

## Proceedings of the British Thoracic Society

# The British Thoracic Society's summer 1992 meeting was held on 8–10 July at the Octagon Centre, University of Sheffield

### Improving hospital asthma management—where next?

CE BUCKNALL, C ROBERTSON, F MORAN, RD STEVENSON *Royal Infirmary and Strathclyde University, Glasgow* Prospective audits of hospital management of acute asthma were carried out in 1985–6 for a calendar year and in 1991 for six months. Patients were interviewed at home two weeks after discharge, when symptoms of poor asthma control were sought and hospital casenotes were reviewed for details of management and evidence of readmission to hospital. Data from 157 episodes in 1985–6 and 86 episodes in 1991 are available. These two groups were similar in terms of age, gender, proportion of current smokers, initial pulse rate on admission to hospital and initial PEF, where this was recorded. Similar proportions had a definite diagnosis of asthma (1985–6 153/152, 89%; 1991 76/83, 92%). There were significant improvements in most aspects of hospital management (table, A, below). However, there was no improvement in outcome as judged by symptoms of poor control two weeks after discharge or readmission to hospital within two months (table, B, below). Possible reasons for this apparently worsening outcome despite better process include: (1) undetected differences between groups being compared; (2) underlying increase in severity of asthma; (3) improvements in process not as important or as substantial as outlined.

	1985–6	1991	p
<b>A</b>			
Initial PEF recorded: No (%)	20/157(13)	48/83(58)	<0.001
Mean (SD) (l/min)	156(72)	172(68)	
PEF charted regularly: No (%)	84/148(57)	71/83(86)	<0.001
Oral steroids given: No (%)	114/153(75)	80/82(98)	<0.001
Oxygen given: No (%)	94/148(64)	60/81(74)	
High concentration oxygen: No (%)	25/94(27)	43/60(72)	<0.001
<b>B</b>			
Sleep disturbance: No (%)	54/155(35)	38/69(55)	<0.01
Morning tightness: No (%)	78/154(51)	43/69(62)	
No (%) readmitted <2 months	10/133(8)	14/76(18)	<0.05

### A trial of steroid tapering in acute asthma

BR O'DRISCOLL, S KALRA, M WILSON, JP ROBSON, CAC PICKERING, KB CARROLL, AA WOODCOCK *Wythenshawe and Hope Hospitals, Manchester* Acute severe asthma is usually treated with a 7–14 day course of oral corticosteroids, either stopped abruptly or with a gradual taper over a further 1–2 weeks. In a controlled double blind study, 35 hospital patients with acute severe asthma (mean PEF 176 l/min) received oral prednisolone 40 mg daily for 10 days. They were then randomised to either prednisolone 5 mg (PRED, n = 18, 7 male, mean age 28, mean daily dose of inhaled steroid = 965 µg) or matched placebo tablets (PLACEBO; n = 17, 10 male, mean age 37, mean dose of inhaled steroid 850 µg/day) in a tapering fashion. Tablets were reduced by one per day from seven tablets on day 11 to zero tablets on day 18. Patients were monitored by diary cards and thrice daily PEF measurements. All patients had an excellent initial response and, by day 10 (at commencement of the taper) the groups remained well matched; (morning PEF: PRED 396 l/min, PLACEBO 391 l/min). The mean PEF of the two groups remained similar throughout the study with no significant difference at any time. For example, the mean morning PEF for days 16–23 was PRED 384 l/min, PLACEBO 415 l/min. The subjective symptom scores of the two groups also remained almost identical during 28 days of observation. No patient required readmission to hospital and one patient in each group had a transient episode of severe asthma. Other outcomes were as follows (PRED v PLACEBO): brittle asthma 3 v 2; moderate symptoms 4 v 3; persistent mild symptoms 5 v 5; complete remission 5 v 7. It is concluded that steroid tapering is unnecessary for most asthmatics provided they are protected by inhaled corticosteroids. This permits the use of simple prednisolone regimens with less likelihood of confusion and a lower overall steroid dose.

### Patient compliance with inhaled medication: does combining β-agonists with corticosteroids improve compliance?

CM BOSLEY, DT PARRY, GM COCHRANE *Departments of Thoracic Medicine and Psychiatry, UMDS, Guy's Hospital, London* Patients treated for asthma tend to take less than their prescribed medication (*Lancet* 1990;335:262) and this non compliance is an important cause of morbidity (Horn *et al*, *Respir Med* 1990;84:67). Compliance may be improved by combining β-agonists and corticosteroids in one inhaler. One hundred and two asthmatic patients were recruited, divided into two groups and given either two inhalers containing terbutaline and budesonide respectively (group A) or one inhaler containing a combination of the two drugs (group B). Patients were told to take two or four doses daily for two six week periods (P1 and P2). Compliance was measured by using the Turbohaler inhalation device (TIC), which registers the time of each inhalation. Seventy two patients completed the study: males = 28, mean age = 44 (20–69), group A = 36. The information obtained from the TICs is shown in the table below. There was no significant difference in compliance with β-agonists and corticosteroids. Combining the two drugs did not significantly improve compliance. The results suggest that other ways of understanding and improving patient compliance should be sought.

	% Compliance (mean (SD))		
	Pulmicort	Bricanyl	Pulmicort beta
P 1	63.0 (37.7)	63.3 (36.9)	73.5 (31.8)
P 2	56.6 (46.4)	61.9 (46.6)	59.8 (41.6)

### Systemic effects of high dose inhaled steroids: a comparison of beclomethasone dipropionate (BDP) and budesonide (BUD)

PH BROWN, SP MATUSIEWICZ, C SHEARING, I TIBI, AP GREENING, GK CROMPTON *Respiratory Medicine Unit, Western General Hospital and Departments of Clinical Chemistry, Western General Hospital and Royal Infirmary, Edinburgh* This randomised double blind crossover study compared the effects of aerosol BDP and BUD, with and without 750 ml spacers, on serum cortisol, 24 h urine free cortisol and plasma osteocalcin. Nine healthy volunteers (mean age 32.7 y; five male) were studied on six days (minimum washout three days). Subjects inhaled 1 mg BDP/BUD with or without a spacer, at 0900 and 2200. Blood samples were taken before the morning dose, at hourly intervals for six hours, and after 24 hours and urine was collected over this period. Cortisol and osteocalcin were measured by radioimmunoassay and results compared by Anova. All results were within normal ranges. Serum cortisol was significantly reduced 5 h and 6 h after inhalation of BDP or BUD (both p < 0.05) but there was no change at +24 hours. Urinary cortisol was not influenced by BUD with (mean 212 nmol) or without (213) a spacer or by BDP with spacer (233 nmol) but fell significantly (p < 0.01) when BDP was used without a spacer (172 nmol). Osteocalcin was significantly reduced (p < 0.01) only by BDP without a spacer at +24 hours (mean 5 µg/l). It is concluded that (1) serum cortisol was reduced 5 h and 6 h after inhalation of 1 mg BDP or BUD; however, only BDP inhaled without a spacer reduced urine free cortisol and 0900 osteocalcin; (2) 24 hour urinary cortisol and +24 hour osteocalcin were more sensitive indices of systemic effect than 0900 serum cortisol.

### Effect of the number of peak expiratory flow readings a day on diurnal variation

PFG GANNON, DT NEWTON, CFA PANTIN, PS BURGE *Occupational Lung Disease Unit, East Birmingham Hospital, Birmingham, Staffordshire Polytechnic, Stafford, and City General Hospital, Stoke* The effect of the number of peak expiratory flow (PEF) readings a day on the

calculation of diurnal variation is not fully understood. Two hundred and twenty five days with 10 readings a day were selected from a database of 283 peak flow records. Diurnal variation was calculated with two to 10 readings a day (evenly distributed over waking hours) for these days. The different diurnal variations (man-min/mean) were compared with that calculated from 10 readings a day (Bland Altman *Lancet* 1986;30:7). These results show that when only two PEF readings a day are used, the diurnal variation may be 1.09% to 16.47% below that calculated using 10 readings a day. These differences fall below clinically significant levels at and above four readings per day. The study was repeated with max-min/predicted as the measure of diurnal variation with similar results. It is concluded that patients should perform at least four readings a day for an accurate assessment of diurnal variation in PEF.

Readings/day	Mean difference (limits of agreement)
2	2.81 (-1.72 to 13.6)
3	1.71 (-1.98 to 5.79)
4	1.29 (-1.57 to 2.65)
5	1.20 (-1.54 to 2.2)
6	1.14 (-1.46 to 1.9)
7	1.07 (-1.33 to 1.53)
8	1.06 (-1.29 to 1.44)
9	1.02 (-1.14 to 1.18)

### Asthmatic symptoms, airway responsiveness (AR) and appreciation of bronchoconstriction

SC STENTON, A AVERY, J BEACH, EH WALTERS, DJ HENDRICK *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne* Epidemiological studies often rely on questionnaires or measurements of AR to diagnose asthma. The agreement between the two is often not close but there is little evidence to suggest that one is a more reliable method of diagnosis than the other. We recently considered this problem in a study of 1126 workers aged 16–30. Each worker completed a questionnaire about current or past symptoms of breathlessness, wheezing, and chest tightness, and AR was measured as  $PF_{20}FEV_1$  to methacholine. At the end of each  $PD_{20}$  measurement, at a time when  $FEV_1$  was >20% below baseline, all subjects with measurable AR were asked "have you ever felt like this before?" Those who answered "yes"—that is, recognised the sensation of bronchoconstriction (BC)—were categorised according to  $PD_{20}$  category and their responses to questions about asthma symptoms recorded on the questionnaire (QR +ve/QR -ve) (table). As AR increased ( $PD_{20}$  decreased), more subjects recognised the sensation of BC as something they had experienced before. By contrast, there was no relation with the responses to the questionnaire symptoms of asthma. This suggests that  $PD_{20}$  is the better method for recognising asthma and that epidemiological studies of asthma that rely on questionnaire responses may be subject to considerable errors.

$PD_{20}$ 1000–6400	95 of 237 (41%) recognised BC
$PD_{20}$ 200–1000	95 of 184 (52%) recognised BC
$PD_{20}$ <200	71 of 86 (83%) recognised BC
QR +ve	73 of 162 (45%) recognised BC
QR -ve	188 of 345 (54%) recognised BC

### Asthma in general practice—prevalence and treatment

MG PEARSON, R SLOAN, I RYLAND *Aintree Hospital and Maghull Health Centre, Liverpool* A 9700 patient practice has prescribed all drugs by computer for four years. Its asthma prescribing costs are 225% of the district mean. From the prescription/diagnosis record on computer we identified three groups: (a) unlikely asthma (one bronchodilator script only), (b) possible asthma (repeated bronchodilators), (c) probable asthma (bronchodilators and inhaled steroids). Of 5456 people aged 18 to 70, 569 (10.4%) were group a, 246 (4.5%) group b and 308 (5.6%) group c. Women outnumbered men 1.4:1 and the distribution was similar across each age decade. One hundred patients (age and sex stratified) were randomly sampled from these groups. Data were collected from the GP notes, from the computer (actual prescriptions prospectively for one year), by nurse questionnaire, and by two week peak flow chart. Cumulative symptom severity and lifestyle interference scores were derived from the questionnaire. 13/26 (50%) of group a, 22/28 (85%) of group b and 42/46 (91%) of group c reported troublesome symptoms. Troublesome interference with lifestyle was less frequent at 20%, 39%, and 54% respectively ( $p < 0.01$ ) suggesting a degree of patient acceptance. A combination of symptoms and lifestyle interference correlated strongly with peak flow variability

>25% ( $p < 0.001$ ). Combining the symptom, lifestyle, and peak flow data suggests that at least six of 26 in group a, seven of 28 in group b and 33 of 46 in group c had definite asthma yielding an overall prevalence of at least 7.6% for the adult population. In groups a and b, nine persons were started on inhaled steroids with good peak expiratory flow control in only four. A further five had both peak expiratory flow (PEF) variability >25% and symptoms that could warrant steroids. In group c, only 29/33 with definite asthma received inhaled steroids but PEF control remained poor in 15. Only 7/47 patients prescribed inhaled steroids collected enough scripts in the year to take the recommended dose. Why patients decline to take inhalers even when reporting significant symptoms interfering with their lifestyle needs to be understood. 25/47 (53%) did not collect enough for even half dosage. This may explain the poor levels of control achieved. These data imply a high prevalence of adult asthma and suggest that this practice's high prescribing level may still not be high enough.

### The effects of acute and chronic hypoxia on the secretion of vasopressin, renin, and aldosterone

DMG HALPIN, D KEMP, DF TREACHER, ML FORSLING, IR CAMERON *UMDS (St Thomas's Campus) London* The pattern of secretion of vasopressin, renin, and aldosterone was studied in 10 men with non-oedematous hypoxic respiratory failure ( $PO_2 < 8$  kPa) due to chronic airflow limitation (CAL), five men with obstructive sleep apnoea (OSA), and nine healthy men. All subjects were aged 60–80 and were not receiving oral steroid or diuretic treatment. They were admitted to the sleep laboratory at 1700 and samples of venous blood were taken at 1800, 2200, 0000, 0100, 0200, 0400, 0800, and 1200. There were no significant differences between the groups in the concentrations of Na, K, urea, or glucose, or in plasma osmolality. There were no significant differences in the concentrations of cortisol in the three groups; they all showed a normal diurnal variation. Median vasopressin concentrations in normal men showed a diurnal variation with a peak of 0.76  $\mu$ g/ml at 0000 and a trough of 0.32  $\mu$ g/ml at 1800. Concentrations in men with CAL were not significantly different from those in normal people, although diurnal variation was less clear. Median vasopressin concentrations in men with OSA were significantly higher at 0800 (1.16  $\mu$ g/ml,  $p < 0.05$ ) compared with the other groups, but were otherwise similar. Median renin concentrations in normal men showed a diurnal variation with a peak of 1.50 pmol/ml/l at 1200. Renin concentrations were similar to normal in men with OSA, but were significantly higher at 0200 h in men with CAL (1.50 pmol/ml/l,  $p < 0.05$ ). Despite this there were no significant differences in the concentrations of aldosterone between the groups, which all showed normal diurnal variations. These data suggest that significant alterations in the pattern of secretion of renin occur in men with CAL. Despite this aldosterone concentrations were normal and there were no significant alterations in the secretion of vasopressin.

### Hypoxia and water retention in chronic obstructive pulmonary disease (COPD)

AG STEWART, JC WATERHOUSE, CB BILLINGS, P HOWARD *Department of Medicine and Pharmacology, University of Sheffield* Twenty four patients with hypoxaemic chronic obstructive pulmonary disease (COPD) received 15 ml/kg of water orally over one hour. Plasma electrolytes, osmolality, aldosterone, renin activity (PRA), and vasopressin were measured before and for four hours after the water load. Glomerular filtration rate (GFR) and renal blood flow (RBF) were measured by a DTPA renogram. Cardiovascular autonomic function (*Br Med J* 1982;285:916) was assessed. Three groups of eight patients: group C ( $Pao_2 > 8.9$ ), group MH ( $Pao_2 7.3-8.9$ ) and group SH ( $Pao_2 < 7.3$  kPa) were compared by ANOVA. The groups were similar for age, weight,  $Paco_2$  and GFR but significantly different for  $FEV_1$ , RBF, and autonomic function ( $p < 0.001$ ) with the worst results in the most hypoxaemic groups. Groups MH and SH had a significant reduction in volume of urine and water load excretion. PRA, aldosterone, and vasopressin were insignificantly raised in groups MH and SH but responded appropriately to the water load. There were no differences in plasma and urine sodium and osmolality. Urine volume correlated with  $Pao_2$  ( $r = 0.54$ ), free water clearance ( $r = 0.53$ ) and parasympathetic autonomic function ( $r = 0.46$ ). The percentage of the water load excreted was inversely correlated with  $Pao_2$  ( $r = -0.44$ ), PRA time 0 ( $r = 0.74$ ), vasopressin (time 0 and 60) ( $r = 0.44$  and  $r = 0.45$ ). Free water clearance correlated with ADH time 60 ( $r = -0.58$ ) and autonomic function ( $r = 0.47$ ). Water excretion correlated with fractional sodium reabsorption ( $r = 0.66$ ) suggesting that increased proximal tubule sodium reabsorption may

be important in the impaired ability to excrete a water load. The mechanism remains obscure but may involve an interplay between renal blood flow, renal sympathetic tone, renin, and vasopressin. The appropriate vasopressin suppression by water loading suggests that there is an important non osmotic release of vasopressin. The possibility that a parasympathetic neuropathy might reset osmoreceptor function needs study.

### Hypoxia and sodium retention in chronic obstructive pulmonary disease (COPD)

AG STEWART, JC WATERHOUSE, CB BILLINGS, P HOWARD *Department of Medicine and Pharmacology, University of Sheffield* Twenty four fasted patients with hypoxaemic chronic obstructive pulmonary disease (COPD) received 6 ml/kg in 2.7% saline. Plasma electrolytes, osmolality, aldosterone renin activity (PRA), and vasopressin were measured before and for four hours after the saline load. Glomerular filtration rate (GFR) and renal blood flow (RBF) were measured by a DTPA renogram. Cardiovascular autonomic function (*Br Med J* 1982;285:916) was assessed. Group C (eight patients with COPD and  $P_{aO_2} > 8.9$  kPa, group MH ( $P_{aO_2}$  7.3–8.9), and group SH ( $P_{aO_2} < 7.3$ ) were compared by ANOVA. The groups were similar for age, weight,  $P_{aCO_2}$ , and GFR but significantly different for  $FEV_1$ , RBF, and autonomic function ( $p < 0.001$ ) with the worst results in the most hypoxaemic group. Urine volume and sodium excretion were significantly less in groups MH and SH ( $p < 0.05$ ). They had a greater fractional sodium reabsorption and an impaired free water clearance ( $p < 0.01$ ). Although aldosterone, PRA, and vasopressin were raised in group SH ( $P > 0.1$ ) they suppressed or increased appropriately. Sodium excretion was significantly correlated with  $P_{aO_2}$  ( $r = 0.74$ ),  $FEV_1$  ( $r = 0.59$ ), RBF ( $r = 0.5$ ), aldosterone time 0 ( $r = 0.58$ ), and autonomic function ( $r = 0.77$ ). Urine volume correlated with  $P_{aO_2}$  ( $r = 0.62$ ),  $FEV_1$  ( $r = 0.61$ ), aldosterone, at time 0 ( $r = 0.62$ ), and autonomic function ( $r = 0.75$ ). Fractional sodium reabsorption correlated with  $P_{aO_2}$  ( $r = 0.5$ ) and aldosterone at time 0 ( $r = 0.62$ ). Parasympathetic autonomic function correlated with the free water clearance ( $r = 0.63$ ), aldosterone suppression ( $r = 0.53$ ), and vasopressin at time 0 ( $r = 0.49$ ). Patients with hypoxaemic COPD have an impaired ability to excrete a sodium load. The mechanism involves a complex interplay between hormones, renal blood flow, and parasympathetic autonomic nerve function.

### Abnormal right ventricular systolic and diastolic function in patients with pulmonary heart disease

RM OLIVER, JS FLEMING, DG WALLER *Clinical Pharmacology Group and Department of Nuclear Medicine, Southampton General Hospital, Southampton* Patients with pulmonary heart disease (PHD) frequently have impaired right ventricular (RV) systolic function but few studies have evaluated diastolic function in such patients. Krypton-81 m radionuclide ventriculography is ideally suited to the non-invasive assessment of RV function. Twelve patients (mean age 69 y) with advanced chronic obstructive pulmonary disease (mean  $FEV_1$  0.82 litres; mean  $P_{aO_2}$  8.4 kPa) and clinical evidence of PHD were studied. Right heart krypton-81 m ventriculography was performed and RV ejection fraction (RVEF) obtained at rest and during submaximal exercise (range 20–50 watts; mean 40.8 watts). Indices of RV systolic and diastolic function were derived at rest. Results were compared with eight normal subjects comparable in age at rest and on submaximal exercise (100 watts). In the controls, mean (SD) RVEF was 0.58 (0.04) at rest and increased to 0.64 (0.05) during exercise ( $p < 0.001$ ). In patients, RVEF was 0.53 (0.06) at rest ( $p < 0.05$  compared with controls) and was unchanged during exercise (0.53 (0.06)). At rest, mean RV peak ejection rate was 2.78 (0.50) EDV/s in controls and 3.04 (0.63) EDV/s in patients (NS). Mean RV early diastolic filling rate was 1.63 (0.41) EDV/s in normals and was 1.00 (0.52) EDV/s in patients ( $p < 0.02$ ) (EDV/s = end-diastolic volumes per second). Right ventricular systolic and diastolic function at rest and systolic function on exercise show significant impairment in patients with PHD. Right ventricular contractility is well preserved at rest and abnormal systolic and diastolic function are a manifestation of altered loading conditions.

### Basal metabolic rate, weight loss, and decline in $FEV_1$ in chronic obstructive pulmonary disease (COPD)

J CONGLETON, JH GREEN, MF MUERS *Respiratory Unit, Killingbeck Hospital, Leeds* Basal metabolic rate (BMR) is raised compared with predicted values and matched controls in many patients with chronic

obstructive pulmonary disease (COPD), (Green, Muers *Eur Resp J* 1991). Weight loss is also a feature of COPD and is associated with a poor prognosis (Vandenberg *Am Rev Respir Dis* 1967). The increase in BMR is thought to be a possible cause of the weight loss. The relation between increase in BMR, weight loss, and decline in lung function was examined. Sixteen patients with COPD had BMR measured while in a stable clinical state (respiratory gas exchange by Datex Deltatrac Metabolic Monitor, urinary nitrogen by Kjeldahl method). Weight change and decline in  $FEV_1$  were calculated from outpatient records over 2–12 y (mean 4.1 y). Nine patients were hypermetabolic and seven normometabolic. There was no significant difference in  $FEV_1$ , carbon monoxide transfer factor, or  $P_{O_2}$  between the two groups. There was no correlation between weight loss and BMR. Mean weight loss was 2.3% body weight/y (SE (0.92)) in the hypermetabolic group and 2.6% body weight/y (SE (2.86)) in the normometabolic group. Mean decline in  $FEV_1$  was higher in the hypermetabolic group 72 ml/s/y (SE (2.7)) cf 32 ml/s/y (SE (13.82)),  $p = 0.1$ . Three patients in the hypermetabolic group and none in the normometabolic group have since died. These results suggest that a hypermetabolic state may be independently associated with worsening lung function and that weight loss may occur despite a normal BMR.

### Breathlessness, hypoxaemia, and survival in a community study

J WATERHOUSE, CG BILLINGS, J NICHOLL, P HOWARD *University Department of Medicine, Royal Hallamshire Hospital, Sheffield* In 1983 a 1:50 sample of the Sheffield community aged over 45 was made: 252 persons were discovered to have a forced expiratory volume ( $FEV_1$ ) of less than 70% predicted or a transcutaneous  $P_{O_2}$  ( $P_{TO_2}$ ) of  $< 8.5$  kPa. In 1989 201 of this group were traced: 73 had died. Cox's proportional hazards model was fitted to the data to investigate the influence of respiratory state in 1983 on survival. Age understandably predicted survival ( $\chi^2 = 13.7$   $p < 0.001$ ). Lower values of  $FEV_1$  and forced vital capacity (FVC) were associated with decreased survival ( $FEV_1$ :  $\chi^2 = 11.1$ ,  $p < 0.001$ ; FVC:  $\chi^2 = 9.4$   $p < 0.01$ ). The effect of  $P_{TO_2}$  was marginal ( $\chi^2 = 2.3$   $p = 0.12$ ). Smoking had no effect ( $\chi^2 = 0.1$   $p > 0.5$ ). The most significant indication was severe breathlessness defined on the medical research council respiratory questionnaire as stopping on the level from a slow walking pace ( $\chi^2 = 28.3$   $p < 0.001$ ). In chronic respiratory disease in the community the important predictors of survival are airways obstruction and severe breathlessness. Hypoxaemia had no influence.

### Prescription of oxygen concentrators: review of patients with $SaO_2$ above 91% at follow up assessment

LJ RESTRICK, EA PAUL, GM BRAID, P CULLINAN, J MORE-GILLON, JA WEDZICHA *Departments of Thoracic Medicine and Epidemiology, London Chest Hospital, and Department of Respiratory Medicine, St Bartholomew's Hospital, London* A study of 176 patients in East London with oxygen concentrators (*Thorax* 1992;47:222P) showed improved compliance with Department of Health and Social Security guidelines for long term oxygen treatment (LTOT) prescription compared with previous studies. We found that 67 (38%) had  $SaO_2 > 91\%$  when breathing air on home assessment. Indications for LTOT in these patients and the adequacy of the initial assessment were therefore reviewed. Hospital records were traced for 52/64 (81%) patients; three patients were under general practitioner care only. Chronic airflow limitation (CAL) was the indication for LTOT in 69%, nocturnal hypoxia in 23%, bronchiectasis in 4%, and heart failure in 4%; LTOT was initiated in 42/55 by respiratory physicians and the remaining 13 prescriptions were initiated by general practitioners without formal assessments. Thirty five of the 42 respiratory physician initiated LTOT prescriptions had formal assessments performed (blood gases and spirometry). Assessment before prescription for nocturnal hypoxia was good; means (SD) daytime  $P_{aO_2}$  in this group was 7.5 (1.3) kPa,  $P_{aCO_2}$  6.8 (1.1) kPa. All 13 of these patients had been assessed by sleep studies; diagnoses were CAL, chest wall or muscle disease, sleep apnoea, and bronchiectasis. Twenty six of the 38 patients with CAL (68%) were prescribed LTOT by a respiratory physician; 20 were prescribed LTOT when stable; the remaining six were prescribed LTOT during an exacerbation.  $FEV_1$  was  $< 1.5$  l in all patients, but in eight of the 21 patients, in whom records of measurement were available,  $P_{aO_2}$  was  $> 7.5$  kPa at assessment. For these 21 patients, mean  $P_{aO_2}$  was 7.5 (1.4) kPa,  $P_{aCO_2}$  6.2 (1.2) kPa. Ninety six per cent of patients were followed up; with spirometry performed in 78%, but blood gases or oximetry in only 59%. Nine of the 11 patients with CAL, who had general practitioner initiated prescriptions were also under hospital follow up; mean  $P_{aO_2}$  recorded

in 5/9 was 9.8 (2.9) kPa, mean FEV<sub>1</sub> in 8/9 was 0.7 (0.3) l. Specific recommendations regarding communication between hospital, general practitioner, and concentrator supplier have previously been made and the need for domiciliary reassessment has been stressed. It has also been suggested that SaO<sub>2</sub> > 91% on air at such assessment should lead hospital physicians to review the adequacy of initial and subsequent investigation; where treatment has been general practitioner initiated, direct advice to refer for such investigation should be given by the domiciliary assessor.

### An audit of lung function laboratories: the West Midlands initiative

M MUSHTAQ, R HAYTON, JM JONES, WH PERKS *Princess Royal Hospital, Telford, Shropshire* On behalf of the West Midlands Thoracic Medical Committee, twenty two lung function laboratories encompassing each district in the West Midlands Regional Health Authority were audited within a two week period in November 1991. Each laboratory performed a full set of lung function studies on the same three normal healthy subjects who travelled to each centre. Also, staff in each laboratory completed a questionnaire. The results showed that 14 laboratories (64%) used European Coal and Steel, whereas six (27%) used Cotes as the source of reference values. Six (27%) provided an information sheet and 15 (68%) required patients to stop bronchodilator treatment before testing. There was wide diversity as to how reversibility studies were performed. Smoking habit was recorded in 16 laboratories (63%). There were significant differences in height and weight ( $p = 0.004$ ) in those laboratories (77%) that measured them. With Friedman's test to compare laboratories, there were significant differences between mean values in all measured variables of lung function and all predicted values except for total lung capacity. Examples of this variability are shown below. An attempt was made to assess what factors had produced this variability and technician's experience of > seven years and age of equipment < three years seemed to be important. The West Midlands is currently attempting to standardise procedures with a view to repeating the audit cycle in 1993.

