 HETE released by the cells were calculated as a percentage of the total radioactivity in the suspension at the end of the reaction. The relative amount of 15 HETE from ‘H- AA by tumour cells was significantly less than that of normal cells (p < 0.001). In six out of 11 patients there was no detectable 15 lipoxigenase activity in the tumour cells. The pathophysiological role of 15 HETE in vivo is not known. In vitro, 15 HETE regulates the adhesion of normal and tumour cells to the basement membrane (Buchanan et al Agents and Actions 1990,29:16) and inhibits proliferation in a variety of normal cells (Spector et al Prog Lipid Res 1985,27:271). Therefore, a reduction in 15 HETE synthesis by lung tumour cells may contribute to the aberrations in growth and differentiation characteristic of lung tumour progression. A causal relation between eicosanoid metabolism and lung cancer has yet to be established, however.

**Smoking related bronchial inflammation**

MI IRISDALE, S WANKLYN, P PHILLIPS, T KRAUSZ, PW IND Departments of Medicine and Cytopathology, Hammersmith Hospital, Du Cane Road, London Quantitative induced sputum cytology provides a simple, non-invasive assessment of bronchial inflammation. Smoking related airway diseases involve inflammation of large and small airways. We examined the effect of smoking by inducing sputum and simultaneously determining bronchial responsiveness in three groups of subjects free of infection. We studied 13 non-atopic non-smokers (mean age 32 years; N), eight smokers (one atopic, mean age 45 years, mean pack-years 34, SM), and four ex-smokers (one atopic, mean age 64 years, mean pack-years 73, who have stopped smoking for a mean 12-5 years; EX). Hypertonic (4-5%) saline (HS) was nebulised for increasing time periods (0-5-16 minutes) as a bronchial challenge. FEV1 was measured at baseline and one minute after each inhalation period. Sputum expectorated during the procedure was collected. Differential cell counts (mean of four counts of 500 cells) were performed on direct smears stained with Chromotrope 2R. Mean baseline FEV1 (% pred) was 107 (95% CI 101–113 for N, 97 (87-106) for SM (p < 0.05), and 69 (40-93) for EX (p < 0.01 v SM, p < 0.001 v N). Mean maximum fall in FEV1, on challenged 4-4 (2-7-6-1) % for SM (p < 0.01), and 22.8 (18-7-26-8) % for EX (p < 0.01 v SM, p < 0.001 v N). Adequate sputum samples were obtained from 11/13 N, 6/8 SM, and 4/4 EX. There were no differences in % lymphocytes, eosinophils, or epithelial cells between the three groups. Neutrophil counts (%) were 23-6 (9-9-29-4) for N, 42-3 (26-5-52-6) for SM (p < 0.002), and 60-2 (15-1-65-7) for EX (p = 0-07 v N). Median (range) % macrophages on differential counts were 62-3 (54-4-74-7), 46-0 (40-1-65-0), and 30-1 (26-6-51-3) for N, SM, and EX, respectively (p < 0.05 v SM, p < 0.005 v N v EX). We have found no previous work on quantification of induced sputum in smokers. We report significantly increased numbers of neutrophils, which have not been found in bronchial biopsies or bronchoalveolar lavage. Preliminary results suggest that this effect persists long after stopping smoking.

**Lung interstitial albumin increases after 24 hours exposure to 100% oxygen**

ENS O’GORMAN, KLI WEIR, DJ GODDEN, JAS ROSS, PW JOHNSTON Departments of Pathology, Medicine, Environmental, and Occupational Medicine, University of Aberdeen, Scotland Exposure of rats to high concentrations of oxygen produces pulmonary interstitial oedema visible microscopically after 48 hours (Kistler et al J Cell Biol 1967,33:605–20), attributed to increased capillary permeability. We postulated that this increase considerably predeates oedema, and used a new model (Langston et al Cell Invest 1986,5:49–56) to study the effect of 100% oxygen on lung lymphatic permeability. Rats were killed by intraperitoneal injection of anaesthetic, lungs were fixed in situ by instillation of glutaraldehyde (1-15%, 350 mOsm, pH 7-4, 4°C), and processed to LR White acrylic resin. Sampling protocols used systematic randomisation to avoid bias, and six large bronchial biopsy blocks from six were sectioned and stained for native albumin with a two stage immunocytochemical technique marked by 10 nm colloidal gold. After morphometric quantification, adapting the method of Johnston et al (Int J Microcirc Clin Exp 1991;10:395), RAC was used as an index of capillary permeability. RAC in interstitial ground substance, expressed as mean (SE) gold particles ×104 per randomly counted point was 17-7(6-2) after 24 hours of air exposure and 31-4 (16-1) after 60 hours of air. After 24 hours 100% oxygen RAC was 98-1 (27-2) and, after 60 hours, 108-4 (18-0). These changes are related to the gas (p < 0.001) and not...
Oxidant induced pulmonary endothelial cell injury is protect-
ed by cAMP analogues

WJ Bourke, TJ McDonald. Department of Respiratory Medicine, St Vincent's Hospital, Dublin and University College, Dublin, Ireland.

The protective effect of the cyclic AMP analogue dibutyryl cyclic adenosine monophosphate (db-cAMP) on in vivo models of lung injury has previously been demonstrated. We have previously shown that db-cAMP protects endothelial cells against injury from exotoxin in vitro. The manner in which db-cAMP exerts its protective influence is unknown and its efficacy against oxidant forms of endothelial cell injury is unclear. We postulated that the protective effect of db-cAMP may be related to a specific property of db-cAMP and not to the elevation of intracellular cAMP associated with cAMP analogues. To test this hypothesis we preincubated a different cyclic AMP analogue, 8-bromo-cAMP, and db-cAMP with endothelial cells before adding hydrogen peroxide (H2O2) as an oxidant injury stimulus. Endothelial cell injury was studied in bovine pulmonary artery endothelial cells (BPAEC) obtained from the American Type Culture Collection (ATCC). Standard tissue culture techniques were used and the release of incorporated radiolabeled cholesterol (3H) (0-01) was used to assess cell injury. Both db-cAMP and 8-bromo-cAMP protected against H2O2 injury. There was no difference between the two agents in the protection conferred. We conclude that the protection afforded by cyclic AMP analogues is not specific to db-cAMP and requires further studies to elucidate the mechanisms involved.

Six year experience in referral, assessment, and transplantation at Freeman Hospital pulmonary transplant unit

D Fishwick, AD Gascoigne, N Wrightson, JH Dark, PA Corris. Department of Cardiopulmonary Transplantation, Freeman Hospital, Cardiothoracic Unit, Newcastle upon Tyne. Over a six year period, commencing June 1986, 297 patients (mean age 39 years) were referred to this unit for assessment of lung or heart-lung transplantation. Six major diagnostic categories emerged (n, mean age): cystic fibrosis n = 55, 24, chronic obstructive pulmonary disease n = 74, 48, fibrotic lung disease n = 70, 48, bronchiectasis n = 29, 42, congenital heart disease n = 30, 31, and primary pulmonary hypertension n = 19, 33. A total of 92 (31%) had received a transplant up to June 1992. The mean time in days (range) from referral to assessment as a group was 81 (0-741), from referral to active listing 186 (3-1322, n = 183), and from referral to transplantation 407 (38-1027). Fifty seven patients died before transplantation while listed at a mean time of 244 days from referral, despite a mean time from referral to assessment of only 53 days reflecting recognition of the clinical urgency of the referral. The mean time from active listing to transplantation was 235 (1-860) days. This value was significantly shorter for the first 10 patients transplanted (mean 80 days, from June 87 to September 88) in comparison with the latest 10 (198, from August 92 to November 92) and peaked (mean 381 days) for the 10 patients transplanted between November 90 and May 91. The main limiting factor imposed on this form of treatment remains donor availability.

Isolated lung transplantation for cystic fibrosis

A Hasan, M Healy, AD Gascoigne, JH Dark, CJ Hilton, PA Corris. Cardiopulmonary Transplant Unit, Freeman Hospital, Newcastle upon Tyne. Heart lung transplantation was initially the operation of choice for patients with cystic fibrosis (CF) referred for pulmonary transplantation; however bilateral sequential lung transplantation (BSLT) is now becoming the operation of choice in many centres with the perceived advantage of recipients retaining their native hearts. We report our experience with this technique. Between August 1990 and March 1993, 14 patients have undergone isolated lung transplantation for CF. Thirteen patients had BSLT and one patient had single lung transplant and contralateral pneumonectomy. Their ages ranged from 15 to 30 (mean age 22) years. There were no intraoperative deaths. There were three early and one late deaths. The early deaths were due to donor organ failure, bronchial dehiscence (n = 1), and CMV pneumonitis (n = 1). The late death was due to bronchiolitis obliterans. Only two patients had significant airway complications, one with dehiscence of the right bronchial anastomosis, the other requiring stenting of the intermedi-
ate bronchus for ischemic stenosis. All surviving patients have demonstrated a significant functional improvement in their pul-
monary function as is shown in the table. Survival at six months was 86%. Actuarial survival at one year was 71% which is comparable with published data for heart lung transplantation. In conclusion isolated lung transplantation offers a good functional result and intermediate survival for patients with CF with acceptable early morbidity and mortality.

Cytomegalovirus antigenaemia: a predictor of cytomegalovirus pneumonitis/pulmonary infection in lung transplant recipients

JJ Egans, L Barber, J Lomas, A Fox, A Turner, A Woodcock. North West Lung Centre, Wythenshawe Hospital, Manchester.

Cytomegalovirus (CMV) is an accepted cause of morbidity and mortality in lung transplant patients. CMV infection carries significant morbidity and mortality. CMV antigenaemia is the demonstration of HCMV p65, an early internal matrix protein, by immunofluorescent staining using a monoclonal antibody (Biosoft) in cytoplasmic preparations of polymorphonuclear leucocytes (PMNL). The technique is rapid (three hours) and quantifiable, avoiding the need for tissue culture enhancement. We prospectively (June 92-February 93) studied the utility of CMV antigenaemia in nine lung transplant recipients surviving 100 days. Seven patients received HCMV matched grafts (two HCMV seropositive recipients, R+, D-), five HCMV seronegative recipient/donors (R-, D-). Two HCMV seropositive recipients received a graft from a seronegative donor (R+, D-). One of the R+ D+ patients was HCMV antigenaemia positive (six positive cells/50,000 PMNLs) at day 60 after transplantation and at day 91 this patient had a bronchoalveolar lavage that was HCMV positive by DEAFF and culture (no HCMV pneumonitis), while remaining IgM nega-
tive. One R+ D- patient became HCMV antigenaemia positive (50 positive cells/50 000 PMNLs) on days 50 and 57 after transplantation. He developed a significant rise in IgM in parallel with the finding of HCMV antigenaemia. One R- D+ dehiscence patient did not develop clinical or histological evidence of HCMV disease and they remained HCMV antigenaemia negative. HCMV antigenaemia may be a useful early indicator for the subsequent development of HCMV pulmonary disease/infection in lung trans-
plant recipients.

Necrotic ulcerative bronchitis as the presenting feature of lymphoproliferative disease after lung transplantation

JJ Egans, NY Yonan, PS Hasletton, KR Carroll, A Woodcock. North West Lung Centre and Departments of Cardiothoracic Surgery and Histopathology, Wythenshawe Hospital, Manchester. After lung transplantation the incidence of post-transplant lymphoproliferative disease (PTLD) is in the region of 8%. At our centre, two of 25 long term survivors, women aged 49 (case 1) and 31 (case 2), have developed PTLD, each presenting as a localised necrotic ulcerative bronchitis documented at flexible bronchoscopy (FIB) before progression of a more typical clinical picture of PTLD. Both had a...
flexible bronchoscopy (FB) and transbronchial biopsy performed because of a 10% fall in FEV1 at four and five months after transplantation respectively. At FB a necrotic ulcerative bronchitis was observed, photographed, and biopsied. Histology showed necrotic material with an inflammatory infiltrate and ulceration in both cases. The bronchial biopsy of case 2 also demonstrated lymphoproliferative disease. Both had a normal chest X-ray film at the time of FB and no evidence of fungal or herpesvirus infection. Case 1 later developed lung nodules and a monoclonal high grade B cell non-Hodgkin's lymphoma was confirmed by open lung biopsy. Each case was Epstein Barr virus seropositive but neither showed evidence of reactivation using IgG capsid antigen serology. Neither case responded to reduction in immunosuppression and intravenous acyclovir. Both patients then received VAPE-C-B chemotherapy. Case 1 died 6 months later from progressive lymphoma and aspergillus pneumonia. Case 2 showed regression of lymphoma and is alive on treatment two months from diagnosis. The features described should alert clinicians to the differential diagnosis and may suggest that the lymphatic follicles in the mucous membrane of the bronchi are the initial site for mitosis in PTLD.

Pulmonary capillary leakage/haemorrhage late after cardiac transplantation

JJ EGAN, NJ MARTIN, PS HASLETON, A WOODCOCK North West Lung Centre and Department of Histopathology, Wythenshawe Hospital, Manchester Diffusion abnormalities are recognised late after cardiac transplantation (Egan et al, Chest 1993, in press). To investigate this phenomenon prospectively, we completed flexible bronchoscopic (FB) and bronchoalveolar lavage (BAL) on 10 heart transplant recipients (HTRs). A consistent feature of the cytological examination of the BAL taken from the right middle lobe of HTR was the presence of haemosiderin laden macrophages. We compared the haemosiderin score (HS) of the BALs of the 10 HTRs with 10 heart lung transplant recipients (HLTRs). All HLTRs had previous transbronchial biopsies but none of the HTRs had. 200 macrophages stained by prussian blue were scored according to scale 0 = no colour, 1 = faint blue, 2 = medium intensity <50%, 3 = deep blue >50%, 4 = deep blue throughout the cell, and the HS was determined by counting 200 stained macrophages and scoring by two. The HTRs had a significantly higher HS than the HLTRs (HTR median = 144, range 2–260; HLTR median = 12, range 0–140; p = 0.019, Mann–Whitney U test, W = 136–5). All the HTRs had a normal right heart catheter measurement before BAL and no patient had cardiac rejection or pulmonary infection. The significantly higher HS scores in the HTRs late after transplant (mean 6.3 months) suggest an interstitial process with microvascular leakage that may contribute to abnormalities of diffusion.

Effectiveness of patient controlled analgesia after thoracic surgery

GW PARRY, CR CAMERON, OJ LAU Cardi thoracic unit, Brook general hospital, London Analgesic response after standard posterolateral thoracotomy was compared in two patient groups with a visual analogue scale. Group A (n = 28) were managed postoperatively with opioid patient controlled analgesia (PCA). Group B (n = 30) were managed postoperatively with either intermittent intramuscular opioids (n = 12) or with continuous intravenous opioid infusion (n = 18). All patients received local (intercostal) infiltration with 0.5% bupivacaine before thoracotomy closure, and all except three received regular oral diclofenac in the postoperative period to discharge. Group A patients achieved significantly lower pain scores than group B (p < 0.003). Total opioid consumption (mg/24 h) was also less in group A than group B (p < 0.05). No adverse effects were seen with PCA; respiratory rate, pulse, and systemic blood pressure were not affected. Patient and staff acceptability of the PCA were both high. We conclude that PCA is safe and highly effective after thoracotomy and would commend more widespread use of this method of pain control in thoracic surgical patients.

Evolving experience in thoracoscopic management of recurrent pneumothorax

MI ISTARABADI, RHUSSAIN, AO DONnell, D LUKE, E MCGOVERN Cardiothoracic Department, St James's Hospital, Dublin In the period between June 1992 and March 1993, 23 operations, 21 patients (14 male, 7 female) ages ranging between 16–67 years had thoracoscopic pleurectomy. The stiff, thickened parietal pleura was removed from the anterior, middle, and posterior axillary line sixth intercostal space. This was followed by apical pleurectomy with bullae resection using an Endo GIA stapler. An intercostal chest drain was inserted into the apex of the cavity at the end of the procedure. Average operating time was 45 minutes and average blood loss was 80 ml. Patients were discharged within 72 hours of their operation. One operation was converted to an open thoracotomy. Thoracoscopic pleurectomy is a satisfactory method of treating recurrent pneumothorax; our evolving experience has resulted in alteration of techniques to improve results.

Exploring the role of video assisted thoracic surgery

J MCCARTHY, J HURLEY, AE WOOD Department of Cardio-Thoracic Surgery, Mater hospital, Dublin Video assisted thoracic surgery (VATS) spares the patient the morbidity associated with formal thoracotomy. It allows excellent visualisation of the intrathoracic structure possibly aiding the diagnostic process. In the hands of an experienced operator, VATS is associated with lower incidence of complications. In the heart of the VATS procedure is the interventional role of the thoracic surgeon. The thoracic surgeon is required to perform diagnostic procedures in relation to the pleura and lung. VATS is used in a range of surgical procedures; most commonly in the resection of primary malignancy. The role of VATS has continued to expand. Using video thoracoscopic techniques in 45 patients, we have been able to perform 48 procedures. We have found the applications of this procedure to be diverse, being both diagnostic (21) and therapeutic (26). The diagnostic procedures included an initial biopsy (eight), intrapulmonary masses (eight), mediastinal mass (one), pleural effusions (four), pleural biopsy (one), and were associated with a high diagnostic yield and allowed accurate staging of lung cancer, in particular nodal status in N2 disease. It also allows assessment of the disease process in patients with malignant pleural effusion. The therapeutic procedures included pleurectomy and blebectomy (seven), excision of emphysematous bullae (two), trauma (three), lung resections (five), pericardial window (one), ligation of patent ductus arteriosus (two), closure of bronchopleural fistula (one), drainage of an empyema space (two), oesophageal resection (one), paraoesophageal hernia repair (one), and evacuation of haemothorax (one). These procedures were associated with minimal morbidity and short hospital stay. There were no intraoperative complications in either group and we did not have to resort to formal thoracotomy in any case. Although we have reservations concerning the use of VATS for resection of malignant disease, our experience indicates an expanding role for video assisted thoracic surgery and we list its chief advantages—namely, reduced morbidity and shorter hospital stay together with a high diagnostic facility and an expanding therapeutic role.