Subject A:	KCO (mmol.min <sup>-1</sup> KPa <sup>-1</sup> l <sup>-1</sup> )
	mean 1.67 SD 0.12 (range 1.41–1.94)
Subject B:	residual volume (l) mean 1.09 SD 0.30 (range 0.43–1.45)
Subject C:	FEV <sub>1</sub> (l) mean 4.55 SD 0.28 (range 3.87–4.97)

### British Thoracic Society (BTS) survey of respiratory function laboratories and technicians

D ERAUT, D PARRY, FOR THE MANPOWER AND RESOURCES COMMITTEE OF THE BTS *British Thoracic Society, London* The BTS conducted a survey in 1991 of respiratory laboratories and their staff. The regional representatives wrote with a questionnaire to all districts in their Region. Replies were received from 177, most districts in all the 16 regions. Of those who replied, 10 districts had no laboratory. (In the 1985 survey 40 districts had no laboratories.) Twenty one admitted a regional responsibility (12%), 69 of the 167 have a research component (41%). Seventy three (44%) were respiratory only and 93 (56%) were combined with cardiology. We were concerned that regrading procedures had led to loss of staff. One hundred (60%) had satisfactory regrading; 54 (32%) did not. Particularly there was a shortfall in the higher grades applied for (MT05 and MT04). Fourteen lost staff because of regrading. The low numbers of the higher grades may lead to problems in retention of the more experienced staff. Eighty five (51%) have had recruitment problems and 49 (29%) have had problems with retention of staff. Fifteen had recently lost posts for technicians. We also thought that the importance of the respiratory laboratory and its resources might be under threat. Ten considered that this was so. Overall respiratory function testing was locally thought to have improved in 77 (46%), not changed in 76 (46%), and deteriorated in nine (5%), 28 (17%) had sessional problems, and 75 (45%) had equipment problems and were it not for charitable sources, this figure would be much higher. All laboratories had a spirometer, 157 (95%) had transfer factor apparatus, 44 (27%) a body box, 142 (86%) had easy access to blood gases, 118 (71%) had means of exercise testing, 121 (73%) had pulse oximetry, 20 (12%) had a sleep laboratory, and 57 (34%) performed challenge testing. Facilities for blood gas analysis and exercise testing seemed to be worse than the 1985 BTS survey, but facilities for transfer factor, oximetry, and sleep studies had improved.

### Use of transcutaneous oxygen and carbon dioxide tensions for assessing gas exchange during exercise

MK SRIDHAR, R CARTER, F MORAN, SW BANHAM *Department of Respiratory Medicine, Glasgow Royal Infirmary* We have validated the use of a transcutaneous electrode for estimation of alveolar arterial O<sub>2</sub> difference (A-aO<sub>2</sub>) and dead space to tidal volume ratio (V<sub>D</sub>/V<sub>T</sub>) during exercise against values calculated from direct arterial blood gas analysis. Fifty measurements were made in 10 patients with various cardiopulmonary disorders who underwent exercise testing. Exercise testing was performed by bicycle ergometry with a specific protocol involving gradual work increments at two min intervals. Transcutaneous gas tensions were measured by a combined O<sub>2</sub> and CO<sub>2</sub> electrode heated to 45° C. Arterial blood was sampled at the midpoint of each stage of exercise and transcutaneous tensions noted at the end of each stage. The mean difference of the A-aO<sub>2</sub> calculated from blood gas tensions obtained by the two methods was 0.14 mm Hg. The limits of agreement (Bland, *Altman Lancet* 1986;i:306) were -3.24 and 3.52. The same values for V<sub>D</sub>/V<sub>T</sub> calculated from gas tensions measured by the two methods were: mean difference 0.001; limits of agreement: 0.0267 and -0.0259. It is concluded that estimation of gas exchange during exercise with transcutaneous gas tensions is reliable so long as the electrode is heated to a slightly higher temperature than usual and the work increments are gradual, allowing for the latency in the response time of the system. The transcutaneous method is particularly valuable in patients undergoing repeated exercise tests.

### Static lung volumes in healthy subjects assessed by helium dilution during occlusion of one mainstem bronchus

B JOHANSEN, Ø BJØRTUFT, J BOE *Department of Thoracic Medicine, The National Hospital, University of Oslo, Oslo, Norway* The function of one single lung is usually assessed by radionuclide imaging, more rarely by bronchspirometric methods. The first provides limited information, the second is poorly tolerated. The method to be described is an alternative to bronchspirometry. During bronchoscopy we temporarily occluded one mainstem bronchus with an inflatable balloon at total lung capacity (TLC) in 12 healthy volunteers, aged 18–29 y. In random order, the functional residual capacity (FRC) of the right, the left, and both lungs was measured in duplicate by the closed circuit helium dilution method and supplemented by vital capacity (VC) manoeuvres to obtain TLC and residual volume (RV). The coefficient of variation (%) for unilateral (u) TLC was 3.3, for u-RV 24.0, for bilateral (b) TLC 4.9, and for b-RV 23.1. The sum of u-TLC (6.12 l) and u-FRC (2.60 l) from each lung was not different from b-TLC (5.95 l) and b-FRC (2.78 l). The sum of u-VC (4.52 l) and u-RV (1.60 l) was lower, and respectively higher than b-VC (4.80 l) and b-RV (1.16 l). For all subdivisions of lung volume, the right lung was larger than the left. The most common complaint was substernal discomfort during complete exhalation. Oxygen saturation rarely fell below 90%. Temporary balloon occlusion of a mainstem bronchus is safe, relatively simple, and allows fairly precise and accurate measurements of unilateral static lung volumes. Occlusion at TLC probably prevents proper emptying of the non-obstructed lung.

### Respiratory muscle function in patients with severe scoliosis

RJ AQUILINA, SW WRAGG, J MOXHAM, M GREEN *Respiratory Muscle Laboratory, Royal Brompton Hospital, London* Severe scoliosis may result in respiratory failure. Respiratory muscle strength has been little studied in patients with scoliosis. Eight male patients with severe scoliosis, Cobb angle 90–120, mean age 54 (range 35–71) were studied. Vital capacity ranged from 0.8–1.4 l (mean 26.5% predicted, range 19–34%). Seven patients were on long term domiciliary nocturnal nasal ventilation. Resting daytime blood gases were mean: (range) Po<sub>2</sub> 8.5 kPa (7.22–9.6) Pco<sub>2</sub> 6.46 (5.0–7.71). We measured the maximum voluntary isometric strength of the right quadriceps muscle (R Quads, maximum static expiratory and inspiratory mouth pressures (PE<sub>max</sub>, PI<sub>max</sub>), and oesophageal (P<sub>oes</sub>) and transdiaphragmatic (P<sub>di</sub>) pressures during an un-occluded sniff. Results (% predicted, mean (SD)) are shown in table below. Thus inspiratory muscle strength was reduced to about 45% of the predicted value. This may be due to loss of muscle bulk especially as quadriceps strength was also reduced, but may also be due to change in configuration. In patients with respiratory muscle weakness ventilatory failure occurs when strength is reduced to less

R Quads	PE <sub>max</sub>	PI <sub>max</sub>	Sniff P <sub>oes</sub>	Sniff P <sub>di</sub>
59 (13)	75 (22)	46 (17)	46 (11)	47 (18)

than 30% predicted (Braun *et al Thorax* 1983;38:616–23). We conclude that, in scoliosis, impairment of respiratory muscle strength is only one factor predisposing to ventilatory failure. An additional factor is likely to be the severe distortion of the chest wall, which impairs the translation of pressure generated into volume change.

**The evaluation of airway distensibility in asthma**

X LI, JW WILSON, MCF PAIN *Department of Thoracic Medicine, Royal Melbourne Hospital, Victoria 3052, Australia* To evaluate conducting airway distensibility, the anatomical dead space Vd was measured at different end inspiratory lung volumes (Vi). Six asthmatic patients and six normal subjects performed a single breath nitrogen washout by inspiring 1 litre of oxygen from residual volume (RV), RV + 15% TLC (total lung capacity), RV + 30% TLC, and RV + 45% TLC. Expired nitrogen concentration and volume were measured by a nitrogen analyser and spirometer simultaneously. Vd was calculated by the “equal area” method of Fowler. Results are given in the table below. This study used a simple and practical technique for evaluation of human airway distensibility. There was a significant difference between asthmatic patients and normal people; the Vd/Vi was reproducible in normal subjects but was variable in asthmatic. Further studies are needed to investigate the relation between this variability and airway structure in asthma by measuring the thickness of subepithelial collagen. The work was supported by the Australian NH and MRC.

Group	FEV 1% predicted	Vd/Vi	r	n
Normal	97	35.9 ml/L	0.97	6
Asthmatic	69	26.1 ml/L	0.85	6
p Value	0.001	0.02	0.05	

Values shown are mean (SD) Vd/Vi = linear regression of change in Vd and increase in Vi as a percentage of TLC. r = correlation coefficient.

**Ultrasonographic evaluation and strength assessment of the respiratory and thigh muscles in patients with chronic asthma**

PF DE BRUIN, J UEKI, A WATSON, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Previously we have shown relatively good preservation of quadriceps and respiratory muscle strength (RMS) in chronic, incompletely reversible asthma. We have now compared the forces generated by these muscles with their dimensions assessed by ultrasound in nine middle aged patients with adult onset asthma (three men, 6 women; mean (SD) age 56.3 (8.6)y; mean weight 65.0 (8.5) kg; forced expiratory volume in one second (FEV<sub>1</sub>) 1.51 (0.33) l; functional residual capacity/total lung capacity (FRC/TLC) 0.62 (0.08) and five normal subjects (three men, two women; age 54.2 (6.2) y; weight 68.4 (16.5) kg; FEV<sub>1</sub> 2.94 (0.67) l; FRC/TLC 0.56 (0.04)). All patients had been diagnosed more than five years earlier, had normal carbon monoxide transfer factor and regularly used inhaled steroids and bronchodilators. Maximum inspiratory and expiratory mouth pressures (MIP, MEP) were measured at FRC and TLC respectively. The isometric strength of the right quadriceps femoris muscle was determined during maximum voluntary contractions (MVC). Thickness of the right hemidiaphragm was assessed at the apposition zone 0.5–2 cm below the costophrenic angle by B-mode ultrasound during the MIP manoeuvre (DMT<sub>MIP</sub>) and while breath-holding at FRC (DMT<sub>relax</sub>). The thickening ratio (TR) was calculated as TR = DMT<sub>MIP</sub>/DMT<sub>relax</sub> (Ueki *et al Thorax* 1992;47:215P). Cross sectional area of the right rectus femoris muscle (CSA) was determined by B-mode ultrasound at mid thigh level. Results are summarised in the table. Thus despite preserved quadriceps and expiratory muscle strength, there was a tendency to less negative MIPs in asthma. Quadriceps

	Asthma	Control	p Value (t test)
MEP (cm H2O)	82.1 (41.8)	83.6 (26.7)	0.944
MIP (cm H2O)	-52.1 (18.3)	-75.4 (27.6)	0.080
DMT <sub>relax</sub> (cm)	0.22 (0.04)	0.18 (0.04)	0.155
TR	2.0 (0.3)	2.2 (0.5)	0.326
Quadriceps MVC (N)	297.1 (86.6)	278.2 (129.5)	0.767
CSA (cm <sup>2</sup> )	60.4 (27.0)	60.6 (14.0)	0.985

strength was highly correlated to CSA (r = 0.927) in normal volunteers with a weaker correlation in the asthmatic patients (r = 0.615). The MIPs tended to be more negative in normal subjects with greater DMT<sub>relax</sub> (r = 0.764) but not in asthmatic patients (r = 0.126). A higher TR was usually found in subjects who produced more negative MIPs, both in asthma and control groups (r = 0.562 and 0.752, respectively). Differences in MIP could be related to bigger FRC/TLC in asthma.

*Supported by the Cons Nac Desenv Cient Tecnológico-CNPq of Brazil*

**Atopy as a risk factor for cryptogenic fibrosing alveolitis**

P MARSH, IDA JOHNSTON, J BRITTON *Human Sciences Department, Loughborough University and the City and University Hospitals, Nottingham* In a recent case control study of occupational and environmental causes of cryptogenic fibrosing alveolitis (CFA), an increased prevalence of self-reported symptoms of wheeze, rhinitis, or conjunctivitis was reported in cases relative to controls (Scott *et al BMJ* 1990;301:1015–7). To determine objectively whether this finding was due to an increased prevalence of atopy amongst cases of CFA, we have now measured skin sensitivity to common allergens (*Dermatophagoides Pteronyssinus*, grass pollen, and cat fur), eosinophil counts and total Immunoglobulin E (IgE) I in venous blood in the twenty two surviving CFA cases from that study who were willing to provide a blood sample, and in one matched control/case. At least one positive skin test (defined as a wheal diameter of 1 mm or more greater than the saline control) was recorded in 13 cases and six controls, the matched odds of one or more positive test being significantly increased in cases by a ratio of 8.0 (95% CI 1.01–64, p = 0.05). Geometric mean eosinophil counts and IgE levels were also increased amongst cases by factors of 1.6 (95% CI 0.96–2.6) and 1.9 (0.9–3.8) respectively, although these differences were not significant. Differences in skin sensitivity, eosinophil counts, and IgE levels all tended to be more obvious in the 13 case control pairs in which the case was not taking steroids or other immunosuppressive treatment. It is therefore concluded that in this study, cases of CFA showed increased skin sensitivity to common allergens, and have evidence of increased IgE and eosinophilia in peripheral blood. These findings suggest that atopy may be an important determinant of susceptibility to CFA.

**Tuberculosis and poverty**

DPS SPENCE, CSD WILLIAMS, J HOTCHKISS, PDO DAVIES *Aintree Chest Centre, Tuberculosis Research Unit, and Public Health Observatory, Liverpool* Historically, tuberculosis has been associated with poverty. In an earlier presentation to this society it was shown that the rise in tuberculosis in England and Wales from 1987 to 1989 had a number of different causes of which poverty may be one (*Thorax* 1991;46:778P). The most recent Office of Population Censuses and Survey data show a further rise in TB in 1991 over previous years. A retrospective study of tuberculosis notifications in the city of Liverpool has been undertaken to determine whether a relation between tuberculosis and poverty is present. Notifications of tuberculosis (all forms) between 1985 and 1990 for the 33 wards of Liverpool have been used to calculate the annual rate/ward. A number of indices of deprivation are now available for each Liverpool ward based on factors such as car ownership, council housing, and immigration; significant relations with tuberculosis and the following indices of deprivation were found. Council housing (r = 0.4), free school meals (r = 0.43), Townsend overall deprivation index (r = 0.59), and Jarman index, (r = 0.73). The strongest correlation was with the Jarman index, a compound index that scores single pensioners, numbers of those under five, single parent families, the unskilled, the unemployed, overcrowding, high mobility, and ethnic minorities. It has been shown that tuberculosis remains strongly associated with social deprivation and poverty although a longitudinal study is required to determine whether the increases of tuberculosis currently being experienced in Britain is related to an increase in numbers suffering social deprivation.

**Audit of pleural biopsies: an argument for setting up a pleural biopsy service**

LJ WALSH, JT MACFARLANE, M SHEPHERD, JSP JONES *City Hospital, Nottingham* Pleural biopsies (P1 Bx) can be poorly performed and also uncomfortable for the patient. An audit of 203 consecutive P1 Bx performed by medical and geriatric firms over a three year period in this hospital (1987–9) was carried out. For firms without a special

respiratory interest only two to three biopsies per year were performed, rising to 23 per year for a respiratory team. Overall 19% of biopsies failed to obtain any pleural tissue, 50% showed normal or non-diagnostic pleural changes, 26% tumours of various types, 5% other diagnoses. For the respiratory team that performed a third (68) of the biopsies the failure rate for obtaining pleura was 9% compared with 27% for other teams. In view of this disparity a P1 Bx service was offered by the respiratory team during routine bronchoscopy lists. A repeat audit (1990–2) after the introduction of this service showed that 60% (84) of 141 biopsies were performed by the respiratory team. Their failure rate for obtaining pleura was lower at 6% compared with 16% for the general physicians. The noted decrease in the failure rate for the general physicians was considered to be the result of improved training of junior staff, also provided by the service. Thirty one per cent of biopsies provided a definitive diagnosis. This was higher for those performed by the respiratory team (37%, as opposed to 23% for general physicians). Data on morbidity was not collected. The figures presented argue strongly for pleural biopsies only being performed by experienced operators. This service is still offered. Other respiratory units may consider a similar approach.

### Interrelations among physiological and psychological function in chronic airflow limitation (CAL) patients

PA FRITH, PE WALKER, S ROWLAND, J ATKINSON *Respiratory Unit, Repatriation General Hospital, Daw Park, South Australia* Chronic airflow limitation has a major impact on health resources and on the subjects enjoyment of life. As part of a comprehensive programme static and exercising lung function and psychological function in patients with CAL were examined. It was thought that exercise endurance would relate as much to psychological as to physiological variables; and that quality of life would associate with the degree of airways obstruction, gas transfer, exercise capacity, and with personality traits. Thirty CAL patients completed spirometry, lung volumes, gas transfer, 12 minute walk with oximetry (12MD), arterial blood gas analysis, cycle ergometry, the chronic respiratory disease questionnaire (CRQ) that is a measure of quality of life, the Eysenck personality inventory (EPI), and a profile of mood states (POMS). Significant correlations ( $p < 0.05$ ) were found between 12MD and  $VO_2$  MAX, tension, fatigue, dyspnoea, and mastery, suggesting that there is greater psychological impact on 12MD. The regression equation that accounted for the greatest proportion of the 12MD variance (43%) included only psychological variables. CRQ variables correlated with FEV<sub>1</sub>, 12MD,  $VO_2$ MAX, and transient personality traits, but not with stable personality items, nor with other lung function measurements. Our results suggest that in CAL the degree of airways obstruction has relatively little bearing on exercise endurance as measured by the 12MD, which seems related more to measures of psychological functioning. Both physiological and psychological functioning have important interactions on the quality of life of patients with CAL.

### Endoscopy assisted microthoracotomy

RAYMUND J DONNELLY, RICHARD D PAGE *The Cardiothoracic Centre, Liverpool* There have been few reports of the use of endoscopy in performing major intrathoracic procedures, normally performed through formal thoracotomy. Thirty nine patients (male: female = 1.44:1, mean (SD) age = 40.5 (19.9) y, range = 15–80) underwent 42 endoscopic intrathoracic procedures. Seventeen had recurrent or persisting pneumothoraces, nine had unidentified peripheral masses on chest radiograph, 11 required lung biopsy, one had an oesophageal duplication cyst causing dysphagia, and one had a recurrent pericardial effusion. General anaesthesia was used. Through a 1 cm stab incision, a laparoscope attached to a video monitor was introduced. Other stab incisions were made as needed for the introduction of surgical instruments. For lung biopsies or resection of tumours, standard or endoscopic linear staplers were used to resect a wedge of lung tissue. In 16 of the 17 patients with recurrent pneumothoraces the parietal pleura was removed from the whole of the inner surface of the ribs and thoracic apex. Apical blebs were isolated with a linear stapler. Five patients underwent bilateral pleurectomies either as staged procedures (three patients) or at the same sitting (two patients). In the remaining patient, who had cystic fibrosis and a persistent air leak, the hole in the pulmonary bleb was sutured with a long needle holder. Pleurectomy was not carried out. The patient with pericardial effusion underwent creation of a pericardial window. All patients survived without complications and were discharged home a mean of 4.1 (2.0) days after surgery. It is concluded

that endoscopic thoracic surgery is a safe and useful technique for certain cases. It merits further investigation and assessment.

### Attitudes to smoking and smoking habit among a hospital staff: a five year follow up

SF HUSSAIN, SONJA TJEDER-BURTON, IA CAMPBELL, PDO DAVIES *Departments of Chest Medicine, Llandough Hospital, Cardiff and Sefton General Hospital, Liverpool* A study of smoking habits and attitudes to smoking was undertaken in October 1991 on 1307 staff working at Llandough Hospital. 82% responded: of these 65% were non-smokers, 15% ex-smokers and 20% current smokers. The prevalence of current smokers was 5% among doctors, between 18–20% among nurses and administrative, and 40–42% among domestic, catering, and portering staff. Prevalence of smoking was highest (24%) under 30 years of age; 38% of the responders wished smoking to be completely forbidden in all areas of the hospital and 90% in certain areas, for example, wards and offices; 48% wanted a smoking facility in rest rooms; 63% wanted a 24 hour facility to smoke for staff, 56% for patients and 44% for visitors, and 39% of smokers wished to join a stop smoking support group. Comparing the results of this study with a similar survey in 1987, response rate was higher (82% v 70%), proportion of smokers fell slightly (20% v 23%) but more smokers wanted help (39% v 26%). More were lifelong non-smokers (65% v 59%) and fewer wanted 24 hour access to smoking for staff (63% v 70%) and for visitors (44% v 59%). There were some aspects of concern: smoking increased in some departments (catering and portering), prevalence of smoking was highest in the younger age group, and 60% of smokers did not wish to stop smoking. Support is being provided to the smokers who wished to stop. Those smokers who have a strong compulsion to continue to smoke should be provided with more information on the risks of smoking. In the meantime those who do not smoke should continue to demand a healthier and smoke free environment at work.

### Relation of passive smoking assessed by salivary cotinine and questionnaire to spirometric values in children

DG COOK, PH WHINCUP, O PAPACOSTA, DP STRACHAN, MJ JARVIS, A BRYANT *Department of Public Health Sciences, St George's Hospital Medical School, London; Department of Public Health and Primary Care, Royal Free Hospital School of Medicine, London; ICRF Health Behaviour Unit, Institute of Psychiatry, London; National Poisons Unit, New Cross Hospital, London* The effects of passive tobacco smoke exposure on lung function have been assessed in a cross sectional survey of 3664 children aged 5.5–7, by both salivary cotinine and questionnaire measurements of exposure. All spirometric indices were negatively associated with cotinine after adjustment for confounding variables that included age, sex, body size, and social class. Most of the associations were highly significant. The strongest association was with FEF<sub>50</sub>, the fall between the bottom and top fifths of the cotinine distribution was 6%, equivalent to a reduction of 20.5 ml/s for doubling of the cotinine concentration (95% CI 11.9 to 29.1 ml/s). A composite questionnaire score based on the number of regular sources of exposure was as strongly related to spirometry as the single cotinine measure. The fall in FEF<sub>50</sub>/smoker to whom exposed was 51.0 ml/s (95% CI 26.5 to 75.5 ml/s). As previous studies have relied on questionnaire measures less comprehensive than these and because a single measure of cotinine will have led to an underestimate of the true association by about 40%, previous studies are likely to have underestimated the true effect of passive smoking on lung function. Nevertheless, the effects on respiratory function seem small in absolute magnitude. They may, however, turn out to be important if the effects of exposure are cumulative. The use of salivary cotinine as a marker of passive smoke exposure in longitudinal studies should help resolve this issue.

### The microbiology of pleural empyema

THE BRITISH THORACIC SOCIETY RESEARCH COMMITTEE *British Thoracic Society, London* A prospective multicentre study of naturally occurring empyema was undertaken to find among other aspects, whether resistance to penicillin in pneumococci or other streptococci was responsible for the occurrence of this disease. Of 100 patients for whom detailed microbiology is available at the central reference laboratory, a microbiological diagnosis was established in 86 (86%). Empyema fluid from 55 patients yielded a single organism (16 Pneumococci, 17 *Streptococcus milleri*, one Group A streptococcus, six *Staphylococcus aureus*, four Enterobacteriaceae, nine Anaerobes, six

other organisms). In 31 patients a mixed bacterial flora was encountered, consisting of a mixture of aerobic organisms in five patients (including three with pneumococci and of aerobic and anaerobic organisms in 26 patients (including 10 with *Streptococcus milleri*). None of the *Pneumococci* or *Streptococcus milleri* were resistant to penicillin: the minimal inhibitory concentration ranged from 0.008–0.03 µg/ml for the *Pneumococci* and  $\leq 0.25$  µg/ml for *Streptococcus milleri*. The wide diversity of organisms isolated requires microbiological determination of the aetiological agents to delineate the appropriate chemotherapy. Initial empirical treatment must include a broad spectrum second generation cephalosporin and a nitro-imadazole, for example, Cefuroxime and metronidazole. No significant association was found between the species of the aetiological agent and a number of clinical assessments on admission, response to treatment, or mortality.

### Clinical course of empyema

THE BRITISH THORACIC SOCIETY RESEARCH COMMITTEE *British Thoracic Society, London* In a prospective multicentre study 119 patients with naturally occurring empyema were analysed. Ages were between 7 months and 85 years with 48% over 65 y. Eight per cent had taken excess alcohol (over 30 units a week), 42% were teetotal, 61% had normal lungs before this illness, and in 29% there was an associated factor favouring aspiration. In 29% however, the lungs were normal with no predisposing factors. Malaise was the most frequently reported symptom, occurring more commonly the longer the diagnosis was delayed. Fever was reported initially in only 47%. Significant laboratory abnormalities were in serum albumin (median 27 g/l), (interquartile range 24–31) and white blood cells (median  $18 \times 10^9/l$ ) 12.1–24.5). A positive microbiological diagnosis was made in 108 subjects (91%), 38 (32%) had anaerobes isolated, 24 (20%) pneumococci, and 35 (29%) other streptococci. There were 114 different isolates. Seventy six per cent of pus specimens containing aerobes were malodorous; specimens with pneumococci rarely smelled (1/24). In 78 patients x ray films were available for assessment: 49 of the films clearly suggested pleural fluid. In the rest an alternative diagnosis of a mass or pneumonia was possible. The interval from first symptom to first general practitioner consultation was five days (1–13). There was then a median delay of 13 days (4–31) before hospital admission. A diagnosis was made in 61% of patients within 48 hours of admission. In 15 the diagnosis was delayed more than two weeks. Median hospital stay from diagnosis was 23 days (15–42). Twelve patients died of empyema and nine from other causes (six carcinoma of the bronchus). Eighty three per cent of survivors were fully ambulatory at six months.

### Surgical treatment of empyema thoracis: analysis of 88 cases between 1987 and 1991

AC DE SOUZA, J GALEA, D BEGGS, TJ SPYT *Cardiothoracic Units of Leicester Groby Road and Nottingham City Hospital* A total of 88 cases of empyema thoracis were treated in the cardiothoracic units of Leicester and Nottingham between 1987 and 1991. Eighty two patients were adults and six were children. The mean age was 48 y. Most patients were male (80%). The commonest underlying cause was pneumonia, then malignancy and iatrogenic injury. The commonest pathogens isolated were *Streptococcus milleri* and *Staphylococcus aureus*. There was an associated systemic disorder in 63% of the adults, most often chronic renal failure or an unrelated malignancy. Thirty three patients (38%) had a failed therapeutic procedure before the referring admission. After admission patients were treated with various procedures including simple intercostal drainage, rib resection, or thoracotomy and decortication. The choice of treatment depended on the age, pulmonary function, nutritional state, underlying pathology, and location of the collection. Most (89%) of the patients were treated with surgery. The commonest procedure was rib resection and drainage by tube (52%). Only 7% of all patients required further intervention. The average postoperative stay was 19.5 days and the hospital mortality was 9%. After this review we recommend early surgical drainage for confirmed empyema thoracis as this has a low mortality with good postoperative results, few requiring further intervention.

### The treatment of empyema

THE BRITISH THORACIC SOCIETY RESEARCH COMMITTEE *British Thoracic Society, London* This paper is based on 119 patients in a

prospective BTS survey. Sixty four patients were recorded as having antibiotics before admission; when organisms were subsequently identified 43 had had appropriate treatment and 16 inappropriate. After diagnosis antibiotics were given according to sensitivities when available. Only 51% of patients received antibiotics after rib resection or decortication. Methods of treatment: (1) Antibiotics only—five patients; three survived, two died (one from empyema, one other cause). (2) Repeated needle aspiration—Forty six patients: 19 required no further treatment, 16 had tube drainage, one rib resection and six decortication, four died (three from empyema, one other cause). (3) Tube drainage—Seventy nine patients: 28 required no further treatment, 20 had rib resection, 17 decortication, 14 died (7 from empyema, 7 other causes). (4) Rib resection and drainage—Twenty four patients: 20 required no further treatment, two required decortication, two died (one from empyema, one other). (5) Decortication—Twenty nine patients: 28 patients survived, one died (not from empyema). For each method the interval from start of treatment to hospital discharge was (median and interquartile range); aspiration 26 days (14–41); tube drainage 23 days (13–43); rib resection 11 days (10–39); decortication 12 days (8–15). Possible prognostic variables were sought to determine any difference between the survivors and deaths from empyema. These show that old age, congestive cardiac failure, and diabetes predict an unfavourable outcome. The mean initial albumin concentration in survivors was 28.7 g/l compared to 21.1 g/l in patients who died from empyema ( $p < 0.001$ ). The probability of successful tube drainage or needle aspiration was relatively high when 20% or less in area of the hemi-thorax on x ray film was involved at diagnosis. This treatment was less likely to succeed in patients with a larger area involved and in whom malaise and fever were early symptoms.

### Malignant pleural mesothelioma: role of the surgeon

D PRAKASH, M CLEE, AN JILAIHAWI, CJ CLARK *Regional Thoracic Surgical Unit, Hairmyres Hospital, Glasgow* Needle biopsy and pleural fluid cytology are often inadequate in making a firm diagnosis of malignant pleural mesothelioma. Clinical and radiological features may give a presumptive diagnosis. An open pleural biopsy through a 4 cm skin incision gives an adequate biopsy and a certain histological diagnosis. Surgical treatment for the disease may vary from palliative pleurectomy to radical pleuropneumectomy with excision and reconstruction of the pericardium and diaphragm. Radical surgical resection is reported to be a feasible procedure with acceptable mortality and good palliation of symptoms in this condition but the procedure is not widely practised. Our experience with 35 cases operated on between May 1987 and December 1991 have been encouraging. The first 15 patients (group 1) had a radical pleuropneumectomy whereas the next 20 patients (group 2) had the same operation followed by four courses of chemotherapy at monthly intervals. In group 1, the tumour recurred six to 18 months post-operatively and only one patient survived two years. In group 2, six patients have had recurrence between 12 and 24 months post-operatively whereas six others are well and tumour and symptom free 12 to 24 months postoperatively. One patient is well (with recurrence) at 36 months and four others have a follow up of less than a year. The palliation in all patients has been gratifying and the duration of survival in group 2 has been worthwhile. The hospital mortality has been 20% and 15% in the two groups. There is a role for the surgeon in the diagnosis and the treatment of mesothelioma. Radical resection is the first step in the treatment of this disease but should be followed by adjuvant treatment that needs further evaluation and improvement.

### A survey of malignant mesothelioma in Portsmouth 1982–91

AW MATTHEWS *Queen Alexandra Hospital, Portsmouth* Between 1982 and 1991, a total of 240 patients with malignant mesothelioma have been identified in the Portsmouth health district (population 530 000). A survey has been made of the clinical and pathological features of 200 patients who have died. A history of asbestos exposure was found in 91%, most having worked in the Royal Naval dockyard. Age at first exposure ranged from 15 to 50 (mean 22) and total exposure was from two to 50 (mean 12) y. The interval from first exposure to the onset of symptoms ranged from 21 to 71 years (mean 44). The sites of origin were: right pleura 60%, left pleura 37%, peritoneum 3%. Of the pleural mesotheliomas 78% presented with effusion and 22% with a pleural mass or diffuse thickening. The presenting symptoms were dyspnoea 91%, pain 58%, cough 46%, weight loss 28%. The diagnosis was made by pleural biopsy in 42%, thoracoscopy in 24%, thoracotomy 6%, skin biopsy 6%, and at post mortem examination in 17%. The mean interval between the start of

symptoms and diagnosis was seven months. The histological types comprised: epithelioid 50%, spindle cell 21%, mixed 25%, anaplastic 4%. Survival from the start of symptoms ranged from two to 86 months (mean survival 16 months, median 13 months). Prolonged survival was associated with epithelioid histology and serous rather than bloodstained effusions or a pleural mass. There was no clear association between survival and any of the other features and treatment seemed to have no effect on survival. At post mortem examination extra thoracic metastases were found in 62% of patients.

#### Activation of CD4+ T cells and increased IL-4, IL-5 and GM-CSF mRNA positive cells in bronchoalveolar lavage fluid (BAL) 24 hours after allergen inhalation challenge of atopic asthmatic patients

DS ROBINSON, Q HAMID, AM BENTLEY, S YING, AB KAY, SR DURHAM *National Heart and Lung Institute, London* Late asthmatic responses (LAR) to allergen inhalation are associated with bronchial mucosal eosinophil infiltration, which may contribute to increased bronchial responsiveness. To test the hypothesis that this local eosinophilia results from cytokine production from activated CD4+ T lymphocytes we have analysed BAL cell differential, T cell phenotype, activation markers, and cytokine mRNA expression in 13 atopic asthmatics 24 hours after inhalation challenge with allergen and after diluent control challenge. Comparing BAL after allergen with BAL after diluent, there was an increase in BAL eosinophils ( $p < 0.01$ ), and flow cytometry showed increased expression of CD25 by CD4+ ( $p < 0.02$ ) but not CD8+ BAL T cells after allergen. Increased numbers of BAL cells per 1000 on cytopins gave positive in situ hybridisation signals for mRNA, for IL-4 ( $p < 0.01$ ), IL-5 ( $p < 0.01$ ), and GM-CSF ( $p < 0.01$ ), but not IL-2, IL-3, or IFN- $\gamma$  after allergen challenge compared with diluent. Associations were found amongst activation of BAL CD4+ T cells and IL-5 mRNA+ve BAL cells (CD4+/CD25+ v IL-5 mRNA+,  $p < 0.01$ ), BAL eosinophils (CD4+/CD25+ v EOS,  $p < 0.05$ , IL-5 mRNA+ v EOS,  $p < 0.05$ ) and the magnitude of the LAR (EOS v LAR,  $p < 0.001$ ). Cytokines from activated Th2 type CD4+ T cells in the airway may contribute to LAR by mechanisms including eosinophil accumulation.

#### Increases in activated T lymphocytes, eosinophils, and cytokine mRNA expression for IL-5 and GM-CSF in bronchial biopsy specimens after allergen inhalation challenge in atopic asthmatic patients

AM BENTLEY, QIU MENG, DS ROBINSON, Q HAMID, AB KAY, SR DURHAM *National Heart and Lung Institute, London* Tissue eosinophilia is a well recognised feature of the late asthmatic response to allergen inhalation and may contribute to the associated increase in airways responsiveness. We have examined the phenotype and activation state of T lymphocytes, eosinophils, and cytokine mRNA expression in bronchial mucosal biopsies after allergen challenge. Fifteen mild atopic asthmatic patients underwent fibreoptic bronchoscopy on two occasions, 24 hours after inhalation challenge with allergen and allergen diluent. The challenges were performed in random order separated by an interval of three weeks. Immunohistology (APAAP method) with a panel of monoclonal antibodies identified increased numbers of activated (EG2+) eosinophils ( $p < 0.05$ ) and IL-2R+ (CD25+) cells ( $p < 0.01$ ) after allergen challenge compared with diluent. Increased numbers of cells expressing positive hybridisation signals for cytokine mRNA for IL-5 ( $p < 0.05$ ) and GM-CSF ( $p < 0.01$ ), but not for IFN- $\gamma$ , were also found. An association was identified between the number of activated (EG2+) eosinophils and the number of IL-5 mRNA positive cells in subjects who developed definite late responses ( $r = 0.92$ ,  $p < 0.01$ ). The results suggest that Th<sub>2</sub> type cytokines possibly from activated T lymphocytes contribute to the local tissue eosinophilia during late asthmatic responses.

#### Up regulation of GM-CSF expression in the bronchial epithelium of asthmatic patients shown by immunohistochemistry

AR SOUSA, SJ LANE, J NAKHOSTEEN, TH LEE, RN POSTON *UMDS Guy's Hospital, London and Augusta Teaching Hospital, Bochum, Germany* Granulocyte macrophage colony stimulating factor (GM-CSF) may play a role in the pathogenesis of bronchial asthma by enhancing the survival, differentiation and activation of eosinophils and other inflammatory cells (Burk LA *et al. J Allergy Clin Immunol* 1991;88:226). Frozen sections were cut from bronchial biopsies from 15 asthmatic and nine normal subjects. They were assessed by

immunoperoxidase for GM-CSF expression with the avidin-biotin complex technique. A polyclonal and a monoclonal antibody were used for this purpose. Control immunoglobulins were used at the same concentration as the test antibodies to exclude non specific staining. Strong staining for GM-CSF was seen in the epithelium of the asthmatic group together with less extensive staining in the sub-epithelial inflammatory cells. Reactions in the normal group were much weaker. Expression in the epithelium was quantified by hue saturation intensity colour image analysis (Poston RN *et al. Am J Pathol* 1992;140:665). This allows measurement of the brown colour produced by the immunoperoxidase reaction product. With the polyclonal antibody, there was staining in 48.0% (5.9%) (mean (SEM)) of the epithelium of the asthmatic group, compared with 14.1% (3.4%) of the controls. With the monoclonal antibody, the figures were 29.8% (4.6%) and 2.7% (1.2%) respectively, with no overlap between the groups. These differences were highly significant ( $p = 0.0013$  and  $p = 0.0003$ ). These data indicate increased production of GM-CSF by bronchial epithelium of asthmatic patients.

#### Expression of the endothelial and leucocyte adhesion molecules ICAM-1, E-selectin and VCAM-1 in the bronchial mucosa in steady state asthma and allergen induced asthma

AM BENTLEY, SR DURHAM, DS ROBINSON, O CROMWELL, AB KAY, AJ WARDLAW *National Heart and Lung Institute, London* We have tested the hypothesis that endothelial and leukocyte adhesion molecules are upregulated in the bronchial mucosa in asthma. Bronchial biopsies were examined with the APAAP method and monoclonal antibodies to ICAM-1, E selectin and VCAM-1 in steady state intrinsic asthmatic (IA) and extrinsic asthmatic patients (EA), and after allergen challenge. Constitutive expression of ICAM-1, E selectin and VCAM-1 was found in IA and EA and normal controls (NC). Staining for ICAM-1 and E selectin was greater in IA than NC for intensity ( $p < 0.02$ ,  $p < 0.05$ ) and extent ( $p < 0.01$ ,  $p < 0.05$ ) respectively. No differences were found between EA and NC. VCAM-1 staining did not differ between IA, EA, and NC. Epithelial expression of ICAM-1 was found in 8/10 IA, 5/8 EA, and only 2/9 NC. Biopsies obtained 24 hours after allergen compared with diluent challenge showed no differences in ICAM-1 or E-selectin expression. Extent and Intensity of VCAM-1 staining was increased in 10/13 and 9/13 subjects after allergen challenge respectively. The eosinophil infiltrate after allergen challenge (MPB+ cells) correlated with the intensity and extent of ICAM-1 and VCAM-1 staining ( $r = 0.63$ ,  $p < 0.03$  for extent and  $r = 0.82$ ,  $p < 0.01$  for intensity of ICAM-1 staining,  $r = 0.69$ ,  $p < 0.01$  for extent and  $r = 0.79$ ,  $p < 0.01$  for intensity of VCAM-1 staining). Epithelial expression of ICAM-1 after allergen challenge was found in 7/13 subjects compared with 2/13 after diluent. The results suggest that in vivo expression of adhesion molecules is more complex than their in vitro expression. Epithelial ICAM-1 expression in asthma may render it susceptible to immune damage and ICAM-1 and VCAM-1 may facilitate eosinophil migration after allergen challenge.

#### Circulating adhesion molecules in asthmatic and non-asthmatic subjects

S MONTEFORT, CKW LAI, P KAPAH, DO HASKARD, PH HOWARTH, ST HOLTGATE *University of Southampton, Hammersmith Hospital, London and Chinese University, Hong Kong* There is accumulating evidence that leucocyte endothelial adhesion molecules are important in inflammatory airway disease, being involved in the primary steps of migration of leucocytes to the site of inflammation. Recently circulating forms of these adhesion molecules have been described, although their origin and function are still unknown. We have used a capture ELISA to measure the baseline concentrations of circulating ICAM-1 and VCAM-1 in the peripheral blood of atopic and non-atopic normal subjects ( $n = 13$  and  $16$ ) and stable asthmatic subjects ( $n = 29$ ). These circulating adhesion molecules were also measured for acute asthmatic subjects on day 1 ( $n = 38$ ), day 3 ( $n = 29$ ), and day 28 ( $n = 13$ ) after an acute asthmatic episode. Circulating ICAM-1 concentrations were significantly raised in acute asthma on all three study days when compared with stable asthmatic patients ( $p = 0.002$ ) atopic controls ( $p = 0.001$ ), and non-atopic controls ( $p = 0.0002$ ). There were no significant differences between the controls and the stable asthmatic patients. The serum concentrations of cICAM-1 were significantly correlated to the decrease in peak expiratory flow rates (expressed as % predicted) seen between the stable and acute asthmatic patients ( $r = 0.359$ ,  $p = 0.002$ ). Circulating VCAM-1 was

not significantly increased in any of the groups studied. We conclude that circulating concentration of ICAM-1 is raised in acute asthmatic episodes and might either reflect the primary inflammatory response in the lung or is possibly a reflection of a compensatory mechanism attempting to control the abnormal reactivity found in acute asthma.

#### Cyclooxygenase inhibition modulates the change in bronchial reactivity to methacholine with inhaled frusemide in normal subjects

R POLOSA, K RAJAKULASINGAM, G PROSPERINI, ST HOLTGATE *Institute of Respiratory Diseases, University of Catania, Italy, and Medicine 1, University of Southampton* Inhaled frusemide (fru) protects the airways of asthmatic subjects against the bronchoconstrictor response to a wide variety of challenges. We have recently shown that both inhaled frusemide and bumetanide attenuate bronchial responsiveness of human airways to methacholine (R Polosa *et al. Eur Resp J* 1991;4:605s) by unknown mechanisms. Generation of bronchoprotective prostaglandins, such as PGE<sub>2</sub>, may underlie the airway action of frusemide and bumetanide, as loop diuretics stimulate release of PGE<sub>2</sub> in renal tubules. To investigate this we have studied the effects of flurbiprofen (F), a potent cyclooxygenase inhibitor, on the protective action of frusemide against methacholine induced bronchoconstriction in eight healthy volunteers in a randomised, double blind placebo controlled study. Eight normal subjects attended the laboratory on four separate occasions to undertake concentration response studies with methacholine. On the first two occasions (not less than three days apart) subjects received nebulised fru (40 mg) or matched placebo 10 minutes before bronchoprovocation tests. In the final two visits (not less than 10 days apart) subjects were pretreated with either F (100 mg/daily) or placebo capsules for three days. Two hours after taking the last capsule, subjects inhaled fru (40 mg) and 10 minutes later they underwent concentration response studies with methacholine. Changes in airway calibre were followed up as forced expiratory volume in (FEV<sub>1</sub>) and methacholine responsiveness expressed as PC<sub>15</sub>. Inhaled fru significantly reduced the airway response to methacholine in all the subjects studied, the geometric mean PC<sub>15</sub> value increasing from 43.5 to 109.0 mg/ml ( $p < 0.01$ ) after placebo and fru respectively. After fru inhalation and oral placebo the airway responsiveness to methacholine increased up to a PC<sub>15</sub> value of 116.3 mg/ml, which was not significantly different from that derived after inhaled fru alone. The combination of inhaled fru and oral F reduced methacholine responses to a PC<sub>15</sub> value of 50.3 mg/ml, which was not significantly different from that found before nebulised placebo alone. The present findings support the view that the production of protective prostaglandins underlies the protective properties of nebulised frusemide against methacholine induced bronchoconstriction in humans.

#### Restriction of peripheral T cell receptor V $\alpha$ gene used in atopy and atopic asthma

CM GELDER, JFJ MORRISON, BJ O'CONNOR, IM ADCOCK PHD, PJ BARNES, S BRENNER *Department of Thoracic Medicine, National Heart and Lung Institute, London, MRC Molecular Genetics Unit, Addenbrookes Hospital, Cambridge* The atopic diseases of asthma, perennial rhinitis and eczema affect up to 30%–40% of the population of industrialised countries. They have an important genetic component that may act via an effect upon the T cell. Using the polymerase chain reaction with primers specific for 18 families of the T cell receptor  $\alpha$  chain variable genes (TCR V $\alpha$ ), we report that in peripheral T cells in atopy and atopic asthmatic subjects there is a restriction of TCR V $\alpha$  gene usage from a mean of 15.6 families (95% CI 14.1–17.2) in normal subjects to 6.8 (95% CI 5.2–8.3) in atopy and 8.4 (95% CI 6.8–9.9) in atopic asthmatic patients ( $p < 0.00001$ ). Non-atopic asthmatic patients used a mean of 13.9 (95% CI 12.3–15.4) gene families, which was statistically identical to normal subjects. There was also a different pattern of TCR V $\alpha$  gene family usage in peripheral blood between normal, atopic and non-atopic asthmatic subjects. Examination of CD4+ T cells from atopic peripheral blood revealed a use of 4.5 (95% CI 2.5–6.5) TCR V $\alpha$  gene families as distinct from 10.3 (95% CI 8.3–12.2) in CD8+ cells ( $p = 0.0003$ ). We detected only 2.5 (95% CI 0.5–4.5) TCR V $\alpha$  gene families in atopic asthmatic lung tissue. This study suggests that the T cell repertoire in atopic subjects is restricted. The occurrence of asthma was not itself associated with clonal T cell restriction, implying that atopic and non-asthma are distinct syndromes. The striking clonal restriction found in lung implies a local selection process which may have important therapeutic implications. *JFJM and CMG are MRC Training Fellows.*

#### In vivo quantification of pulmonary $\beta$ adrenoceptor density using <sup>11</sup>C-S-CGP 12177 and positron emission tomography (PET)

J UEIKI, CG RHODES, R DE SILVA, D LEFROY, F QING, C STEEL, S WATERS, T JONES, PG CAMICI, PW IND, JMB HUGHES *MRC Cyclotron Unit and Respiratory Division, Department of Medicine, RPMS, Hammersmith Hospital, London* In a previous report (Rhodes *et al Thorax* 1991;46:757P), <sup>11</sup>C-S-CGP 12177 was used to measure pulmonary  $\beta$  adrenoceptor ( $\beta$ AR) density ( $B_{max}$ ) in the dog lung. We have extended these measurements to normal male volunteers ( $n = 6$ ) and patients with hypertrophic cardiomyopathy (HCM,  $n = 8$ ). PET scanning consisted of transmission (tissue volume), C<sup>15</sup>O (blood volume) and <sup>11</sup>C-CGP ( $\beta$ AR) emission scans. The C<sup>15</sup>O data were subtracted (a) from the transmission images to produce quantitative images of extravascular tissue volume ( $V_{ev}$ , (ml gas-free tissue) cm<sup>-3</sup> thorax) and (b) from the <sup>11</sup>C-CGP images to correct for intravascular ligand activity (with simultaneous venous blood sampling). To estimate  $B_{max}$  of pulmonary  $\beta$ AR, a high specific activity <sup>11</sup>C-CGP (4–11  $\mu$ g) was first given intravenously, followed 30 minutes later by a second injection of low specific activity <sup>11</sup>C-CGP (28–43  $\mu$ g). Dynamic PET scanning was started at the time of the first <sup>11</sup>C-CGP injection and continued for 60 minutes. Regions of interest (ROIs) were drawn on the transmission images and projected onto the dynamic <sup>11</sup>C-CGP data to general pulmonary tissue time-activity curves. A graphical approach was used to calculate  $B_{max}$  of pulmonary  $\beta$ AR in each ROI (Delforge *et al J Nucl Med* 1991;32:739), modified to express  $B_{max}$  as pmol (ml gas-free tissue)<sup>-1</sup> by normalising to the local  $V_{ev}$  value. Both in normal subjects and HCM patients, there were no differences in pulmonary  $\beta$ AR density (mainly alveolar) between peripheral and central regions nor between right and left lungs. In normal subjects, average  $B_{max}$  for all ROIs was 15.4 (0.7) (mean (SEM)) pmol/ml<sup>-1</sup> which was consistent between subjects and similar to in vitro values for human lung  $12.6 \pm 0.9$  pmol/ml<sup>-1</sup>. (Carstairs *et al AM Rev Respir Dis* 1985;132:541). There was no difference in pulmonary  $\beta$ AR density between normal subjects and HCM patients (16.4 (0.9) pmol/ml<sup>-1</sup>), although  $V_{ev}$  was increased in HCM patients (0.163 (0.010) ml/cm<sup>-3</sup> v 0.132 (0.006) in normal subjects,  $p < 0.05$ ). We now have a quantitative method to begin to assess pharmacological regulation of pulmonary  $\beta$ ARs in normal subjects and asthmatic patients in vivo.

#### Time trends in respiratory symptoms in childhood over a 24 year period

DG COOK, PH WHINCUP, DP STRACHAN, O PAPANOSTA *Department of Public Health Sciences, St George's Hospital Medical School, Department of Public Health, and Primary Care, Royal Free Hospital School of Medicine, London* Whereas reports have suggested that the prevalence of childhood asthma is increasing, few have supported their observations with lung function measurements. Moreover, trends in respiratory symptoms other than wheeze have received little attention. Using data from the 1966 Schoolchild Chest Health Survey and the 1990 Ten Towns Study, the prevalence rates of cough, phlegm, and wheeze in urban British children aged 6.0 to 7.5 years have been compared. In both studies the same respiratory questions were used and measurements of PEF were carried out. The percentage of children reported as wheezing on most days or nights increased from 3.9% to 6.1% (95% CI for increase -0.2 to 4.6), with a proportionately smaller increase in ever wheeze. The percentage of children with day or nighttime cough increased from 21.1% to 33.3% (95% CI for increase 3.8 to 20.6) and the percentage with day or nighttime phlegm increased from 5.8% to 10.0% (95% CI for increase 0.4 to 8.0). Smaller increases in persistent cough (from 9.0% to 12.4%) and persistent phlegm (from 2.4% to 3.5%) were also found, whereas morning cough and morning phlegm showed little change. The increases in cough and phlegm were apparent in subjects with and without a history of wheeze. The increases were at least as great in northern towns as in southern ones, and occurred in all social classes. The mean difference in PEF between subjects with and without wheeze was smaller in 1990 than in 1966, but this result was strongly dependent on subjects receiving antiasthmatic treatment. The data suggest that the prevalence of persistent wheeze has increased, but a lower parental threshold for symptom reporting may be partly responsible. There has also been an increase in the prevalence of childhood cough and phlegm that is independent of the increase in wheeze.

### Changing patterns of respiratory disease in HIV positive patients 1986-7 and 1990-1

AD PITKIN, AD GRANT, NM FOLEY, RF MILLER *Department of Medicine, UCMSM, Middlesex Hospital, London* We compared 73 consecutive HIV positive patients admitted for respiratory investigation in 1986-7 with 122 consecutive patients in 1990-1 to identify changes in patterns of respiratory disease. We also assessed the effects of prophylaxis with nebulised pentamidine (NP) on the yield for *P carinii* from bronchoalveolar lavage (BAL) and on the chest radiographic (CXR) appearances in patients with pneumocystis pneumonia (PCP). Results are given in the table below. *S aureus*, *Str pneumoniae* and *Ps aeruginosa* were the commonest causes of bacterial pneumonia. In patients with PCP the yield from BAL was 56% in those who had received NP and 79% in those who had not; CXR were atypical (apical shadowing or lymphadenopathy) in 7.5% of those who had not received prior NP and 21% who had. Although KS and bacterial infections have become more frequent, PCP remains the commonest cause of respiratory illness in HIV positive patients. In patients with PCP use of NP prophylaxis reduces the yield of BAL and increases the proportion with atypical CXR appearances, factors which may make the diagnosis more difficult to sustain.

Diagnosis	1986-7 (n = 73)	1990-1 (n = 122)
PCP	50	59
KS	3	14
Mycobacterial infection	2	8
Bacterial infection	5	26
Other diagnoses*	10	8
Negative investigation/self-limiting episodes	3	7

KS = pulmonary KS. \*Includes fungal pneumonia, lymphoma, lymphoid pneumonitis, chronic inflammation, non-specific fibrosis.

### Osteoporosis, corticosteroids, and bone disease: comparison of oral and intravenous bisphosphonates

K ANDERSON, S GALLACHER, JAK FENNER, T SPEEKENBRINK, F BRYDEN, IT BOYLE, SW BANHAM *University Department of Medicine, Departments of Respiratory Medicine and Radiology, Royal and Victoria Infirmary, Glasgow* Oral etidronate treatment was recently shown to be effective in the management of postmenopausal osteoporosis (Reid *et al Lancet* 1988;i:143); however the role of bisphosphonates in general is unclear in corticosteroid associated osteoporosis. We have compared the effect of oral cyclical etidronate (400 mg for two weeks followed by 11 weeks calcium supplement) with intermittent infusions of pamidronate (APD 30 mg/three months) in two groups of patients with corticosteroid dependent lung disease. Overall, 36 patients were studied—19 given APD, 17 given etidronate. The age distribution was similar—APD, mean 58.4 years, range 42-79; etidronate 57.6, range 42-78. The weekly oral corticosteroid dose was just less in the etidronate group (mean 95 mg, range 35-280) than in the APD group (mean 98 mg, range 38-280). The duration of treatment was also lower in the etidronate group—mean 8.3 v 14 years. Vertebral fractures were present in 15 APD and 10 etidronate subjects. Pretreatment bone density was similar—L2-4 APD 0.906/cm<sup>2</sup>, range 0.603-1.307 v 0.831, 0.474-1.215; neck of femur APD 0.739 g/cm<sup>2</sup>, range 0.529-0.965 v 0.741, 0.492-1.020. After one year of treatment with APD, L2-4 density increased by a mean of 3.4% (95% CI 1.1 to 5.2) and by 3.7% with etidronate (95% CI -0.4 to 7.5), but no significant change was found in neck of femur density. The effect of the two drugs on bone density was similar (p < 0.07) by one way analysis of variance. Within the limitations of the groups studied, our findings suggest that the response to oral or intravenous bisphosphonate is similar after one year of treatment.

### Subepithelial fibrosis in asthmatic airways

JW WILSON, X LI, I KUNG, L WILSON, MCF PAIN *Department of Thoracic Medicine and Anatomical Pathology of Royal Melbourne Hospital, Victoria 3052, Australia* Airway collagen deposition and myofibroblast proliferation are now recognised in asthma; however their extent and clinicopathological significance remains unclear (Brewster *et al. Am J Respir Cell Mol Biol* 1990;3:507). We measured the thickness of subepithelial collagen by electron microscopy in endobronchial biopsies from six asthmatic and six normal subjects and attempted to correlate subepithelial collagen deposition with clinical and physiological indices of asthma. Airway distensibility was evaluated by measuring anatomical dead space (Vd) (nitrogen washout method) at different end inspiratory lung volumes (Vi) and expressed

by linear regression of Vd/Vi (see separate abstract). Thickness of subepithelial collagen from the lamina densa to the submucosa was significantly greater in asthmatic than normal subjects (mean 7.26 (SD 2.16)  $\mu\text{m}$  v 3.73 (0.53)  $\mu\text{m}$ , p = 0.014). Thickness did not correlate with either VD/Vi (r = -0.257), methacholine PC<sub>20</sub> or FEV<sub>1</sub> (% predicted), nor was there any association with disease duration, severity, or use of steroids. These results confirm the presence of subepithelial fibrosis in mild asthma and suggest that further studies are needed to evaluate its pathophysiological significance and its relation to fixed airflow obstruction.

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### Bronchial reactivity and airways obstruction in rheumatoid arthritis

WU HASSAN, NP KEANEY, CD HOLLAND, CA KELLY *The Royal Infirmary, New Durham Road, Sunderland* It is presently unclear whether small airways disease should be considered part of the spectrum of lung involvement in patients with rheumatoid arthritis (RA). We have assessed the prevalence of bronchial reactivity (BR) to methacholine and airways obstruction in 57 consenting patients with RA. Fifteen patients were men and the mean population age was 60.6 years (range 22-74). Autoantibodies, erythrocyte sedimentation rate, and radiographs of hands and chest were performed in all patients. Atopy and smoking were assessed and Schirmer's tear tests performed to identify secondary Sjogren's Syndrome (SSS). All patients had spirometry, static lung volumes, flow volume loops, and gas transfer measurements performed within one month of formal methacholine challenge testing to quantify BR. Five patients were atopic on skin prick testing to five common allergens. 13 (22%) patients were active smokers and 23 (40%) ex-smokers, and only 4 (7%) patients had evidence of SSS. Twenty six patients (45%) had a measurable PC<sub>20</sub> FEV<sub>1</sub>, whereas only 10 (17%) patients were totally unresponsive (less than 5% fall in FEV<sub>1</sub>) to methacholine up to 32 mg. There was no statistical relation between baseline FEV<sub>1</sub> or FEF<sub>25-75%</sub> and PC<sub>20</sub> FEV<sub>1</sub>. Ten (40%) patients with a measurable PC<sub>20</sub> FEV<sub>1</sub> were active smokers, one had evidence of SSS, and three were atopic. We have shown a high prevalence of BR in patients with RA independent of base line FEV<sub>1</sub>, smoking, and SSS.

### How progressive is bronchopulmonary aspergillosis?

A SEATON *Department of Environmental and Occupational Medicine, University Medical School, Foresterhill, Aberdeen* Allergic bronchopulmonary aspergillosis is often regarded as a chronic and progressive condition, usually requiring long term oral corticosteroids for its control. I have looked after five such patients, diagnosed on the basis of recurrent pulmonary infiltrations, positive skin tests, and serum precipitating antibodies to *Aspergillus fumigatus*, since 1979 or before. All have managed with inhaled corticosteroids and intermittent self administered oral steroids for exacerbations. None has shown evidence of abnormal radiological or functional decline and all remain fully active. The patients averaged just less than one course of oral steroids per year (61 courses over 78 years in the five patients after starting inhaled steroids). The patients between them recorded 56 attacks requiring oral steroids (sometimes an unduly short course was prescribed and had to be repeated once or twice), over a total of 83 years from the time of diagnosis, including episodes before inhaled steroids were started. Of those, 24 occurred in the winter, 12 each in spring and autumn, and eight in summer. The apparent success of this method of management is explainable on the basis of knowledge of the ecological relations between *Aspergillus fumigatus*, its natural predators in the soil, and the defences of the asthmatic lung (Seaton and Robertson. *Lancet* 1989;1:893; Robertson *et al Brit J Med Vet Mycol* 1989;27:295).