A vascularised rib strut technique: an improved chest wall fixation for correction of pectus excavatum

J KHALL-MARZOUK Regional Department of Thoracic Surgery, East Birmingham Hospital, Bordeley Green East, Birmingham Reassessment of pectus excavatum (pectus deformity) is the consequence of abnormal cartilaginous and osseous structures, restoration of normal contour, and sternal fixation in the correct anatomical position. Techniques of sternal fixation include the use of wires, metal struts, pins, synthetic mesh, and plates. Infection remains a serious problem when associated with the use of synthetic material, and recurrence of chest depression after removal of the supporting strut is often encountered. The use of an autologous vascularised rib as a strut for supporting the elevated sternum should overcome these problems of infection and recurrence; due to maintenance of vascularisation there is also no potential contribution to the deformity. The chosen rib is dissected with its vascular pedicle based on the internal thoracic artery and the intercostal artery. It is then turned 180 degrees behind the sternum and fixed to rib ends bilaterally. We have used this method in eight cases, with ages ranging between seven and 22 years. The results have all been satisfactory up to 30 months. Postoperative ventilatory control was not routinely used. Two children required artificial ventilation postoperatively. None of the adolescents or adults required rethoracotomy. This technique is currently
Aetiology and outcome of congenital tracheobronchial obstruction in neonates and children

J McCARTHY, J HURLEY, M NELIGAN, AE WOOD Our Lady’s Hospital for Sick Children, Crumlin Recognition of the aetiology of congenital tracheobronchial obstruction is essential for a logical approach to management and an assessment of likely outcome. We have reviewed all cases of congenital tracheobronchial obstruction presenting to our unit since 1964. Seventeen patients were shown to have congenital tracheobronchial obstruction. The aetiology of the airway obstruction was congenital tracheal stenosis including funnel shaped and segmental stenosis (n = 2), vascular rings (n = 7), vascular compression (n = 3). One patient died before surgery. The surgical procedures carried out on the remaining 16 patients included tracheal resection with end to end anastomosis using absorbable monofilament suture (n = 7) and sleeve resection of the bronchus with a similar anatomostic technique (n = 2). Seven patients had vascular ring division, two of this group also required tracheal resection. There was one aortopty and pulmonary anastomosis and mortality was 12%. The major independent predictor of mortality and morbidity was associated cardiac anomalies. In a follow up ranging from two months to nine years there has been one death at one month after operation due to inoperable cardiac anomalies. The remaining 13 patients are well. In conclusion we have found the aetiology of congenital tracheobronchial stenosis to be divided equally between extrinsic and intrinsic causes, that the majority can be managed in a single stage procedure with a low operative mortality and incidence of post-operative strictures, and that the single most important predictor of mortality is associated intracardiac anomalies.

Changes in gastric tissue oxygen tension during mobilisation for oesophageal replacement

GJ COOPER, KM SHERRY, JAC THORPE Departments of Thoracic Surgery and Anaesthetics, Northern General Hospital, Sheffield We have measured changes in gastric tissue oxygen tension (P_{O_{2}} mm Hg), using a modified Scholander electrode, in eight patients (n = 7) and sleeve resection of the bronchus with a similar anatomostic technique (n = 2). Seven patients had vascular ring division, two of this group also required tracheal resection. There was one aortopty and pulmonary anastomosis and mortality was 12%. The major independent predictor of mortality and morbidity was associated cardiac anomalies. In a follow up ranging from two months to nine years there has been one death at one month after operation due to inoperable cardiac anomalies. The remaining 13 patients are well. In conclusion we have found the aetiology of congenital tracheobronchial stenosis to be divided equally between extrinsic and intrinsic causes, that the majority can be managed in a single stage procedure with a low operative mortality and incidence of post-operative strictures, and that the single most important predictor of mortality is associated intracardiac anomalies.

Relation of static lung compliance to dyspnoea and exercise capacity in chronic heart failure

SA EVANS, WJM KINNEAR, L WATSON, AJ COWLEY, IDA JOHNSTON University Hospital, Nottingham The pathogenesis of dyspnoea in chronic heart failure (CHF) is poorly understood. Static lung compliance (SLC) is reduced in CHF and may be a useful index of dyspnoea experienced in this condition. To examine this hypothesis we have investigated the relation of SLC to exercise capacity and levels of dyspnoea in CHF. SLC was calculated from expiratory pressure-volume curves in 20 patients (three women) with CHF, mean age 61 years. SLC was measured using a pneumotachograph (Gaeltrec) used to measure changes in oesophageal pressure. Changes in lung volume were determined by integrating flow at the mouth as measured by a pneumotachograph (Fleish). New York Heart Association (NYHA) class for dyspnoea was determined by a single observer. Patients underwent treadmill exercise to symptom limited maximum using staged and fixed rate protocols. Borg ratings for dyspnoea at submaximal exercise were also measured. SLC, whether expressed as % total lung capacity (TLC)/cm H_{2}O, or % predicted TLC/cm H_{2}O was unrelated to NYHA class. Similarly, there was no significant relation between SLC and exercise capacity with either protocol, or with Borg ratings for dyspnoea at submaximal exercise, with the exception of that measured after 11 minutes of the staged protocol (n = 7, r = 0.8, p < 0.02). SLC is not related to treadmill exercise capacity in CHF, and its relation to measures of dyspnoea is variable. It is unlikely that lung elasticity has a role in determining the symptomatology of CHF.

Basal metabolic rate in patients with chest bellows disease

MK SRIDHAR, MEJ LEAN, SW BANHAM Department of Respiratory Medicine, University Department of Human Nutrition, Glasgow Royal Infirmary, Glasgow Patients with chest bellows disease (CBD)-like kyphoscoliosis (KS) and thoracoplasty (T) are characterised by an increased work of breathing. We studied 12 patients (mean age 58 years) with CBD (seven KS; five T) and six healthy matched controls to determine whether increased work of breathing is associated with a raised BMR as measured by an indirect calorimeter.
This ratio is known as the inspiratory effort quotient (IEQ). As a working approximation, $P_{mus} = (kVT/C_{dyn}) (TI/TTOT)$, where $V_T$ is the tidal volume, $C_{dyn}$ is the effective dynamic compliance, $TI/TTOT$ is the inspiratory duty cycle, and $k$ is a constant ($0.75$ in intensive care unit patients). From this:

$$\text{IEQ} = (kVT/C_{dyn}) \times (TI/TTOT)$$

where $P_{mus}$ is the maximum inspiratory pressure. This study aimed to evaluate the bedside use of IEQ to predict successful weaning given that this should occur when IEQ is less than 0.15. Factors for the equation were deduced from ventilator settings. Dynamic compliance was taken as the product of ventilator tidal volume and peak airway pressure deflection. Positive end expiratory pressure produces the highest tidal volume, and the lowest pressure. The duty cycle was taken as $0.3$ with a $V_T$ of $400$ ml. Pimox was recorded with a commercially available pressure manometer. Twelve patients were studied. The decision to wean was made on clinical grounds only. Six weaned successfully at the first attempt. IEQ on day of extubation ranged from $0.06$ to $0.18$. Six failed to wean at first attempt (IEQ range $0.13$ to $0.45$).

Change in lung density by computed tomography: measure of microscopic emphysema with age

H MOUGDIL, D MORRISON, K SKWARSKI, S PHILLIPS, M CONNELL, JK BEST, W MACNIE University Department of Respiratory Medicine, City Hospital, Edinburgh Lung density by computed tomography corre-

lated with mean and the lowest fifth percentile of the distribution density value of the lateral 2/5th of the lungs and age for the group as a whole. CT density on expiratory scans separated smokers from non-smokers better than inspiratory CT lung density. We con-

cluded that CT lung density does decrease with age and that expira-

tory CT scans may be the better method to quantify microscopic emphysema from CT lung density. [This work was supported by the Norman Salvesen Emphysema Research Trust.]

Use of the inspiratory effort quotient in predicting weaning outcome

P AGARWAL, K CHATHAM, K MCCONNOCHIE Section of Respiratory Medicine, University of Wales College of Medicine, Llandough Hospital, Penarth, South Glamorgan Inspiratory muscle fatigue may occur when the mean inspiratory pressure $(P_{mus})$ developed during a breathing movement expressed as a fraction of the maximum static inspiratory muscle pressure exceeds a critical ratio of $0.15$ to $0.20$. This study aimed to evaluate the bedside use of IEQ to predict successful weaning given that this should occur when IEQ is less than 0.15. Factors for the equation were deduced from ventilator settings. Dynamic compliance was taken as the product of ventilator tidal volume and peak airway pressure deflection. Positive end expiratory pressure produces the highest tidal volume, and the lowest pressure. The duty cycle was taken as $0.3$ with a $V_T$ of $400$ ml. Pimox was recorded with a commercially available pressure manometer. Twelve patients were studied. The decision to wean was made on clinical grounds only. Six weaned successfully at the first attempt. IEQ on day of extubation ranged from $0.06$ to $0.18$. Six failed to wean at first attempt (IEQ range $0.13$ to $0.45$).

Nasal masks for positive pressure ventilation: survey of patient use and complications

DJ MECHAM JONES, GM BRAID, JA WEDZICHA Department of Thoracic Medicine, The London Chest Hospital, Bower Road, London Lung intermittent positive pressure ventilation (NIPPV) and nasal continuous positive airway pressure (CPAP) are used in the domiciliary treatment of chronic ventilatory disorders, with ventilation administered through tightly fitting nasal silicone masks. The success of the technique depends on long term patient acceptance of the masks, which may cause complications, although the incidence of mask problems is unknown. We have carried out a survey of nasal mask use and complications in all patients using NIPPV or nasal CPAP with the Respironics nasal mask at the London Chest Hospital. 66 patients (46 men 20 women) were surveyed, median age 55 (range 21-75); 26 patients were using NIPPV (median age 13 (2-58) months), 40 CPAP (use 16 (3-60) months). The median daily use of ventilation was seven (3-13) hours. Complications were categorised as major: broken skin or open sores, or minor: slight skin irritation, red or painful areas of skin. 29 patients (44%) described no mask problems, 12 (18%) had major problems, and 25 (38%) had minor problems, with no difference between the NIPPV and CPAP patients. Of those with major problems, eight patients had broken skin or ulceration for less than four weeks. Four patients had problems for longer. 16 patients (23%) (six NIPPV, 10 CPAP) experienced disruption of treatment on at least one night per week due to mask discomfort. 20 patients (12 NIPPV, eight CPAP) started using the nasal mask during an acute exacerbation; five of these developing problems (two major, three minor). Of the remaining 46 patients with problems, 25 (55%) used CPAP and 21 (46%) used NIPPV. Attention to mask complications will improve the compliance and efficacy of home ventilatory support. [This work is supported by The British Lung Foundation.]

Prediction of dangerous hypoxaemia during aircraft flight

AOC JOHNSON, RL PAGE, SB PEARSON, D SAPSFORD, JG JONES Respiratory Unit, Kellinghe Hosp, Leeds and Department of Anaesthesia, University of Leeds passengers with impaired gas
exchange are at risk of developing dangerous hypoxaemia during air travel and should receive in flight oxygen if their saturation will fall below 85%. We investigated a new method for predicting altitude related desaturation. Arterial saturation (SaO₂) is measured at five different inspired oxygen pressures (P(O₂)) and the data used to plot a curve relating P(O₂) and SaO₂. The curve is similar to the oxyhaemoglobin dissociation curve but is displaced downwards where there is intrapulmonary shunting, similar to the right when there is ventilation perfusion inequality. The curve should then allow prediction of SaO₂ at differing P(O₂) without exposing the subject to that P(O₂) (Br J Hosp Med 1989;42:140). We initially studied 13 subjects with chronic obstructive pulmonary disease. Each had SaO₂ measured on five different P(O₂) between 21 and 40 kPa. The data were used to construct a P(O₂)/SaO₂ curve as above. Each subject also inhaled 15-17.5 kPa oxygen to simulate aircraft cabin P(O₂). This observed cabin SaO₂ was then compared with the predicted value (derived from the curve) for the same P(O₂). The results as mean (range) were (1) SaO₂ on air: 93-1 (89-95%); (2) observed cabin SaO₂: 85.4 (81-91.3); (3) predicted cabin SaO₂: 73.5 (51-86.5); (4) difference (observed - predicted): 12-0 (5-33%). Predicted cabin SaO₂ was always lower than the observed indicating that a compensatory mechanism is being activated to protect against more severe hypoxaemia. This is currently being studied in detail. In a larger group of 23 subjects, we found a good correlation between rightward displacement (shift) of the P(O₂)/SaO₂ curve and observed cabin SaO₂ (r = 0.83, p < 0.0001). Correlation between saturation on air and observed cabin SaO₂ was less good (r = 0.56, p = 0.0054). More importantly, each subject who had a cabin saturation below 85% had a shift of greater than 9 kPa, whereas there was no particular saturation on air that could identify subjects at risk of in-flight desaturation. We propose a novel method of assessing the risk of dangerous hypoxaemia in flight. It requires only the measurement of saturation on air and four different levels of P(O₂) delivered by face mask. (This obviates the need for special equipment, for example, oxygen analyser, nitrogen source as required in conventional assessment.) The data are entered into a computer and shift calculated. Patients with a shift of >9 kPa are at high risk of dangerous hypoxaemia and require in flight oxygen.

Determination of effective inspired oxygen concentration (F(O₂)eff) during oxygen treatment

CB COOPER, JM STRAKOVA, JS WILSON, JR COLTHURST UCLA School of Medicine, Los Angeles, California, USA During oxygen treatment inspired oxygen concentrations fluctuate because of variations in inspiratory flow rate and tidal volume. Determination of the "effective F(O₂)eff" is therefore difficult. We used a graphical analysis of respiratory gas exchange as described by Rahn and Fenn (Am Rev Respir Dis 1955) to derive a linear relation between expired concentrations of CO₂ and O₂. We extrapolated to obtain the "inspired point" and this was taken to represent F(O₂)eff. We studied 10 subjects (three men, seven women) with chronic hypoxia. Breath concentrations of CO₂ and O₂ were measured from a standard blood gas analyser using a sampling frequency of 100 Hz. Four subjects had transtracheal catheters allowing direct sampling of tracheal gas. We compared a molecular sieve (SI) producing 96% O₂ with a membrane separator (SE) producing 47% O₂. We compared three types of O₂ delivery: standard nasal cannulae (NC), occluding cannulae (OC), and transtracheal catheters (TC). Mean values of F(O₂)eff are given in the table. The "effective F(O₂)" with oxygen treatment is lower than previously believed. Fifty-nine paired determinations of F(O₂)eff showed agreement between tracheal and mouthpiece sampling (r = 0.92). Two types of nasal cannulae gave similar values of F(O₂)eff, reaching 33-6% with the 97% O₂ and 28-5% with the 47% O₂ supply. Transtracheal delivery gave significantly higher values of F(O₂)eff, reaching 45-2% with the 97% O₂ and 32-0% with the 47% O₂ supply.Expired gas analysis is vital in determining effective F(O₂)eff in chronically hypoxaemic patients receiving oxygen treatment.

Effect of hyperoxia on renal blood flow in normal humans

M LONG, R COSTELLO, D O’DONNELL, S O’NEILL Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland The effect of high inspired oxygen concentration (O₂) on renal blood flow (RBF) in humans is unknown. Studies in animals show hyperbaric O₂ to have a vasocostrictor effect on renal, cerebral, retinal, and limb vessels. In a previous study we investigated patients with hypoxaemic respiratory failure (a condition where RBF is known to be reduced) correction of hyperoxia was associated with an improvement in RBF (Long et al. Eur Respir J 1992;5(suppl 15):486s). This study examines the response of the renal vasculature to high concentration of inspired O₂ in nine healthy male volunteers. RBF was assessed non-invasively with duplex Doppler ultrasound. An Acuson 128 system with a 2 MHz probe was used to scan the renal interlobar vessels via the transplanar route. Pulsatility index (PI) was calculated as a measure of renovascular resistance. PI is obtained by dividing the difference between the maximum systolic and the minimum diastolic velocity by the mean velocity. A fall in PI corresponds to a fall in distal resistance to flow. PI is measured sequentially while the subject is breathing room air/100% O₂ for 10 minutes and after discontinuation of 100% O₂. We found an immediate and significant (p < 0.005) fall in PI while breathing 100% O₂. We conclude that hyperoxia is associated with renal vasodilation in normal subjects.

Patient no.

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PI = on room air; B = on 100% O₂.

Autonomic nerve function and cardiac arrhythmias in patients with chronic obstructive airways disease

W BIERNACKI, S SCHOLEY, G CLAPHAM, S DEAN, MD PEAKE The Chest Unit, General Infirmary, Pomefract, West Yorkshire A previous study showed impaired autonomic function as measured by metabolic tests in nine patients with chronic obstructive airways disease (COAD) (Stewart et al. Eur Respir J 1991;4(suppl 14):522). This included prolongation of the QTc interval. Cardiac arrhythmias are common in these patients and may be a cause of sudden death. There is no published work on the relation between autonomic function and cardiac arrhythmias in these patients or its relation to hypoxaemia. We have studied 15 patients (eight men) aged 65 (8) years with severe COAD (FEV₁, 34% (9%) of predicted) and a wide range of emphysema as judged by gas transfer (Kco 22-125% of predicted). All patients underwent a battery of autonomic function tests and had 24 hour ambulatory ECG monitoring. Seven out of 15 patients had impaired sympathetic postural tone, but only three had demonstrable parasympathetic nerve abnormalities. Mean QTc interval for these three patients was prolonged at 0.54 (0.03) s whereas it was normal in others. There was no obvious correlation between the degree of airflow obstruction, resting arterial Po₂ or transfer factor and the presence or absence of autonomic abnormalities. Four out of 15 had significant cardiac arrhythmias but these seemed unrelated to the abnormalities in autonomic nerve function.

Phosphodiesterase inhibitors may not have a long term therapeutic role in chronic obstructive pulmonary disease (COPD)

AY BUTT, TW HIGENBOTTAM, M TAKAO, G CREMONA Respiratory Physiology Department, Papworth Hospital, Papworth Everard, Cambridge Enoximone is a type III phosphodiesterase inhibitor and has been shown to reduce pulmonary hyperventilation and airway resistance in decompensated chronic obstructive pulmonary disease (COPD) (Leeman et al. Chest 1987;91:662-6). Its role as a long term treatment of COPD is, however, not known. We have prospectively studied 12 patients with severe but stable COPD (mean age (SD) 61 (5-8), six men and six women, mean FEV₁, 0.56 (0-2) litres). Right heart catheterisation was performed during which vasodilatory responsiveness to intravenous prostacyclin was assessed. Patients were then randomised either to oral enoximone (100 mg three times daily) or placebo for two six week periods.
intervened by a two week washout period with a placebo followed by a crossover. Pulmonary function tests and exercise tolerance during a six minute walk were measured at baseline and at 1, 3, 6, 9, 11, and 14 weeks of the study. The results (mean (SD)) are shown in the table. By comparison with placebo, enoximone did not cause any significant improvement in airway obstruction or exercise tolerance in this group of patients. Phosphodiesterase inhibitors may not have a long term therapeutic role in the management of COPD.