### Computed tomography of the lungs in chronic allergic bronchopulmonary aspergillosis and in asthmatic patients skin test positive for *Aspergillus fumigatus*

RM ANGUS, MD COWAN, ML DAVIES, C MCHARRY, NC THOMSON *Departments of Respiratory Medicine, Radiology and Immunology, Western Infirmary, Glasgow* Allergic bronchopulmonary aspergillosis (ABPA) is a disease of asthmatic patients that follows a protracted course resulting in chronic lung damage such as central bronchiectasis. The incidence of bronchiectasis in asthmatic patients with immediate type skin reactions to *Aspergillus fumigatus* but without the other features of ABPA has not been clearly defined. We performed computed tomography scans on 17 asthmatic patients with ABPA (all

with current or previous positive precipitins to *A fumigatus*) and 11 asthmatic patients, skin test positive for *A fumigatus* but without the clinical or serological features of ABPA (non-ABPA group). A Philips Tomoscan 310 with a 9.5 second scan time was used. Thin section studies were performed using a 3 mm slice thickness scanning at 9 mm increments. Results are given in the table below. Bronchial dilatation was more common in the ABPA group affecting 12 patients compared with two in the non-ABPA group. Bronchial wall thickening (BWT) was common to both affecting 16 and nine respectively. When both groups were combined the presence of bronchiectasis correlated positively to the specific IgE and specific IgG concentrations and inversely to the FEV<sub>1</sub> (% of predicted  $p < 0.05$ ). There was no correlation with age, duration of asthma, smoking history, total IgE or eosinophilic cationic protein (ECP) concentrations. Bronchiectasis is common in ABPA but occurs occasionally in asthmatics skin test positive to *A fumigatus*. The presence of bronchiectasis correlates to the specific humoral immune response to *A fumigatus* and is seen in association with more severe airflow obstruction.

	ABPA (n = 17)	Non-ABPA (n = 11)
Age (y)	60.1 (2.5)	49.5 (4.5)
Asthma (y)	27.6 (5.3)	23.2 (5.4)
Current/ex-smoker	11	4
Bronchiectasis	12	2*
Bronchiectatic (lobes)	41	3*
BWT	16	9
Total IgE (mg/ml)	676 (169)	387 (429)
Rast IgE to <i>A fumigatus</i> (IU/ml)	4.6 (4.2)	1.32 (1.0)
ELISA IgG to <i>A fumigatus</i> (U/ml)	41.9 (16.7)	2.2 (1.6)*
FEV <sub>1</sub>	1.3 (0.14)	2.1 (0.3)*
FEV <sub>1</sub> (% predicted)	49.4 (5.8)	75.5 (6.5)*
ECP µg/l	17 (2.5)	15.5 (5.3)

Variables expressed as mean (SE).  
\* $p < 0.05$ .

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**Effect of addition of increasing doses of salbutamol to salmeterol**

ET SMYTH, J WILLIAMS, A WISNIEWSKI, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* It is recommended that salmeterol should be given twice daily and that salbutamol should be added for break through symptoms although the effect of combining the two drugs has received little attention. We have performed a double blind placebo controlled crossover design study on 12 patients with mild asthma to assess the effect on FEV<sub>1</sub>, serum K<sup>+</sup>, QTc interval, heart rate, and tremor of placebo or salmeterol (Sm) at 50, 100, and 200 µg followed two hours later by inhaled salbutamol (Sb) in cumulative doses up to 3600 µg. Two hours after placebo Sm 50, Sm 100 and Sm 200 µg the ΔFEV<sub>1</sub> was 0.03, 0.45, 0.52, and 0.64 l and the ΔHR was -5.4, -2.7, 0.9, and 1.6 beats per minute. The addition of salbutamol caused a large increase in FEV<sub>1</sub> after placebo (0.72 l) and a very small further increase after Sm 200 µg. Heart rate however increased in parallel on the four study days to produce a mean (SE) maximum increase of 7.5 (2.6) beats per minute after placebo and 18.1 (1.6) beats per minute after Sm 200 µg compared with post-placebo baseline. The increase in HR after Sm 200 µg alone was similar to that seen after Sm 200 µg suggesting that salmeterol is less β<sub>2</sub> selective than salbutamol or that salmeterol is some 10-fold more potent than salbutamol. Dose equivalence for serum K<sup>+</sup> and tremor (two β<sub>2</sub> effects) were similar to those with heart rate suggesting that the second is the correct explanation.

**Sleep disturbance due to respiratory symptoms: a marker of generalised impairment of health and wellbeing**

PW JONES, CM BAVEYSTOCK *Division of Physiological Medicine, St George's Hospital Medical School, Cranmer Terrace, London* To examine the relation between sleep disturbance and disturbances of daily life in patients with airflow limitation, 152 outpatients (99 men) were studied. All were stable at the time—defined as requiring no consideration of change in medication for the six weeks preceding the study. Arterial saturation (SaO<sub>2</sub>) was measured at rest. The patients performed a six minute walking test (6MWD) and completed the MRC dyspnoea scale, the hospital anxiety and depression scale, and the sickness impact profile (SIP)—a valid measure of impaired health in airways disease. The patients were categorised into those with disturbed sleep (Disturbed) and those without sleep disturbance

(Undisturbed) by their response to an item from the St George's respiratory questionnaire: "my cough or breathing disturbs my sleep." Age and sex distribution were not significantly different between the two groups ( $p > 0.1$ ); Undisturbed: 79 patients (56 men), mean age 63 years; Disturbed: 73 patients (43 men), mean age 62 years. Results for the two groups are tabled below as means together with  $p$  values for the difference (unpaired  $t$  test). The SIP scores were skewed so results are given as medians with non-parametric CIs and a Mann-Whitney U test was used. Disturbed patients had higher scores in eight of 12 areas of life covered by the SIP compared with undisturbed ( $p > 0.01$  in each case). Sleep disturbance due to respiratory symptoms seemed to be a marker of widespread impairment of daily life and wellbeing. This was not related to spirometry or daytime oxygen saturation.

Variable	Undisturbed		Disturbed		p Value
	Mean	95% CI	Mean	95% CI	
FEV <sub>1</sub> (% pred)	52	47-57	54	48-60	0.6
SaO <sub>2</sub> (%)	96	95-96	96	95-97	0.97
6MWD (m)	405	385-425	334	307-362	0.0001
MRC dyspnoea	2.4	2.2-2.7	3.3	2.9-3.6	0.0002
Anxiety	5.8	4.9-6.7	8.8	7.8-9.9	0.0001
Depression	4.4	3.6-5.1	6.2	5.3-7.0	0.002
SIP	3.1	3.0-6.5	10.0	5.2-12.6	0.0002

**The size of statistically significant late asthmatic reactions (LARs)**

SC STENTON, A AVERY, EH WALTERS, DJ HENDRICK *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne* We have used statistical techniques to examine the validity of convention criteria (>15% late falls in FEV<sub>1</sub> or PEF following inhalation challenges) to diagnose LARs. The statistical techniques depend on obtaining time matched FEV<sub>1</sub> or PEF measurements on at least three control days to assess day to day variability of lung function. A lower boundary (effectively a pooled lower 95% confidence limit) is calculated from the control data and expressed graphically. Any measurement on a subsequent active challenge day which falls below the boundary suggests a statistically significant ( $p < 0.05$ ) late fall in lung function that might be due to an LAR. The false positive rate is roughly the 5% expected. In this study, the lower PEF boundary was calculated for 18 asthmatic subjects (age 18-35 years), before an inhaled challenge with *D pteronyssimus*. In nine subjects, the lower boundary was within 10% of the baseline PEF, the narrowest being only 4.2%. This suggests that for many asthmatic subjects, falls of considerably less than 15% represent statistically significant late changes in PEF. These might be due to LARs that would not be detected using conventional criteria. On the other hand, one subject with pronounced day to day PEF variability had a lower boundary that was 62% below baseline making a statistically significant late fall almost impossible to show. For him, applying the conventional 15% criteria would have resulted in a false positive diagnosis. We conclude that statistical techniques can increase the sensitivity with which LARs can be diagnosed while protecting against false positive diagnoses.

**Is the variation in bronchial reactivity greater in patients with severe unstable asthma compared with patients with milder stable asthma?**

AS VATHENEN, S COOPER, JR BRITTON, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* The variation in bronchial reactivity with time in a patient with asthma and its relation with variation in airway calibre is not clear. We hypothesised that the variation in bronchial reactivity would be greater in patients with severe unstable asthma than in patients with milder stable asthma. A cohort of adult patients with mild to moderate asthma who had never been admitted to hospital with an exacerbation of asthma (Group A, 19 patients) and a group with severe unstable asthma with a history of at least one hospital admission with a life threatening attack of asthma (Group B, nine patients) were followed up for one year with monthly measurements of PD<sub>20</sub> methacholine (PD<sub>20</sub> histamine in five patients). A control group of patients with chronic airflow limitation and bronchial hyperreactivity (Group C, 10 patients) was also studied. Mean baseline FEV<sub>1</sub> for Groups A, B, and C were 2.6, 2.4 and 1.5 l respectively; corresponding geometric mean baseline PD<sub>20</sub> values were 0.7, 0.3 and 2.4 µmol. There was a significant within subject correlation between FEV<sub>1</sub> and PD<sub>20</sub> in Group A ( $p < 0.0001$ ) and Group B ( $p$

< 0.01) but not in Group C ( $p = 0.4$ ). The mean variation in FEV<sub>1</sub> (calculated as standard deviation for each subject) over the 12 months was smaller in Group C (0.10 l) than in Group A (0.25 l,  $p < 0.005$ ) and Group B (0.21 l,  $p < 0.005$ ) with no significant difference between groups A and B. The mean variation in PD<sub>20</sub> (calculated as standard deviation for each subject) was 1.03, 1.01, and 1.17 doubling doses for Groups A, B, and C respectively with no significant difference between the three groups. Thus our hypothesis that there would be greater variation in PD<sub>20</sub> with time in patients with more severe unstable asthma was rejected.

### The cardiovascular effects of isoprenaline are increased under conditions of combined hypoxaemia and hypercapnia in healthy males

C BURGESS, P BREMNER, D GALLETTY, B ROBINSON, D MCHAFFIE, G PURDIE, R BEASLEY *Departments of Medicine, Surgery, and Community Health, Wellington School of Medicine, Wellington, New Zealand* Hypoxaemia and hypercapnia can occur during severe asthma. Both these conditions can affect the cardiovascular system and may alter the responses to  $\beta$  agonist drugs. We investigated whether different gas mixtures influenced the cardiovascular effects of inhaled isoprenaline. Nine healthy males were randomly assigned to receive each of three gas mixtures via a close fitting mask to achieve normoxia-normocapnia (RA); hypercapnia (HC; end tidal pCO<sub>2</sub> 50 mm Hg), or hypoxia-hypercapnia (HOHC; arterial oxygen saturation 90%, Pco<sub>2</sub> 50 mm Hg). Isoprenaline (400  $\mu$ g) was administered during inhalation of the gas mixture (at 20 minutes). Cardiovascular measurements of heart rate (HR), blood pressure (BP), QTc interval, cardiac index (CI), ejection fraction (EF), and fractional shortening (FS) were made before administration of the gases, before and five minutes after isoprenaline administration while the gas mixture was maintained. There were no differences between the baseline measurements of the gas mixtures. The changes after HC were not significantly different from those after RA. Compared with RA, HOHC increased HR (19.3  $v$  1.5,  $p < 0.001$ ); SBP (6.9  $v$  -4.0,  $p < 0.009$ ); DBP (7.1  $v$  -1.7,  $p < 0.004$ ); QTc (25.4  $v$  2.7,  $p < 0.002$ ); CI (1.00  $v$  0.06,  $p < 0.001$ ); EF (7.4  $v$  0.9,  $p < 0.005$ ); and FS (6.2  $v$  0.8,  $p < 0.006$ ). Isoprenaline increased HR (5.8 bpm); systolic BP (6.3 mm Hg); QTc interval (14.1 ms); CI (0.51 l/min/m<sup>2</sup>); EF (6.0%), and FS (4.9%) and decreased diastolic BP (-2.3 mm Hg), while breathing RA. It caused similar changes with the other gas mixtures; thus the combined effects were additive. The changes with isoprenaline and HOHC will increase myocardial oxygen demand and these could prove detrimental in severe asthma.

### Factors determining bradykinin responsiveness and refractoriness in asthma

K RAJAKULASINGAM, MK CHURCH, PH HOWARTH, ST HOLTGATE *Immunopharmacology Group, University of Southampton, England* We have examined the relation of bronchial hyperresponsiveness induced by bradykinin to that of histamine (H). We also assessed the incidence and factors influencing the development of refractoriness to bradykinin. A randomly chosen group of 21 atopic asthmatic subjects made two visits to our laboratory to undergo two concentration-response studies separated by one hour with either inhaled histamine or bradykinin. On the histamine study day, the geometric mean PC<sub>20</sub> was 0.87 (range 0.04-8.4) mg/ml for the first test, and 0.88 (0.04-6.8) mg/ml for the second test ( $p > 0.05$ ). On the bradykinin study day, the geometric mean PC<sub>20</sub> was 0.63 (0.01-11.73) mg/ml for the first, and significantly higher at 1.55 (0.01->16.0) mg/ml for the second test ( $p = 0.001$ ). For the group ( $n = 12$ ) with less histamine bronchial reactivity (PC<sub>20</sub> > 1.0 mg/ml), the geometric mean PC<sub>20</sub> bradykinin was 1.18 (0.02-11.73) mg/ml for the first challenge and 3.55 (0.07->16.0) mg/ml for the second challenge ( $p = 0.004$ ). For the group ( $n = 9$ ) with histamine bronchial reactivity < 1.0 mg/ml, the geometric mean PC<sub>20</sub> values were 0.28 (0.01-4.92) and 0.51 (0.01-9.43) mg/ml for the first and second challenges respectively ( $p > 0.05$ ). No significant correlation was found between the first PC<sub>20</sub> histamine and first PC<sub>20</sub> bradykinin. The index of bradykinin refractoriness was not related to baseline histamine reactivity, but it showed a weak negative correlation with baseline bradykinin reactivity. We conclude that refractoriness to inhaled bradykinin is not universally seen in asthmatic subjects but there is a tendency for it to occur with ease in subjects with mild bronchial responsiveness to histamine. We have failed to confirm any correlation between baseline histamine and bradykinin bronchial responsiveness, giving support for an indirect mechanism of action for bradykinin in asthma.

### A survey of airway responsiveness to methacholine and urinary sodium excretion

JR BEACH, CL YOUNG, JH DENNIS, SE WILLIAMS, AJ AVERY, EH WALTERS, DJ HENDRICK *Chest Unit and Department of Biochemistry, Newcastle General Hospital, University of Newcastle upon Tyne* Several investigations have reported a relation between dietary salt intake or urinary sodium (Na) excretion and airway responsiveness (AR) to histamine. We consequently included measurements of AR (in fact to methacholine) and urinary Na in a recently completed survey of shipyard workers. Subjects comprised all welders and caulkers in the shipyard who had commenced employment in 1980-7, and prospective new employees for 1989-90. Matched groups of other shopfloor trades and office workers from the same shipyard were also included. Airway responsiveness was measured by a conventional dosimeter technique and the result expressed as PD<sub>20</sub>/FEV<sub>1</sub>. A 24 hour urine collection commencing the next morning was requested from all men with measurable AR and a group of age and trade matched controls without measurable AR. Subjects were given oral and written instructions on collecting the samples. The overall study included 1036 men of whom about 500 agreed to a 24 hour urine collection. Two hundred and ninety three samples were returned, 59% of which gave creatinine excretion levels within the normal range of the evaluating laboratory. Analysis using generalised linear models showed no significant relation between either the presence or the magnitude of AR to methacholine and 24 hour urinary Na excretion. Although there was poor compliance in supplying urine samples, we can detect no obvious bias to our findings, which do not support the hypothesis that a high intake of dietary salt may be implicated in causing asthma.

PD <sub>20</sub> ( $\mu$ g)	n	Na excretion (mmol/24 h)	
		Mean	(95% CI)
< 200	43	176.7	(156.7-196.7)
200-1000	62	162.7	(144.7-180.7)
1001-6400	77	191.4	(172.7-210.1)
> 6400	109	181.1	(169.0-193.2)

### Molecular genetic analysis shows *Pneumocystis carinii* is closely related to the ustomycetous red yeast fungi

AE WAKEFIELD, JM HOPKIN *Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford* The source of infection of *Pneumocystis carinii*, the major cause of potentially fatal pneumonia in the immunosuppressed, is unknown but animal experiments suggest airborne transmission of infection. Recent data question current opinion that *Pneumocystis carinii* pneumonia results from the reactivation of latent infection acquired during childhood. Progress on the understanding of the epidemiology of this infection has been hampered by the lack of an effective in vitro means of propagation of the parasite. As an alternative strategy we have cloned seven contiguous mitochondrial genes from *Pneumocystis carinii*. We show that *Pneumocystis carinii* can be unequivocally assigned to the fungal kingdom and that organisms infecting different mammalian hosts are genetically distinct. Using DNA amplification we have screened a wide range of organisms representing the major orders of the fungal kingdom. We show that *Pneumocystis carinii* is closely related to the ustomycetous red yeast fungi, a group which includes organisms that are extensively distributed throughout the environment and which release many widely dispersed airborne spores. These observations suggest that *Pneumocystis carinii* pneumonia in the immunosuppressed may result from freshly acquired infection from an environmental source.

### Absence of latent *Pneumocystis carinii* infection in post-mortem lung samples

SE PETERS, AE WAKEFIELD, PR MILLARD, JM HOPKIN *Institute of Molecular Medicine, University of Oxford and Department of Pathology, John Radcliffe Hospital, Oxford* The epidemiology of infection by the opportunistic fungal pathogen *Pneumocystis carinii* has not been satisfactorily clarified. Of particular importance is whether pneumonia in the immunosuppressed develops, by analogy with tuberculosis, as a reactivation of dormant pulmonary infection or by a fresh infection. We have developed oligonucleotide primers which, in the polymerase chain reaction, specifically amplify a portion of the *Pneumocystis carinii* mitochondrial gene encoding the ribosomal RNA. In calibration experiments using this technique, we show that the

method can detect *Pneumocystis carinii* to a lower limit of one to two organisms. We have conducted, using DNA amplification, a search for *Pneumocystis carinii* in postmortem lung samples from 15 non-immunosuppressed subjects, age at death 15–70 years. No *Pneumocystis carinii* DNA was detectable in triplicate amplification reactions from 45 (3 × 15) 1g samples. Amplification of DNA for the human anti-thrombin gene (a positive control for PCR conditions) occurred efficiently in each sample. *Pneumocystis carinii* is not detectable in non-immunosuppressed human lungs; the finding suggests that pneumonia in the immunosuppressed arises as a result of fresh infection.

#### Subclinical *Pneumocystis carinii* (PC) detected at routine bronchoscopy in a proportion of patients with small cell lung cancer

SP MATUSIEWICZ, RJ FERGUSSON, AP GREENING, GK CROMPTON, S BURNS *Respiratory Unit, Western General Hospital and Virology Department, City Hospital, Edinburgh, Scotland* Traditionally, PC has been regarded as a commensal protozoal agent becoming pathogenic when allowed to proliferate in the immunocompromised patient. Recent evidence, however, suggests PC is of fungal origin and there are few data to show the presence of PC in the lungs of the immunocompetent. We have tested for PC in BAL fluid or bronchial washings (BW) or patients undergoing routine diagnostic or research bronchoscopy. BAL fluid (10 ml) or BW were analysed for PC by fluorescent antibody test (FAT; GENETIC SYSTEMS CORP, SEATTLE). HIV positive patients or those on immunosuppressive therapy were excluded. One hundred and ten unselected stored and 110 sequential prospective samples were analysed (patients; mean age 61; 134 men: diagnoses: healthy volunteers/no active disease 40, asthma/COPD 18, bronchial carcinoma 128, interstitial lung disease 16, infection/pneumonia 18). A total of 5/220 (three BAL, two BW) were FAT positive. All had small cell lung cancer (5/26 SCLC). None had clinical or radiographic appearances to suggest PCP. One patient had received chemotherapy three months previously. One had ectopic ACTH production. *Pneumocystis carinii* was not identified in BAL fluid or BW from a large number of normal subjects or patients with various chest diseases except for a proportion (20%) of patients with SCLC. We suggest PC is not a normal commensal organism. Testing BAL fluid of all patients with suspected lung cancer at bronchoscopy may be of benefit for those who subsequently require cancer chemotherapy.

#### DNA amplification for *Pneumocystis carinii* from a saline mouth rinse

AE WAKEFIELD, RF MILLER, LA GUIVER, JM HOPKIN *Institute of Molecular Medicine, John Radcliffe Hospital, Oxford and Department of Medicine, UCMSM, Middlesex Hospital, London* We have developed a highly sensitive and specific diagnostic technique for human *Pneumocystis carinii* using the polymerase chain reaction (PCR) to amplify a portion of the *Pneumocystis carinii* using the polymerase chain reaction (PCR) to amplify a portion of the *Pneumocystis carinii* mitochondrial gene encoding ribosomal RNA. In bronchoscopic lavage and induced sputum from AIDS subjects, the method offers a diagnostic sensitivity and specificity of 98% for clinical pneumocystis pneumonia. We have applied the method now to fluid expectorated from an early morning mouth and throat rinse with 10 ml normal saline in 30 patients with AIDS. The results were compared with silver stain microscopy for *Pneumocystis carinii* on subsequent bronchoscopic alveolar lavage. Of the 19 patients with *Pneumocystis carinii* specific DNA amplification product of 346 base pairs was detected in the mouth rinse by ethidium bromide staining (sensitivity > 100 organisms) in nine patients, and by oligohybridisation alone (sensitivity one to two organisms) in a further five patients—a diagnostic rate of 73% (14 of 19). All the patients without pneumocystis pneumonia (negative silver stain on lavage) were negative by PCR on mouth rinse. Diagnostic PCR for *Pneumocystis carinii* can usefully be applied to the simple sample of saline mouth rinse.

#### A qualitative and quantitative comparison of the polymerase chain reaction and immunofluorescence for diagnosing *Pneumocystis carinii* pneumonia in AIDS patients

TR LEIGH, BG GAZZARD, A ROWBOTTOM, JV COLLINS *Westminster Hospital, London, and Brompton Hospital, London* Immunofluorescence staining, the most sensitive stain for the detection of *Pneumocystis carinii* in AIDS patients, frequently gives equivocal results with

fewer than five cysts per slide. DNA amplification by the polymerase chain reaction (PCR) has recently been shown to be more sensitive than immunofluorescence (IF) for the detection of *P carinii* (Leigh *et al. BTS* July 1991), but a quantitative comparison of the two techniques has not been made. We set out to compare IF with PCR with bronchoalveolar lavage (BAL) specimens from symptomatic AIDS patients, and to estimate quantitatively their relative sensitivities. Over a three month period, 28 BAL specimens were analysed from AIDS patients undergoing investigation for suspected *P carinii* pneumonia. All patients had previously been *P carinii* negative by IF on sputum induction. Specimens were examined for *P carinii* by IF (Northumbria Biologicals) and by PCR (Wakefield *et al. Lancet* 1990;336:451). *P carinii* specific PCR products were shown by gel electrophoresis (GEL), and by Southern hybridisation with a <sup>32</sup>P end labelled oligonucleotide probe (BLOT), which gives a further 100 fold increase in sensitivity over the GEL result. Specimens unequivocally positive by IF were also used for a quantitative comparison of IF with PCR. Serial (powers of 10) dilutions of the DNA template from these specimens were each amplified by PCR, and PCR products examined for *P carinii* by gel electrophoresis. Twenty of the 28 specimens were negative for *P carinii* by IF. Two of these 20 were BLOT positive alone, the remaining 18 were GEL + BLOT negative. Of the remaining eight specimens, four were equivocally positive and four unequivocally positive by IF. Of the four patients with equivocal IF results, three were GEL + BLOT negative, and one, who almost certainly had *P carinii* pneumonia clinically, was solely BLOT positive after receiving two days of anti-pneumocystis chemotherapy before the BAL. Of the four unequivocal results, three were GEL + BLOT positive, and one was GEL + BLOT negative. This patient, who almost certainly had *P carinii* pneumonia on clinical grounds, had received nine days of anti-pneumocystis treatment before the BAL. Of the 28 patients, all survived apart from one GEL + BLOT positive patient. Dilutions of the three GEL + BLOT positive specimens gave positive GEL results down to dilutions of 10<sup>-4</sup>, 10<sup>-5</sup>, and 10<sup>-6</sup>. In conclusion, false positive results may occur with IF. We estimate PCR to be 10<sup>4</sup>–10<sup>6</sup> times as sensitive as IF. PCR results may become negative rapidly after the start of antipneumocystis chemotherapy, and may therefore be a useful measure of organism viability.

#### Atypical *Pneumocystis carinii* pneumonia

NM FOLEY, M GRIFFITHS, RF MILLER *Department of Medicine, UCMSM, Middlesex Hospital, London* *Pneumocystis carinii* pneumonia (PCP) remains the most common pulmonary opportunistic infection in patients infected with the human immunodeficiency virus (HIV). We have studied the incidence and mode of presentation of PCP that was clinically or histologically atypical in a cohort of patients with the acquired immunodeficiency syndrome (AIDS). During the period July 1989 to December 1991, we treated 138 patients for PCP. Of these, 11 (8%) had atypical disease. All patients were caucasian men (10 homosexual), who had been diagnosed HIV antibody positive (mean 41 months previously) and their median age was 45 y. Seven patients had a history of AIDS related illnesses including previous PCP in two. Six patients were taking no PCP prophylaxis at the time of presentation, four were receiving nebulised pentamidine and one patient weekly Fansidar. Presenting symptoms were fever, cough, and dyspnoea in most cases. In seven patients atypical radiographic abnormalities were present: cavitation and upper lobe infiltrates in four, a solitary mass lesion in two, pulmonary nodules and consolidation in one. The diagnosis of PCP was made by bronchoalveolar lavage (BAL) in two patients, open lung biopsy (six patients), and computed tomographic guided needle biopsy (one patient). All seven of the patients biopsied had negative BAL. Diagnosis was made at postmortem examination in the remaining two cases, one of whom had been treated for PCP but was too sick to undergo bronchoscopy and the other who had not been diagnosed before death. Histology showed *Pneumocystis carinii* by silver staining in all nine patients. Four patients had a granulomatous response, two pneumocystomas, one obliterative bronchiolitis and a plasma cell infiltrate, and one patient had diffuse pulmonary haemorrhage. Special stains and culture did not show other pathogens such as acid fast bacilli, fungi, bacteria, or viruses in any patient. With treatment, eight patients survived. Of the three patients who died, two had rapidly progressive respiratory failure and did not respond to specific anti-pneumocystis treatment. Atypical PCP remains an uncommon but clinically significant problem in patients with AIDS and may be the AIDS defining illness in patients who have not been on anti-PCP prophylaxis.

### Sustained maximum voluntary ventilation causes diaphragm fatigue

S WRAGG, R AQUILINA, J MORAN, C HAMNEGARD, M GREEN, J MOXHAM *Kings College, and Royal Brompton Hospitals, London* When highly motivated normal subjects perform maximal voluntary ventilation there is a fall to roughly 70% of initial values within two min. The importance of respiratory muscle fatigue in the decline of ventilation is not clear. The slowing of maximum relaxation rate (MRR) suggests the respiratory muscles are excessively loaded (Mulvey *et al. J Appl Physiol* 1991;70:2173). We measured transdiaphragmatic twitch pressures (Pdi) before and after two minutes isocapnic maximum voluntary ventilation (MVV) in six normal subjects. The phrenic nerve roots were magnetically stimulated by a magstim 200 with the neck flexed and the coil placed over C6. Initial MVV was 157.2 l/min (range 116–211) falling by 36% (range 19–51) at 2 min. After MVV sniff MRR was reduced by 30.6% (range 15.7–51;  $p < 0.01$ ). After MVV there was a sustained reduction of twitch Pdi that at 20 minutes was reduced by 25.1% (range 16.4%–36.3%;  $p < 0.01$ ). During control studies subjects were investigated with the same protocol but omitting MVV. Twitch Pdi was not reduced. We conclude that maximum voluntary ventilation in humans causes peripheral diaphragm fatigue. Diaphragmatic fatigue may be a factor limiting maximum voluntary ventilation and could contribute to acute ventilatory failure in patients.