<table>
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<th>Tests</th>
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</table>

Exhaled nitric oxide is not diminished in primary pulmonary hypertension

G CREMONA, BA MIST, TW HIGENBOTTAM Department of Respiratory Physiology, Papworth Hospital, Cambridge Impaired endothelium dependent relaxation has been found in the conduit pulmonary arteries of patients with secondary pulmonary hypertension (Dinh Xuan et al. Br J Pharmacol 1990). Endogenous NO can be measured in the exhaled air in vivo (Gustafsson et al. Acta Physiol Scand 1992). We have measured NO in the exhaled air of eight patients with primary pulmonary hypertension (PPH) and six healthy volunteers by chemiluminescence (Model 42, Themoelectron, Warrington, UK). The subjects breathed NO free air (NO concentration <0.5 parts per billion) for 15 minutes through a non-rebreathing valve into a metabolic gas analyser (Model 2900s, Sensormedics, Rugby, UK) that allowed measurement of NO, NO was measured directly from the mixing box. The NO signal was stable after five minutes of steady breathing and the measurements taken during the past five minutes were used to calculate NO production. Mean NO production was 4+02 (1-15) = 2-84 (1-97) nmol 1-1 min -1 (p = 0-59) in the control and PPH group respectively. Predicted KCO was lower in patients with PPH (89 (8) = 63 (20) mmHg; p = 0-01) probably reflecting the decrease in pulmonary capillary blood volume.

Effect of norepinephrine (LNA) on the adaptation of the pulmonary capillary bed to increased flow in perfused pig lungs

G CREMONA, M TAKAO, TW HIGENBOTTAM Department of Respiratory Physiology, Papworth Hospital, Cambridge The arterial and venous occlusion techniques divide the total resistance of the pulmonary vascular bed into: a) intraparenchymal (IA), b) autogenous venous (RV), and c) middle (RM) (Hakim et al. J Appl Physiol 1982). We have used arterial and venous occlusion in isolated pig lungs to investigate the changes in the various segments with increased flow before and after treatment with norepinephrine (LNA), an inhibitor of NO production. The perfusion consisted of 1.5 to 2 liters of autologous blood and 1 to 1.5 litres of Krebs with 3-5% dextan. Perfusion packed cell volume was 20-25%. The lungs were ventilated with a gas mixture containing 30% O2 and 5% CO2 in N2. Perfusion was instituted at 1 min -1 and after an equilibration period of one hour, arterial and venous occlusions were performed. This was repeated at varying flow rates (50, 75, and 100 ml min -1 kg -1) before and after giving LNA (10 -4M). With increasing flow there was an increase in the resistance of the arterial segment. After addition of LNA the slope of the Q-Ra relation increased. By contrast the resistance of the middle segment decreased with increasing flow both at baseline and after LNA. LNA increased the Rm but the Q-Rm relation remained constant. Ra increased with flow but did not change after LNA. The results indicate that LNA increases the ohmic resistance of the arterial segment and the critical pressure of the middle segment.

Magnitude of acute hypoxic pulmonary vasocostriction (AHPV) during lobar hypoxia in man

NW MORRELL, KS NIHAN, T BIGGS, WA SEED Departments of Medicine and Nuclear Medicine, Charing Cross and Westminster Medical School, London AHPV plays an important role in the maintenance of ventilation-perfusion balance in many species. Despite this, few studies have investigated the magnitude and time course of the response in man. Using fiberoptic bronchoscopy we have produced localised regions of alveolar hypoxia by placing balloon tipped catheters to occlude lobar bronchi in six young normal volunteers. The PAO2 and PACO2 inside the occluded lobe were monitored continuously by a mass spectrometer connected to the proximal end of the catheter. During the occlusion 2-3 mCi 99mTc labelled macroaggregated albumin (MAA) were injected into a peripheral vein with the subject lying supine. The occluding balloon was then deflated and the bronchoscope removed. The resulting defect in perfusion was imaged with a gamma camera. Multiple view lung scans were performed collecting 300 000 counts per view. A control perfusion scan was performed one week after the experiment to allow calculation of percentage reduction in blood flow to the occluded lobe as measured by the distribution of 99mTc activity. During lobar occlusion the mean (SE) PAO2 and PACO2 rapidly approached mixed venous levels of 42.9 (2.5) mm Hg and 39.8 (1.2) mm Hg, respectively. The calculated mean reduction in blood flow for the six subjects was 42% (5%) (range 27% to 58%). The mean time from occlusion to injection of 99mTc-MAA was 147 seconds (range 80 to 300 seconds). Blood flow was redistributed to the unoccluded lobes, with the largest increases in flow observed in the ipsilateral unoccluded lobes. This study demonstrates that AHPV at the lobar level is a strong reflex in normal subjects and that the response is greater than that previously reported in studies of unilateral hypoxia in an entire lung.

In vitro tension-reactivity relationship in isolated rat pulmonary artery

F ZHANG, JS THOMPSON, AH MORICE Department of Medicine, University of Sheffield, Royal Hallamshire Hospital, Sheffield Mean pulmonary artery (PA) pressure ranges from approximately 15 mm Hg in normal animals to 35 mm Hg in hypoxic pulmonary hypertension. What tension should be used in vitro to simulate these physiological conditions? Using a small vessel myograph it is possible to investigate the vasoactive properties of isolated blood vessels under various conditions. In this study we have investigated the tension-reactivity relationship of isolated pulmonary resistance vessels (PRV) and PA. PRV (<300 μm) and PA (>800 μm) were dissected and mounted on an automated myograph (Cambustion, Cambridge). Vessels were maintained in oxygenated physiological saline solution (3 ml) at 37°C. Resting tensions equivalent to intra-mural pressures of 15, 17.5, 20, 25, 30, and 35 mm Hg were set. It has been suggested (Muhlavey and Halpern, Circ Res 1971:41: 19-26) that in systemic vessels vasoactivity is greater when vessel tension is reduced by an amount corresponding to 90% of the internal diameter. We therefore tested the vasoreactivity of each pulmonary vessel at 90% and 100% of the diameter at each preset pressure. KCl (100 mM) was added to the bath and tension (mmHg) recorded when the contractile response was stable. Results were shown as active tension divided by vessel diameter (mm/mm²). Analysis of active/passive tension (signal to noise ratio) suggests that the lowest pressure should be used as both PA and PRV had the greatest active/passive tensions at 15 mm Hg. The analysis of vascular responses requires a consistent tension-reactivity relationship. This occurred over the range of physiological passive tensions, provided that results were expressed as mm/mm².

![Graph showing the relationship between tension and active tension](http://thorax.bmj.com/Thorax: first published as 10.1136/thx.48.10.1052 on 1 October 1993. Downloaded from http://thorax.bmj.com/ on September 15, 2023 by guest. Protected by copyright.)
Are the effects of atrial peptide on pulmonary artery specific?

W SHEEDY, AH MORICE Department of Medicine and Pharmacology, University of Sheffield, Royal Hallamshire Hospital, Sheffield Brain natriuretic peptide (BNP) is a hormone which is closely related in its structure and some physiological actions to atrial natriuretic peptide (ANP). We have previously shown that both human and rat ANP are vasodilators of prostaglandin (PGF₂α) contracted rat pulmonary arteries (PA). Here we report the effects of human and rat BNP compared with human ANP on rat pulmonary arteries contracted in response to PGF₂α. Vessels were dissected and mounted as ring preparations in the organ bath of an automated small vessel myograph (Cambustion, Cambridge). A concentration of 100 μM PGF₂α was used to obtain maximum contraction. When the contraction had stabilised dose-response curves were obtained using up to a maximum of 165 nM peptide. These results suggest that, unlike ANP, BNP is species specific in its actions.


D MCKEOWN, F KELLY, L CLANCY Peamount Hospital, Newcastle, Co. Dublin, Republic of Ireland All public health specialists, hospital clinical consultants, and heads of diagnostic laboratories were surveyed by postal questionnaire to determine a profile of tuberculosis in 1991 and the results compared with our previous survey for 1986 (Proc SEP, Freiburg, 1986). Preliminary analysis showed that the incidence of tuberculosis has decreased from 21.4 to 16.7 per 100,000 with no significant change in age distribution; some 30% are <15 years; proven bacteriologically/histologically (30%). There is still no uniformity in terms of tuberculin testing, both the Heaf and Mantoux technique being used. Analysis of the incidence of tuberculosis in those aged <15 years showed that there is a significantly lower incidence (p = 0.0000019) in this age group in areas that have a policy of neonatal BCG vaccination. HIV associated tuberculosis now comprises 3% of all reported cases with drug resistant tuberculosis and atypical mycobacterial infection (other than in HIV positive patients) comprising less than 1% each. Despite a slight increase in reported incidence of tuberculosis in the late 1980s, overall the trend in incidence of tuberculosis in the Republic of Ireland is downward. Approximately 30% are younger than 35 years. Neonatal BCG vaccination appears to offer significant protective benefit against tuberculosis in the younger age group in the Republic of Ireland.

Consumption and underconsumption: a minority problem?

DPS SPENCE, J HOTHCISS, CSR WILLIAMS, PDO DAVIES Aintree Chest Centre, Tuberculosis Research Centre and Public Health Observatories, Liverpool We have previously shown a link between indices of poverty and the rate of notification of tuberculosis within the city of Liverpool. It has been suggested that this may be due to increased rates of tuberculosis among ethnic minorities from Asia, the Indian subcontinent and Africa who also suffer the highest levels of deprivation. We have re-examined by electoral ward all notifications of tuberculosis over the period 1985–90 and identified cases from ethnic minorities. Data on the ethnic mix of each electoral ward is available from 1991 census returns. Rates of tuberculosis among the white population were correlated with several indices of deprivation, free school meals (FSM), council housing (CH), Townsend overall deprivation index (ODI) and Jarman index (JI) using Spearman rank correlations. The population of Liverpool during the period studied was 452,486 of whom only 378% were non-white: 24% described their ethnic origin as Asian, 9% from the Indian subcontinent, and 14% from Africa. During the period studied there were 344 cases of tuberculosis of whom 49 were among ethnic minorities.

Rates of tuberculosis among the white population correlated with all indices of poverty (FSM, r = 0.49; CH, r = 0.42; ODI, r = 0.58; JI, r = 0.65). We conclude that increased rates of tuberculosis among the poorest in our city are not explained by high incidences of the disease in socially deprived ethnic minorities.

Changing trends of presentation of pulmonary tuberculosis in one Liverpool hospital

FC LESLIE, MJ WALSHAW, CG EVANS, CRK HIND The Cardiothoracic Centre and Broadway Hospital, Liverpool There has been an increase in the number of reported cases of pulmonary tuberculosis both in the UK (OPCS data 1991) and in the USA (Am Rev Respir Dis 1989;140:1788). It is our impression that both the proportion of atypical presentations and cases due to non-tuberculous mycobacteria are also rising. To study this further we have analysed all 68 cases of pulmonary tuberculosis seen at this hospital over 9 months up to June 1992 (43 men, mean age 51.2 years, range 16–83; 65 white). Whilst the majority presented with classical symptoms and chest radiographic changes of pulmonary tuberculosis, seven presented with lower zone shadowing only. A further nine were initially thought to have bronchial carcinoma and the diagnosis of tuberculosis was only made after thoracotomy. We divided the study period into two halves: more cases presented in the latter half (43, 63%). There were also significantly more atypical presentations in the latter half (14/43 v 2/25; x² = 2.75, p < 0.01) and more atypical mycobacterial infections (9/43 v 3/25); seven M kanamui, three M malmoense, one M chelonae, one M avium intracellulare. A history of previous tuberculosis was found in 13 (19%) patients and of tuberculosis contact in eight (12%). None of the patients was in a high risk group for HIV infection, and none was shown to be HIV positive. These results confirm our impression of an increasing incidence of pulmonary tuberculosis locally. They also demonstrate increasing numbers of not only atypical mycobacterial infection but also atypical presentations in a predominantly white population not thought to be at a high risk of HIV infection.

Comparison of human and bovine Mycobacterium bovis infection in south west Ireland 1983–90

TP COTTER, S SHEEHAN, B CRYAN, HN CUMMINS, CP BREEDIN Departments of Respiratory Medicine and Microbiology, Regional Hospital and University College, Cork and District Vetricinary Office, Cork, Republic of Ireland A comparison of Mycobacterium bovis infection in humans with M bovis infection in cattle in south west Ireland in 1983–90 inclusive was made. Pasteurised milk was introduced in this region in the 1950s. Human M bovis infection was identified by culture of sputum or other body fluids at the Regional Microbiology Laboratory. Cases of M bovis infection were identified using standard tuberculin testing methods. Results show a gradual decline in positive bovine tuberculin tests over the period: 472 per 100,000 animals in 1983 compared with 126 per 100,000 animals in 1990. This compares with 0.56 cases per 100,000 human M bovis infections in both 1983 and 1990. Human M bovis cases occurred in an elderly/middle aged group of patients (mean age 57±1), probably as reactivation disease of primary infection acquired by ingestion of unpasteurised milk 40 or more years previously. The low incidence plateau of human M bovis infection together with the declining incidence of animal infection suggests a cutoff in the animal to human chain of infection at two points: the animal source and the ingested (now pasteurised) milk. Accordingly the virtual elimination of active human M bovis disease in south west Ireland in the next 10–15 years may occur.
Tuberculosis conversion in medical students after elective periods in the developing world

TP COTTER, G GIBSON, BA ABERNETHY, L PLANT, CP BREDIN Department of Respiratory Medicine, Regional Hospital and University College, Cork, Republic of Ireland We conducted a retrospective case study of patients with positive Mantoux and a random group of students. From 1982-91 inclusive 38 patients fulfilled these criteria. The initial chest radiograph in each case was staged using the Siltzbach method. We identified the number of patients with positive Mantoux tests (10 tuberculin units) and compared their radiological staging with those who were Mantoux negative (see table). Ten patients (29%) had a positive Mantoux test (10 mm or more induration). No patient had any other disease known to cause false positive Kveim tests or affect Mantoux status. No patient had evidence of active tuberculosis or had developed it since. The chest radiograph stage was not correlated with Mantoux status. Scadding calculated that only 14% of his patients with sarcoïdosis reacted to 10 tuberculin units (Scadding JG, Mitchell DM. Sarcoïdosis, 2nd ed, London: Chapman & Hall, 1985). The high proportion of patients in our series with a positive Mantoux test is likely to be related to the relatively high incidence of microbiologically proved tuberculosis in south west Ireland, although the incidence has fallen from 15-3 per 100 000 in 1983 to 9-0 per 100 000 in 1992. We would expect the proportion of Kveim test positive patients with positive Mantoux tests to fall in the next decade as a result of the gradual decline in the tuberculosis incidence in the region.

Chest radiograph stage Mantoux positive cases Mantoux negative cases
0 0 0
1 3 3
2 1 3
3 2 3
4 6 19
5 2 3
6 2 3
7 2 3
8 2 3
9 2 3
10 2 3

Tuberculin reactivity in sarcoidosis: relationship to Kveim test and chest radiograph staging

TP COTTER, CP BREDIN Department of Respiratory Medicine, Cork Regional Hospital and University College, Cork, Republic of Ireland We conducted a retrospective case study of patients with positive Kveim and a random group of students. From 1982-91 inclusive 38 patients fulfilled these criteria. The initial chest radiograph in each case was staged using the Siltzbach method. We identified the number of patients with positive Mantoux tests (10 tuberculin units) and compared their radiological staging with those who were Mantoux negative (see table). Ten patients (29%) had a positive Mantoux test (10 mm or more induration). No patient had any other disease known to cause false positive Kveim tests or affect Mantoux status. No patient had evidence of active tuberculosis or had developed it since. The chest radiograph stage was not correlated with Mantoux status. Scadding calculated that only 14% of his patients with sarcoïdosis reacted to 10 tuberculin units (Scadding JG, Mitchell DM. Sarcoïdosis, 2nd ed, London: Chapman & Hall, 1985). The high proportion of patients in our series with a positive Mantoux test is likely to be related to the relatively high incidence of microbiologically proved tuberculosis in south west Ireland, although the incidence has fallen from 15-3 per 100 000 in 1983 to 9-0 per 100 000 in 1992. We would expect the proportion of Kveim test positive patients with positive Mantoux tests to fall in the next decade as a result of the gradual decline in the tuberculosis incidence in the region.

Influence of cigarette smoking on Haed grade

DPS SPENCE, CSD WILLIAMS, E MAZOUK, M NISAR, PDO DAVIES Aintree Chest Centre and Tuberculosis Research Centre, Liverpool Tobacco smoke increases the risk of carcinoma of the bronchus and COPD but little is known of its effect on Mycobacterium tuberculosis infection. To examine the relationship between smoking habit and Mycobacterium tuberculosis infection we have studied 146 consecutive patients attending our tuberculosis screening clinic. Tuberculin sensitivity was measured by Heaf testing. Current smoking habit, previous tobacco consumption and years since BCG vaccination were also recorded. Mean (SD) or median (range) summary data are given in the table. Haed grades are expressed as percentages. Haed grade was significantly correlated with age (r = 0.18, p < 0.05), and cigarette consumption (r = 0.37, p < 0.001). In those who had received BCG Haed grade correlated with years since vaccination (r = 0.24, p < 0.05). We conclude that inhalation of tobacco smoke may increase the risk of Mycobacterium tuberculosis infection through its effect on both mucus clearance and local lung immunological defence mechanisms. Continued subclinical infection with Mycobacterium tuberculosis will result in continued stimulation of cell mediated immunity and can be measured by tuberculin sensitivity. This may be important in interpreting Heaf test results.

Haed grade

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Tuberculin Association of neonatal BCG vaccination with tuberculosis in the paediatric population in Ireland

D MCKEOWN, P KELLY, L CLANCY Peamount Hospital, Newcastle, Co. Dublin, Republic of Ireland Analysis indicates that a policy of neonatal BCG is associated with significantly fewer cases of tuberculosis in people <15 years (p < 0.0000019). We estimate that 900-1100 children need vaccination to prevent one case of paediatric tuberculosis and that in 1991 neonatal BCG was associated with preventing 60-70 cases of tuberculosis in the paediatric population (<15 years). The incidence of tuberculosis in the survey was 16.5 per 100 000 (<600 cases of tuberculosis reported) for the entire country. Previous studies have shown benefit associated with neonatal BCG vaccination (Eur Respir J 1991;4:778-82, Am Rev Respir Dis 1990;141:A894, Eastern Health Board BCG Committee Report, Dublin, Proc Irish Thoracic Soc, November 1992). We conclude that neonatal BCG vaccination is associated with significant protection against tuberculosis in the paediatric age group in Ireland. With a declining overall incidence of tuberculosis the benefits of neonatal BCG will probably be outweighed by the disadvantages towards the end of this decade.

Use of sputum induction for establishing a diagnosis in patients with suspected pulmonary tuberculosis in Malawi

CM PARRY, O KAMOTO, AD HARRIES, JJ WIRIMA, CM NYIRENDA, DS NYANGULI, CA HART Department of Medicine, Queen Elizabeth Central Hospital, Blantyre, Malawi, Malawi National Tuberculosis Control Programme, Longue, Malawi and Tropical Medical Microbiology Centre, Liverpool University, Liverpool. Adults with suspected pulmonary tuberculosis in whom the expectorated sputum smear is acid fast bacilli negative or who are unproductive of sputum are increasingly seen in Malawi. Limited diagnostic facilities mean the potential for misdiagnosis in this group is high, particularly if there is coinfection with HIV. We have investigated 82 Malawian adults with suspected pulmonary tuberculosis using the technique of sputum induction. Sputum was successfully induced in 73 patients. The induced sputum was smear and culture positive for Mycobacterium tuberculosis in 18. In a further 38, in whom the clinical and radiological features suggested pulmonary tuberculosis, 12 were smear negative but culture positive. Of the 56 patients commenced on antimicrobial chemotherapy, tuberculosis was confirmed in 45 (80%), by positive bacteriology in 30 (54%) and satisfactory response to treatment in 15 (27%). Other significant pathogens were detected in only two patients (one Pneumocystis carinii and one Strongyloides terricola). Sputum induction is a useful technique in Malawian adults with suspected pulmonary tuberculosis. Significant pathogens other than Mycobacterium tuberculosis are uncommon. [This work was supported by the Overseas Development Administration and the Scadding-Morrison Davies Fellowship].

Who converted remain free of active disease to date. This study demonstrates that there is a significant incidence of tuberculin conversion associated with medical student electives in the developing world.
Is the Tine test useful in HIV disease?

C DIMIAN, SP HIGGINS, CS BRADBEE, NT BATEMAN Departments of Genitourinary Medicine and Thoracic Medicine, St Thomas’ Hospital, London

It is assumed that the loss of skin reactivity to purified protein derivative (PPD) occurs with deteriorating cellular immunity, casting doubt on the reliability of tuberculin testing in HIV positive patients (BMJ 1992;304:1231–3). In a study of 167 HIV positive patients who were tine tested PPD reactivity was maintained despite a CD4 count of 200/mm³ or less (Higgins et al. Thorax 1992; 47:877). As part of this longitudinal study 62 patients were retested either because their CD4 count dropped by more than 100/mm³ or it was a year since they were last tested. Skin reactions were graded as nil, low (grade 1–2), or high (grade 3–4). The results are shown in the table. Five of those becoming PPD reactive had CD4 count <200/mm³. Three of the eight patients with initial CD4 <200/mm³ maintained their reactivity though their counts continued to be <200/mm³. Three of the six patients who were PPD reactive whose CD4 counts were initially >200/mm³ maintained their reactivity though their count dropped below 200/mm³. Of the 12 patients becoming PPD negative seven had CD4 counts >200/mm³ but their counts had dropped by more than 100/mm³. Tine test is useful in HIV positive patients as it can be maintained in patients with CD4 counts <200/mm³. It can be lost in some patients with CD4 counts >200/mm³, particularly when it is falling rapidly.

<table>
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</table>

Interleukin 2 receptor expression is increased on peripheral blood lymphocytes in patients with moderate to severe symptomatic asthma

SP MATUSIEWICZ, WAH WALLACE, D COSSAR, SEM HOWIE, AP GREENING Respiratory Unit, Western General Hospital and University Department of Pathology, Edinburgh

Lymphocyte activation may play an important part in regulating the inflammation of bronchial asthma. Markers of activation such as CD25 (IL-2 receptor) on blood lymphocytes have been shown to be elevated in acute severe asthma and to decline with treatment. We examined peripheral blood lymphocytes and monocytes for evidence of activation in 60 asthmatic patients with persistent symptoms despite treatment with >800 µg inhaled steroid per day (including 20 also receiving long term systemic steroids), eight mild asthmatics taking prednisolone alone and 30 healthy volunteers as controls. All subjects were non-smokers. Mononuclear leucocytes were separated by density centrifugation. Using flow cyrometry, lymphocytes were tested against a panel of 17 monoclonal antibodies (including positive and negative controls) to assess cell surface markers of activation and results were given as % positive cells. CD25 expression was increased in asthmatics on inhaled (median % positive; 8-6%) or systemic steroids (10-8%) compared with normals (3-4%) (p = 0.001; p < 0.001 Mann Whitney U test). CD25 expression was not increased in relatively mild asthmatics (2-1%). Expression of HLA-DR and DQ histocompatibility antigens was reduced in chronic asthmatics taking inhaled or systemic steroids. Despite high dose inhaled or systemic steroids patients with chronic symptomatic asthma show some continued evidence of T cell activation.

Neutrophil influx and increased bronchial reactivity associated with inhaled tumour necrosis factor a

DH YATES, PJ BARNES, PS THOMAS National Heart and Lung Institute, Dovehouse Street, London

Allergen-induced mast cell activation releases tumour necrosis factor a (TNFα), a potent pro-inflammatory cytokine known to be stored within the mast cell granule. TNFα upregulates leucocyte adhesion molecules and may therefore mediate allergen associated inflammatory cell influx. We hypothesised that exogenous TNFα may cause an inflammatory infiltrate and thus induce bronchial hyperreactivity. The effect of inhaled recombinant TNFα in normal subjects was studied by serial evaluation of inflammatory cell influx in induced sputum and measurements of bronchial reactivity. Six subjects (four men, mean age 36-8) were studied in a single blind crossover manner; two were atopic. All subjects had a non-asthmatic methacholine PC20. Baseline spirometry and methacholine dose-response curves (4-128 mg/ml) were performed, sputum was induced by inhalation of 3-5% saline. Nebulised recombinant TNFα (60 ng) or saline control was inhaled and spirometry, methacholine and sputum induction repeated 1-5, 24, and 48 hours later. Sputum cell differential counts showed an influx of neutrophils starting at 1-5 hours and persisting up to 48 hours after inhalation (mean (SD) saline control at 24 hours 19-4% (8-1%), recombinant TNFα at 24 hours 50-9% (29-7%), p < 0.05). At baseline a PC20 was measurable in one of the subjects but was detectable in four subjects at 24 hours after recombinant TNFα. There was a significant shift to the left in the mean dose-response curves (p < 0.05) 24 hours after recombinant TNFα. We conclude that TNFα is capable of causing an inflammatory cell influx and increasing bronchial reactivity.

Bronchoalveolar lavage differential cell counts in patients with severe chronic asthma

SP MATUSIEWICZ, PH BROWN, E RAMAGE, SEM HOWIE, AP GREENING Respiratory Unit, Western General Hospital and University Department of Pathology, Edinburgh

Bronchosopic procedures have increased our understanding of asthma immunopathology. While bronchoscopy, bronchoalveolar lavage (BAL), and mucosal biopsy have been shown to be safe, most have studied relatively mild asthmatics. Such studies have tended to show a predominance of lymphocytes and eosinophils. We have examined BAL cell profiles in patients with severe chronic asthma receiving therapy. Bronchosopic examinations with BAL were performed on a group of non-smoking, clinically stable, severe asthmatics with chronic daily symptoms despite using high dose inhaled (800–3200 mg/day) with or without systemic steroids (mean: age 49 years; histamine PC20 <2 mg/ml; FEV1, 64% pred.). Asthmatics were defined as relatively corticosteroid resistant (CR) by a failure of FEV1, or mean PEF to improve by >15% following two weeks of prednisolone despite >15% response to β2 agonists (Am Rev Respir Dis 1991; 144:1016) or corticosteroid sensitive (CS). Normal non-smoking volunteers were used as controls. A standardised BAL was performed. Cytosin preparations were coded, Giemsa stained and cells counted (without knowledge of clinical details). The results are expressed as mean (SD) % BAL cells (table). Statistical analyses refer to Mann-Whitney tests comparing asthmatics with controls. Asthmatics with chronic symptoms despite high dose inhaled (± systemic) corticosteroids have more lymphocytes and eosinophils in BAL than normal controls. There was a trend (p = 0-1) for a greater proportion of lymphocytes in BAL in corticosteroid resistant than corticosteroid sensitive asthma.

<table>
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<th>Cell</th>
<th>Control</th>
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<th>CR asthma</th>
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<tbody>
<tr>
<td>n</td>
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<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Macrophages</td>
<td>95 (3)</td>
<td>81 (12)*</td>
<td>73 (18)*</td>
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<td>Lymphocytes</td>
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<td>11 (10)*</td>
<td>20 (17)*</td>
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<td>0-8 (0-8)</td>
<td>6-0 (9)*</td>
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</tbody>
</table>
*p < 0.02.

Relationship between cytokines IL-1β and TGFβ and macrophage subsets in the bronchoalveolar lavage fluid in asthma

S SREENAN, P DEBENHAM, CM BURKE, LW POULTER Department of Respiratory Medicine, James Connolly Memorial Hospital, Dublin and Department of Clinical Immunology, Royal Free Hospital, London

Previous work has shown alterations in the proportions of macrophage subsets in the bronchi of asthmatic subjects. This pilot study was designed to test whether or not such alterations are reflected in changes in the profile of macrophages in bronchoalveolar lavage (BAL) fluid and related levels of cytokines in BAL supernatants. BAL was performed on asthmatic and control subjects. Lavage supernatants were tested with ELISA for levels of IL-1β and TGFβ. Double immunofluorescent staining with monoclonal antibodies RFD1 and RFD7 was used to document the proportions of...
antigen presenting cells (D1+), effector cells (D7+), and suppressor macrophages (D1+, D7+). Results showed lower TGFβ and IL-1α levels in asthmatics than in control subjects. There was an increase in the proportion of D1+ and an associated reduction in D7+ macrophages in asthmatic subjects (table). These data suggest that alterations in the populations of macrophage subsets in airways of asthmatic subjects may be reflected in alterations in the cytokines of BAL fluid.

Cytokine production by bronchoalveolar lavage cells from atopic asthmatics and normal subjects

IL RESTRIKK, AP SAMPSON, PJ PIPER, JF COSTELLO Department of Thoracic Medicine, King’s College School of Medicine and Department of Pharmacology, Royal College of Surgeons, London We have previously shown a reduction in the capacity of bronchoalveolar lavage (BAL) cells, the majority of which are alveolar macrophages, from mild atopic asthmatics to generate LTB4 compared with cells from normal subjects (abstract at Thorax, 1993). This may be due to altered exposure of alveolar macrophages to cytokines such as GM-CSF, IL-1, or IFN-γ which may regulate macrophage mediator release. To test this hypothesis we assessed spontaneous and stimulated cytokine production by mixed BAL cells in vitro in 12 mild atopic asthmatics using β2 agonists only (7F5;5M; mean age 23 (range 20–29) years), with mean (SD) methacholine PC20 1–40 (1–29) mg/ml and mean (SD) FEV1 FEV1 3–7 (0–8) l and in nine non-smokers (6F;3M; mean age 24 (20–32) years; FEV1 3–5 (0–9) l). Washed BAL cell aliquots (approximately 80% alveolar macrophages; no significant differences in % alveolar macrophages or lymphocytes between atopic asthmatics and normal subjects) were incubated in RPMI 1640 at 1 × 10⁶ cells/ml for 24 hours, with or without 5 μg/ml lipopolysaccharide, and GM-CSF, IL-3 and IFN-γ were measured in the supernatants by enzyme immunoassay. LTB4 from cell aliquots stimulated with 4 μM A23187 over 0–30 minutes was measured by radioimmunoassay. Mixed BAL cells from atopic asthmatics produced less GM-CSF than normal controls, both spontaneously [atopic asthmatics GM-CSF median (range) 2.5 (0.0–148.4) pg/million cells/24 hours, normal subjects 39.7 (0.0–371.9) pg; p = 0.071] and when stimulated [atopic asthmatics 7.5 (0.0–226.7), normal subjects 43.7 (0.0–467.5); p = 0.05]. There were no significant differences in IL-3 (n = 12) or IFN-γ (n = 6) production between atopic asthmatics or normal subjects. There was no relationship between GM-CSF, IL-3 or IFN-γ production and LTB4 generation, although significantly less LTB4 was generated by cells from atopic asthmatics than from normal subjects (p = 0.03). In conclusion, there were a trend to reduced GM-CSF production by BAL cells from atopic asthmatics, but no change in IL-3 or IFN-γ production, and no relationship between cytokine levels and LTB4 generation. The reduced capacity to generate LTB4, and GM-CSF probably reflects generalised downregulation of alveolar macrophage function in asthma.

Interleukin 8 protein (IL-8) in bronchoalveolar lavage (BAL) fluid in human asthma

IK TAYLOR, J SHUTE, J DOUGLAS, DM MITCHELL, PJ SHAW Department of Respiratory Medicine, St Mary’s Hospital Medical School, London, UK and St George’s School of Medicine, Southampton There is increasing evidence that cytokines are important in the development of airway inflammation in asthma. IL-8 is a recently described polypeptide released from various cells including monocyte/macrophages, T lymphocytes, neutrophils, and bronchial endothelium. In vitro IL-8 is principally recognised by a neutrophil chemotaxtractant and functional activator and has been shown to induce neutrophil adherence and transendothelial migration. By contrast, in vivo, whilst IL-8 has been implicated in the pathogenesis of idiopathic pulmonary fibrosis and the adult respiratory distress syndrome (Donnelly et al. Lancet 1993;341:643–7) little is known regarding a role in asthma. In this study we have evaluated IL-8 protein in supernatants of bronchoalveolar lavage. Three patient groups underwent bronchoscopy delineated by their inhalational therapy: (A) steroid-dependent asthmatics (ASTd, n = 20, 8M, age 19–59, FEV1, 60–119% predicted, daily inhaled steroid dose 200–2000 μg [median 1000 μg], duration of steroid usage 13 ± 24 months, T > 24 months; (B) steroid-independent asthmatics (ASTin, n = 15, 13M, FEV1, 22–44, FEV1, 70–117% predicted); (C) normal non-asthmatic controls (n = 20, 10M, age 18–41, FEV1, 95–142% predicted). IL-8 in BAL supernatants was quantified using a double sandwich ELISA technique and mean (SE) results expressed as both ng/ml and ng/mg protein are shown in the table. There were no significant differences in IL-8 concentrations, either between groups or between all asthmatics (ASTa, Controls). Thus, in contrast to other pulmonary pathologies in which IL-8 has been implicated in the pathogenesis, we have found no evidence that this is the case in bronchial asthma. Further, these data support the view that chronic administration of therapeutic doses of inhaled glucocorticosteroids does not modulate IL-8 in BAL in vivo in asthma.

Bronchial epithelial cytokine production in asthmatics and non-asthmatics

AE REDINGTON, P BRADDING, JA DOUGLASS, LM TERAN, JA ROBERTS, ST HOLGATE, PH HOWARTH Immunopharmacology Group, University of Southampton, Southmam. Although the bronchial epithelium has traditionally been viewed as a target for the immunological process of asthma, it is now apparent that it has the potential itself to contribute to inflammatory events as it is a metabolically active cell population. To investigate the cytokine expression within the epithelium in vivo we have undertaken immunohistochemical staining of endobronchial biopsy samples with monoclonal antibodies directed against IL-1β, IL-6, IL-8 and TNFα, all cytokines described in relationship to cultured bronchial epithelial cells in vitro. Endobronchial biopsies were obtained at fibroptic bronchoscopy from mild asthmatics treated with inhaled bronchodilators only (n = 9) and from normal control subjects (n = 7). The biopsies were processed into glycol methacrylate resin and immunostaining of 2 μm sections was performed using an avidin biotin peroxidase technique. The intensity of staining was assessed semiquantitatively using a grading system. Immuneactivity for interleukin (IL)-8 was detected in the epithelium of both asthmatics and non-asthmatics with the intensity being significantly greater in the former (p < 0.05, χ² test). IL-1β immuneactivity was also localised to airway epithelium but, in contrast to IL-8 immuneactivity, there was no significant difference between asthmatics and non-asthmatics. Immuneactivity for IL-6 and TNFα was not localised to the bronchial epithelium. These findings confirm the potential importance of cytokine production by the bronchial epithelium in the inflammatory processes of asthma.

Increased expression of CD44 and LFA-1 in bronchial biopsies from mild asthmatic patients and normal controls and correlation with leucocyte influx

DG PERONI, R DJUKANOVIC, CP BRADDING, IH FEATHER, PH HOWARTH, DB JONES, ST HOLGATE Departments of Medicine and Pathology, University of Southampton, Southmam. We have investigated by immunohistochemistry in bronchial biopsies from 10 mild asthmatic asthmatics and eight normal subjects, the expression of leucocyte endothelial cell adhesion molecules (LECAMs) such as ICAM-1, CD11a (LFA-1), CD44 (a tissue selective adhesion molecule), CD49d (VLA-4), CD49f (VLA-6), and the expression of cell surface markers CD3, CD4, CD8 for T lymphocytes subsets and their activation (CD25), AA1 for mast cells and EG2 for activated eosinophils. Analyses showed a significant increase in the number of eosinophils (p = 0.02) in the asthmatic submucosa. The staining for endothelial ICAM-1 was constitutively expressed and the
monoclonal antibodies for VLA-4 and VLA-6 stained the basement membrane of the bronchial epithelium in both groups. In the epithelium there were more CD44+ (p = 0.002) and LFA-1+ (p = 0.06) leucocytes in asthmatics than in the normals. The CD44 staining was present in the bronchial epithelial cells in both the groups, but when the staining was expressed as the percentage of the total basement membrane a significant increase was observed in the asthmatic subjects (p = 0.003). In asthmatic patients a positive correlation (p < 0.03, \( r = 0.69 \)) was found between LFA-1+ and CD44+ cells both in the epithelium and submucosa and between LFA-1+ and eosinophils EG2+ in the submucosa (p < 0.005, \( r = 0.80 \)). These results suggest that LECAM-1 plays a significant role in the influx of leucocytes into the bronchial asthmatic tissue.