### Right ventricular hypertrophy in chronically hypoxic rats is associated with increased IGF-1 gene expression

RM LEACH, DL RUSSELL-JONES, CR THOMAS, IR CAMERON, JPT WARD *Divisions of Medicine, Endocrinology, and Chemical Pathology, UMDS (St Thomas Campus), London* Increased insulin-like growth factor (IGF-1) gene expression is associated with work induced skeletal muscle growth (De Vol *et al. Am J Physiol* 1990;259:E89). The mechanism of right ventricular hypertrophy and pulmonary vascular remodelling in response to prolonged alveolar hypoxia has not been established but may involve the release of locally produced growth factors (Vender *et al. Am Rev Respir Dis* 1987;135:622). In this study northern blot analysis was used to determine the expression of IGF-1 mRNA in cardiac tissue from controls (C,  $n = 7$ ) and chronically hypoxic (H,  $n = 8$ ) rats. Weight matched male CSE rats (224 (7) g) were maintained in two identical normobaric environmental chambers breathing either air or 10% oxygen. After five weeks the rats were killed, the hearts dissected, weighed, and snap frozen. Weight gain was less in hypoxic (67.5 (10) g) than in control (107 (14.3) g,  $p < 0.05$ ) rats. Right ventricular weight was greater in hypoxic than control rats (H = 0.37 (0.02) g, C = 0.26 (0.01) g;  $p < 0.01$ ) but the left ventricular weight did not differ between the two groups (H = 0.8 (0.04) g, C = 0.9 (0.04) g). Concentrations of IGF-1 mRNA were determined by laser densitometric analysis of the autoradiograph of the 0.7–1.8 Kb transcripts on northern blots of total RNA extracts, probed with  $^{32}P$  labelled cDNA for rat IGF-1. Laser densitometric values were expressed as the ratio of right ventricle/left ventricle for each rat. This ratio was significantly higher in chronically hypoxic (1.34 (0.2)) than in control (0.72 (0.07);  $p < 0.02$ ) rats. These results show that IGF-1 mRNA expression is increased in the right ventricles of chronically hypoxic rats, and imply that IGF-1 may play a part in cardiac hypertrophy under these conditions.

### Effect of ambulatory oxygen treatment on symptoms and exercise capacity in chronic heart failure

LJ RESTRICK, SW DAVIES, L NOONE, JA WEDZICHA *Departments of Thoracic Medicine and Cardiology, London Chest Hospital, London* Ambulatory oxygen treatment reduces breathlessness and improves exercise tolerance in patients with chronic lung disease. It is not known whether it is of benefit in patients with chronic heart failure (CHF). We therefore assessed the effect of portable oxygen treatment on exercise tolerance and arterial oxygen saturation ( $SaO_2$ ) during both six minute walking tests and endurance walks in 12 patients with stable CHF. The median age of patients (11 men, one woman) was 64.5 (range 28–74) y; All had Grade III New York Heart Association CHF (nine due to coronary artery disease, two mitral regurgitation, and one dilated cardiomyopathy). Respiratory disease was excluded clinically and by spirometry; mean (SD) FEV<sub>1</sub> 2.4 (0.6) l, mean  $PaO_2$  11.8 (1.5) kPa. The mean (SD)  $Vo_2$  max was 14.6 (3.8) ml/min/kg. Standard protocols for assessment of ambulatory oxygen were used with randomisation of the order of walks and blinding of the observer, and subject as to the gas content of the portable cylinder (air or  $O_2$  at 2 l and 4 l/min). Median baseline six minute walking distance was 250 (90–

450) m. The mean (SD)  $SaO_2$  fell significantly from 94.4 (3.7)% at rest to a minimum of 90.1 (6.1)% on exercise ( $p = 0.014$ ; CI 1.1%–7.6%). Ambulatory oxygen at 2 l/min only increased mean resting  $SaO_2$  to 96.5 (3.0)% ( $p = 0.081$ ) and minimum  $SaO_2$  on exercise to 91.2 (4.9)% ( $p = 0.402$ ) and had no effect on six minute distance walked or breathlessness assessed by visual analogue and Borg scales. Median endurance walk distance was 275 (19–2690) m, with  $SaO_2$  falling from 94.5 (2.7)% to a minimum of 88.0 (8.8)% ( $p = 0.037$ ; CI 0.5%–12.4%). Oxygen at 4 l/min significantly increased the minimum  $SaO_2$  on exercise to 93.5 (4.7)% ( $p = 0.030$ ; CI 0.7–10.3%) and reduced breathlessness, but had no effect on endurance distance walked. Supplementary oxygen at 2 l/min during endurance walking only raised the minimum exercise  $SaO_2$  to 92.1 (4.9)% ( $p = 0.124$ ; CI –1.3–+9.6%). Ambulatory oxygen at 2 l/min is not of clinical benefit in patients with CHF and during endurance walking was insufficient to correct  $SaO_2$ . Higher flow rates of oxygen may be more effective in preventing arterial oxygen desaturation on exercise and reducing dyspnoea but are of less practical value because of the limited capacity of the small oxygen cylinders currently available.

### Nasal ventilation v doxapram in the treatment of type II respiratory failure complicating chronic airflow obstruction

AH AHMED, L FENWICK, RM ANGUS, AJ PEACOCK *Department of Respiratory Medicine, Western Infirmary and Gartnavel General Hospital, Glasgow* Type II respiratory failure ( $PaO_2 < 8$  kPa;  $Paco_2 > 6.7$  kPa) complicating chronic airflow obstruction (CAO) remains a significant cause of death. In a study of patients with CAO admitted to our hospital group in one year with this condition 23% died (Angus *et al. Thorax* 1991;46:764P). Short of full mechanical ventilation the only supportive treatment available until recently has been intravenous doxapram. This drives respiration but does not improve lung function. Nasal intermittent positive pressure ventilation (NIPPV) is a new bedside treatment for type II respiratory failure. In several studies, NIPPV has been shown to improve arterial blood gases (ABGs) in these patients. We therefore compared NIPPV to doxapram in a group of similar patients. Each new admission with acute type II respiratory failure was randomised to receive either doxapram IV or NIPPV through a pressure cycled ventilator (Ventimate: Thomas Respiratory systems, London). We studied 11 patients (five men, mean (SEM) age 63 (2) y and FEV<sub>1</sub> = 0.7 (0.1) l). Blood gases were taken breathing oxygen (1–3 l/min by nasal cannulae) and 1, 2, 3, and 4 hours after the start of doxapram or NIPPV. Oxygen treatment was continued at the same rate as before randomisation. After the period of study patients continued on the randomised form of respiratory support. Changes in arterial blood gases (ABG) during the four hour monitoring period are shown expressed as mean (SEM) kPa (see table). The improvements in ABGs with intervention were significant and maintained except in the doxapram group where at four hours the  $Paco_2$  was unchanged. In the subsequent 24 hours three patients died in the doxapram group so we changed the protocol such that any patient deteriorating in one arm was switched at four hours to the other. Two patients were switched from doxapram to NIPPV, but no patient from NIPPV to doxapram. These two patients showed mean improvements in  $PaO_2$  from 7.62 kPa to 11.25 kPa and  $Paco_2$  from 8.7 kPa to 8.3 kPa. We conclude that NIPPV is a useful non-invasive treatment for type II respiratory failure complicating CAO. It may be more effective and may be safer than doxapram.

	Doxapram (n = 5)			NIPPV (n = 6)		
	Baseline	Best achieved	4 h	Baseline	Best achieved	4 h
$PaO_2$	5.3 (0.5)	7.2 (0.6)*	6.7 (0.7)*	5.3 (0.3)	8.8 (0.8)*	8.4 (0.7)*
$PaCO_2$	9.9 (0.9)	8.7 (0.7)*	9.8 (0.9)	9.8 (0.5)	8.6 (0.4)*	8.3 (0.4)*

\*Gases are significantly different from baseline:  $p < 0.05$ .

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### The role of expiratory positive airway pressure (EPAP) during nasal ventilation

MW ELLIOTT, R AQUILINA, AK SIMONDS *Royal Brompton National Heart and Lung Hospital, London* The effects of expiratory positive airway pressure during nocturnal nasal ventilation have been examined in 15 patients with nocturnal hypoventilation. Eight patients had chronic obstructive pulmonary disease (COPD) (mean (SD) FEV<sub>1</sub> 700 (72) ml, diurnal  $PO_2$  6.7 (1.6) kPa,  $Pco_2$  7.9 (1.7) kPa), and seven had primary neuromusculoskeletal disorders (mean (SD)

forced vital capacity 1090 (214) ml, diurnal  $P_{O_2}$  9.1 (0.6) kPa,  $P_{CO_2}$  6.8 (0.9) kPa). Polysomnography was carried out on two occasions with patients receiving inspiratory positive airway pressure (IPAP) on one night and IPAP + (expiratory positive airway pressure) (EPAP) on the other night in random order through a BiPAP ventilator (Respironics, Inc) in spontaneous or timed mode. The IPAP was set at near maximum (mean 19.4 cm  $H_2O$ ). End expiratory oesophageal pressure (EEPoes) was measured as an index of intrinsic positive end expiratory pressure in 12/15 subjects, and EPAP level matched to EEPoes value. In patients with no significant EEPoes, EPAP was set at 5 cm  $H_2O$ . Nocturnal mean (SD) minimum arterial oxygen saturation (min  $SO_2$ ) and maximum transcutaneous  $CO_2$  (max  $T_{CCO_2}$ ) improved on IPAP/EPAP compared with IPAP alone in the neuromusculoskeletal group (min  $SO_2$  83.6 (4.2)% v 77.7 (6.7)%,  $p < 0.05$ ; max  $T_{CCO_2}$  7.3 (0.9) kPa v 8.1 (1.4),  $p < 0.05$ ). Overall there was no change on IPAP v IPAP/EPAP in the COPD group, although 3/8 patients did show improvement in min  $SO_2$  or max  $T_{CCO_2}$  or both with the application of EPAP. Total sleep time, percentage rapid eye movement time, and sleep efficiency did not differ significantly on IPAP and IPAP/EPAP nights. Patients receiving EPAP of 5 cm  $H_2O$  ( $n = 10$ ) showed improvement in nocturnal arterial blood gas control, whereas the five subjects receiving higher levels of EPAP (6–12 cm  $H_2O$ ) showed no significant change over IPAP alone. In conclusion, EPAP can be helpful in patients with neuromusculoskeletal disorders and in selected patients with COPD. High levels of EPAP (> 5 cm  $H_2O$ ) may offset any beneficial effects on functional residual capacity by increasing expiratory muscle load or reducing effective IPAP or both especially in patients with severe airflow obstruction.

#### Nasal intermittent positive pressure ventilation: assessment and comparison of volume and pressure preset ventilator systems in chronic respiratory failure

DJ MEECHAM JONES, G BRAID, JA WEDZICHA *Department of Thoracic Medicine, Royal Brompton Hospital, London* Nasal intermittent positive pressure ventilation (NIPPV) has been widely used for domiciliary ventilatory support in patients with chronic respiratory disease and for treating patients with acute on chronic respiratory failure. Although originally volume preset equipment was considered appropriate for NIPPV, pressure preset ventilators may have advantages in adjusting for nasal mask leaks, although no formal comparison is available. We have assessed four different nasal positive pressure ventilators (2 volume preset—Brompton Pac (pneuPAC (UK) Ltd) and Monnal D; 2 pressure preset—Respironics BiPAP and NIPPY (Thomas systems)). Eight patients mean age 60 (range 48–71) y, with chronic respiratory disease (six with chronic airflow obstruction (CAO) and two with thoracoplasties) were studied; mean (SD)  $P_{aO_2}$  7.16 (0.21) kPa,  $P_{aCO_2}$  7.02 (0.35) kPa, FEV<sub>1</sub> 0.76 (0.24) l, FVC 1.58 (0.49) l. All patients had previously used NIPPV, either for domiciliary ventilatory support or during acute admissions to hospital. Each patient was initially acclimatised to each ventilator on the first day but no recordings were taken. After this the patients were all established on each ventilator for a two hour period, with blood gases taken at the start and end of ventilation. Visual analogue scale scores (VAS) and a patient questionnaire about the acceptability of the equipment were given. There were significant changes in blood gases with each ventilator—mean change (95% CI); BiPAP  $P_{aO_2}$  + 1.52 (0.95–2.09) kPa,  $P_{aCO_2}$  – 1.04 (1.55–0.54) kPa; NIPPY  $P_{aO_2}$  + 1.63 (0.85–2.41) kPa,  $P_{aCO_2}$  – 1.1 (1.86–0.34) kPa; Brompton PAC  $P_{aO_2}$  + 1.22 (0.75–1.67) kPa,  $P_{aCO_2}$  – 1.14 (1.52–0.76) kPa; Monnal D  $P_{aO_2}$  + 1.14 (0.42–1.84) kPa,  $P_{aCO_2}$  – 1.19 (2.14–0.23) kPa. Analysis of variance showed no significant difference between ventilators in the blood gas changes achieved; VAS scores showed no differences between pressure and volume preset ventilators, but there were individual variations in acceptability. All nasal ventilators studied delivered satisfactory levels of ventilation and proved to be acceptable. There were no significant differences in the efficacy of the volume or pressure preset equipment in these stable patients studied with chronic respiratory disease.

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#### The protective effects of subminimal inhibitory concentrations of antibiotics on non-typable *Haemophilus influenzae* (NTHi) infection of human respiratory epithelium in vitro

K TSANG, A RUTMAN, J BELCHER, D ROBERTS, PJ COLE, R WILSON *Host Defence Unit, National Heart and Lung Institute, Emmanuel Kaye Building London* Antibiotics penetrate poorly into mucus and so bacteria may only be exposed to subminimal inhibitory concentration (MIC) during treatment of bronchial infections. We have examined

the effects of 1/4 and 1/2 MIC amoxicillin, loracarbef, and ciprofloxacin on the interaction of a clinical isolate of NTHi with human adenoid tissue in organ culture. Pieces of human adenoid tissue (5 mm) were embedded in agar so that only the mucosal surface was exposed. Minimum essential medium containing NTHi with or without antibiotics was added to the organ cultures and incubated with 5%  $CO_2$  at 37°C for 24 hours. The organ cultures ( $n = 6$ ) were assessed for several variables by light (LM) and transmission electron microscopy (TEM). Bacterial viable counts after 24 hours were not significantly different in all organ cultures ( $4 \times 10^2$ – $8.2 \times 10^8$  cfu/ml). Compared with uninfected controls at 24 hours, NTHi infection caused significant ( $p < 0.05$ ) changes in LM assessment: slowing of cerebral blood flow, disruption of epithelium integrity, reduction in the amount of the epithelial surface that was ciliated; and in TEM assessment: extrusion of epithelial cells from the epithelial surface, loss of cilia from ciliated cells, cytoplasmic blebbing, and mitochondrial damage. In the presence of 1/4 and 1/2 MIC concentrations of antibiotic all these variables of mucosal damage were significantly reduced ( $p < 0.05$ ), but a dose-response effect was not shown. Bacteria were found associated with the mucosal surface in all sections (six of six) where there was no antibiotic present and less often (1/4 MIC six of 18, 1/2 MIC five of 18) in the presence of antibiotics. We conclude that in the presence of subMIC concentrations of amoxicillin, ciprofloxacin, and loracarbef, NTHi infection causes less functional cerebral blood flow change and less mucosal damage.

#### Interaction of fimbriate (F+) and non-fimbriate (F–) clinical isolates of non-typable *Haemophilus influenzae* (NTHi) with human respiratory tract mucus in vitro

W BARSUM, R WILSON, RC READ, A RUTMAN, P WEBB, HC TODD, PJ COLE *Host Defence Unit, Department of Thoracic Medicine and Department of Microbiology, Royal Brompton National Heart and Lung Institute, London* Adherence to mucus is the first interaction of inhaled bacteria with the respiratory mucosa. Fimbriae have been identified as one of the determinants of epithelial cell adherence but other adhesins are also involved. With a microtitre plate assay, we have previously shown that fimbriae of two laboratory strains of NTHi enhance adherence to sputum sol phase and to purified mucin and its constituent glycopeptides. Six fresh clinical isolates were found to be fimbriated by negative staining transmission electron microscopy and were stored in 20% glycerol broth in liquid nitrogen. The strains were passaged six times on agar at daily intervals, and were then found to be non-fimbriate. Microtitre plate wells were coated by overnight incubation with sol phase obtained by high speed centrifugation of sterile mucoid sputum from a patient with mucus hypersecretion. The F+/F– pairs of NTHi were cultured to mid-log phase, washed, then added to wells and incubated at 37°C for 30 minutes. Unbound bacteria were removed by flooding the wells with phosphate buffered saline. Bound bacteria were then desorbed by agitation with Tween 0.5% and quantified. Adherence index (AI) and specific adherence index (SAI) were calculated as  $X \times Z^{-1}$  and  $(X - Y) \times Z^{-1}$  respectively where  $X$  = number of bacteria desorbed from coated wells,  $Y$  = number of bacteria desorbed from uncoated wells (that is adherent to the plastic),  $Z$  = number from initial inoculum. Fimbriation was unchanged at the end of the experiment. For AI six out of six, and for SAI five out of six F+ clinical isolates were more adherent to sol phase than their respective F– partners ( $p < 0.05$ ,  $n = 6$  for each strain except one where  $n = 7$ , Wilcoxon rank). We conclude that fimbriation of clinical isolates of NTHi increases adherence to the sputum sol phase.

#### Experimental bronchiectasis producing potential of bacteria frequently isolated from purulent sputum of patients with bronchiectasis (Bx)

D GUERREIRO, H TODD, J ROHDE, M SHEPPARD, PJ COLE *Host Defence Unit and Department of Lung Pathology, Royal Brompton National Heart and Lung Institute, London* The ability of *Pseudomonas aeruginosa* (*P aer*), *Haemophilus influenzae* (*H infl*), and *Staphylococcus aureus* (*S aur*), frequent isolates from the sputum of patients with chronic bronchial sepsis, to produce Bx in an experimental model was compared. The rat apical lobe was partially ligated (LIG) and 10<sup>9</sup> bacteria from a single clinical bacterial isolate were injected into the bronchial lumen distal to the ligation. Three groups of rats ( $n = 5$ ) were prepared with either *P aer*, *H infl*, or *S aur*, and 12 control groups (normal; sham-operated; LIG alone; each of the three viable bacteria alone; each of the three bacteria killed: with and without LIG). Rats were killed from each group one, two and three months after surgery, the lungs inflated, apical lobes orientated, sectioned and stained with

Haematoxylin and eosin, periodic acid-Schiff's reagent alone, Alcian blue and periodic acid-Schiff's reagent, or Miller's elastin stain. Axial bronchus luminal diameter (mm), epithelial cell hyperplasia (per 1.5 mm), neutral and acid mucus-containing goblet cells, and stainable elastin were quantified in the apical lobe by standard point counting techniques. Severity of bronchiectatic changes was  $P_{aer} + LIG > H_{infl} + LIG > S_{aur} + LIG > controls$  at all time points. Data (SD) at three months were examined by Kruskal-Wallis analysis of variance. The Bx producing potential of these microbes in an experimental model parallels clinical experience in man.

Experimental group	Bronchial dilation (mm)	Epithelial hyperplasia (1.5 mm)	Goblet cells (%)	Bronchial elastin (%)
$P_{aer} + LIG$	2.53 (0.65) p < 0.0001	636.4 (26.7) p < 0.0001	77.9 (4.06) p < 0.0001	10.2 (0.3) NS
$H_{infl} + LIG$	0.99 (0.11) p < 0.0001	363.8 (6.9) pNS	59.1 (6.3) p < 0.0001	9.3 (2.0) p < 0.0001
$S_{aur} + LIG$	0.68 (0.06) NS	364.4 (52.3) p < 0.0001	41.6 (3.1) p < 0.0001	14.7 (1.1) p < 0.0001
Normal	0.62 (0.07)	79.2 (23.9)	27.0 (5.2)	23.2 (2.8)

### Survival in non-small cell lung cancer in relation to epidermal growth factor receptor expression

D VEALE, N KERR, GJ GIBSON, AL HARRIS *Department of Respiratory Medicine, Freeman Hospital, Newcastle upon Tyne and ICRF Cancer Research Unit, Oxford* Increased expression of epidermal growth factor receptor (EGFR) has been reported in non-small cell lung cancers (NSCLC) when compared to normal lungs. We have examined post-operative survival in 19 surgically treated patients with NSCLC who had full characterisation of EGFR on primary tumour membrane preparations. There were 10 squamous, seven adeno, and two large cell carcinomas. The median concentration of high affinity sites was 31 fmol per mg of protein (4–1532) and the median dissociation constant (Kd) of these high affinity sites was  $2.3 \times 10^{-10}$  per mol ( $1.2-30 \times 10^{-10}$ ). Seven patients survived over five years. Twelve patients died between 8.5 and 55 months from the time of surgery. When survivors were compared with non-survivors there was no difference as regards tumour size or stage, or age or sex. The survivors had a median concentration of high affinity EGFR sites of 16.1 fmol/mg protein compared with a median concentration of 68.6 fmol/mg protein in the non-survivors. All patients with EGFR concentration > 35 fmol/mg had died within five years, whereas seven out of 11 patients with EGFR < 35 were still alive after five years. Thus EGFR quantitation may give independent prognostic information in NSCLC and help to select patients for adjuvant therapy after surgery.

### Changes in neutrophil motility, shape and adhesiveness produced by a glucocorticoid induced peptide

RD STEVENSON, S CHETTIBI, AJ LAWRENCE *Respiratory Medicine, Glasgow Royal Infirmary and Cell Biology, Glasgow University* Previous studies by one of us (RDS) showed that glucocorticoid treated monocytes produce a peptide factor that stimulates the migration of human neutrophils using a capillary tube system. This effect correlated with the anti-inflammatory potency of the steroid and was also evident using leucocytes from steroid treated patients. We have further investigated this steroid activity using a computerised cell tracking system and cell adhesion assays. Human monocytes were cultured at  $4 \times 10^6$ /ml with and without  $10^{-6}$ M dexamethasone for 24 hours and the supernatants added to neutrophils in protein coated glass migration chambers. Steroid treated culture supernatants considerably increased the speed of locomotion of neutrophils compared with culture medium alone ( $15-16 \mu\text{m}/\text{min}$  v  $4-5 \mu\text{m}/\text{min}$ ). Neutrophil motility was slightly stimulated by control monocyte supernatants ( $7-8 \mu\text{m}/\text{min}$ ) but was unaffected by steroids alone. Steroid treated culture supernatants also induced increased neutrophil pseudopodia formation. Neutrophil adhesiveness to glass was reduced by 65% by steroid treated culture supernatants and was increased by 200% by control monocyte supernatants. There was no correlation between changes in motility and adhesiveness. Antibodies to lipocortins 1–6 and to interleukin 8, factors modulated by glucocorticoids, did not inhibit the effects of the steroid-induced factor. Colchicine ( $10^{-5}$ M) also stimulated neutrophil locomotion ( $11-12 \mu\text{m}/\text{min}$ ) and affected cell shape in the same way as the steroid induced factor. It is suggested that this factor may be an anti-inflammatory glucocorticoid mediator that acts by inhibiting microtubular function.

### Modulation of tracheobronchial clearance by inhaled bradykinin and [desArg9]-bradykinin in normal subjects

R POLOSA, A HASANI, D PAVIA, JE AGNEW, SW CLARKE, ST HOLGATE *Institute of Respiratory Diseases, University of Catania, Italy, Thoracic Medicine, Royal Free Hospital, London, Great Britain, and Medicine 1, University of Southampton* Kinins may have an important modulatory effect on mucociliary clearance in humans (Polosa *et al. Am Rev Respir Dis* 1991;143:A619) by interacting with specific surface receptors named as B1 and B2 receptors. The comparative effects of kinins on airways have been widely investigated in animals but not in humans. We therefore set out to look in more detail at the effects of inhaled bradykinin (Bk) and [des Arg9]-bradykinin (dA-Bk) on tracheobronchial clearance (TBC) of a group of normal subjects. Four healthy non-smokers attended the laboratory on three occasions separated by at least two weeks at the same time of the day to undertake TBC studies by a non-invasive radioisotopic method consisting of inhalation of polystyrene particles labelled with  $^{99m}\text{Tc}$ . These were followed by inhalations of Bk (8 mg/ml), dA-Bk (8 mg/ml), or vehicle placebo in a randomised, double blind manner. Regular whole lung counts were measured with two collimated scintillation counters and a TBC curve was plotted for each subject on each occasion. Baseline pulmonary function, inspiratory flow rates, alveolar depositions, and penetration indices were not significantly different on the three study days. Mucociliary clearance, expressed as the area under the tracheobronchial radionuclide retention curve calculated for the first six hours (AUC 0–6 hours), was significantly enhanced in all subjects after inhaled Bk. On the contrary dA-Bk exposure significantly prolonged TBC in all subjects when compared with placebo. The mean values (SEM) for AUC 0–6 hours were 92 (18)%/hours, 253 (43)%/hours and 120 (18)%/hours after Bk, dA-Bk and placebo administration respectively. The data of the present investigation indicate that in normal human airways Bk accelerates TBC whereas dA-Bk inhibits it. These findings suggest that kinins may have complex effects on mucociliary clearance in humans.

### Second messenger regulation of the isolated chloride current in human airway epithelium

DM STEEL, EFW ALTON, DM GEDDES *Ion Transport Laboratory, National Heart and Lung Institute, London* Studies have shown that the regulation of Cl<sup>-</sup> channels in cystic fibrosis is defective. To study the regulation of Cl<sup>-</sup> transport by the three principal second messenger pathways in human airways, bronchial epithelia from non-cystic patients were mounted in Ussing chambers of area 0.28 cm<sup>2</sup> under short circuit conditions. The basal Cl<sup>-</sup> current was isolated by the mucosal addition of phloridzin (200  $\mu\text{M}$ ), substitution of mucosal Na<sup>+</sup> with choline and serosal addition of acetazolamide (100  $\mu\text{M}$ ) to inhibit NA glucose cotransport, Na<sup>+</sup> absorption, and HCO<sub>3</sub><sup>-</sup> secretion respectively. Addition of a combination of forskolin (1  $\mu\text{M}$ ) and zardaverine (100  $\mu\text{M}$ , a phosphodiesterase inhibitor), to stimulate the protein kinase (PK) A pathway, significantly increased the short circuit current (Isc),  $4.2 (1.3) \mu\text{A}/\text{cm}^2$  (n = 6), compared with paired diluent controls. Similarly, stimulation of the Ca<sup>2+</sup> dependent pathway with the Ca<sup>2+</sup> ionophore A23187 (10  $\mu\text{M}$ ) increased the Isc by  $5.1 (1.9) \mu\text{A}/\text{cm}^2$  (n = 4). Stimulation of the PK C pathway with phorbol dibutyrate (10 nM), however, inhibited the Isc by  $2.3 \mu\text{A}/\text{cm}^2$  (n = 3). We conclude that activation of the PK A and Ca<sup>2+</sup>-dependent pathways stimulates the isolated Cl<sup>-</sup> current whereas the PK C pathway is predominantly inhibitory in human airways.

### Passive smoking does not change lung permeability acutely

DH YATES, K HAVILL, J CHU, A GLANVILLE *Respiratory Unit and Department of Nuclear Medicine, Concord Hospital, Sydney, New South Wales Australia* Active smokers have significantly increased whole lung epithelial permeability but the effect of passive smoke inhalation has not been reported. Accordingly, we measured the half life (T1) clearance of an aerosol of  $^{99m}\text{Tc}$  diethylene pentacetic acid (TcDTPA) from lung to blood in 16 normal patients (American Thoracic Society criteria) two days before and immediately after a one hour passive smoke exposure. Cigarette smoke was generated mechanically to raise ambient CO concentrations with the challenge chamber from 0 (SD1) ppm (control day) to 22 (SD6) ppm (smoke day) (p < 0.001) equivalent to concentrations obtained in social settings. Spirometry, lung volumes, and KCo were measured before each period in the challenge chamber and after each TcDTPA scan. Passive

smoking did not cause a significant change in any lung function variable. Mean half life TcDTPA clearance rose from 71 (SD15) minutes to 79 (SD17) minutes after passive smoke exposure but this change is within the reproducibility of the test. We conclude that lung epithelial permeability is not increased immediately after one hour of short term passive exposure to smoke, when measured within 30 minutes of cessation of exposure.

### Interaction between current smoking, leanness, and physical inactivity in the prediction of hip fracture

L FORSÉN, K BJARTVEIT, A BJØRNDAL, T-H EDNA, J HOLMEN, V JESSEN, G WESTBERG *National Institute of Public Health, Geitmyrsveien 75, N-0462 Oslo, Norway and National Health Screening Service, Imherred Hospital and Namdal Hospital* Several studies show that smoking is associated with the incidence of hip fracture but none of them show that the effect of smoking varies with body mass index and physical activity, probably due to small data sets. We have analysed 38 356 adults older than 50 years of age who were screened in Nord-Trøndelag in 1984–6 (90% of those invited). Four hundred and twenty four had a hip fracture in the years 1986–9. In the Cox regression model the relative risk of a person suffering a hip fracture being a current smoker *v* a non-smoker was 2.3 for the physically inactive and 1.4 for the physically active. These results pertain to people with body mass index equal to 26 kg/m<sup>2</sup> (which is the mean body mass index for the population in this study). For thin people, however, the effect of smoking was much stronger. For thin people with body mass index below 18 the relative risk was more than 5 for the physically inactive and more than three for the physically active. Assuming the model to be valid for various hypothetical smoking prevalences in the future, We will be able to predict future incidence of hip fracture with and without smoking in the population.

### Passive smoke exposure in children

DG COOK, PH WHINCUP, O PAPACOSTA, DP STRACHAN, MJ JARVIS, A BRYANT *Department of Public Health Sciences, St George's Hospital, Medical School, London, Department of Public Health and Primary Care, Royal Free Hospital School of Medicine, London, ICRF Health Behaviour Unit, Institute of Psychiatry, and National Poisons Unit, New Cross Hospital* There is considerable interest in the health hazards of passive smoking in children. Cotinine, a metabolite of nicotine, is the biochemical marker of choice for quantifying recent exposure. We have examined the determinants of salivary cotinine in a sample of 3630 European children aged 5–7 from 10 towns in England and Wales. Cigarette smoke in the home was clearly the most important source of exposure, with average cotinine ranging from 0.30 ng/ml in non-smoking households to 5.40 ng/ml in households where the mother, father, and another smoked. People from outside the household who smoked and looked after a child for more than two hours per week were also an important source of exposure. There was clear evidence that other factors modify exposure. Cotinine concentrations fell with age from 1.08 ng/ml at age 5 to 0.78 ng/ml at age 7.5, were higher in manual workers than among non-manual workers (0.33 ng/ml in SC1, 2.08 ng/ml in SC5), were higher in towns with high adult respiratory mortality, and were slightly higher in girls than in boys (0.99 *v* 0.86 ng/ml). There was clear evidence of exposure among "non-exposed" children; 88% of children from non-smoking households and not looked after by a smoker had detectable cotinine, with 5% being in the top two fifths of the cotinine distribution. Moreover, similar trends in cotinine with age, social class, town, and sex were seen in this group. Cotinine in children not exposed at home or by a carer, was also related to the general level of parental smoking in their schools and towns of residence, emphasising the community nature of passive exposure to smoke in this age group.

### Nocturnal symptoms, morning symptoms, and night time inhaler use in patients with asthma

FH QUIRK, PW JONES *Division of Physiological Medicine, St George's Hospital Medical School, London* Patients with asthma may have nocturnal and early morning symptoms and use their inhalers at night. To examine inter-relationships between these measures of asthma severity, 49 asthmatic outpatients were studied. Their mean age was 46 (range 15–79), and their mean FEV<sub>1</sub> was 66% of predicted normal (range 22–116%). The mean duration of their disease was 16 years (range 1–48). They were asked to respond either yes or no to five items relating to nocturnal disturbance and early morning symptoms. These

were: item 1—"wake in the morning with wheeze or other chest symptoms" (yes 69% of patients); item 2—"wheeze worse in the morning" (yes 57%); item 3—"trouble getting to sleep" (yes 37%); item 4—"woken in the night by cough or breathing" (yes 55%); item 5—"need inhaler in the night" (yes 63%). With one exception, the responses to these items were intercorrelated (median  $r = 0.36$ , range 0.31–0.77,  $p < 0.05$ ). The exception was the absence of a significant correlation between items 2 and 3 ( $r = 0.23$ ). Principal components analysis with a varimax rotation was performed on the responses to the five items. Three factors were extracted with eigen values of 2.68, 1.0, and 0.66. These factors accounted for 0.54, 0.20, and 0.13 of the original variance respectively. The table gives the varimax orthogonal solution tabulated. The three identified factors were: night time symptoms, morning symptoms, and night time use of inhalers. We conclude that, whereas these measures of asthma severity are to a degree inter-related, they each reflect different aspects of the disease. In particular, nocturnal inhaler use may not be a reliable reflection of the severity of night or early morning asthma.

Item	Factor 1	Factor 2	Factor 3
1	0.90	0.28	0.08
2	0.91	0.08	0.26
3	0.08	0.88	0.15
4	0.26	0.82	0.16
5	0.22	0.23	0.94

### Acute asthma management: audit after feedback and guidelines

D BELL, A LAYTON *Department of Thoracic Medicine, Central Middlesex NHS Trust, London* Audit has confirmed deficiencies in overall asthma management but more recently has shown evidence of improvement (Bucknall *et al. Qual Health Care* 1992;1:15; Lim *et al. R Coll Phys* 1992;26:71). We have analysed a random systematic sample of 114 acute asthma adult admissions over a three year period (April 1988–March 1991) covering the introduction of hospital audit; local asthma, and British Thoracic Society guidelines; and feedback of results. The best recorded severity measures on admission are pulse (100%) and PEF (97%) 109/112. Chest physicians (CPs) tended to record other severity measures: paradox (71% *v* 54%, NS); difficulty speaking (63% *v* 72%, NS); arterial blood gases (78% *v* 74%, NS); K<sup>+</sup> (82% *v* 59%,  $p = 0.016$ ) more often than non-chest physicians (NCPs). Over the three year period arterial blood gases were measured significantly more often by both CPs and NCPs ( $p = 0.0001$ ). Immediate therapy (nebulised  $\beta_2$  agonists, ipratropium, and steroids) is given more frequently by CPs but is only significant for steroids ( $p = 0.035$ ). About a third of patients still do not receive systemic steroids within one hour of arrival at hospital. For these 33% of patients the median delay in steroid treatment remains 5 hours and has not improved. There was a tendency for increased immediate use of ipratropium and a general reduction in the use of antibiotics. A pre-discharge plateau of PEF and reduction of "morning dips" was achieved in about 50% of cases and documentation of inhaler techniques remains poor. The NCPs have increased their referral rate for chest follow up. Local audit is needed to identify local needs. Severity measures assessed by nurses are better recorded than those performed by doctors. Although CPs in general perform better than NCPs in asthma management the NCPs in our hospital have in general shown improvement after the introduction of audit, guidelines, and feedback. This suggests we are closer to closing the feedback loop but there are no grounds for complacency and the increase in the emergency use of ipratropium without an increase in systemic steroids confirms that underuse of steroids remains a problem.

### Long term follow up of pleuroperitoneal shunts for malignant pleural effusion

PS WONG, V TSANG, D KAPLAN, P GOLDSTRAW *The Royal Brompton Hospital, London* Survival is short in patients with recurrent malignant pleural effusion. Pleuroperitoneal shunts provide effective palliation in patients in whom a cortex limits lung expansion and pleurodesis would fail. It is important to recognise this situation as a shunt avoids repeated stays in hospital for thoracocentesis and the attendant risks of empyema. Since 1986 we have implanted 42 Denver pleuroperitoneal shunts in 40 patients with malignant effusion unsuitable for pleurodesis. There were 21 men and 19 women with a mean age of 60 (37–85). Thirty eight patients required multiple thoracocentesis, one as many as nine times. Twelve patients had failed attempts at medical pleurodesis. All shunts were inserted under

general anaesthesia. One patient had a concomitant peritoneovenous shunt insertion and one the creation of a pericardial window. There was no operative mortality. The mean hospital stay was 6.3 days (range 2–21 days). Short term morbidity included two patients with surgical emphysema and one patient requiring ventilatory support. Mean follow up was 8.3 months (range 0.1–48 months). There was good symptomatic relief in all patients. Mean survival was 6.8 months (range 2–23 months). Six patients (15%) developed shunt complications requiring nine surgical procedures. They included revision of the existing shunt in three patients, replacement of the shunt in two patients, and in four, it was necessary to remove the shunt for infection and establish open drainage. Only one patient developed symptomatic peritoneal deposits. In another, peritoneal deposits were found at postmortem examination.

### Bronchial carcinoma, airflow obstruction, and breathlessness

J CONGLETON, MF MUERS *Respiratory Unit, Killingbeck Hospital, Leeds* Breathlessness is a common symptom in patients with primary bronchial carcinoma and is often not well controlled. Most patients have a significant smoking history and therefore potentially co-existing chronic obstructive pulmonary disease of which airflow obstruction (AFO) is a feature. The incidence of AFO in bronchial carcinoma, its relation to breathlessness, and response to bronchodilator therapy was examined. All patients with bronchial carcinoma diagnosed in the preceding six months who were attending our outpatient clinic were assessed. Spirometry was performed and breathlessness rated. Those with AFO and significant breathlessness were offered a trial of bronchodilator therapy. The response to regular inhaled Duvent via a spacing device, and to nebulised salbutamol and ipratropium bromide (each over a two week period), was assessed by improvement in peak flow, spirometry, and symptom impact scores. Of the 40 patients with bronchial carcinoma 16 (40%) had AFO. Only two of these were taking bronchodilator therapy. Of the 14 patients with significant breathlessness 12 had AFO. There was no significant difference in the mean age, time from diagnosis, tumour site (central, large airway, peripheral), or smoking history (pack-years) between the groups with and without AFO. There were more adenocarcinomas present in the group with AFO (5/16 v 0/20). Eleven patients had a trial of bronchodilator therapy. This gave subjective benefit in eight, and of these five had objective benefit with increase in peak flow or FEV<sub>1</sub> of >15%. There was no significant additional benefit from nebulised drugs in most patients. There was no significant increase in breathlessness scores. We conclude that untreated AFO is commonly present in patients with bronchial carcinoma, is more common in patients with breathlessness, and that these patients may benefit from appropriate treatment.

### Gas mixtures for estimated CO transfer factor

AH KENDRICK *Respiratory Department, Bristol Royal Infirmary, Bristol* The American Thoracic Society recommends that the magnitude of each component of the CO transfer factor mixture (TLCO) should be 0.25%–0.35% CO, 10%–14% Helium (He) 17%–21% O<sub>2</sub>, and as balance, nitrogen. The recommended inspired O<sub>2</sub> (FIO<sub>2</sub>) in North America is 21%, whereas in Europe it is 18%. The FIO<sub>2</sub> influences the alveolar O<sub>2</sub> (PAO<sub>2</sub>) and hence CO uptake. TLCO increases by 0.35%/mm Hg decrease in PAO<sub>2</sub> (Kanner, Crapo. *Am Rev Respir Dis* 1986;133:676). To standardise the TLCO calculations, either a known FIO<sub>2</sub> should be used, or TLCO corrected to a standard FIO<sub>2</sub>. A questionnaire was sent to 185 respiratory units in the United Kingdom requesting information on (1) the mixture used, (2) whether "medical quality" gas was ordered, and (3) the satisfaction with supplier service. 106 units replied. Most units used the single breath, breath holding method. Seventeen mixtures were ordered for this method, 12 for Morgan and five for Jaeger/Inmed equipment. One unit made up their mixture, whereas another also used the single breath exhalation method. FIO<sub>2</sub> ranged from 17.94% to 25%, giving a wide variation in PAO<sub>2</sub>. Forty seven units ordered a specific FIO<sub>2</sub>, the rest ordering "air" as balance. The cost/l of gas varied greatly, with the mixtures 14% He, 0.28% CO, balance air (17.9% O<sub>2</sub>), and 10% HE, 0.28% CO, balance air (18.8% O<sub>2</sub>) being cheapest. Ordering a specific FIO<sub>2</sub> increased the cost by up to 125%/l. Large cylinders of gas were up to 75%/l cheaper for the same mixture. The mixture for the exhalation method, containing methane and acetylene, was up to 185% more expensive/l than the cheapest mixture. Sixty seven units ordered "medical quality" gas and six assumed that this was supplied. Twenty nine (27%) were dissatisfied with their supplier due to (1) poor service, (2)

long delivery times, (3) costs, or (4) wrongly labelled cylinders. It is recommended that (1) two mixtures be available—(a) 14% He, 0.28% CO, balance air for Morgan equipment and (b) 10% He, 0.28% CO, balance air for Jaeger/Inmed/Chest equipment; (2) the mixture should be produced under a medical product licence.

### Investigation of microorganisms in wedge-bellows spirometer tubes

AH KENDRICK, EC SMITH, D SMITH, D PRYCE-ROBERTS, J LEEMING *Respiratory and Microbiology Departments, Bristol Royal Infirmary, Bristol* Transmission of respiratory pathogens is a potential complication of lung function testing. We investigated the microbiological contamination of spirometer tubes from three wedge-bellows spirometers (Vitalograph) in routine use. At the start of each day a tube that was cleaned, washed, and dried by a commercial dishwasher at 90°C was used. At the end of the day the tubes were sealed with sterile bungs and the inside washed with 20 ml of sterile 1% peptone water; 20 µl of washings of a 1:10 dilution were spread onto blood agar and organisms counted after 24 h at 37°C and 24 h at 30°C. Studies were done with (Ia, IIIa) and without (I, II, III) a one way exhalation valve (Vitalograph). The results (table) show the number of days each tube was sampled, the number of patients using that tube, and the number of organisms grown/20 µl of washings. The organisms isolated were mainly those found in the upper respiratory tract including α and non-haemolytic streptococci. Environmental gram negative bacilli were also cultured. No organisms were cultured from unused clean tubes after drying or after storage. Numbers of organisms cultured were not related to the number of patients using the tube. The organisms isolated were not pathogenic, but many were clearly markers of upper respiratory tract contamination, emphasising the potential for this equipment to disseminate pathogenic organisms. The one way valve did not reduce the number of colonies isolated, but offers a low cost alternative to bacterial filters for the prevention of cross infection.

Tube	Days	Patients	Organisms
I	16	253	0 to > 1000
II	12	42	0 to 650
III	12	34	0 to > 1000
Ia	7	117	0 to > 1000
IIIa	6	31	0 to 1

### Dependence of resistance during interruption of airflow on rate of change of flow before interruption

PJ CHOWIENCZYK, CP LAWSON, D PARRY, GM COCHRANE *Clinical Pharmacology, St Thomas's Hospital, Micro Medical, and Guy's Hospital, London* Interruption of airflow at the mouth produces a biphasic response in airway pressure recorded just upstream of the interrupting valve. An initial step response is followed by a more gradual curvilinear rise in pressure. The step response reflects airway resistance but cannot be measured directly due to superimposed high frequency oscillations arising as a result of airway blockage. Airway resistance (Rint) is thus found by extrapolating the slow phase of the pressure increase back to the time of interruption. The form of the backward extrapolation used becomes more critical with increasing rate of rise of pressure (dPdif/dt) during the slow phase. Consideration of chest wall viscoelastic properties, alveolar gas compliance, and chest wall inertia, suggests that dPdif/dt is in part determined by the flow and volume of the respiratory system before interruption. In particular dPdif/dt may be dependent on the rate of change of flow (dV/dt) immediately before the interruption. In six normal subjects during tidal breathing we found dPdif/dt to be strongly positively correlated to dV/dt ( $r > 0.7$ ,  $p < 0.001$ , in all six subjects) but not to the value of flow at the time of interruption or to Rint. We suggest that Rint should be measured at the time of peak tidal flow or late in expiration when dV/dt is at a minimum.

### Comparison of six minute walk test performance between patients with cystic fibrosis and with emphysema

D FISHWICK, S PIRRIE, T SMALL, A GASCOIGNE, GJ GIBSON, PA CORRIS *Respiratory Division, Department of Medicine, Freeman Hospital and University of Newcastle upon Tyne* The six minute walk test is used as

a simple indicator of exercise capability in patients with respiratory disease. We report differences in six minute walk performance between a group of patients with cystic fibrosis (CF) and emphysema, matched for degree of airflow obstruction. Fourteen patients with end stage emphysema (mean age 50.3 y, 95% (CI) 47.2–53.4) and 20 patients with CF (22.9 y, 21–24.7) underwent a standard six minute walk test as part of assessment for lung transplantation. None of the patients selected for this study required supplementary oxygen. The mean FEV<sub>1</sub> in the emphysema group was 19.5% of predicted (15.0%–24.0%) and did not differ significantly from the CF group; mean 23.1%. Despite this the mean distance walked in metres was significantly greater in the patients with CF (543.74 m, (499–588)) compared with patients with emphysema; 242.43 m. There were no differences in resting oxygen saturation nor degree of maximum desaturation on exercise between the two groups (the maximum percentage desaturation in the CF group; 8.55% (6.1–11), emphysema group; 9.21%. Although mean % predicted KCO was significantly higher in the group with CF (mean 121.2%, (112–131)) compared with 39.9% in the emphysema group, there was no relation in each diagnostic group between distance walked and % predicted KCO. Most of the difference in walking distance could be explained by the greater proportion of time spent resting in the emphysema group (34%) in comparison with 4.5% for the CF group and also may reflect differences in motivation. These data suggest that despite similar % predicted FEV<sub>1</sub>, patients with CF far outwalk those with emphysema. When using this test to help assess suitability for lung transplantation, it is important to consider the underlying diagnosis.

#### Assessment of patients for home nebulisers: survey of present practice in Yorkshire

HSR HOSKER, C TEALE, MF MUERS, MA GREENSTONE *Departments of respiratory Medicine, Castle Hill Hospital, Hull, and Killingbeck Hospital, Leeds* There is debate concerning the best way to assess adults with chronic airways limitation for home nebuliser treatment. A postal survey of the present practice (excluding children and cystic fibrosis) of all 22 thoracic physicians in the Yorkshire region showed that 21 (95%) assess patients for home nebuliser treatment and all use objective assessment as well as history. Eighteen (86%) physicians use laboratory lung function tests as part of their assessment. Of these, three (17%) use baseline tests only, and 15 (83%) use either response from baseline (three) or comparison with inhaler (12) as criteria for response. Three (14%) rely solely on a trial of home nebuliser assessed by symptom improvement and home peak flow monitoring, although 15 others (71%) use a trial of home use as part of their assessment. Ten physicians (48%) incorporate functional measurement (walking distance) into their assessment. But not used this as the only method of assessment. Criteria for a positive assessment varies considerably, four use objective criteria alone and 17 take into account symptomatic response to a home nebuliser trial. Prescribing information was available from 19 physicians. All use a  $\beta$  agonist, 17 preferring salbutamol to terbutaline (90%). Two physicians (10%) did not prescribe ipratropium. A further seven (37%) used it only in some of their patients. Initial tuition for patients is available in all but one case. This is usually provided by the chest clinic nurse (six), pulmonary function technician (five), or physiotherapist (four). Five districts have a service for visiting patients at home by the respiratory support nurse. Although all physicians use objective methods of assessment, there is a variable emphasis on laboratory studies, home peak expiratory flow rate response and walking distance. Many physicians take into account subjective response in deciding whether to recommend a home nebuliser.

#### Lung function and symptom scores during three years of home nebuliser use

BR O'DRISCOLL, C WORTHY, A BERNSTEIN *Hope Hospital, Salford* Concern has been expressed that regular use of bronchodilator treatment may cause an accelerated decline in lung function (van Schayck *et al.* *BMJ* 1991;303:1426). We have studied serial measurements of lung function and subjective assessments of breathlessness among a group of 21 patients who have used home nebulised treatment for severe asthma (eight cases) or chronic obstructive pulmonary disease (COPD) (13 cases) over a period of three years. All patients inhaled nebulised salbutamol (10–30 mg daily) and 17 patients also used nebulised ipratropium bromide (1.5–2.0 mg daily). All patients kept a diary of respiratory symptoms and thrice daily peak expiratory flow rate (PEF) measurements before and after starting home nebuliser treatment and this diary was reinstated for one month after three years of home nebuliser use. Laboratory spirometry

was also recorded at baseline at six, 12, and 36 months. The mean early morning PEF was (a) baseline (before home nebuliser treatment commenced); (b) first month of nebulised treatment; (c) month 36 of nebulised treatment) a = 175; b = 196; c = 172 l/min. The PEF 30 minutes after the first morning treatment was a = 216; b = 244; c = 220. Subjective symptom scores for breathlessness and restriction of activity also improved during the first month of home nebuliser use and were similar to baseline values by 36 months. The laboratory PEF was 7% below baseline at 36 months but mean FEV<sub>1</sub> remained 7% above baseline at 36 months and mean FVC was 9% above baseline at 36 months. We conclude that these highly selected patients continue to derive subjective and objective benefit from home nebuliser treatment after 36 months of regular use. Symptoms and lung function values were similar to baseline values but not as good as the values achieved in the early months of nebuliser use. We found no evidence for an accelerated decline in lung function among these patients.

#### Provision of home nebulisers in Yorkshire

HSR HOSKER, C TEALE, MF MUERS, MA GREENSTONE *Departments of Respiratory Medicine, Castle Hill Hospital, Hull, and Killingbeck Hospital, Leeds* Home nebulisers for adults with chronic airways disease are being increasingly used despite some doubts about their benefits. All 22 thoracic physicians from 17 districts in Yorkshire replied to a postal survey of the local provision of a home nebuliser service for adults. Eleven districts (65%) have a centralised service that is coordinated by a wide variety of nursing, technical, and clerical staff. Six allow other adult physicians independent access to nebulisers. All 11 offer loan of compressors, and a repair service (10 provide a replacement during repair). Ten (91%) supply masks and tubing, and three routinely prescribe nebulised drugs. Compressors are recalled for maintenance in eight districts. A total of 11 compressor types are used, the commonest being the Portaneb 50 and the Medix traveller. There is considerable variation between districts in the numbers of compressors available ranging from 12 to 213 per 100 000 population, with an estimated total of 2000 provided in Yorkshire. Six districts have no centralised adult home nebuliser service. Three of these have no service at all, and one offers a repair service for patients' own compressors. The two districts that provide compressors also offer repair and replacement facilities. Eight districts (47%) receive Health Authority funding for nebuliser provision and one receives funding only for spares and servicing. None of the six districts without a centralised service receives direct funding. Other sources (trust funds, charities) are sometimes used but three districts are unable to provide any assistance. Only four districts reported no difficulties in funding. There is wide variation in the provision and funding of the home nebuliser service for adults in Yorkshire. A coordinated service for each district seems to offer a more comprehensive service with more reliable information on the compressors available. A consensus on all aspects of nebuliser provision might enable districts to obtain more reliable funding.

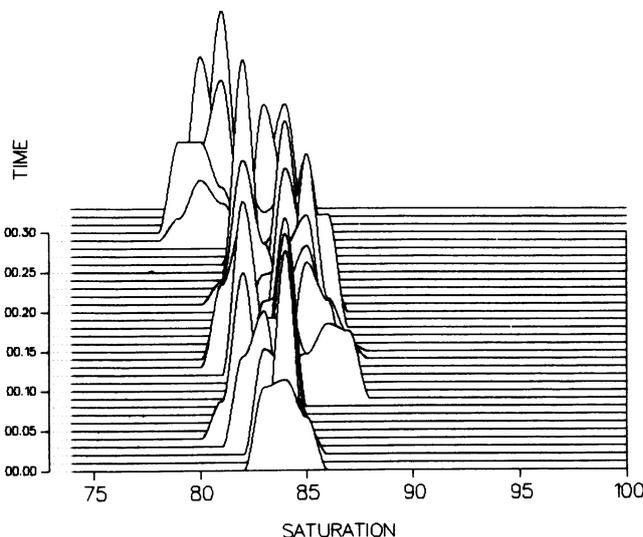
#### Costs of a district nebuliser compressor service

ME DODD, SP HANLEY, SC JOHNSON, AK WEBB *Chest Unit, Monsall Hospital, Manchester* Nebulisers driven by electrical compressors are increasingly being used to give drugs for the treatment of lung disease. In north Manchester the bulk of compressors supplied to hospital treated patients are funded and supplied by a district service based at Monsall Hospital Physiotherapy Department. Little data are available on the costs of such a service, that encompasses initial purchase, preventive maintenance, repair costs, and replacement. We present an analysis of our service for the years 1982 to 1991. Compressors were supplied to 416 patients. Some compressors were reused. The annual issue between 1982 and 1987 was 20 to 40 a year, but rose to 100 a year by 1991. A total of 280 compressors were purchased, including 47 bought as replacements for machines considered beyond repair. No preventive maintenance was undertaken. Of the 280 compressors, 136 required one or more repairs. The average time and range from purchase to first repair (n = 136), from first to second repair (n = 62), and second to third repair (n = 20) were, 3.6 y (0.5–9.8), 2.2 y (0.16–5.16), and 1.5 years (0.33–3.58), suggesting that repaired compressors were less reliable. For compressors two to 10 years old an average of 15% a year required repair. The percentage of compressors beyond economical repair each year increased with their age, being <2% for those <3 years old, but >10% for those aged >9 years, however >50% of 10 year old compressors remained in service. The calculated costs for 1982–91 for the actual and possible permutations of service provision including

replacement but excluding initial purchase costs, based on current prices (new compressor £100, average repair £20, maintenance £15/y) were; (1) repair and replace as necessary £8120 (actual practice); (2) repair once only and replace as necessary £10 200; (3) replace and never repair £13 600; (4) regular annual maintenance £17 625. This would suggest that the most economical policy is one of repair and replace as necessary. These data also allow prediction of future costs for any given population of compressors.

### Short term variability of saturation in patients being assessed for long term oxygen treatment

AOC JOHNSON *Respiratory Unit, Killingbeck Hospital, Leeds* Long term domiciliary oxygen treatment (LTOT)—the only treatment shown to improve the survival of hypoxaemic patients with chronic obstructive pulmonary disease—is expensive and troublesome and any improvement in identifying patients most likely to benefit is worthwhile. Selection criteria for LTOT usually include two measures of  $P_{aO_2}$  below 7.3 kPa (calculated  $S_{aO_2}$  about 90%) taken three weeks apart. We have noticed recently that arterial oxygen saturation ( $S_{aO_2}$ ) as measured by pulse oximetry is very variable in many patients assessed for home oxygen. We therefore recorded  $S_{aO_2}$  over a 30 minute period on 10 patients. Mean (SD)  $S_{aO_2}$  was 85.2% (5.97) and the mean spread of  $S_{aO_2}$  was 7.3% (range 5%–10%). A typical example is shown in the figure. In this example the mean  $S_{aO_2}$  was 83.2%, (1.67%) and spread 79%–87%. Each curve shows the distribution of  $S_{aO_2}$  over a one minute period, with successive one minute curves plotted above the first. The degree of spread can be explained by a curve similar to the oxyhaemoglobin dissociation curve but with  $S_{aO_2}$  plotted against  $P_{iO_2}$ , rather than  $P_{aO_2}$ . A similar curve is produced, but in this case the shape of the curve is dependent on a number of factors including ventilation perfusion relations in addition to haemoglobin dissociation characteristics. The explanation for the wide spread of  $S_{aO_2}$  appears to be related to the position on this curve. Patients on the steep part of this curve show large changes in  $S_{aO_2}$  with small changes in  $P_{iO_2}$ , ventilation or shunt. They will therefore have larger rises in  $S_{aO_2}$  with oxygen treatment than patients on the flatter part of the curve. We would suggest that in addition to blood gas sampling useful information may be obtained by measuring  $S_{aO_2}$  over a 30 to 60 minute period as those patients with a larger spread of  $S_{aO_2}$  are likely to respond better to oxygen treatment.



### The East Anglian GP domiciliary oxygen treatment survey

M JACKSON, JM SHNEERSON *The Respiratory Support and Sleep Centre, Papworth Hospital, Papworth Everard, Cambridge* One thousand two hundred and twenty six GPs in East Anglia were sent a questionnaire to survey their attitudes to and how they prescribe domiciliary oxygen. Replies were received from 529 GPs whose lists totalled 853 614 patients and who were treating 489 patients with domiciliary oxygen. Thirty five per cent of GPs did not indicate that they thought that chronic bronchitis and emphysema should be treated with long term oxygen treatment (LTOT), 31% stated that they might initiate LTOT without referral to a hospital physician, 23% considered that their prescription of oxygen was constrained by a

lack of expert advice about when and how to use oxygen, and 25% expressed doubts about the usefulness of oxygen treatment. Only 42% thought that they would always prescribe an oxygen concentrator for LTOT. The flow rates that GPs would prescribe for LTOT varied widely. Only 60% indicated a flow rate that they might recommend. The mean was 3.4 l/min. Similarly 22% of GPs did not have an opinion of how many h each day was the minimum that should be prescribed for LTOT. Of those who did indicate a figure the mean was 11.7 hours. 57.5% of these recommended less than 15 h/day. This survey shows that many GPs remain unclear about the indications for LTOT, the need for specialist assessment, and the practicalities of delivering this form of treatment.