**Relationship of T lymphocyte activation to lung function in glucocorticoid dependent asthma**

SH LOCK, NC BARNES, C CORRIGAN, AB KAY National Heart and Lung Institute, London, and The London Chest Hospital, London

In acute severe asthma elevated numbers of peripheral blood T lymphocytes express activation markers and their reduction following therapy could be correlated with improvement in lung function (Carrington et al. Respir. Med. 1991;85:970-7). To investigate the possible role of T lymphocytes in glucocorticoid dependent asthma we studied 35 glucocorticoid dependent asthmatics (mean age 51 years, range 26-67 yrs, FEV\(_1\), 66% (33-112%) of the predicted value) and six normal control subjects. Patients’ lung function was kept stable for four weeks on their lowest maintenance dose of prednisolone (12 mg/day, 2-22.5 mg/day). Peripheral blood mononuclear cells were then separated from the asthmatics and controls. The expression of activation markers CD25 (IL-2 receptor), HLA-DR, VLA1, CD45RA (naive T lymphocytes) and CD45RO (memory T lymphocytes) were measured on CD4 and CD8 T lymphocytes using flow cytometry. The percentages of CD25 expressed on CD4 T lymphocytes in asthmatics (median 11.0%, range 2-22.9) was significantly higher than in controls (8.0%, 5.0-17.8%, p = 0.02). The percentages of total CD4 and CD8 T lymphocytes and expression of other activation markers on CD4 and CD8 T lymphocytes were not significantly different in the two groups. The percentages of CD4 T lymphocytes expressing CD25 in asthmatics correlated with their spirometry (% predicted FEV\(_1\), \( r = 0.46, p = 0.05 \)). Thus glucocorticoid dependent asthmatics showed evidence of ongoing CD4 T lymphocyte activation which can be correlated to lung function and CD25 expression may be a useful marker of disease severity.

**Clinical response to cyclosporin A therapy in chronic severe asthma is associated with a decrease in serum soluble interleukin 2 receptor (IL-2R)**

AG ALEXANDER, CJ CORRIGAN, P JARDEAU, NC BARNES, AB KAY National Heart and Lung Institute, Royal Brompton and London Chest Hospitals, London, UK and Genentech Inc, San Francisco, USA

In a randomised placebo controlled double blind crossover trial of oral cyclosporin A in steroid dependent chronic severe asthmatics, cyclosporin A therapy for 12 weeks resulted in a mean increase above placebo of 12.0% in PEF and 17.6% in FEV\(_1\) (Alexander et al. Lancet 1992;339:324-8). To investigate the mechanism of action of cyclosporin A in asthma, peripheral blood samples were obtained from 29 patients at the mid points of both the cyclosporin A and placebo treatment periods and serum stored at 80°C pending measurement of soluble IL-2R concentration by enzyme linked immunosorbent assay. Soluble IL-2R was detected in all samples with a range of 0.006 to 0.10 U/ml, considerably above the 50.0 U/ml lower limit of sensitivity of the assay. Mean concentrations of soluble IL-2R were significantly lower (p = 0.017) on cyclosporin A (519.6 U/ml) compared with placebo (616.4). This decrease in soluble IL-2R concentration was correlated with the cyclosporin therapy and with the % increase in morning PEF (p = 0.375, p < 0.05). These data suggest that in patients with chronic severe asthma clinical response to cyclosporin A is associated with a decrease in serum soluble IL-2R concentration. This is compatible with the hypothesis that the IL-2R may act in vivo, at least in part, by inhibition of T cell activation.

**Nutrition and lung function in the elderly**

J DOW, MTA VILLAR, ST HOLGATE Department of Care of the Elderly, Frenchay Hospital, Bristol, and University Medicine, Southampton General Hospital, Southampton

The relationship between nutrition and lung function was examined in a sample of elderly men and women in a longitudinal study of airways disease. Spirometry was measured in 1986-7 and 1990-1. Nutritional information was only collected at the second examination and consisted of: food frequency data from a questionnaire, weight, body mass index, triceps skinfold thickness, and upper midarm muscle circumference. The mean (SD) age of this sample of 1289 (76.3±5.2) years. From 1990-1 data 36 subjects had an FEV/FVC ≤60% and 155 had FEV/FVC >60%. Obstructed subjects had marginally higher energy intake (kcal) through higher intakes of protein, fat and carbohydrate, but were lower in weight (kg) and body mass index (lb/ft\(^2\)), triceps skinfold thickness and upper midarm muscle circumference were lower for obstructed than non-obstructed subjects. Change in FEV, between the two examinations was calculated as average yearly change in FEV, and categorised as: gain < 0-150 ml (n = 31), loss > 4-9 ml (n = 62), 50-99 ml (n = 66), 100-149 ml (n = 25), >150 ml (n = 14). Nutritional status and food intake did not show any consistent pattern across these different groups. We conclude that an association exists between nutrition and lung function cross sectionally, but is not detectable in this study with longitudinal measurements of lung function.

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<th>FEV/FVC &gt;60%</th>
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<tbody>
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<tr>
<td>Women 1917 (573)</td>
<td>1648 (515)</td>
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<td>Weight (kg)</td>
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<td>Men 67-8 (13-9)</td>
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<td>Women 62-3 (11-1)</td>
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</tbody>
</table>

**Relation of selenium and glutathione peroxidase with atopy and bronchial hyperreactivity in adults and children**

B BEGISHVILI, JM DOULL, R BEASLEY, ST HOLGATE University Medicine, Centre Bloch, Southampton General Hospital, Southampton

Selenium is an essential component of the antioxidant glutathione peroxidase. Non-atopic asthma is associated with decreased whole blood selenium and in some studies with decreased glutathione peroxidase activity. We have investigated the relationship of bronchial hyperreactivity and atopy to selenium and glutathione peroxidase in 29 families (58 adults, 94 children) randomly selected without reference to atopy or asthma, who attended our department for bronchial challenge to histamine and skin prick testing to 12 allergens. To prevent the loss of censored data, bronchial hyperreactivity was expressed as area under the curve (AUC). Total IgE, serum selenium and glutathione peroxidase activity were measured by standard assays. There was no difference in mean selenium or glutathione peroxidase between atopics and non-atopics. Glutathione peroxidase was negatively correlated with IgE (r = 0.226, p = 0.011) in the families as a whole and in patients separately (r = 0.338, p = 0.015), but there was no relation between selenium and IgE. In atopics there was no relation between selenium or glutathione peroxidase and AUC; however, in non-atopics both selenium (r = 0.378, p = 0.012) and glutathione peroxidase (r = 0.433, p = 0.008) correlated with AUC. When the children were analysed separately there was no relationship between selenium, glutathione peroxidase, and AUC or IgE.

**Effects of atopy, cigarette smoking and dietary vitamin C intake on lung function in the general population**

J BRITTON, I FAVORD, K RICHARDS, A KNOX, A WINSIEWSKI, S LEWIS, A TATTERSFIELD, S WEISS Respiratory Medicine Unit, City Hospital, Nottingham, and Harvard Medical School, Boston, USA

Cigarette smoke and other inhaled pollutants cause lung damage by oxidation, both as a direct effect and by recruitment of host defence systems. Individual susceptibility to oxidative damage may therefore be influenced by dietary intake of antioxidants, including vitamins C and E. We have estimated the potential importance of differences in
dietary intake of these vitamins, relative to the effects of cigarette smoking and atopy, as determinants of lung function in a cross-sectional survey of a sample of 2873 people of 15–78 years of age living in a district of Nottingham. Dietary intakes of vitamins C and E were measured by a semiquantitative food frequency questionnaire, lifetime smoking in pack-years from self-reported smoking histories, atopy as the mean skin weal response to histamine, grass pollen and for allergic rhinitis by standard prick testing, and lung function as the FEV₁, analysed as a standardised residual after adjustment for age, sex and height within the study population. We found that, significantly and independently related to pack-years smoked (mean fall in FEV₁ per pack-year = 5.5 ml, 95% confidence interval 4.4–6.6 ml), allergen skin weal diameter (mean fall per mm = 15.4, 95% confidence interval 5.8 to 25.1 ml), and to average dietary intake of vitamin C (mean increase in FEV₁ per standard deviation increase in vitamin C intake = 25.0 ml, 95% confidence interval 5.2 to 44.8 ml). There was no significant interaction between the effects of dietary vitamin C and smoking or atopy, and no additional independent effect from dietary vitamin E intake. These data demonstrate that, in cross sectional analysis of this population, vitamin C intake is an independent determinant of lung function in a magnitude such that a standard deviation decrease in vitamin C intake is associated with a change in FEV₁, approximately equivalent to five pack-years smoking.

Is screening of schoolchildren for asthma a worthwhile procedure?

RG DENT, M HUMBLE, P MCINTYRE, E ATTFIELD East Hertfordshire NHS Trust, Hertford Previous studies have outlined a significant number of children with undiagnosed asthma in primary schools (Speight BMJ 1978;2:331; Hill et al. Arch Dis Child 1989;64:246). These studies have been in urban areas and the implication has been that identification of such children and subsequent intervention would lead to an improvement in morbidity from asthma. We have studied 1003 children in eight primary schools in rural Hertfordshire using a questionnaire and an exercise peak flow test. Eighty seven of the children were already known to have asthma or were receiving treatment for asthma (8.7%). A further 89 (8.9%) had a positive questionnaire or exercise test but, after a further questionnaire completed by the child’s parents, only 19 (1.9%) children had clear evidence of undetected asthma sufficient to warrant further investigation. Parents of these 19 children were encouraged to seek advice about their child from their GP who was informed of the results of the screening study. Eight of the 19 visited their doctor of whom only four were subsequently commenced on treatment. Sixty of the 87 children with known asthma were considered to be “inadequately” controlled on the basis of their symptoms and exercise test results. It is concluded that screening schoolchildren for asthma in rural Hertfordshire is not a profitable use of resource, but that children with known asthma should be identified and an attempt made to improve their control. The results support the much larger urban study of Hill in Nottingham in 1991 (BMJ 1991;303:1169).

Case note review as a means of identifying potential asthma in 10 500 children

RA CLARK, RG NEVILLE, P BRYCE, J PHILLIPS Departments of General Practice and Respiratory Medicine, University of Dundee, Dundee The case notes of 10 685 children aged 1–5 from 12 rural, country town, or urban general practices in Tayside were reviewed by a nurse facilitator who identified 3373 children with symptom complexes suggestive of past or present asthma. The GPs were given the names of the 1585 intervention patients and asked to assess and follow them up according to standardised asthma protocols. Follow up of the 1563 children in the control group was as per standard practice, their names remaining secret. Intervention and control groups were closely matched for age, sex, previous asthma diagnosis and current asthma treatment. The records of both groups were reviewed after one year. A total of 943 intervention children had been assessed (292 asthma, 258 probable asthma, 393 not asthma); 351 had had no recent symptoms and were not assessed and 291 had not yet been seen. The same number of children in the intervention and control groups continued on bronchodilators, INH, and inhaled steroids throughout both years but there was a significant increase in use of bronchodilator, INH, spacer device, and PEF meter and the diagnosis of asthma in the intervention but not the control arm during the second year. Persistent cough with one or more episodes of bronchospasm was most commonly associated with the diagnosis of asthma although less than 30% of persistent coughers had proven asthma.

High prevalence of asthma-like symptoms in East Anglia

D JARVIS, E LAJ, C LUCZYNSKA, B HALL, BWD HARRISON, J STARK, S CHINN, P BURNEY Department of Public Health Medicine, UMDS, St Thomas’ Campus, London, Department of Respiratory Medicine, Addenbrooke’s Hospital, Cambridge, Department of Respiratory Medicine, Ipswich Hospital, Ipswich, Department of Respiratory Medicine, West Norfolk Hospital, Norwich As part of the British arm of the European Community Respiratory Health Survey (ECRHS) 15 000 people aged between 20 and 44 years, living in Cambrige, Ipswich and Norwich, were sent the ECRHS questionnaire, a seven item self-administered questionnaire asking about respiratory symptoms over the preceding year. The response after three mailings was lowest in Cambridge (50.9%) and highest in Ipswich (66.8%), with Norwich at 60.8%, but increased to 65.0%, 74.7%, and 70.2% respectively when people known to have moved, died, or to be the wrong age were excluded. Response was greater in women and increased with age. The prevalence (%) of a positive response to the following questions: (1) wheeze or whistling in your chest at any time (whz), (2) waking with an attack of asthma (att ast), (3) attack of asthma (att ast), and (4) currently taking medication for asthma (ast med) is given in the table. The range of prevalence obtained in a similar study of young men of the same age using the same questions conducted in 20 local authority areas in 1986 (Burney et al. Thorax 1991;46:574–9) is also shown. The prevalence of asthma-like symptoms in Cambridge, Ipswich and Norwich is higher than has previously been reported elsewhere. [This work was supported by the National Asthma Campaign]

<table>
<thead>
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<th>Cambridge</th>
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<tr>
<td>wake SOB</td>
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Quality of life in asthma

A WRIGHT, J PORTLOCK, E NEVILLE, AP ROBERTS School of Pharmacy and Biomedical Sciences, University of Portsmouth and St Mary’s Hospital, Portsmouth An asthma specific questionnaire was developed to investigate the quality of life that asthmatics experienced. The questionnaire was administered by one interviewer and consisted of 71 items, of which 15 were positive and 55 negative. A variety of modes of response were used including binary, multi-category, descriptive, and visual analogue scales. Fifty patients aged 15–78 were interviewed, of whom 20 were judged to have mild, 14 moderate, and 16 severe asthma. There were no significant correlations with age. Men were twice as likely as women to become annoyed with their asthma and to feel anxious, but were more confident that they coped with their medicines. A small number of men had problems going to sleep, but found family members more supportive. A highly significant correlation was found between increasing duration of asthma and embarrassment, using three separate modes of assessment. Severity of asthma did not correlate with social activities or emotions, but correlated well with clinically related questions and familial life and energy. Deteriorating spirometry correlated with breathlessness while talking, but not with the degree of distress caused by talking. The major causes of distress were ranked as follows: inability to do my job, inability to sleep well, inability to perform everyday tasks, not feeling in control, inability to have the social life I would like, inability to participate in activities, having to avoid certain places, embarrassment, attitudes of other people, becoming short of breath when talking and having to use inhalers; i.e. broadly speaking, functional problems were rated as causing more distress than psychological ones. Quality of life is a subjective measurement of how well a person functions in everyday life, incorporating subjective wellbeing, health and objective welfare. This questionnaire has been found to satisfactorily integrate these three areas.
Audit of acute asthma in the North West region

R FEINMANN, P ORMEROED, G COOK, P PHILLIPS, Stepping Hill Hospital, Stockport, Cheshire, Blackburn Royal Infirmary, Bolton Road, Blackburn, and North Western Regional Health Authority, Gateway House, Piccadilly South, Manchester The North West region has considerable acute admissions with asthma to all district hospitals in the region. Twenty per cent of all asthma admissions in the age range 16–46 years who were admitted over a 12 month period were audited. Using the BTS guidelines it was decided what information should be collected from the hospital notes to indicate good practice. In total 343 records of capsaicin required to elicit reactions were audited, 23% of whom had been seen by their GP or in the Accident and Emergency department within two weeks of being subsequently admitted. Peak flow recording was disappointing in that only half had initial recordings and, although 90% had daily measurements, only 15% had QDS before and after bronchodilator measurements. Discharge peak flows were recorded in only one quarter and in 25% of patients nebulisers were not stopped 24 hours prior to discharge. One quarter of all were not followed up after discharge. Despite well publicised national guidelines and many local protocols and audits, acute asthma management remains inadequate. This audit also compared the management of asthma in adults and, despite being slightly better, the results were still disappointing.

Darlington prospective study of childhood asthma: pulmonary function and treatment

AA GATNASH, CK CONNOLLY, SM ALCOCK Darlington Memorial Hospital and University of Newcastle upon Tyne All children with asthma referred to one author (CKC) between 1972 and 1983 and likely to remain in the district were entered into a prospective study of the outcome. One hundred and eighty six subjects aged 5–14 (128 boys, 58 girls) were reviewed at the age of 21. Any visit after 18 years was accepted for those not attending, the remaining being traced through their last known address or general practitioner. Data were obtained for 149 (80%), of whom 109 (73%) were seen and two (1-3%) died. A boy (14 years) died from progressively severe steroid resistant asthma, and a girl (16 years) in remission from a catastrophic attack on exposure to exceptional pollen levels. Of those known to be alive, 20 (14%) were on no treatment, 65 (44%) were prescribed bronchodilators only, and 62 (42%) were on preventative treatment (oral corticosteroids 0, inhaled steroids 43 (29%), cromoglycate 19 (13%).) Peak expiratory flow (PEF) was available in 125 (82 boys, 43 girls) and forced expiratory volume in one second (FEV1) in 115 (74 boys, 40 girls). The mean peak flow was 501 L/min (85-64% predicted) in boys and 429 L/min (86-8%) in girls. Mean FEV1 was 3.57 (83-5% predicted) in boys and 2.88 (86-7%) in girls. PEF was >80% in 86 (69%) and FEV1, in 70 (61%). PEF was 83% predicted (range 71–116%) in those on no treatment, 87% (62-120%) on bronchodilator only, 85% (66-101%) on cromoglycate, and 81% (51–106%) on inhaled corticosteroids. Of the 127 receiving treatment, 111 (87%) claimed little or no disruption to their lives, while 16 (13%) had at least moderate disruption. This was less than would be expected from published population surveys and may reflect good initial training in coping with asthma. On the other hand, the range of pulmonary function was large within the treatment groups and the differences between them small, suggesting that there might still be under-recognition of asthma, particularly in those on no treatment at all.