### Community management of long term domiciliary oxygen therapy: an outline plan

J WATERHOUSE, CG BILLINGS, J NICHOLL, P HOWARD *University Department of Medicine, Royal Hallamshire Hospital, Sheffield* We have previously reported data on patients prescribed an oxygen concentrator for hypoxaemic lung disease in the months of August 1990 and February 1991 in six of the nine areas of England and Wales. An analysis has been made of measurements of  $S_{aO_2}$  through pulse oximetry in the home. Response to supplemental oxygen was judged by plotting resting  $S_{aO_2}$  breathing air against proportional improvement in  $S_{aO_2}$  breathing oxygen at the prescribed flow rate for 237 patients in whom full measurements were obtained. We considered 90.5%  $S_{aO_2}$  at rest on air as the division between adequate and inadequate oxygenation and at least 30% improvement towards maximum  $S_{aO_2}$  (97%) as a therapeutic response to oxygen. The results were plotted on a figure that divides into quadrants. Patients where there is no indication for therapy may be separated from those who clearly need it and response judged. Six per cent were prescribed long term oxygen treatment (LTOT) with no benefit where no need existed, 7% required LTOT but responded inadequately at the prescribed flow rate; 54% seemed to have appropriate responses to LTOT, and 32% achieved improvement of  $S_{aO_2}$  even though seeming not to be in the hypoxaemic range. It is proposed that the oxygen provider service is extended to measure  $S_{aO_2}$  and response to oxygen. Those with a hypoxic response need specialist rereferral, the inappropriately prescribed should stop LTOT. Mildly hypoxaemic patients not severe enough for the guidelines should cease LTOT but be closely monitored.

### Estimation of resting energy expenditure (REE) in patients with chronic lung disease: comparison of a ventilated hood and mouthpiece systems

MK SRIDHAR, R CARTER, MEJ LEAN, SW BANHAM *Department of Respiratory Medicine and University Department of Human Nutrition, Glasgow Royal Infirmary* In healthy subjects estimation of REE by indirect calorimetry with different methods of data collection (hood, mouthpiece, and mask) are comparable (Segal KR. *Am J Clin Nutr* 1987;45:1420). We compared a ventilated hood (V) system (Deltatrac metabolic monitors inc, Helsinki) with a mouthpiece plus noseclip (M) system (PK Morgan, Rainham, Kent) in estimating REE in 10 patients (six emphysema, four thoracoplasty; mean  $FEV_{1.0}$ : 37% predicted). Indirect calorimetry was performed by both methods on two consecutive days after an overnight fast. Both systems were calibrated by a certificated gas mixture (BOC special gases) before each measurement. Mean REE (SEM) estimated by the two methods on the two days were: H (Day 1) 1452.3 (70.5) kcal; H (Day 2) 1467.7 (70.8); M (Day 1) 1692.7 (74.6) kcal M (Day 2) 1618.0 (48.8). There was no significant day to day variation in the REE estimated by each method. There was however a significant difference in the REE as estimated by the hood and mouthpiece systems ( $t$  test  $p < 0.01$ ). The limits of agreement between the two systems (Bland and Altman. *Lancet* 1986;i:306) were 691.8 kcal and  $-301.0$  kcal. We believe that the effect of respiratory apparatus on the breathing pattern of patients (Ashkenazi *et al. Journal of Applied Physics* 1980;48:577) results in a tendency for the mouthpiece system to overestimate REE in comparison with the hood. We conclude that by contrast with the situation in healthy subjects methods of data collection may influence the estimation of REE in patients with severe lung disease.

**Chronic airflow limitation (CAL): cognitive functioning, pulmonary physiology and quality of life**

PE WALKER, PA FRITH *Respiratory Function Unit, Repatriation General Hospital, Daw Park, South Australia* There has been little investigation into the relations between neuropsychological functioning and quality of life in patients who have CAL. Also, past neuropsychological examinations did not analyse the different subtests that are embedded in the aggregate test scores but which may be differentially affected in CAL. We hypothesised (1) that deficits in physiological functioning resulting in impaired cognitive performance are associated with poor quality of life, (2) that patients with deficits in gas exchange perform poorly on several neuropsychological sub-tests of memory, and (3) that a high proportion of CAL patients have clinically significant impairment of memory. A sample of 30 CAL patients completed a Wechsler memory scale-I, a Rey auditory verbal learning test, a Rey complex figure, a profile of mood states, an Eysenck personality inventory, and the chronic respiratory disease questionnaire. The physiological measurements taken were spirometry, resting arterial blood gases, and oximetry on exercise. There were several significant correlations between mental control, visual and verbal short term memory, and subjects' perception of mastery over their condition. There were no significant correlations between PO<sub>2</sub> values and any of the neuropsychological results; however, TLC<sub>0</sub> correlated with visual and verbal memory and PCO<sub>2</sub> with only verbal learning. *t* Tests showed significant differences in mastery and visual and verbal memory between good and poor groups for PCO<sub>2</sub> and gas transfer. Clinically significant memory impairment was found in up to 40% of all patients assessed. The results show the adverse effect of poor gas transfer on cognitive functioning in CAL patients and highlight the importance of considering the impact of cognitive deficits on quality of life.

**Relation between diurnal variability in peak expiratory flow (PEF), symptoms, reversibility of FEV<sub>1</sub>, and bronchial responsiveness in patients with severe chronic airflow obstruction (CAO)**

DC WEIR, P SHERWOOD BURGE *Chest Research Institute, East Birmingham Hospital, Birmingham* In asthma variability in PEF correlates with bronchial responsiveness to histamine, reversibility to salbutamol, and with symptoms. The relation in patients with non-asthmatic CAO is not clear. We examined this in 104 patients with CAO, mean (SEM) FEV<sub>1</sub> 1.05 (0.05) l. Peak expiratory flow was measured five times daily, a breathlessness score once daily, and patients completed an oxygen cost diagram, and a quality of life and modified MRC symptom questionnaire. Reversibility of FEV<sub>1</sub> to salbutamol and ipratropium were measured, and PD<sub>20</sub> to histamine determined in patients with an FEV<sub>1</sub> >0.75 l. Mean daily PEF correlated with the oxygen cost diagram (rho = 0.38), and breathlessness score (rho = 0.4), but less so with reversibility of FEV<sub>1</sub>. Variability in PEF (as amplitude % mean) showed a weak correlation with salbutamol reversibility (rho = 0.33), but not with ipratropium (rho = 0.09). No correlation between measures of breathlessness or PD<sub>20</sub> and amplitude % mean was seen. Variability of PEF (as amplitude % mean) was similar in patients showing an improvement in FEV<sub>1</sub> after inhaled beclomethasone, and those not improving (mean (SEM) amplitude % mean responders 21.3 (2.2), non-responders 21.1 (0.9)), and in patients with and without symptoms of bronchial irritability (BI) (mean (SEM) amplitude % mean BI absent 21 (0.9), BI present 21 (0.9)). Variability in PEF in this group of patients with severe chronic airflow obstruction seems to have few clinical correlates.

**Significance of symptoms of bronchial irritability in patients with non-asthmatic chronic airflow obstruction (CAO)**

DC WEIR, P SHERWOOD BURGE *Chest Research Institute, East Birmingham Hospital, Birmingham* Mortagy *et al* (BMJ 1986;293:525) defined a collection of symptoms which they considered indicated bronchial hyperresponsiveness, and possibly response to steroids, as the bronchial irritability syndrome (BIS). We have investigated the significance of BIS in 105 patients with non-asthmatic CAO, mean (SEM) FEV<sub>1</sub> 1.05 (0.05) l 40 (1.5)% predicted, in whom response to inhaled beclomethasone (BDP) was assessed in a placebo controlled trial. The presence of BIS was determined during the baseline run in phase of the trial. Forty three patients had symptoms of bronchial

irritability. These patients had more severe airflow obstruction than those without BIS, but similar FEV<sub>1</sub> reversibility to salbutamol, bronchial responsiveness to inhaled histamine, and PEF variability. The BIS did not predict the response to inhaled BDP. In this group of patients with non-asthmatic CAO, the presence of bronchial irritability indicates more severe airflow obstruction only.

	Bronchial irritability	
	Present	Absent
Number (female)	43 (11)	62 (19)
Age (y)	65.6 (0.8)	66.1 (1.0)
FEV <sub>1</sub> (l)	0.91 (0.06)	1.15 (0.06)*
FEV <sub>1</sub> /FVC %	34.5 (1.8)	42.5 (1.5)*
Mean PEF (l/min)	212 (13)	249 (11)*
FEV <sub>1</sub> reversibility to salbutamol (as % predicted FEV <sub>1</sub> )	5.6 (0.7)	5.8 (0.8)
Diurnal variation in PEF as % mean PEF	21 (1.5)	20 (1.4)
PD <sub>20</sub> histamine		
Geometric mean (μmol)	0.56	0.49
Responders to BDP (%)	37	28

\*p < 0.05.

**Predictors of symptomatic and functional benefit after oxitropium in COPD**

DPS SPENCE, MG PEARSON, PMA CALVERLEY *Aintree Chest Centre, Fazakerley Hospital, Liverpool* Improvements in six minute walking distance (6MD) and breathlessness (SOB) after bronchodilator drugs in COPD patients are poorly related to changes in resting spirometry (Hay *et al*, *Eur Resp J* in press). We speculated that dynamic measurements of inspiratory flow and expiratory airway collapse would be more sensitive indices of bronchodilator action in COPD. We studied 32 patients with severe COPD mean age (SEM) 62.5 (1.3), FEV<sub>1</sub> 0.8 (0.05) l. Each attended on two practice days and on two successive days. Flow volume loops, airways resistance, lung volumes, and 6MD were measured before and after 200 mcg inhaled oxitropium bromide administered in double blind random fashion. Breathlessness was assessed by Borg scaling before and after each walk. Oxitropium increased 6MD from 279 (10) m to 298 (11) m and reduced initial and final breathlessness from 2.2 (0.3) to 1.9 (0.2) and 3.5 (0.3) to 3.1 (0.3) respectively. Spirometry did not predict the size of these effects. Baseline 6MD was predicted by FVC and resting breathlessness (R<sup>2</sup> = 0.43), while resting breathlessness was related only to FRC (R<sup>2</sup> = 0.31). Changes in 6MD correlated only with increased tidal flow rates after bronchodilator (R<sup>2</sup> = 0.24). Changes in resting breathlessness could not be predicted by changes in any measured variable, but reduction in end exercise dyspnoea related to increased PIFR and F<sub>50</sub>/PERF, an index of airway collapsibility (R<sup>2</sup> = 0.54). These data suggest that measurements of inspiratory flows may be a use in predicting those patients who will derive benefit from bronchodilators.

**Bronchodilator effect of oxitropium bromide compared with ipratropium bromide**

JPR HARTLEY, PL GOGGIN, P GRAHAM *Hove General Hospital and Clinical Pharmacy Unit, Brighton Polytechnic* The anticholinergic bronchodilator oxitropium bromide (OX) has recently become available to treat chronic airflow obstruction and has been claimed to have a longer duration of action than ipratropium bromide (IB). There have been few comparative studies using a currently accepted dose of IB of 80 mcg (= 2 puffs Atrovent Forte). (Peel *et al*. *Eur J Respir Dis* 1984;65:106). Eleven patients completed the study. They had stable chronic airflow obstruction, were aged 50-72 (mean 62) and showed potential to improve FEV<sub>1</sub> by 15% after salbutamol or IB. The subjects attended on two days and were given either 200 mcg OX or 80 mcg IB in double blind random fashion. Measurements of PEF, FEV<sub>1</sub> and FVC were made at intervals over 12 hours. There was no significant difference in baseline lung function on the study days (FEV<sub>1</sub> 1.15 l OX; 1.11 l IB). Peak response was similar (FEV<sub>1</sub> 1.51 l OX; 1.52 l IB) and the median time to peak effect was 90 minutes for both drugs. The duration of action of OX and IB was not significantly different. Patients required rescue medication or FEV<sub>1</sub> fell below baseline before 12 hours in eight patients after OX and seven after IB. The area under the curve was not significantly different between OX and IB for either FEV<sub>1</sub> or PEF (FEV<sub>1</sub> AUC for OX 15.1 l and for IB 14.7 l; p = 0.43). We conclude that there is no significant difference in

magnitude or duration of bronchodilator effect between 200 mcg OX and 80 mcg IB in a population of patients especially likely to be given these drugs.

### Comparison of clinical features in cystic fibrosis patients with different genotypes

GE PACKE, ZH MIEDZYBRODZKA, G RUSSELL, JAR FRIEND, NE HAITES, KF KELLY, JCS DEAN *Chest Clinic, City Hospital, Aberdeen, and Departments of Child Health and Medical Genetics, Medical School, Aberdeen University, Aberdeen* We have studied the genotype of 71 patients with cystic fibrosis in the Grampian Region of Scotland and compared the clinical features of patients with different mutations. In 62 patients genotype was ascertained by direct testing for the mutations delta F508, G551D, G524X, 1717-iG→A, delta I507, R553X, R117H, and 621+1G→T. Genotype in the remainder was inferred from family studies. Patients were divided into three groups: 44 patients who were delta F508/delta F508 homozygotes (group a); nine who were delta F508/G551D compound heterozygotes (group b); and a miscellaneous group of 18 patients who were compound heterozygotes, including nine with the genotype delta F508/mutation unknown (group c). For each patient, where available, annual data were collected retrospectively from the case notes on weight, height, PEF, pancreatic supplementation, and Schwachman score. Weight was plotted against time and a logarithmic transformation applied to linearise the data. The regression coefficient was calculated and used as a summary measure for each patient. The median coefficients for weight regressed against time, in groups a, b, and c were compared (Kruskal-Wallis test). Similar calculations were performed for height and PEF. Median Schwachman scores were compared in all three groups at ages 5 and 10 (Kruskal-Wallis test). The proportion of patients who were and who were not taking pancreatic supplements were compared in the three groups at ages 5 and 10 ( $\chi^2$  test). There were no differences between groups a, b, and c for any of the measurements made. These data support the suggestion that factors other than genotype influence the severity of the clinical features of cystic fibrosis.

### Chronic supplemental enteral nutrition via the nasogastric route in cystic fibrosis

DL SMITH, JM CLARKE, DE STABLEFORTH *Adult Cystic Fibrosis Unit, East Birmingham Hospital, Birmingham* Adult patients with advanced cystic fibrosis (CF) often fail to maintain adequate body weight despite maximal daytime nutritional support. Supplemental nocturnal enteral nutrition can reverse the decline in body weight and may result in improvement in lung function. Gastrostomy and jejunostomy routes are currently popular; we have had success using the simpler nasogastric (NG) route. Fourteen patients, mean age 23 (18–35 (4.5) (range (SD))) with advanced CF (mean % predicted FEV<sub>1</sub>, FVC: 29.5, 46.6) and low body weight (mean % IBW 73.5 (67–85.5)) have undertaken chronic nocturnal NG tube feeding for a mean duration of 14.7 (6–18 (4.4)) months. A high energy feed, "fortison energy plus" (1.5 kcal/ml; 1042 (800–1200, (116)) ml) was delivered for five nights out of seven together with an enzyme capsule dose determined by individual daytime requirements (mean 19 (10–35, (7.4))). Patients were trained to pass and remove their own NG tubes daily. All patients gained weight (mean weight gain 5.4 (1–17, (4.4)) kg); those with high compliance (50%) gained more than those who missed feeds on a frequent basis, 6.9 v 3.9 kg. Over the period of feeding lung function deteriorated in six patients (mean change in FEV<sub>1</sub>, –233 ml), remained stable in three, and improved in five (mean change in FEV<sub>1</sub>, +370 ml). Nine patients (60%) developed hyperglycaemia requiring insulin treatment during the feeding period. Chronic nocturnal NG feeding is acceptable to most adult CF patients in our care and results in weight gain and for some, improvements in lung function. The development of carbohydrate intolerance is common and regular monitoring of blood sugars is advised.

DLS is supported by the Cystic Fibrosis Trust, UK

### Increased incidence of *Pseudomonas cepacia* infection in an adult CF centre: management issues

DL SMITH, LB GUMERY, T TURNER, EG SMITH, DE STABLEFORTH *Adult Cystic Fibrosis Unit, East Birmingham Hospital, Birmingham* *Pseudomonas cepacia* (PC) infection in cystic fibrosis (CF) patients is associated with a poor outcome in a proportion of those affected.

Concern about person to person transmission of PC has led some centres to separate PC from non-PC patients. Despite a policy of separation within the hospital environment (both inpatient and outpatient) we have experienced a sudden increase in new PC infections over the last 12 months. In a clinic of 100+ patients the annual incidence of new PC infections was one in 1988, none in 1989, two in 1990, nine in 1991 and two in the first two months of 1992. Prevalence of PC infected patients attending the centre was one in 1988, one in 1989, three in 1990, nine in 1991, and 12 in the first two months of 1992. Mean age at first isolation of PC was 23 (range 17–28). Mean % predicted FEV<sub>1</sub> and FVC were 30.6 and 53, mean % ideal body weight was 87. In this group of 14 patients, three had mild to moderate disease at the time of first PC isolation, the remaining 11 patients had moderate to severe disease. Sputum microbiology before first PC isolation showed chronic infection with *P aeruginosa* (PS) in 13 of the 14 patients, all of whom were receiving nebulised colomycin as part of their routine treatment. Of 14 cases of PC infection, two have undergone successful heart lung transplantation 19 and 22 months after PC isolation. Four patients have died, all within an average of 4.5 months (3–6) from first PC isolation. One further patient died after transplantation complicated by postoperative infection. Seven patients remain under regular follow up a mean of 5.3 (1–9) months from first PC isolation. This high incidence of new PC infections despite a policy of separation that has been in operation for four years leads us to suspect that contact between patients outside the hospital environment may be important in the acquisition of PC.

DLS and LBG are supported by the Cystic Fibrosis Trust, UK

### Cystic fibrosis related diabetes mellitus: prevalence and insulin responses in adults

DL SMITH, MB O'LEARY, GP GILLERAN, WA BARTLETT, AF JONES, PM DODSON, DE STABLEFORTH *East Birmingham Hospital, Birmingham* Cystic fibrosis related diabetes mellitus (CFRDM) is increasingly recognised among adult CF patients. Glycosylated haemoglobin (HbA1c) measurements in 92 patients attending an adult CF centre showed results ranging from 2.3%–8.1% (median 4.0%). In 34 of these patients (eight with treated insulin dependent diabetes mellitus (IDDM) and 26 who underwent formal oral glucose tolerance tests (OGTT)) HbA1c measurements showed a sensitivity of 54% and a specificity of 91% for the diagnosis of DM (World Health Organisation (WHO) criteria) using a cut off value of HbA1c of 5.0%. The OGTTs in 26 patients without clinical DM showed 12 patients with a normal OGTT, 11 with IGT OGTT, and three with DM OGTT (WHO criteria). Time to peak (t/p) insulin response (t/p (minutes)) in 15 CF patients (OGTT normal in four, IGT in eight, DM in three) who underwent prolonged OGTT (180 minutes) showed a delayed response in all groups compared with four healthy non-CF controls; t/p normal OGTT = 112.5, t/p IGT OGTT = 112.5, t/p DM OGTT = 160, t/p controls = 30 (p < 0.01) Insulin/glucose ratios (I/G) for three groups of CF patients and controls at 0 and 120 minutes during OGTT are shown in the table. Increased I/G for all CF patients (DM at 0 min, IGT and controls at 120 min) suggest a degree of peripheral insulin resistance. We conclude that HbA1c is a poor predictor of IGT and DM in CF adults. Insulin resistance and delayed insulin response time may be important factors in the genesis of CFRDM.

	I/G at 0 min	I/G at 120 min	n
CF patients			
normal OGTT	1.7	6.7	12
IGT OGTT	1.3	4.7	11
DM OGTT	3.2	2.3	3
Controls	1.1	3.2	4

DLS is supported by the Cystic Fibrosis Trust, UK

### Glutathione state in adults with cystic fibrosis

D SCHOFIELD, N SHIEL, M SUMMAN, M JONES, J MADDISON, AK WEBB, JM BRAGANZA *Departments of Medicine and Pharmacy, Royal Infirmary and Adult CF Centre, Monsall Hospital; Manchester* Published studies of markers of lipid oxidation show oxidative stress affecting internal organs as well the vascular compartment in patients with cystic fibrosis. Glutathione (GSH) is a key antioxidant of both sites. We are therefore assessing GSH state in adults with cystic fibrosis by

analysing whole blood and plasma for GSH as pointers to the biological availability of the tripeptide, and plasma GSSG (the oxidised form as % of the total) as an index of its oxidation. There was no difference in whole blood GSH of 18 healthy volunteers and 10 patients with stable disease on prophylactic oral flucloxacillin or inhaled colomycin (medians 0.22 and 0.20 nmol/10<sup>6</sup> red cells), nor in plasma GSH concentrations (5.4 v 5.1 μM). A group of six patients with clinical signs of deterioration showed subnormal red cell (0.18 nmol GSH/10<sup>6</sup> red cells, *p* < 0.01) and plasma (3.72 μM, *p* < 0.05) GSH concentrations but there was no discernable change in plasma GSSG. By contrast, two weeks of iv antibiotic treatment was associated with a clear increase in plasma GSH (*n* = 4, 12.6 μM) resulting in a significant fall in the proportion as GSSG. These results suggest that the reduction in *Pseudomonas* load through iv antibiotic is associated with a reduction in oxidative stress.

Study supported by the Cystic Fibrosis Trust

### Effect of addition of exercise to chest physiotherapy on sputum expectoration and lung function in adults with cystic fibrosis

AL HILL, DR BALDWIN, J LOCKWOOD, DG PECKHAM, AJ KNOX *Department of Respiratory Medicine and School of Physiotherapy, City Hospital, Nottingham* Promotion of sputum expectoration by chest physiotherapy is an important aspect of management of cystic fibrosis. We have investigated whether the addition of exercise improves sputum expectoration and lung function in eight adult subjects (four men) with a recent exacerbation of cystic fibrosis. Subjects were treated on two non-consecutive days of the second week of inpatient treatment in a randomised cross over fashion. On the physiotherapy alone day, subjects rested for 60 minutes after which spirometry was recorded and expectorated sputum weight measured. Physiotherapy was given (postural drainage, percussion, deep breathing, vibrations, forced expiratory technique, and coughing) for 60 minutes after which lung function was recorded. Finally sputum weight and spirometry were recorded after a further 30 minutes rest. On the other study day subjects exercised during the first 60 minutes before physiotherapy. The table shows that mean (SEM) sputum expectoration was increased during the first 60 minutes if subjects exercised and that exercise also augmented sputum expectoration for the period during and after physiotherapy. No significant difference in FEV<sub>1</sub>, FVC, FEF<sub>25-75</sub>, and PEF was shown between the exercise and no exercise days. In conclusion, exercise itself leads to more sputum expectoration than occurs at rest and further increases sputum clearance by physiotherapy. Neither physiotherapy nor exercise have significant effects on acute lung function.

	Sputum wt before physiotherapy (g)	Sputum wt during and after physiotherapy (g)	Total
Exercise	7.0 (1.9)	14.5 (3.6)	21.5 (4.8)
No exercise	2.6 (1.4)	11.4 (3.9)	14.0 (5.2)
<i>p</i> Value	0.05	0.007	0.023

### Trial of nebulised amiloride in patients with cystic fibrosis

A GRAHAM, A HASANI, EFW ALTON, ME HODSON, DM GEDDES *Royal Brompton and National Heart Hospital, and Royal Free Hospital, London* In cystic fibrosis (CF) sodium absorption across conducting airways is increased two to threefold. This may be inhibited by application of the sodium channel blocker amiloride to the airway surface. A randomised, double blind, placebo controlled, crossover trial of the effects of nebulised amiloride was performed in patients with CF. Trial medication was given by nebuliser four times daily for two six month periods separated by a one month washout period. Existing medications were continued and infective exacerbations treated in the usual way. Fourteen (12 male, two female) of 23 patients successfully completed the study. Mean (SEM) age was 23.8 (2.3), forced expiratory volume in one second (FEV<sub>1</sub>) 40% of predicted (five) and forced vital capacity (FVC) 68% of predicted (six). Eight were colonised with *Pseudomonas aeruginosa*, one with *Pseudomonas cepacia*, nine with *Staphylococcus aureus*, and one with *Haemophilus influenzae*. No significant change occurred in mean FEV<sub>1</sub>, FVC, oxygen saturation, body weight, white cell count, erythrocyte sedimentation rate, or serum urea and electrolytes during either the

active or placebo treatment periods. The mean numbers of courses of oral and intravenous antibiotics and microbiological counts were not different between the two treatment periods. Sputum rheology was measured monthly in 10 patients and no overall difference in rheological variables was found between the two treatment periods. We conclude that over a six month period nebulised amiloride seems to provide no additional clinical benefit in CF patients if established treatment is continued.

### Vitamin A and E concentrations in cystic fibrosis

SC BELL, JS ELBORN, S WATKIN, S WYNNE, EJ HILLER, DJ SHALE *Department of Paediatrics, City Hospital Nottingham and Section of Respiratory Medicine, Llandough Hospital, Cardiff* Patients with cystic fibrosis (CF) usually have fat malabsorption and consequently low serum concentrations of vitamins A and E. As these vitamins scavenge toxic oxygen derived free radicals we postulated that low serum concentrations may be related to increased pulmonary morbidity. We studied 58 patients with CF, all of whom were receiving A and E supplementation. Patients were divided into two groups; group 1 within the normal range for healthy controls of A (1.1–1.7 μmol/l) and E (17–47 μmol/l) and group 2 with low concentrations of one or both vitamins. Patients in the two groups were of similar age, group 1 (*n* = 25) 14 (1.3) years (mean (SEM)) and group 2 (*n* = 33) 14 (1.1) years. Median social class was three in both groups. Vitamin A concentrations were significantly higher in group 1, 2.09 (0.13) μmol/l compared with group 2, 1.03 (0.11), *p* < 0.001; as were vitamin E concentrations, group 1 29.8 (1.55) μmol/l, group 2 11.5 (1.4), *p* < 0.0001. Fifty six per cent of group 1 and 64% of group 2 were chronically infected with *Pseudomonas aeruginosa*. Shwachman score (SS) was 71 (3) in group 1 and 68 (3) in group 2 and FEV<sub>1</sub> 72% (5%) and 63% (3%) predicted respectively (NS). In patients with low concentrations of both vitamin A and E (*n* = 16) SS was 66 (4) and FEV<sub>1</sub> 61% (7%) predicted, both *p* < 0.05 compared with group 1. Weight for height was significantly nearer normal in group 1, 99% (1.9%) compared with 93% (1.6%) in group 2 (*p* < 0.05). Patients in group 1 spent a median of 0 days in hospital for antibiotic treatment compared with a median of 14 days in group 2 (*p* < 0.05). These data suggest that in patients with CF low vitamin A and E concentrations are associated with a poorer clinical state, lung function, and increased morbidity from respiratory infection. Low concentrations of vitamins should be aggressively treated with appropriate supplements and consideration of compliance to achieve normal concentrations.

### Comparison of intravenous ceftazidime and aztreonam in the treatment of respiratory exacerbations in cystic fibrosis

S ELBORN, A COLVILLE, S CORDON, E HILLER, D SHALE *Section of Respiratory Medicine, University of Wales; College of Medicine and Respiratory Medicine Unit and Department of Microbiology, University of Nottingham* Respiratory exacerbations in patients with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* infection are usually treated with intravenous (iv) antibiotics. As many patients administer treatment at home, use of a single drug is attractive because it simplifies the procedure. As ceftazidime is currently the only antibiotic used as a single agent routinely for iv treatment we compared its efficacy with aztreonam. Twenty four patients, 12 male, mean age 20 (range 14–48), all chronically infected with *Pseudomonas aeruginosa*, were randomly allocated to receive either C (2 g three times daily (tid)) or A (2 g tid) for two weeks. Spirometry, sputum weight, symptom score, and inflammatory markers (Norman *et al. Thorax* 1991;45:91). were assessed before and two weeks after treatment. FEV<sub>1</sub> increased significantly ceftazidime, 1.25 (0.8) l to 1.63 (0.9) l, *p* < 0.05; aztreonam, 1.14 (0.6) l to 1.4 (0.7) l, *p* < 0.05 (mean (SD)). Sputum weight and symptom scores were reduced significantly in both groups. There was no significant difference between groups for any of these variables. Markers of inflammation were reduced in both groups (c-reactive protein; ceftazidime 11.4 (9) to 0.45 (6.3) μg/ml, *p* < 0.05; aztreonam, 13.7 (4) to 5.5 (2.5) μg/ml, *p* < 0.05; neutrophil elastase α-1-antitrypsin complex; ceftazidime, 1.01 (0.69) to 0.82 (0.5) μg/ml, *p* < 0.05; aztreonam, 0.66 (0.42) to 0.47 (0.21) μg/l, *p* < 0.05; tumour necrosis factor-α; ceftazidime, 163 (207) to 78 (52) pg/ml, *p* < 0.05; Aztreonam, 103 (90) to 68 (60) pg/ml, *p* < 0.05). No significant difference was shown between the effects of each drug on inflammatory markers. Two weeks iv treatment with ceftazidime or aztreonam resulted in similar improvements in patients with CF chronically infected with *Pseudomonas aeruginosa*. Aztreonam is a useful alternative to ceftazidime for single agent iv treatment.