Airway a adrenoreceptors inhibit sensory neurotransmission in guinea pigs but not humans

F O’CONNELL, VE THOMAS, RF FULLER, NB PRIDE Departments of Clinical Pharmacology and Respiratory Medicine, Royal Postgraduate Medical School, London Little is known about the central neuro-transmitters involved in mediation of respiratory reflexes in humans. Previous studies have shown that systemic opiates suppress capsaicin induced cough without affecting respiratory resistance, while inhaled opiates suppress capsaicin induced rise in respiratory resistance without affecting cough, suggesting that the antinociceptive effect of opiates is a central effect. A further study has shown that clonidine, a centrally acting a2 agonist, has no effect on these reflexes in humans. We have now examined the effects of central acting agonists and antagonists of cholinergic and dopaminergic receptors on capsaicin induced cough and reflex rise in respiratory resistance in healthy human volunteers. In eight subjects baseline measurements of heart rate, blood pressure, capsaicin induced cough and respiratory resistance were performed (pre-C) and after (post-C) capsaicin were made. These measurements were repeated five and 30 minutes after a single intravenous dose of atropine 0·6 mg, phystostigmine 0·5 mg, or saline. Atropine caused a significant increase in heart rate (HR) at five and 30 minutes compared with saline and phystostigmine (mean (SD) AHR at five minutes: atropine 28 (5), phystostigmine 5 (4), saline – 4 (3); at 30 minutes: atropine 21 (4), phystostigmine – 2 (3), saline – 5 (3)). Atropine also caused a fall in pre-C respiratory resistance of 21 (4%) at five minutes and 19 (4%) at 30 minutes compared with baseline and abolished the post-C rise in respiratory resistance. Phystostigmine and saline had no significant effects on pre or post-C respiratory resistance and capsaicin induced cough was unaffected by any treatment. In a second study in 12 subjects, baseline measurements of heart rate, blood pressure, capsaicin induced cough and post-C respiratory resistance were made and repeated one, two, and four hours after a single oral dose of levodopa 100 mg, bromocriptine 1 mg, haloperidol 1·5 mg, or matched placebo. None of the parameters measured was affected by any of the treatments. The changes in respiratory resistance after administration of atropine are most probably explained by an effect at postganglionic cholinergic nerve endings in bronchial smooth muscle. It is unlikely that central cholinergic or dopaminergic receptors are involved in mediation of capsaicin induced respiratory reflexes in humans. [This study was supported by The National Asthma Campaign.]
Comparison of the effects of inhaled frusemide and ethacrynic acid on sodium metabisulphite induced bronchoconstriction in subjects with mild asthma

S PYE, P PAVORD, P WILDING, J BENNETT, A KNOX, A TATTERSFIELD Respiratory Medicine Unit, City Hospital, Nottingham Inhaled frusemide prevents bronchoconstriction induced by a number of challenges in asthma. One approach to determine the mechanism of this protection has been to examine the effects of related diuretics. We have compared the effects of frusemide on sodium metabisulphite induced bronchoconstriction with those of ethacrynic acid, a loop diuretic which, unlike frusemide, does not interact with the membrane Na/K/Cl cotransporter protein or inhibit carbonic anhydrase. Eight subjects with mild asthma were studied on five occasions, receiving nebulised frusemide (20 and 40 mg), ethacrynic acid (25 and 50 mg), or placebo (normal saline) in random order and double blind 10 minutes before a cumulative dose challenge with inhaled sodium metabisulphite. The response to sodium metabisulphite was described as the provocative dose causing a 20% fall in FEV1 (PD20) and differences in PD20 were expressed as doubling doses. The geometric mean sodium metabisulphite PD20 was 7.9 μmol after placebo. Frusemide 20 mg increased the PD20 by 1.1 doubling doses to 17.1 μmol (p < 0.05) and frusemide 40 mg by 1.6 doubling doses to 24.7 μmol (p < 0.02). Ethacrynic acid was irritant to the inhaled, but also inhibited bronchoconstriction induced by sodium metabisulphite. The geometric mean PD20 was increased by 0.9 doubling doses to 14.5 μmol (p < 0.05) after 25 mg and by 1.5 doubling doses to 22.4 μmol (p < 0.05) after 50 mg. Thus equivalent diuretic doses of frusemide and ethacrynic acid have a similar effect on sodium metabisulphite induced bronchoconstriction in asthma. This suggests that interaction with the Na/K/Cl cotransporter protein or carbonic anhydrase inhibition is not relevant to the effects of frusemide in asthma.

Comparison between formoterol and salbutamol in reversing methacholine induced bronchoconstriction

JR BEACH, CI YOUNG, EH WALTERS, DJ KENDRICK Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne Formoterol is one of a new class of long acting β agonists intended for regular use in the treatment of asthma. β agonists are also used as rescue medication for episodes of acute bronchospasm, and in this role a long duration of action is not so important as a rapid onset of action. This study was undertaken to detect any difference in speed of action between placebo, two doses of formoterol, and salbutamol in reversing methacholine induced bronchoconstriction. Sixteen asthmatic subjects were recruited from a chest clinic. Each underwent four methacholine tests a minimum of two and a maximum of 10 days apart, on each occasion a 20% decrement in FEV1 being attained. Following each test they received one of four treatments from a dry powder inhaler: placebo; formoterol 12 μg; formoterol 24 μg; salbutamol 400 μg. Following each treatment FEV1 was recorded every two minutes for 10 minutes, and every five minutes for 80 minutes thereafter. All three active drugs produced a greater FEV1 than placebo at each time point during recovery. Analysis of variance showed salbutamol produced a statistically significant greater FEV1, two and eight minutes after inhalation than formoterol 12 μg, and formoterol 24 μg a greater FEV1 at 10, 25, and 30 minutes than formoterol 12 μg, but there were no significant differences between the three active medications at other time points. Although significant, these differences in FEV1 were not large. We conclude that formoterol 24 μg and salbutamol 400 μg act equally rapidly in reversing methacholine induced bronchoconstriction, but that formoterol 12 μg is marginally less effective.

Airway responsiveness to nebulised salbutamol under different conditions of sustained methacholine exposure

JUBBER, NAGM HASSAN, RW FOSTER Smooth Muscle Research Group, Department of Physiological Sciences, Manchester University, Manchester We have previously suggested (Jubber et al, Thorax 1992;47:152, 253) that, when inhaled salbutamol causes bronchoconstriction by dilatation by functional antagonism of methacholine, the airway responsiveness to salbutamol is composed of independent sensitivity and reactivity parameters, each linked to the corresponding methacholine parameter. It is less the amount of constriction produced and more the amount of methacholine producing it that determines both the sensitivity and reactivity to salbutamol. We have now explored the correlations between the indices of sensitivity and reactivity to nebulised salbutamol under different conditions of methacholine exposure. Fourteen normal subjects each underwent three methacholine dosage individualisations (Foster et al, Br J Clin Pharmacol 1991;31:445) and three cumulative log dose-response curves to salbutamol from an Emin (the smallest sGaw caused by repeated methacholine inhalation) of 62-5% reduction from baseline sGaw. In order to challenge our suggestion 10 of the subjects were used to estimate in triplicate the responsiveness to salbutamol from an uncontrasted baseline and six of these also underwent three cumulative log dose-response curves to salbutamol from an Emin of 35% bronchoconstriction. Interpolation in the salbutamol log dose-response curve at the mean Ems was half way between the mean Emin and the line (the largest effect recorded). Therefore repeated determination of the mean log ED50. There were no significant differences over the three bronchodilator protocols between the baseline states (p = 0.76). Naturally there were significant differences between the Emins (p < 0.001 to 0.005). In uncontrasted airways the salbutamol ED50 state (the Eds used was that v methacholine PD20) was significantly larger (p = 0.006) than the Ems state. Also, the log ED50 v methacholine PD20 was significantly smaller (p = 0.048) than that v methacholine PD50 s. The Epeak state v methacholine PD50 s, was significantly smaller (p = 0.045) than v the unconstricted airways but did not differ significantly (p = 0.35) from that v methacholine PD50 s. These results largely sustain the above suggestion, relating sensitivity and reactivity to salbutamol to the amount of methacholine producing constriction.

Comparison of airway responsiveness to nebulised salbutamol and ipratropium in methacholine bronchoconstricted normal subjects

JUBBER, NAGM HASSAN, RW FOSTER Smooth Muscle Research Group, Department of Physiological Sciences, Manchester University, Manchester We have previously confirmed (Jubber et al, Thorax 1992;47:152, 253) that airway responsiveness to inhaled salbutamol is composed of independent sensitivity and reactivity parameters. In this study the component parameters of airway responsiveness to the functional antagonist salbutamol and those of the antagonist at muscarinic cholinoreceptors ipratropium bromide have been compared in a model of bronchospastic asthma created by methacholine inhalation in normal subjects. The index of sensitivity was represented by log ED50 (half maximally effective dose), while the index of reactivity was represented by Epeak (maximal effect). Six subjects each underwent three dosage individualisation experiments (log dose-response curve and offset time-effect effect, Foster et al, Br J Clin Pharmacol 1991;31:445), three cumulative log dose-response curves of salbutamol and three cumulative log dose-response curves of ipratropium. A loading dose (D0) and a sequence of maintenance doses (Dn) of methacholine were inhaled over two minutes at 10 minute intervals, aiming to cause a sustained 60-65% reduction from baseline sGaw. After the first Dn salbutamol was inhaled over two minutes and at 20 minute intervals in cumulative doses of 7, 44, 278, and 1760 μg and ipratropium was inhaled over two minutes and at 30 minute intervals in cumulative doses of 5, 10, 20, and 80 μg. Both mean log ED50 salbutamol and ipratropium were determined from the corresponding mean log dose-response curves.
EFFECT OF CESSATION OF SHORT-TERM TREATMENT WITH IPRATROPIUM BROMIDE ON LUNG FUNCTION IN ASTHMA

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Vagotomy and atropine upregulate muscarinic receptors and enhance the response to muscarinic stimuli in animals. Antimuscarinic drugs may therefore cause increased responsiveness to endogenous acetylcholine and vagus nerve activity in the asthmatic lung. A similar effect could occur in patients when their bronchodilator effect has worn off. We have investigated this in 13 subjects with mild stable asthma who inhaled ipratropium bromide 80 µg four times daily or placebo for 14 days in a crossover fashion with a one week run-in period before each treatment period. PEV, and histamine PD20 were measured on day −1 and 24 hours after the last dose of ipratropium/placebo on day 15 of each treatment period, followed one hour later by methacholine PD2 and 6–8 hours later by sodium metabisulphite PD20. Methacholine was included as a cholinergic stimulus to heterologous smooth muscle, and sodium metabisulphite as a neural stimulus. Subjects used the short acting anti-remotrol hydrobromide as rescue bronchodilator throughout and recorded twice daily symptom scores and rimiterol use and PEF four hourly for three days after the last dose of placebo/ipratropium. Four subjects were withdrawn from the study, two following a respiratory tract infection (one placebo, one ipratropium) and two for personal reasons. Following ipratropium there was a fall in PEF, maximal at 30 hours and lasting less than seven days. The mean changes in FEV, at 30 hours were −220 ml (−28%) and −358 ml with ipratropium and placebo respectively (mean difference −220; 95% CI −82 to −358 ml; 𝑝 < 0.002). Histamine, methacholine and sodium metabisulphite PD20 did not differ significantly after ipratropium or placebo. There were no significant changes in symptom scores or rimiterol use. Our findings suggest a trend towards a lower PEF after ipratropium. Thus cessation of regular treatment with inhaled ipratropium bromide 80 µg four times daily is associated with a transient deterioration in lung function. The mechanism remains unexplained since there was no change in cholinergic or non-cholinergic airway responsiveness. The fall in PEF, in our study after two weeks may be comparable to that seen in some long term studies (Van Schayck et al. BMJ 1991;303:1426–31) and is reversible.

Comparison of ouabain binding sites in airway smooth muscle and airway epithelium

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Na/K ATPase has important roles in fluid transport across airway epithelium and in determining the contractile state of airway smooth muscle. The number of Na/K ATPase pumps and binding characteristics of ouabain in bovine airway epithelium and airway smooth muscle has not been previously characterised. We therefore characterised ouabain binding in both tissues. Studies were performed on fresh specimens of bovine trachea obtained from the abattoir. Membrane particulates were prepared from both airway epithelium and airway smooth muscle by homogenising the tissue and then using a differential centri-fugation technique. Saturation isotherms to ouabain were then performed in the absence and presence of H-ouabain. Non-specific binding was measured as binding in the presence of 10 M cold ouabain. Kd and Bmax values were estimated using a non-linear curve fitting programme. In both epithelium and airway smooth muscle ouabain binding was to a single homogenous population of receptors. In airway epithelium mean (SE) Kd was 8.6 (2.3) nM with a Bmax value of 44.9 (5.2) pmol/mg of protein. In airway smooth muscle mean (SE) Kd value was 4.9 (1.2) nM with a Bmax value of 41 (9.9) pmol/mg of protein. There was no significant difference in the Kd values between airway epithelium and airway smooth muscle, but an 11-fold difference in Bmax values (𝑝 < 0.001). The large number of Na/K ATPase pumps in airway epithelium relative to muscle is likely to reflect the importance of the basolateral Na/K ATPase in sodium resorptive processes in airway epithelium.

Bradykinin increases release of PGE2 from cultured bovine airway smooth muscle cells

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PGF have been shown to have negative modulatory effects on inflammatory processes in vitro and in vivo. We have studied the regulation of PGE2 production by cultured bovine airway smooth muscle cells. Cultures were prepared by enzymatic digestion of whole tissue, and experiments were performed while cells were at confluence on their first passage. Cells were grown arrested by incubating in serum free medium for 24 hours before studying PGE2 production over a six hour period. PGE2 was measured by radioimmunoassay. Mean (SE) PGE2 production was increased to 148 (17%) of control values after the addition of arachidonic acid 10−4 M (𝑝 < 0.05). Bradykinin (10 M) increased PGE2 production by 230 (80%) (𝑝 < 0.01). To determine whether the effects of bradykinin were mediated via protein kinase C (PKC) we studied the effects of 4-bromoliporol 12, 13 dibutyrate, an activator of PKC, and its 4-a isoform (which does not activate PKC). 10 M 4-bromoliporol dibutyrate increased PGE2 production to 175 (17%) of control values (𝑝 < 0.05); 4-a dibutyrate was without effect. In conclusion, bradykinin stimulated PGE2 production from airway smooth muscle cells. The effects of 4-bromoliporol dibutyrate suggested that bradykinin increased PGE2 production was mediated through protein kinase C. Production of PGE2 by airway smooth muscle after exposure to spasmodgens may be a mechanism whereby airway smooth muscle cells are able to feed back and inhibit the inflammatory process.

Lack of bronchial responsiveness to bradykinin in mildly asthmatic children

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As part of a large scale study in 104 children to assess the effects of inhaled steroids on viral induced wheezing episodes, we investigated underlying mechanisms of bronchial hyperreactivity in children by comparing inhalation of methacholine and bradykinin. Thirty three children aged 7 to 9 years with mild episodic wheezing took part in this part of the study. Following baseline challenges to both agents, the children received treatment or placebo for three months during which they had monthly challenges to both agents, with at least a week between each challenge. Both methacholine and bradykinin were given by hand held nebuliser as described by Yan et al. Methacholine was given in increasing concentrations from 2 mg/ml to 64 mg/ml (cumulative concentration 512 mg/ml) and bradykinin in concentrations from 0.03 mg/ml to 32 mg/ml (cumulative concentration 58-655 mg/ml). Cumulative PC20 was calculated by interpolation and extrapolation up to one doubling dilution above the maximum concentration given. Thirteen children had measurable PC20 to methacholine at baseline, and on each subsequent challenge a mean of 12 children had a measurable PC20. In contrast only four children had a measurable PC20 to bradykinin either at baseline (two had a PC20 to both) or subsequently, and there was no relationship between hyperresponsiveness to methacholine and bradykinin. Because of the number of children responding to bradykinin no conclusions were made on the action of inhaled steroids. Even though our children were only mildly asthmatic, the discrepancy in response to the two agents suggests that the underlying mechanisms of bronchial hyperresponsiveness differ between children and adults.

Increased urinary leucotriene E, (LTE) excroution following inhalation of leucotriene C, (LTC) and leucotriene E, (LTE) in asthmatic subjects

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Urinary LTEA concentration was measured.
before and 1:5 and 3:5 hours after inhalation of bronchoconstrictive doses of LTC₄ or LTE₄ in eight asthmatic subjects. Airway response to inhaled LTC₄ or LTE₄ was measured using specific airway conductance (SGaw) in a total body plethysmograph and increasing doses of agonist inhaled until a 35% fall in SGaw was achieved. There was no significant difference between the 52 (3)% fall in SGaw following inhalation of 616-9 ng LTC₄ (GM, range 5-5-508 ng) and the 43 (4)% fall in SGaw following inhalation of 724 ng LTE₄ (GM, range 48-3569 ng). The LTE₄ elicitation rate increased significantly more (2:9 ng/h) (GM, range 0:6-17:5 ng/h) to 4:7 ng/h (GM, range 0:8-20 ng/h) at 1:5 hours after LTC₄ inhalation (p < 0:05) and from 1:7 ng/h (GM, range 0-07-67 ng/h) to 6:9 ng/h (GM, range 2-9-273 ng/h) at 1:5 hours after LTE₄ inhalation (p < 0:05) and had returned to baseline by 3:5 hours. There was a correlation between the dose of LTC₄ and LTE₄, inhaled and LTE₄ excreted in the urine (p < 0:05, r = 0:8 and p < 0:05, r = 0:7 respectively). The % recovery of LTE₄ in the urine of the total dose of inhaled LTC₄ or LTE₄ administered was 7:3 (4:3)% and 1:0 (0:6)% respectively. Thus inhalation of bronchoconstricting doses of LTC₄ or LTE₄ alters urinary LTE₄ excretion in a dose dependent fashion. Changes in urinary LTE₄ excretion may reflect pulmonary levels of eicosanoid mediators in asthma.

Comparison of airway responsiveness to histamine leukotriene C₄ (LTC₄) and leukotriene E₄ (LTE₄) in aspirin sensitive asthmatic subjects with that of aspirin tolerant subjects

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Airway responsiveness to histamine, leukotriene C₄ (LTC₄) and leukotriene E₄ (LTE₄) was determined in seven aspirin sensitive and 13 control asthmatic subjects who were tolerant of aspirin. The dose of agonist which produced a 35% fall in specific airways conductance (PD₃5, SGaw) was determined by linear interpolation from the log dose-response curve. There was no difference in airway responses to histamine and LTC₄ between the groups of asthmatic subjects. Aspirin sensitive asthmatic subjects were significantly more responsive to LTE₄ (p = 0:02) than control asthmatic subjects. The relative responsiveness of LTE₄ to histamine (PD₃5, histamine/PD₃5 LTE₄) was significantly greater in aspirin sensitive asthmatic subjects than in control asthmatic subjects (p = 0:05) There was no difference in relative responsiveness of LTC₄ to histamine between each group of asthmatic subjects. Thus the airways of aspirin sensitive asthmatic subjects but not aspirin tolerant asthmatic subjects demonstrate a selective hyperresponsiveness to LTE₄, which is not observed for LTC₄.

Single high dose budesonide does not affect AMP challenge

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Glucocorticosteroids when inhaled regularly suppress airway inflammation and bronchial hyperresponsiveness in a dose and time dependent manner. We have previously demonstrated a decrease in airway responsiveness to AMP after regular treatment with budesonide (1-2 doubling dilutions after AMP following doubling dilutions of AMP) and we have investigated the acute effect of glucocorticosteroids on mast cell function we conducted a randomised double blind placebo controlled trial in 18 mild atopic non-smoking asthmatic subjects (nine men, nine women) using inhaled budesonide and AMP challenge. All subjects were treated with inhaled beta agonists only, which were withdrawn for at least two weeks before entering the trial. The study consisted of two single treatments, budesonide 4 mg administered in a single dose via turbohaler, and identical placebo, separated by 3 weeks. Each subject inhalated five breaths of doubling doses of AMP from 0-78 to 800 mg/ml via a Mefar dosimeter until a PC₉₀ was reached. Despite a small overall rise in mean log PC₉₀ (log PC₉₀ (SE) placebo 1:0 (0-19), 1:12 (0-16) active treatment), there was no statistically significant change (p = 0-82) from baseline. A significant increase by over 1-5 doubling dilutions, PC₉₀ decreased in two (>1:5 doubling dilutions). There was no correlation between baseline AMP PC₉₀ or FEV₁, and degree of response. We conclude that, despite the marked effect of regular inhaled budesonide on mast cell function, a single high dose has no demonstrable effect in vivo.

Contrasting effects of inhaled and oral WEB 2086, a specific platelet activating factor antagonist (PAF) receptor antagonist on airway and systemic responses to inhaled PAF in man

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WEB 2086 is a specific PAF receptor antagonist with therapeutic potential in allergic and inflammatory diseases. In two double blind placebo controlled studies we compared the ability of four different doses of inhaled WEB 2086 with the known ability of oral WEB 2086 to inhibit PAF induced bronchoconstriction. In study 1, 12 healthy non-atopic men attended on four separate occasions, each at least a week apart, to inhale three doses of WEB 2086, 0-25, 0-5 and 1 mg, or placebo from an MDI 30 minutes before PAF inhalation challenge. Airway responses to PAF (24 mg) were measured as changes in SGaw from baseline at serial intervals for up to 60 minutes. At 30 minutes we measured ex vivo PAF induced platelet aggregation. In study 2, 12 healthy non-atopic men attended on three separate occasions, each at least a week apart, to inhale from an MDI 10 mg or take a 40 mg oral dose of WEB 2086 30 and 90 minutes respectively before PAF inhalation challenge using a double dummy design. PAF induced neutropenia at five minutes and rebound neutrophilia at 30 minutes were measured. In study 1, none of the three inhaled doses of WEB 2086 inhibited PAF induced bronchoconstriction and platelet aggregation. In study 2, PAF induced bronchoconstriction was almost completely abolished by 40 mg orally, but was only partially attenuated by 10 mg inhaled WEB 2086 (NS), PAF induced neutropenia and rebound neutrophilia was significantly affected; mean (SD) % change from baseline at five and 30 minutes after PAF were respectively: −55±4 (8-8) and 132 (40) after placebo; −35±5 (6-8) and 23±9 (8-2) after 10 mg inhaled (NS); −4±5 (2-3) and 8±6 (2-8) after 40 mg oral (p < 0-001) (see table). Thus inhaled WEB 2086 has no effect on airway and systemic responses to PAF inhalation challenge. These data suggest that an oral formulation is required for further evaluation of the therapeutic potential of this compound in airway inflammation.

Are oral antibiotics as effective as intravenous in treating chest infections?

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We studied the effectiveness of oral antibiotics alone or a combination of intravenous and oral antibiotics in the treatment of mild to moderate community-acquired lower respiratory tract infections treated by 328 consecutive non-ventilated inpatients hospitalised in one of three treatment groups: (1) amoxicillin and clavulanic acid, 375 mg orally three times a day for seven days; (2) amoxycillin and clavulanic acid 1·2 g intravenously for three days followed by 375 mg orally three times a day for four days; or (3) cefotaxime 1 g intravenously three times a day for three days followed by cefuroxime axetil 500 mg orally twice daily for four days. Patients were assessed every alternate day until discharge or death. The outcome for each patient on discharge was classified as cure, partial failure, failed or relapse, antibiotic changed, or death. Each group had 180 patients and all were comparable. The final outcome and mean duration of stay in hospital are shown in the table. There was a non-significant trend for a higher cure rate in the oral group which had a significantly reduced duration of hospitalisation. The combination "triple" use was associated with an increased risk of infection which was unrelated to hospitalisation. The effectiveness of oral antibiotics in patients with mild to moderate lower respiratory infections is no longer supported by our data. [Supported by The Health Research Board.]
Airborne transmission of Pseudomonas cepacia in cystic fibrosis

DG PECKHAM, H HUMPHREYS, AJ KNOX Respiratory Medicine Unit, City Hospital and Department of Microbiology, University Hospital, Nottingham

Increased prevalence of Pseudomonas cepacia in the cystic fibrosis clinic has led to inpatient segregation according to sputum cultures. We are presently investigating how patient to patient transmission of P cepacia may occur. Room air was sampled using an SAS sampler before, during, and after the occupancy of a room by six P cepacia positive patients with cystic fibrosis. Samples were obtained during coughing, immediately afterwards, and 18 hours after the patient had left the room. Contact and settle plates were also used. A total of nine experiments on six patients (mean FVC 59%, FEV 36%) have so far been conducted. All patients had been colonised by P cepacia for longer than six months. All sputum samples obtained during testing were positive for P cepacia. In four subjects P cepacia was isolated from air after vacating the room and in one patient it persisted for 45 minutes. Settle plates were negative in most instances. During coughing the mean count was 40 cfu/cm² compared with 15 cfu/cm² when patients were not coughing. During outpatient clinical similar experiments were undertaken with air sampling during and after spirometry of P cepacia positive patients and all results proved to be negative. Our results suggest that P cepacia positive patients should be separated from P cepacia negative patients to minimise cross infection.

K M MURPHY, S O'HICKEY, G SMITH, DE STABLEFORTH Adult Cystic Fibrosis Unit, East Birmingham Hospital Between 1989 and 1992, 18 of 140 adult patients with cystic fibrosis attending our unit have developed sputum colonisation with Pseudomonas cepacia: five of these have died, three have received transplantation, and two subjects with insufficient data are not reported further. We compared the rate of decline of FVC and FEV1 of patients with P cepacia with 18 age, sex and severity matched control patients colonised with Pseudomonas aeruginosa. Body weight and FEV1 were recorded daily in hospital, and number of outpatient visits per six months were also studied. These patients were studied for 24 months before known colonisation with P cepacia and for as long as possible afterwards. The mean (SD) rate of change of FVC for the patients with P cepacia was −2.9% (0.05)% per month (p = 0.05) compared with −8.8% (1.6)% per month for P pseudomona aeruginosa. The mean rate of change of FEV1 for the patients with P cepacia was −3.6% (0.05)% per month compared with −2.2% (0.05)% per month. Days of hospitalisation for treatment of acute infective exacerbation and number of outpatient visits per six months were significantly increased for the patients with P cepacia group (p = 0.05), the mean (SD) being 9.7 (10) days/six months, 3.1 (1.5) visits/six months before and 6.2 (3.6) visits/six months after colonisation respectively compared with 11.7 (19.6) days/six months, 2.9 (1.25) visits/six months in the control group. The differences in body weight per six months did not show any significant difference between the two groups. The acquisition of P pseudomona cepacia is associated with a significant decline in lung function, increased days of hospital treatment, and number of outpatient visits.

Five year survival on home nebuliser treatment

BR O'DRISCOLL, K WORTHY, S JOHNSTONE, A BERNSTEIN Hope Hospital, Salford It has been suggested that home nebuliser treatment of asthma and chronic airflow obstruction may be dangerous either because of the potential hazards of high dose sympathomimetic treatment or because of over-reliance on self-administered treatment. We assessed 50 patients (16 asthma, 34 COPD) for home nebuliser treatment in 1986-7 and now report the five year mortality data of 49 of these patients (one left the area and cannot be traced). Thirty two patients (mean FEV1, 0.87 l) requested long term home nebuliser treatment and 17 patients (mean FEV1, 0.89 l) chose conventional metered dose inhaler treatment (MDI) with or without a large volume spacer. Five year survival was 53% for MDI users and 56% for nebuliser users, the two survival curves being parallel throughout the five year period. Most deaths were due to respiratory failure (14), lung cancer (four), or myocardial infarction. These (three cases, one MDI, two nebuliser users). The risk of death was mainly determined by initial FEV1 (27 survivors FEV1, = 1.1 l; 22 deaths FEV1, = 0.9 l; p < 0.001). We conclude that home nebuliser treatment and metered dose inhaler treatment are associated from post mortem examination, with similar mortality rates in patients matched for the severity of their asthma and COPD. Mortality was related to severity of airflow obstruction in both groups. These data would support the view that the increased mortality amongst nebuliser users in other studies may reflect disease severity rather than factors that may improve survival.

Domiciliary oxygen cylinders: a survey of indications and usage

AA OKUBADEJO, EA PAUL, JA WEDZICHA Department of Thoracic Medicine, London Chest Hospital, Bonner Road, London In 1989, 935 831 oxygen cylinders were supplied in England and Wales at an average cost of £140. A survey of each FHSA (Health Trends 1991:23:166), although concentrations have been available since 1985. Uses of oxygen cylinders include short burst treatment for breathlessness, refilling of portable oxygen cylinders, and as back-up for concentrators. We identified from FHSA records 116 patients in the Tower Hamlets district (population 165 000) who had a home oxygen cylinder. Information on each patient was collected from questionnaire and hospital reports. Two groups of patients were identified: those with an oxygen concentrator and home cylinder, and those who solely used cylinders. There were 60 (37 men, 23 women) concentrator users and 54 (26 men, 28 women) cylinder users. Sixty six (92%) used oxygen cylinders for 69 (range 20–94) years: 12% used the cylinder to refill a portable cylinder, 87% used the cylinder only as a back-up for the concentrator, but 74% stated that they had never actually used the cylinder. In the second group there were 56 patients (32 men, 24 women) of median age 71 (range 29–96) years: 43 (77%) had a diagnosis of COPD, 40 had asthma, three had cardiac failure, two had carcinoma, and in four patients the indication was not known, 41% under regular chest clinic review. Of this group, 44 (79%) replied to the questionnaire on usage: 26 (59%) used oxygen every day, further 12 (27%) used it more than six days a week, and 14% used it less. Thirty eight (86%) patients used it for acute attacks of breathlessness and exacerbations of COPD, six (14%) patients used oxygen before a period of exertion. Only two patients had portable oxygen cylinders. Arterial blood gas results for the previous year were available for 15 patients, 24/26 (92%) had an arterial oxygen tension <7.3 kPa; 20% of patients had an O2 tension <7.3 kPa; 20% of patients had an O2 tension <7.3 kPa. Patients were asked if they were bound. From patient usage data an average of 29-2 cylinders per patient year were delivered. We found that oxygen cylinders in the community are used mainly for regular short term relief of breathlessness, though benefits are controversial. The view of cost implications we suggest that the long term prescription of oxygen cylinders should be limited to patients refilling portable cylinders, to those using a cylinder as a back-up to concentrators, and to where the benefit of short burst treatment has been clearly established and reviewed.

Oxygen therapy and the medical wards: drug or harmless panacea?

C BELL, CC HARDY Manchester Royal Infirmary, Oxford Road, Manchester Oxygen therapy administered in inappropriate circumstances is at best of no benefit, and at worst potentially dangerous. The current plethora of oxygen masks on the market brings potential confusion to both hospital and home users. Clinical trials with patients receiving oxygen therapy on medical wards were identified and their treatment sheets and case notes scrutinised with particular reference to its prescription, whether "prn" or continuous, indication of flow rate, and the duration of time the oxygen was prescribed in an appropriate concentration was not addressed. Oxygen had not been prescribed to 25% of patients receiving it. Of the 75%...
with a prescription, 94% specified an Fio2. However, 36% of patients were not receiving the concentration prescribed, either because of an incorrect mask (77%) or an inappropriate flow rate (23%). Oxygen was prescribed "prn" in 66% of cases, continuously in 25%, and unknown in the remainder. Of the patients prescribed continuous oxygen 78% were not receiving it at the time the ward was visited. Arterial blood gases or oxygen saturation (oximetry) were recorded in 65% of patients, with an Fio2 recorded in 52%. Twenty-five five house officers were interviewed about their understanding of oxygen therapy and its prescription; 24% felt it sufficient to make a verbal request to nurses. Only 4% could name a mask suitable for asthmatic patients, and only 20% knew the principle of delivering controlled oxygen therapy. This study shows that both nursing and medical staff require more training on safe, appropriate, beneficial oxygen therapy. By limiting the number of masks available on our wards we hope to circumvent some of the current problems.

Prevalence and symptoms of air travel amongst patients with respiratory disease

AOC JOHNSON, J CONGLERON, RL PAGE Respiratory Unit, Kellinghe Hospital, Leeds The inspired oxygen pressure in a commercial air-line cabin at maximum cruising altitude is only 15 kPa. While this is sufficient to maintain oxygenation in normal subjects, those with impaired gas exchange may become profoundly hypoxaemic. The prevalence of, and difficulties experienced by, passengers with respiratory disease has been examined in the USA but not, to our knowledge, in the UK. We surveyed outpatients attending our respiratory unit by means of an administered questionnaire. All patients over 40 years with COPD, chronic asthma (CA), bronchiectasis (B), or interstitial lung disease (ILD) were included. A total of 97 patients were surveyed; 35 (36%) said that their chest disease alters their travel plans, 34 (35%) had flown on 63 occasions in the preceding two years (table 1). Of the 34 subjects who flew 15 (44%) developed respiratory symptoms; nine (26%) during the flight, and 10 (29%) while abroad. Only nine (26%) sought medical advice before flying (five GP and four hospital doctor). This included five of the subjects who developed symptoms. No special arrangements or further assessments were made and no patient was advised not to fly. There was no significant difference in FEV1, FVC or FEV1/FVC between flyers and non-flyers, nor between those with and without symptoms (table 2). All subjects were asked if the oxygen level in the aircraft was lower than, higher than, or the same as on the ground. Only 15% answered correctly. These findings, in agreement with Dillard et al (Arch Intern Med 1991:151:1793–5), suggest that patients with chronic respiratory disease fly frequently and often experience symptoms. Patients and doctors should be more aware of the potential problems of flying, and the advantages of preflight assessment.

Table 1 Data on patients in study

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<thead>
<tr>
<th>n</th>
<th>COPD</th>
<th>CA</th>
<th>B</th>
<th>ILD</th>
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<th>FEV1/Sped (mean)</th>
<th>FVC% (mean)</th>
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<td>52-8</td>
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<tr>
<td>Non-flyers</td>
<td>63</td>
<td>36</td>
<td>21</td>
<td>1</td>
<td>5</td>
<td>61-4</td>
<td>49-1</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
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</tbody>
</table>

Table 2 Number of patients experiencing symptoms during flight

<table>
<thead>
<tr>
<th>n</th>
<th>Age (mean)</th>
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<th>FVC% (mean)</th>
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<td>Symptoms</td>
<td>9</td>
<td>63-1</td>
<td>43-7</td>
<td>68-1</td>
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<tr>
<td>No symptoms</td>
<td>25</td>
<td>57-9</td>
<td>56-1</td>
<td>75-9</td>
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</table>

Association of smoking with depression in the elderly

BH GREEN, JMA COPELAND, ME DEWEY, V SHARMA, PA SAUNDERS, IA DAVIDSON, C SULLIVAN, CM WILIAM II, PDO IAVIES Department of Psychiatry, Institute of Human Ageing, University of Liverpool and South Liverpool Chest Clinic As part of a prospective survey to identify risk factors for depression in the elderly, subjects were asked about their smoking habit. A total of 1070 individuals were interviewed and assessed using the Geriatric Mental State package. Smoking data were available for 628 subjects, of whom 183 (29%) were never smokers and 218 (35%) current smokers. Three years later the same individuals were interviewed and 44 incident cases of depression were diagnosed. The control group was taken from the remaining non-depressed individuals. Of 31 risk factors assessed in the interview feelings of loneliness, satisfaction with life, and smoking for the first time were the only factors that remained on analysis after univariate analysis. Smoking at the year of initial interview, but not necessarily a past history of smoking, appeared to predict depression (X2 = 5.45, p < 0.02). Previous studies have shown an association between smoking behaviour and depression and an inverse relationship between quit ratio (former smokers or non-smokers) and depression scale scores. Suggestion of a causal link between current smoking and the onset of late life depression remains intriguing but speculative.

New portable information system for research and clinical use in a sarcoidosis clinic

C QUIGLEY, RM MOFFED, G LUG, C G CONNOR, MA FITZGERALD Medical Professonal Unit, University College, Dublin and St Vincents Hospital, Dublin, Republic of Ireland 'The accumulation of clinical, physiological, radiological and other details over many years of regular follow up will provide greater information about the natural history and long term management of chronic lung diseases. Relational databases organise data in a logical structure, usually from a relational database, which allow easy retrieval of complex interrelated information. We have developed a relational database specifically designed for rapid retrieval of complex clinical and basic research details facilitating continued clinical care and research in patients with chronic lung conditions. Sarcoidosis was used as a model for our database because of the many different types of data required in the full assessment and management of over 600 consecutive biopsy confirmed patients attending our special sarcoidosis clinic. We used a powerful relational database software package, 4thDimension, held on a Macintosh Powerbook 170. This allows access to all previous computer held data and data are entered once only to a single format using electronic transfer where possible. The system takes advantage of the "Mac" user interface which is easy to use, requiring minimal computing skills acquired within 2–3 hours, and is preferable for use in clinics on ward rounds, and at a research laboratory. All data on patients with sarcoidosis are entered into a structure designed for use during consultation. Separate files are used for clinical, biochemical, lung function, bronchoalveolar lavage, and radiological data. Individual patient information is reviewed at a glance and updated during the consultation. Laboratory data can be transferred electronically at intervals. Patient confidentiality is preserved by strict password protection. The database is currently used to support comprehensive analysis of two year and five year follow up data and response to treatment over time in different patient subgroups. This new sarcoidosis information system will give access to complex clinical data and enhances the effective long term management of sarcoidosis. Similar specifically designed databases may be of value in the management of asthma, cystic fibrosis, and other chronic lung conditions, and will allow comparison of epidemiological and other information.'

Review of requests for respiratory consultation

NC MUNRO, D FISHPICK, PA CORRIS, JG GIBSON, RAL BREWS Royal Victoria Infirmary (RVI) and Freeman Hospital (FHI), Newcastle upon Tyne Details were collected prospectively on 508 requests for a consultation with a respiratory physician (RVI, 378 over 33 months; FHI, 130 over four months). Both hospitals include general and specialist medical and surgical services, intensive care, and renal units. Consultations were performed by a consultant (56%) or respiratory registrar or senior registrar (44%). There were no significant differences between the pattern of referrals at the two hospitals studied. The largest single source of referrals (35%) was the general medical wards, followed by medical subspecialties (25%) and general surgery (14%). Renal medicine provided 6% of referrals and intensive care 2.5%. The most common reasons for referral were tumour (27%), COPD (16%), and asthma (10%). The respiratory consultation resulted in the diagnosis of the patient's condition being made or altered in 39% of cases, the majority of the remaining consultations being advisory. Bronchoscopy was required following 29% of consultations; 77% of consultations were seen within 24 hours of the request being received and 33% required more than one visit. The time spent undertaking the consultation was up to 30 hours.
minutes in 47% of cases, 31–60 minutes in 37%, and over an hour in 11%. In 15% of cases, care of the patient was taken over by the respiratory team. Problems encountered were unavailable radiographs in 9%, no appropriate lung function tests performed in 8%, and delay in seeking a respiratory opinion in 6%. Pulmonary disease is commonly present in patients admitted under all specialties and frequently the specialist respiratory opinion for optimal diagnosis and management.

Antiglomerular basement membrane disease: the long term pulmonary outcome

P CONLON, G O’NEILL, M LONG, M CARMDY, B KEOGH, J DONOHUE, J WALSHIE, S O’NEILL Department of Respiratory Medicine, Beaumont Hospital, Dublin, Republic of Ireland Evidence of pulmonary involvement occurred in only 65% of patients with antiglomerular basement membrane disease (anti-GBM) at presentation. The long term functional sequelae of this involvement are unclear. We studied the pulmonary function of 14 patients (seven men, seven women) with biopsy proven anti-GBM disease of a mean of 7.8 (1–17) years after initial presentation. All patients were anti-GBM antibody negative and lacked radiographic evidence of lung disease at the time of study. Patients had measurements of forced vital capacity, forced expiratory volume in one minute, vital capacity, total lung capacity, residual volume, and single breath carbon monoxide transfer factor corrected for alveolar volume (Kco). All patients also participated in a modified Bruce protocol using a respiratory exercise system measuring maximal O2 uptake, CO2 output, expired minute volume, and O2 saturation. As a control group 14 patients attending the renal clinic were chosen. These patients were matched for age, sex, smoking history, level of renal function, method of renal replacement, and duration of renal replacement. The Kco was significantly lower in the anti-GBM patients (53% (15%) compared with the control group (69% (15%), p = 0.02). The anti-GBM patients without pulmonary haemorrhage (n = 6; Kco 0%, 8%) did not differ significantly from the control group in contrast to patients with pulmonary haemorrhage (n = 8; Kco 46% (10%), p = 0.006). We conclude that patients with anti-GBM disease and pulmonary haemorrhage have evidence of a persistent reduction in Kco when compared with patients matched for levels of renal dysfunction.

Sclerosing mediastinitis: Royal Brompton experience

T MOLL, MN SHEPPARD Department of Surgery and Lung Pathology, Royal Brompton Hospital, Sydney Street, London Sclerosing mediastinitis is a rare condition involving dense fibrosis of the mediastinum. We have collected 18 cases from 1970 to 1993. The sex ratio was M:F 2:1, age range 9–64 years. Twelve were British (66%), two Spanish, one Turkish, one Asian and two Greeks. Twelve had shortness of breath, eight developed superior vena cava obstruction, six had haemoptysis, three had hoarseness, four had pleuritic chest pain, two had pleural effusion, three general weakness, and one patient had no symptoms. Twelve (66%) patients had previous disease. Two had autoimmune disease. Three had malignancy and were treated with chemotherapy and radiotherapy. Seven patients (43%) had a history of previous pulmonary tuberculosis with positive Mantoux test. Serological tests showed one positive reaction to histoplasma and this patient had lived for five years in the USA. Erythrocyte sedimentation rate was raised in nine patients. In seven patients (43%) liver function tests were abnormal. Immunoglobulins were raised in six cases. Diagnosis was usually based upon thoracotomy with biopsy. No positive culture results were obtained in any case. All cases showed fibrosis and chronic inflammation with no granulomas of the soft tissue of the mediastinum. Ten cases are alive up to 15 years later while six are lost to follow up. Six cases had superior vena cava bypass graft and are doing well. Only two deaths occurred and this was in cases treated for malignancy with chemotherapy and radiation.

Histological diagnosis of cryptogenic organising pneumonia: value of transbronchial biopsies

R DNA, MN SHEPPARD Department of Histopathology, Royal Brompton Hospital, London and Institute of Pathology, Bologna Hospital, Bologna, Italy Eleven cases of clinically diagnosed cryptogenic organising pneumonia were examined in order to establish the histological features found at transbronchial biopsy and to correlate this with the results of open lung biopsy which followed in five cases. The essential pathological feature was the presence of buds of granulation tissue (Masson bodies) indicating organisation of a persistent exudate by fibroblasts and capillaries within alveoli with preservation of the alveolar architecture. In addition, both acute and chronic inflammatory cells were present in the interstitium. These features, combined with the clinical history, were sufficient to come to a diagnosis in seven of the 11 cases by transbronchial biopsy. However, four biopsies lacked these features and proceeded to open lung biopsy in addition to the two cases with histological features of cryptogenic organising pneumonia on transbronchial biopsy where the patient wanted to explore their lung disease by open lung biopsy. In the long term, four of the five cases undergoing open lung biopsy confirmed cryptogenic organising pneumonia with Masson bodies within alveoli, but changes were focal in three cases with few Masson bodies in one case. In addition, one case which had the features on transbronchial biopsy lacked them in the open lung biopsy which is explained by the evolution of the disease and time delay. The possibility of sampling error is also considered. In summary, transbronchial biopsy can yield diagnostic material in the majority of patients with cryptogenic organising pneumonia while open lung biopsy, which is considered the gold standard, may yield negative results because of the rapid evolution and changing pattern of the disease.

Midazolam sedation for fibroptic bronchoscopy

M HQ HATTON, MB ALLEN, NJ COOKE Department of Respiratory Medicine, General Infirmary at Leeds, Great George Street, Leeds Sedation is often given before fibroptic bronchoscopy, most routinely using an opiate and benzodiazepine. In a previous study comparing an opiate/sedative combination with placebo we found the active drugs conferred no advantage over placebo and patients were significantly less willing to have the investigation repeated (Thorax 1991;46:65). To formally evaluate the benefits of midazolam sedation we compared, in a double blind randomised study, midazolam 70 μg/kg (35 μg/kg for those >70 years) given immediately before fibroptic bronchoscopy with matched placebo; all received atropine. Eighty one patients undergoing routine fibroptic bronchoscopy but not transbronchial biopsy were studied. The assisiting nurse (N), bronchoscopist (B) and patient (PT) completed a 100 mm visual analogue scale (VAS) relating to comfort, ease of procedure, and willingness to have the test repeated. Higher scores represent a less favourable view. Fifty one patients received sedation, 30 placebo. The results, expressed as medians and compared with the Mann-Whitney U test, are shown in the table. The bronchoscopist felt the investigation was easier to perform on those patients given active drug, but none of the participants thought midazolam made fibroptic bronchoscopy more comfortable for the patient. Active sedation made no difference to the willingness to have the procedure repeated. Sedation for fibroptic bronchoscopy has recognised risks and the benefit of the active drug in this study may not be sufficient to justify its use.

<table>
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<th>Active (VAS)</th>
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<tr>
<td>Patient comfort (B)</td>
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<td>14</td>
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Research bronchoscopy in HIV positive patients with no respiratory disease: does it adversely affect future health care decisions?

MC LIPMAN, D STOBBS, R MILLER, MA JOHNSON Royal Free Hospital and School of Medicine, London Patients are often asked to take part in research projects. We studied the response of HIV positive patients with no respiratory disease to a request to have a research bronchoscopy. A structured interview and questionnaire were completed at first approach, subsequent bronchoscopy, and follow up. Sixty subjects were approached (50 men, 10 women); 44 (73%) agreed to bronchoscopy. The commonest reason for this was "to help others" (76%). Comparison of those agreeing and not agreeing revealed generally higher CD4 counts (median 505 v 415 x 10^9 l^-1), lower β2 microglobulin (median 2.8 v 3.1 mg/ml), and a shorter
duration of known HIV positivity (14-5 to 18 months) in the former group. To date 30 patients have undergone bronchoscopy. None found it worse than expected, although 82% had symptoms after the procedure (commonly sore throat); 86% would have a repeat research bronchoscopy, those declining having symptoms lasting >4 days after the procedure. All would have one for diagnostic purposes if a second was necessary at an increased rate to an invasive research procedure which, although associated with short term after effects, is well tolerated and does not appear to compromise future health care decisions.

Audit of transbronchial lung biopsy in one Liverpool hospital
MJ WAlSHAW, CC EVANS, CRK HIND The Cardi Thoracic Centre, Liverpool It has been suggested that transbronchial lung biopsy is of limited value in patients at risk of significant complications (Am Rev Respir Dis 1974;109:67) and some patients are now referred directly for lung biopsy at microthoracotomy (Thorax 1992;47:490–3). As part of an ongoing audit of lung biopsy techniques in our unit we have analysed all transbronchial biopsy carried out during fibroptic bronchoscopy under local anaesthesia since June 1990. Fifty two such biopsies have been performed (4% of all fibroptic bronchoscopies) by seven operators, the majority (44, 85%) by two operators. The mean age was 57 (range 21–79), mean FEV1, 72% predicted (28–115) and mean FVC 78% predicted (24–132). Ten patients (19%) had a history of other diseases which would have made them poor risks for general anaesthesia, and 37 had diffuse shadowing on chest radiography. Uniplanar fluoroscopic positioning of the biopsy forceps was used in 49 cases (94%), the remainder were carried out “blind”. Most cases (45) were taken from the left upper lobe, one from the lower lobes. On average four biopsies were taken (range 1–6). There were no cases of post biopsy pneumothorax, although seven cases (13%) had haemoptysis. Alveolar tissue was obtained in 46 cases (88%); all were cases performed with fluoroscopy. The samples were considered inadequate for pathological examination by the histopathologists in 42 cases (81%); 11 malignancy, seven fibroblastic alveolitis, five sarcoidosis, six pulmonary fibrosis, three extrinsic allergic alveolitis, two amiodarone lung, one tuberculosis, one pulmonary eosinophilia, six normal lung. Of the remaining cases, three went on to surgical lung biopsy (one malignancy, one fibrosing alveolitis, one honeycomb lung). Our results reiterate that transbronchial lung biopsy using uniplanar screening can provide a diagnosis in over 80% of cases and has a low morbidity. It should be considered before patients are referred for more invasive diagnostic procedures.

Bronchoscopic diagnosis of malignancy in patients whose chest radiograph showed only a pulmonary infiltrate
VL SCOTT, E NEVILLE, R BUCHANAN Chest Clinic, St Mary's Hospital, Portsmouth A total of 2453 bronchoscopies were performed at St Mary's Hospital between January 1983 and January 1993. Of these, 163 (6-6%) had radiological evidence of diffuse interstitial disease, with or without hilar enlargement. Of these cases, 13 were diagnosed as malignant, one squamous metaplasia, two by the time and one, by the radiologist. Of these, three went on to have a surgical lung biopsy (one squamous metaplasia, one squamous cell alveolitis, one squamous cell carcinoma). One of these patients went on to have an open lung biopsy which showed metastatic breast carcinoma. Eight of the 18 with definite malignancy had additional radiological features suggestive of carcinoma. In 10 patients there was chest radiographic evidence of pulmonary infiltrate without visible tumour there were three female and seven male patients, with ages ranging from 43 to 81 years (mean 61-9 years). Three of these 10 were known to have other forms of malignant disease, namely non-Hodgkin's lymphoma, carcinoid of the gut, and a cervical carcinoma. A spirometry a restrictive defect was seen in seven out of eight patients. At bronchoscopy three patients had visible tumour, all of which proved to be squamous cell carcinoma. The remaining patients had normal bronchoscopic appearances. The patient with lymphoma had this confirmed on biopsy and the patient with prostatic and gastric carcinoma had histological evidence of metastatic disease. Of the four remaining patients two had squamous cell carcinoma and two adenocarcinoma. One of the latter went on to have a mammogram which confirmed a primary breast lesion. The distribution of the pulmonary infiltrate gave no clue to the underlying diagnosis of malignancy. Histological diagnoses of malignancy were reported in 10 of 163 (6-1%) of those bronchoscopied with interstitial lung disease, but no radiological evidence of cancer. This corresponds to 0-4% of all patients undergoing bronchoscopy in a 10 year period.

Evaluation of computed tomography and sputum cytology in the diagnosis of bronchial carcinoma
GA G OULD, A TROUGHTON, PR GODDARD, JR CATTERALL Departments of Respiratory Medicine and Radiodiagnosis, Bristol Royal Infirmary, Bristol Investigation of suspected bronchial carcinoma usually includes a bronchoscopic examination followed by computed tomography (CT) to stage disease. We prospectively studied 55 consecutive patients in whom a diagnosis of bronchial carcinoma was considered to determine the roles of CT, bronchoscopy, and sputum cytology. Adequate sputum specimens were not obtained in seven patients and, in a further four bronchoscopy was not performed for clinical reasons. The remaining 44 patients had all three investigations and were classified by CT appearance into three groups: group 1: carcinoma highly probable, with pulmonary mass/collapse and hilar, mediastinal or local invasion (n = 17); group 2: equivocal, with pulmonary mass/ collapse/consolidation or hilar enlargement (n = 17); group 3: carcinoma unlikely, with an alternative diagnosis (tuberculosis four, aortic aneurysm two, fibrosing alveolitis one, empyema one, McCloud's syndrome and cardiac fatpad one, bronchectasis and consolidation one) (n = 10). Bronchoscopy confirmed the diagnosis of carcinoma in all patients in group 1, five patients in group 2, and none in group 3. However, sputum cytology also confirmed malignancy in nine patients in group 1, all of whom were considered inoperable due to local invasion. These results indicate that in nine of 44 patients bronchial carcinoma was confirmed by a combination of CT and sputum cytology. When bronchial carcinoma is clinically suspected and CT is negative or equivocal, bronchoscopy is mandatory, irrespective of sputum cytology results if active treatment is being considered. However, when CT confirms inoperable malignancy and sputum cytology is positive, bronchoscopy may not be necessary. Expert CT interpretation and sputum examination may avoid inappropriate bronchoscopy in a significant minority of patients, thereby reducing patient discomfort and costs.

Cervical cordotomy for the relief of pain in pleural mesothelioma
AW MATTHEWS, A PROSSER, E NEVILLE, D FOUNDER Queen Alexandra Hospital, Cosham, Portsmouth Severe chest pain is common in pleural mesothelioma. In a survey of 200 patients with pain was a presenting symptom in 58% and most were taking large doses of opiates by the time of their death (Matthews, Thorax 1992;47:851–2). Percutaneous cervical cordotomy interrupts the spinothalamic tract at C1–2 by means of a radiofrequency burn and produces contralateral loss of pain and temperature sensation below the level of the lesion (Rosomoff, J Neurosurg 1965;23:6). Twenty one patients have been treated by this technique. All were suffering from severe chest pain and taking large doses of opiates. Good pain relief was achieved in 18 and partial relief in three. The interval between onset of pain and cordotomy ranged from two to 16 months (mean 7-6), and between cordotomy and death from eight days to 11 months (mean 3-6 months). The mean daily dose of opiate was reduced by 170 mg before the procedure to 32 mg, and in 11 patients opiates were withdrawn. There were no major complications. One patient developed mild ipsilateral weakness and one experienced dysaesthesia. Recurrence of pain requiring opiates occurred in 11 patients, usually due to spread to the mediastinum or abdomen.

Relation between age and treatment of lung cancer
JS BROWN, A DAIVISON, E BRAUT Department of Cardi Thoracic Medicine, Southend Hospital, Essex We have previously shown a high incidence of lung cancer in patients over 70 years of age. How the treatment of the elderly differs from the younger patients has important implications for the provision of care. The initial treatment given to patients including those not cared for by a respiratory physician over a 30 month period from 1 January 1990 was analysed. A total of 563 new patients were diagnosed, 240 (42-6%) aged 75 or over, 190 (33-7%) between 65 and 74 years, and 133 (23-6%) under 65. For proven non-small cell cancer (n = 308) the relation between age and type of treatment was significant (p < 0.001). For small cell cancer (n = 109) the relation between age and type of treatment was also significant (p < 0.01). The
performance status (ECOG values) at presentation of those aged 75 and over was worse than those aged under 75 (p < 0.001). Three month survival of those aged 75 and over was 37% and for those under 65 years of age was 50% (p < 0.001). The main differences in treatment are that surgery and chemotherapy are more frequently performed in the younger patients, whilst more in the 65–74 age group receive radiotherapy, and more older patients receive symptomatic care only (table).

### Table: Treatment by Age Group

<table>
<thead>
<tr>
<th></th>
<th>Under 65 years</th>
<th>65–74 years</th>
<th>75 years and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>16.3</td>
<td>10.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>38.4</td>
<td>44.4</td>
<td>33.9</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>18.6</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>26.7</td>
<td>38.9</td>
<td>64.3</td>
</tr>
</tbody>
</table>

Values are percentages.

**Outcome in lung cancer: a comparison between those seen by chest physicians and by other doctors**

JS BROWN, A DAVISON, D ERAUT  Department of Cardiothoracic Medicine, Southend Hospital, Essex  Few studies of lung cancer include patients who have not been under the care of chest physicians or surgeons. It is therefore important to characterise these patients and see how they differ from other patients with lung cancer. All new patients with lung cancer in the Southend district for a 30 month period from 1 January 1990 were analysed by all available methods to obtain every case, including laboratory reports and death certificates. A subgroup was formed from patients who were not under the care of a chest physician. There were 563 patients (mean age 71) with a subgroup of 102 patients (18%) who were not under the care of a chest physician. Sixteen patients only diagnosed at necropsy were excluded, leaving 86 patients (15%) with a mean age of 76 years (mean age of those seen by a chest physician 70). 63% men and 37% women. Care was provided by a physician in 13%, a geriatrician in 57%, and an oncologist in 23%. Histology showed non-small cell cancer in 35%, small cell cancer in 13% with no histology obtained in 52% compared with 22% in the patients seen by a chest physician. One patient underwent surgical treatment, four had chemotherapy, and 13 were given radiotherapy. The six month survival was 6% in patients not seen by a chest physician and 32% for patients seen by a chest physician. In this preliminary study patients with lung cancer not seen by a chest physician are more elderly, less likely to have "active" treatment, and have a poorer prognosis. This survey poses a number of questions regarding the care of elderly patients with lung cancer.