### Tumour necrosis factor- $\alpha$ , resting energy expenditure and cachexia in cystic fibrosis

S ELBORN, D SHALE, S CORDON, P WESTERN, I MACDONALD *Respiratory Medicine Unit, University of Nottingham and Section of Respiratory Medicine, University of Wales College of Medicine, Cardiff* Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) has an essentially protective role in the host inflammatory response to infection. In highly localised infection, such as that in the lung in cystic fibrosis (CF), TNF  $\alpha$  probably has both local and systemic effects. Plasma concentrations of bio and immunoreactive TNF  $\alpha$  are raised in CF (Norman *et al. Thorax* 1991;46:91). We hypothesised that a relation existed between circulating TNF  $\alpha$  and the cachectic state seen in such patients. Twenty clinically stable adults with matched healthy subjects had their resting energy expenditure (REE) determined by the ventilated hood method after a 12 hour fast. Catecholamines, TNF  $\alpha$ , and intermediary metabolites were determined in arterialised venous blood. The REE was greater in patients (mean (SD); 121 (9%) predicted) compared with controls (101 (11%) predicted;  $p < 0.01$ ) and was related to plasma TNF  $\alpha$  concentration ( $r = 0.58$ ;  $p < 0.02$ ), which was greater in patients (93 (63) pg/ml) than in controls (24 (19) pg/ml;  $p < 0.01$ ). Concentrations of TNF  $\alpha$  were related to arm muscle area, a measure of muscle wasting ( $r = -0.54$ ;  $p < 0.003$ ), which was less for patients (23 (10) cm<sup>2</sup>) than controls (34 (10) cm<sup>2</sup>;  $p < 0.01$ ). Circulating adrenaline, glycerol, and non-esterified fatty acids were increased in patients compared with controls ( $p < 0.05$ ;  $p < 0.01$ ;  $p < 0.01$  respectively). Although the gene defect in cystic fibrosis might increase energy demands, changes in REE, body composition, and intermediary metabolism suggest that systemic effects of the host inflammatory response may be largely responsible for cachexia in adult patients with chronic pulmonary sepsis. In particular these changes are consistent with the physiological effects of TNF  $\alpha$ , which was detected in the circulation during apparent clinical stability.

### Tumour necrosis factor $\alpha$ (TNF $\alpha$ ), leukotrienes (LT), and airflow obstruction in cystic fibrosis (CF)

P GREALLY, MJ HUSSAIN, AP SAMPSON, D VERGANI, PJ PIPER, JF PRICE *Departments of Child Health, Thoracic Medicine and Immunology, King's College Hospital and Department of Pharmacology, Royal College of Surgeons, London* TNF  $\alpha$  is a proinflammatory cytokine that activates and is chemotactic for granulocytes. In vitro studies suggest that it may prime the 5-lipoxygenase pathway (Roubin *et al. Clin Exp Immunol* 1987;70:484). In CF, sputum LT concentrations are sufficient to contribute to airways inflammation (Sampson *et al. Br J Clin Pharmacol* 1990;30:861). We investigated whether TNF  $\alpha$  was present in the sputum of CF children and whether any relation existed between sputum concentrations of TNF  $\alpha$  and the LTs, and airflow obstruction. Sixteen children (mean age 11.2, range 5–16) provided sputum samples and performed spirometry. TNF  $\alpha$  was measured by ELISA; the LTs were separated by HPLC and quantified by RIA. TNF  $\alpha$  (geometric mean (95% CI) was 129.7 pg/ml (48.2–348.3). LTB<sub>4</sub> (Mean (SEM) was 97.8 (22.9) pmol/g and total cysteinyl LTs (Mean (SEM) were 60.9 (14.8) pmmol/g. FEV<sub>1</sub> (Mean (SD) of the group was 53 (15)% of predicted and FVC (Mean (SD) was 65 (14)% of predicted. There was a significant direct correlation between TNF  $\alpha$  and both LTB<sub>4</sub> ( $r = 0.624$ ,  $p < 0.01$ ) and the total cysteinyl LT sputum content ( $r = 0.52$ ,  $p < 0.05$ ). An inverse relation existed between TNF  $\alpha$  and FEV<sub>1</sub> ( $r = 0.58$ ,  $p = 0.02$ ) and FVC ( $r = -0.625$ ,  $p < 0.01$ ). Moreover, a negative correlation was found between the sputum LTB<sub>4</sub> concentration and FEV<sub>1</sub> ( $r = -0.47$ ,  $p = 0.06$ ) and FVC ( $r = -0.56$ ,  $p = 0.02$ ) respectively. Although cause and effect cannot be confirmed, these results would support the hypothesis that TNF  $\alpha$  upregulates the production of the LTs and that they both participate in airways inflammation in CF.

### An airway epithelial chloride channel which functions normally in cystic fibrosis

EWFW ALTON, SN SMITH, F MUNKONGE, A LINDSAY, D GRUENERT, PK JEFFERY, AJ WILLIAMS, DM GEDDES. *Ion Transport Laboratory, Departments of Cardiac Medicine and Lung Pathology, National Heart and Lung Institute, London, and Cardiovascular Research Centre, San Francisco, USA* We have previously described the properties of a calcium dependent, voltage gated epithelial chloride channel (*J Physiol* 1991;443:137) present in both sheep and human airways. We have now studied the functioning of these channels in transfected cystic fibrosis (CF) airway cells (*Nature* 1991;349:793). Plasma cell and intracellular membranes were separated on discontinuous sucrose gradients and vesicles from the former fraction incorporated into

planar bilayers under voltage clamp conditions. Single channels ( $n = 14$ ) showed alterations in gating induced by both voltage and calcium. Channel open probability was reduced by both ATP (1  $\mu$ M–1 mM) and the chloride channel blocker NPPB (10–100  $\mu$ M). These effects were indistinguishable from comparable properties of non-CF channels. The channel was not seen in 47 consecutive incorporations using vesicles from the intracellular fraction. We conclude that CF airway epithelial plasma membranes possess a calcium activated chloride channel that functions normally under the described conditions. This channel is, therefore a potential target for therapeutic intervention.

### Culture filtrates obtained from growth of non-typable *Haemophilus influenzae* with subminimal inhibitory concentrations of antibiotics cause less ciliary slowing of human respiratory epithelium in vitro

K TSANG, K KANTHAKUMAR, A RUTMAN, D ROBERTS, PJ COLE, R WILSON *Host Defence Unit, National Heart and Lung Institute, Emmanuel Kaye Building, Manresa Road, London* Non-typable *Haemophilus influenzae* (NTHi) broth culture filtrates slow ciliary beat frequency (CBF) of human respiratory epithelium *in vitro* (Wilson R, *et al. Thorax* 1985;40:125). Subminimal inhibitory concentrations (MIC) of antibiotics have previously been shown to alter extracellular toxin production of other bacteria. We have studied the CBF slowing effects of 24 hour culture filtrates (0.2  $\mu$ m) of a clinical isolate of NTHi (SH9) in Herriot's defined medium (HDM) containing no antibiotics or 1/4 MIC of amoxycillin, ciprofloxacin, and loracarbef ( $n = 6$ ). Five slides were constructed for each experiment. Human nasal epithelium strips in minimal essential medium plus (1:1) broth alone (control), culture filtrate of SH9, and culture (with antibiotic) filtrate of SH9 for each of the antibiotics. The mean control and culture filtrate CBF at four hours were 13.7 Hz and 7.2 Hz respectively. The mean ( $n = 6$ )% ciliary slowing was calculated at four hours by control CBF-test CBF/control CBF  $\times 100$ : culture filtrate 47.4, amoxycillin culture filtrate 19.0, ciprofloxacin culture filtrate 23.4, loracarbef culture filtrate 35%. Ciliary beat slowing by culture filtrates was significantly less ( $p < 0.05$ ) when bacteria were grown in the presence of 1/4 MIC of all three antibiotics. We conclude that subMIC concentrations of antibiotic inhibit ciliary slowing factor production by NTHi. This effect is not confined to a particular antibiotic class. Antibiotics penetrate poorly into sputum and thus bacteria may not be exposed to bactericidal concentrations of antibiotic in this site. These findings may therefore have clinical relevance.

### Factors from non-typable *Haemophilus influenzae* inhibiting neutrophil locomotion in vitro: gel filtration and HPLC analysis

DR CUNDELL, GW TAYLOR, M WILKS, R WILSON, PJ COLE *Host Defence Unit, Royal Brompton National Heart and Lung Institute, Department of Clinical Pharmacology, Royal Postgraduate Medical School and Department of Medical Microbiology, St Bartholomew's Hospital, London* Non-typable *Haemophilus influenzae* (NTHi) is a pathogenic bacterium commonly causing infections of the lower respiratory tract. Six clinical NTHi isolates, obtained from the sputum of infected patients, were investigated for their ability to generate factors affecting neutrophil migration in vitro. Culture filtrates obtained during the early phase (0–18 hours) of bacterial growth increased neutrophil migration, and those obtained during the late stationary phase of growth (24–72 hours) significantly depressed the migratory response towards both the chemotactic peptide N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP) and leukotriene B<sub>4</sub> ( $p < 0.003$ ). Culture filtrates obtained after 72 hours of culture failed to enhance either chemotaxis or chemokinesis, as assessed by checkerboard analysis, and had no effect on neutrophil viability. Pooled, freeze-dried 72 hour culture filtrates from the same six strains of NTHi were chromatographed on Sephadex G50. Three major peaks of neutrophil chemotaxis inhibitory activity were obtained. The activity in fraction I ( $V/V_0 = 1.3$ ) was completely removed by passage through Detoxigel, showing it to be endotoxin. Fraction II ( $V/V_0 = 2.1$ ) consisted of a hydrophobic fraction that bound to and could be eluted from a C18 Sep-pak column by methanol, and a hydrophilic fraction that remained unbound. Fraction III ( $V/V_0 = 3.3$ ) was hydrophobic in nature, being completely bound by Sep-pak and eluted by methanol. These gel filtered fractions could be further separated by reverse phase HPLC. The production of substances by NTHi which alter neutrophil function could contribute to the persistence of this organism in vitro.

### *Pseudomonas aeruginosa* pyocyanin slows human ciliary beating via a cyclic AMP dependent mechanism

K KANTHAKUMAR, DR CUNDELL, GW TAYLOR, PJ COLE, R WILSON *Host Defence Unit, National Heart and Lung Institute, Manresa Road, London and the Department of Clinical Pharmacology, Royal Post-graduate Medical School, Du Cane Road, London* Pyocyanin is a phenazine pigment produced by *Pseudomonas aeruginosa* which is present in the sputum of colonised patients. We found that whereas desferrioxamine protected against pyocyanin induced cell damage, it did not prevent pyocyanin induced ciliary slowing. This suggested that epithelial damage by pyocyanin was caused by generation of superoxide (via substrate cycling) and the formation of hydroxyl radical by an iron dependent mechanism. We have now investigated the mechanism of action of pyocyanin on human nasal ciliary beat frequency (CBF; each experiment n = 6). Pyocyanin caused slowing of CBF in a dose dependent manner (5–40 µg/ml). Pyocyanin (20 µg/ml) caused CBF to fall to 42% of control values after four hours, disruption of epithelium integrity at three hours, and ciliary dyskinesia at four hours. The cAMP analogue dibutryl cAMP largely prevented slowing of CBF by pyocyanin (84%, p < 0.05) and partially prevented disruption of epithelium integrity. 3-Isobutyl methyl xanthine, an inhibitor of phosphodiesterase, and forskolin, a stimulator of adenylate cyclase, both prevented pyocyanin slowing of CBF (78% and 74% respectively, p < 0.05). Both agents partially inhibited disruption of epithelium integrity in a similar way to dibutryl cAMP. Concentrations of cAMP and ATP in nasal epithelium were measured using enzyme immunoassay and quantitative spectrophotometric kits respectively. Pyocyanin (20 µg/ml) for two hours resulted in a 68.1% fall in intracellular cAMP, and a 63.4% fall in intracellular ATP. We conclude that pyocyanin induced slowing of ciliary beat involves a cAMP dependent mechanism. This is associated with a fall in intracellular ATP. The cAMP dependent mechanism also partially protects the cells against pyocyanin induced damage.

### Interference of *Streptococcus pneumoniae* with the oxidative response of neutrophils: role of oxidation of cytochrome C by *S pneumoniae*

FE PERRY, CJ ELSON, JR CATTERALL *Department of Pathology and Microbiology, University of Bristol, and Respiratory Department, Bristol Royal Infirmary* Previous work has shown that *S pneumoniae* (S pn) interfere with the oxidative burst of polymorphonuclear leukocytes (PMNs, Perry *et al. Thorax* 1991;46:743P). Three possible explanations for this are that S pn scavenge superoxide (O<sub>2</sub><sup>-</sup>) or prevent its formation, or interfere with the assay by reoxidizing any cytochrome c (cyt c) that becomes reduced. To determine which explanation is correct, we first investigated whether S pn can oxidise cyt c. Cyt c solution was reduced using sodium dithionite to a concentration comparable with that reduced by PMA stimulated PMNs; S pn were then added and the change in absorbance at 550 nm monitored over 90 min. The S pn were able to oxidise reduced cyt c: initial concentration of reduced cyt c 3.65 (1.07) nmol, oxidation by type 1 S pn 3.58 (1.42) nmol (90.8%), by type 14 S pn 3.49 (1.48) nmol (89.8%), n = 7, means (SD). As it has been reported that hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) can reoxidise cyt c and H<sub>2</sub>O<sub>2</sub> is a product of S pn, it was possible that endogenous production of H<sub>2</sub>O<sub>2</sub> by the pneumococci was causing the oxidation of cyt c and that this in turn was causing the apparent inhibition of PMN O<sub>2</sub><sup>-</sup> production. We therefore examined the effect of the H<sub>2</sub>O<sub>2</sub> scavenger catalase and found that 50 µg/ml catalase blocked the reoxidation of cyt c by S pn: oxidation of reduced cyt c by type 1 S pn 2.70 (1.68) nmol/90 minutes, by type 1 S pn + catalase 0.18 (0.45) nmol, by type 14 S pn 2.82 (1.49) nmol, by type 14 S pn + catalase 0.26 (0.33) nmol, n = 7. Experiments were then set up to determine the effect of catalase on the ability of S pn to inhibit PMN O<sub>2</sub><sup>-</sup> production; 50 µg/ml catalase reduced the inhibitory effect (inhibition by type 1 S pn 2.02 (1.25) nmol/90 minutes, by type 1 + catalase 0.96 (0.74) nmol, p < 0.05 n = 7, inhibition by type 14 S pn 3.02 (0.52) nmol, by type 14 + catalase 2.34 (0.78) nmol n = 6, ns) but the effect was only partial by contrast with the effect on reoxidation. These results show that S pn can reoxidise cyt c and thus interfere with the assay, indicating a potential pitfall of this method we have not seen discussed elsewhere. They also show that S pn exert a separate inhibitory effect independent of the effect on cyt c as S pn still inhibited —48% (type 1) and 77% (type 14) of the PMN respiratory burst when reoxidation was blocked by catalase. Thus *S pneumoniae* must scavenge O<sub>2</sub><sup>-</sup> or inhibit its production.

*This work was supported by the British Lung Foundation*

### Characterisation of the respiratory burst inhibitor produced by *Streptococcus pneumoniae*

FE PERRY, JR CATTERALL, CJ ELSON *Department of Pathology and Microbiology, University of Bristol, and Respiratory Department, Bristol Royal Infirmary* Recent results from our laboratory have shown that *S pneumoniae* inhibit the respiratory burst of neutrophils (PMNs). This inhibitory activity may help explain the pathogenicity of the organism. We have therefore sought to analyse the inhibitory substance. In log phase cultures of *S pneumoniae*, the inhibitory activity was confined to the organisms themselves but in autolysis phase cultures it was also present in the filtered supernatants, indicating that the inhibitory factor is released during autolysis. The factor was destroyed by heating at 60°C for 30 minutes. Filtered supernatants from autolysis phase *S pneumoniae* cultures were dialyzed (10 000 molecular weight exclusion pore size) against Todd-Hewitt broth. The ability of dialysed supernatant to inhibit PMA stimulated O<sub>2</sub><sup>-</sup> production by PMNs was compared with that of non-dialysed supernatant. The sensitivity of the inhibitory activity of each supernatant to catalase was also examined as it was possible that the inhibitory activity might be attributable to hydrogen peroxide. The results are given in the table. These results indicate that there are two fractions in the supernatant with inhibitory activity—one of high molecular weight (> 10 000) that is sensitive to catalase and one of low molecular weight (< 10 000) that is insensitive to catalase. These results show that the inhibitory activity is not due to hydrogen peroxide and that it does not reside in a single substance.

	Nanomoles superoxide/ 90 minutes	
	No catalase	+ 50 µg/ml catalase
PMNs + PMA (control)	4.72 (0.43)	4.35 (0.25)
PMNs + PMA + non-dialysed supernatant	3.21 (0.49)*	3.10 (0.35)**
PMNs + PMA + dialysed supernatant	3.82 (0.34)*	4.15 (0.17) NS

\*p < 0.05; \*\*p < 0.01.

*This work was supported by the British Lung Foundation*

### Susceptibility of *Streptococcus pneumoniae* to killing by reactive oxygen species

FE PERRY, CJ ELSON, JR CATTERALL *Department of Pathology and Microbiology, University of Bristol and Respiratory Department, Bristol Royal Infirmary* Previous studies of microbial killing by phagocytes have stressed the importance of reactive oxygen species (ROS). We have therefore attempted to establish whether ROS are important in the killing of *S pneumoniae* (S pn). To help answer this question we have studied the susceptibility of *S pneumoniae* to killing by ROS generated by the cell free purine-xanthine oxidase system. The results of mixing type 1 *S pneumoniae* with purine in the presence or absence of xanthine oxidase (xo) indicate that pneumococci are killed by ROS: *S pneumoniae* in the absence of xanthine oxidase: 225 colony forming units (cfu) per plate; *S pneumoniae* in presence of xanthine oxidase: 28 cfu per plate, mean of 10 experiments each with at least four replicates per condition. The extent of killing was dependent on the concentration of xanthine oxidase. To establish which ROS was primarily responsible for killing, a sub-optimal concentration of xanthine oxidase (xo) was used and the effect of different ROS inhibitors on killing assessed. Superoxide dismutase (SOD, which scavenges superoxide) and mannitol (which scavenges the hydroxyl radical) did not protect *S pneumoniae* from killing (S pn-xo: 229 cfu/plate; S pn + xo: 11 cfu/plate; S pn + xo + SOD: 2 cfu/plate; S pn + xo + mannitol: 9 cfu/plate, n = 3). Catalase (which scavenges hydrogen peroxide) showed a dose dependent ability to protect *S pneumoniae* from the deleterious effects of ROS (S pn-xo: 279 cfu/plate; S pn + xo: 31 cfu/plate; S pn + xo + 0.05 mg/ml catalase: 34 cfu/plate; S pn + xo + 0.5 mg/ml catalase: 108 cfu/plate; S pn + xo + 5 mg/ml catalase: 202 cfu/ml—means of a typical experiment, n = 6), indicating that hydrogen peroxide is the toxic species. This was further borne out by the fact that SOD, which catalyses the dismutation of superoxide to hydrogen peroxide and water, augmented killing in this experiment (S pn + xo + SOD: 1 cfu/plate n = 6). These results show that *S pneumoniae* are susceptible to killing by hydrogen peroxide. It follows that the respiratory burst of phagocytes may provide an effective microbial defence against pneumococci if stimulated.

*This work was supported by the British Lung Foundation*

### Stimulation of the oxidative response of neutrophils by cell associated *Streptococcus pneumoniae*

FE PERRY, CJ ELSON, JR CATTERALL *Department of Pathology and Microbiology, University of Bristol and Respiratory Department, Bristol Royal Infirmary* Reactive oxygen species are thought to play an important part in the microbicidal activity of polymorphonuclear leucocytes (PMNs). However, we have recently found that *S pneumoniae* in suspension inhibit rather than stimulate the oxidative burst of PMNs (Perry *et al. Thorax* 1991;46:743P). The purpose of this study was to determine whether *S pneumoniae* stimulate an oxidative response when they are adherent to PMNs. Type 1 *S pneumoniae* were mixed at a ratio of 20:1 with PMNs in suspension and incubated in a shaking water bath at 37°C for 30 minutes. The mixture was centrifuged and the supernatant discarded to remove non-cell associated bacteria. The PMNs were resuspended in cytochrome c solution and the change in absorbance at 550 nm measured over 90 minutes. The PMNs that had been exposed to *S pneumoniae* generated significantly more superoxide than PMNs exposed to medium alone (PMNs alone 1.55 (0.94) nmol O<sub>2</sub><sup>-</sup>/90 minutes; PMNs + cell-associated *S pn* 2.13 (0.96) nmol O<sub>2</sub><sup>-</sup>/90 minutes, means (SD) of seven experiments each with at least six replicates per condition, *p* < 0.01 paired *t* test). Neither pooled normal nor immune serum stimulated greater O<sub>2</sub><sup>-</sup> production. To determine whether the O<sub>2</sub><sup>-</sup> release could be due to low numbers of pneumococci rather than to cell association, PMNs were incubated with *S pneumoniae* in suspension using the bacterial concentration which had been seen to become cell associated. This concentration of pneumococci did not stimulate O<sub>2</sub><sup>-</sup> but rather inhibited it, in keeping with our previous results for *S pneumoniae* in suspension. These results show that, whereas pneumococci in the extracellular medium inhibit O<sub>2</sub><sup>-</sup> production by PMNs, *S pneumoniae* that become adherent to PMNs do stimulate a small oxidative response. As *S pneumoniae* are killed by reactive oxygen species generated by the purine—xanthine oxidase system (Perry *et al*, unpublished) it is possible that the ability of PMNs to generate O<sub>2</sub><sup>-</sup> in response to adherent pneumococci may provide an effective microbicidal defence against *S pneumoniae*.

*This work was supported by the British Lung Foundation*

### Serum cytokines and salivary platelet aggregation factor (PAF) in acute severe asthma, acute myocardial infarction, and stable asthma

KP JONES, SP REYNOLDS, J BANKS, BH DAVIES *Asthma and Allergy Unit, Sully Hospital, Penarth, South Glamorgan* Salivary concentrations of PAF and lysoPAF together with serum cytokines and receptors IL-1, IL-2, IL-3, IL-4, IL-2R, CD23 and TNF were measured and compared in 26 patients with acute severe asthma, 10 with stable asthma, 10 with acute myocardial infarction, (MI) 13 with active pulmonary tuberculosis, and 10 healthy controls. Salivary PAF was considerably higher (median 9.4 ng/ml range 1.73–12.2 ng/ml *p* < 0.01) in patients with acute MI compared with healthy controls (median 1.96 ng/ml range 1.74–2.7 ng/ml) and MI patients had higher PAF/lysoPAF ratios compared with other groups. There were no differences otherwise between any of the groups with regard to salivary PAF and lysoPAF. IL-2R and CD23 were detected in all cases. IL-2R was significantly raised in MI patients and those with pulmonary tuberculosis (median 920U/ml and 1530U/ml respectively, compared with controls (median 675U/ml, *p* < 0.001). Patients with stable asthma had higher serum CD23 than those with acute asthma (*p* < 0.025). IL-1, IL-2, and IL-4 were not measurable in any of the patients or control subjects. IL-3 was detected in only two patients both of whom had pulmonary tuberculosis. TNF was present in only one patient, who had acute severe asthma and evidence of a respiratory tract infection. Raised concentrations of PAF in acute MI may reflect the degree of platelet activation that occurs in this condition. Serum concentrations of cytokines and soluble receptors were not related to severity of asthma or presence of atopy.

### Effect of clonidine on sensory nerve mediated cough in guinea pigs and humans

F O'CONNELL, RW FULLER, NB PRIDE, JA KARLSSON *Departments of Clinical Pharmacology and Respiratory Medicine, Royal Postgraduate Medical School, Du Cane Road, London and Rhone-Poulenc-Rorer Ltd, Rainham Road South, Dagenham, Essex* We have examined the effects of the  $\alpha_2$  receptor agonist clonidine on citric acid and capsaicin induced respiratory reflexes in guinea pigs and healthy humans respectively. Groups of guinea pigs (*n* = 8–10) were pretreated orally

with 10 or 100  $\mu\text{g}/\text{kg}$  clonidine (Cl) or vehicle (V) one hour before exposure to citric acid aerosol (0.4 M). In a second study groups of guinea pigs (*n* = 8) were pretreated for 10 minutes with Cl aerosol (10–1000  $\mu\text{M}$ ) or V 15 minutes before exposure to citric acid aerosol. The number of coughs (CC) elicited in the first three minutes of exposure and the time to onset of bronchoconstriction (TTB) were measured. Oral Cl had no effect on citric acid induced cough or bronchoconstriction (CC with V = 4.4 (SEM 1.1), Cl 10  $\mu\text{g}/\text{kg}$  = 4.4 (1.4), Cl 100  $\mu\text{g}/\text{kg}$  = 5.8 (1.3), TTB with V = 75 (14) seconds, Cl 10  $\mu\text{g}/\text{kg}$  = 75 (10), Cl 100  $\mu\text{g}/\text{kg}$  = 90 (12)). Nebulised Cl dose dependently suppressed cough and reflex bronchoconstriction (CC with V = 6.5 (0.9), Cl 10  $\mu\text{M}$  = 9.9 (3.7), Cl 100  $\mu\text{M}$  = 4.5 (1.7)\*, Cl 1000  $\mu\text{M}$  = 1.7 (1.0)\*, TTB with V = 191 (24) seconds, Cl 10  $\mu\text{M}$  = 204 (43), Cl 100  $\mu\text{M}$  = 221 (43), Cl 1000  $\mu\text{M}$  = (317) (33)\*). In a third study 12 healthy human volunteers had capsaicin induced cough and reflex rise in respiratory resistance (Rrs) measured before and one and two hours after 150  $\mu\text{g}$  oral Cl or placebo (P). Compared with P, Cl caused a significant fall in resting heart rate (P = 3.6 (1.7) beats per minute, Cl = 7.7 (3.2)\*) and systolic blood pressure (P = 1.3 (3.3) mm Hg, Cl = 15.4 (3.0)\*) and a significant increase in drowsiness as indicated on visual analogue scale [P = -0.5 (6), Cl = 42.3 (7)\*]. Despite these responses, Cl had no effect on cough threshold [ $\Delta\log\text{C}2$  (lowest concentration causing  $\geq 2$  coughs) with *p* = 0.17 (0.15)  $\mu\text{M}$ , Cl = 0.25 (0.1)], near maximal cough response [ $\Delta\log\text{C}5$  (lowest concentration causing  $\geq 5$  coughs) with *p* = 0.02 (0.17), Cl = 0.19 (0.15)], or reflex rise in Rrs [ $\Delta$  rise in Rrs with *p* = 0.06 (0.15) cm H<sub>2</sub>O/l/s, Cl = -0.19 (0.15)] to inhaled capsaicin. We conclude that peripheral  $\alpha_2$  receptors inhibit activity in the afferent nerves involved in irritant induced respiratory reflexes in the guinea pig.  $\alpha_2$  Receptors are not involved in central mediation of these reflexes in either guinea pigs or humans.

\**p* < 0.05 *v* placebo.

### Imaging allergen evoked airway inflammation in asthmatic patients: a pilot study using [<sup>18</sup>F]-fluorodeoxy-glucose and positron emission tomography

KM O'SHAUGHNESSY, C RHODES, H JONES, T JONES, CT DOLLERY, RW FULLER *Department of Clinical Pharmacology, Royal Postgraduate Medical School and MRC Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London* Airway inflammation as a cardinal feature of chronic asthma is currently only visualisable using bronchial lavage and biopsy. Inflammatory foci can, however, be imaged non-invasively using positron emission tomography (PET) and <sup>18</sup>F-labelled 2-deoxy-D-glucose (FDG, a non-metabolisable analog of D-glucose) to quantify the rapid glucose uptake of activated granulocytes. We have investigated, therefore, the effect of an allergen-challenge on FDG uptake in the lungs of four mild asthmatic patients (aged 21–40; FEV<sub>1</sub> > 90% predicted; PC<sub>20</sub> histamine < 16 mg/ml; on inhaled  $\beta_2$  agonists only). In response to inhalation of allergen all subjects showed a fall in FEV<sub>1</sub> of  $\geq 15\%$  (PC<sub>15</sub> is the cumulative concentration needed) and at least a doubling dose shift in PC<sub>20</sub> histamine repeated six hours after challenge. On each of two study days, subjects rested supine within the PET scanner after an overnight fast. Roughly 5 mCi of FDG was injected intravenously having inhaled saline (day one) or their PC<sub>15</sub> dose of allergen (day two) at one of four times (0 minutes, 30 minutes, four hours or 18 hours) before FDG injection. Blood was sampled from a contralateral arm vein while a total of 16 time frames (each of 15 7 mm planes) were acquired over the next 65 minutes. Regions of interest (ROI) were drawn manually from an initial transmission scan to include the total lung parenchyma but excluding all hilar structures. From the extravascular time course of <sup>18</sup>F, the rate of uptake of FDG was expressed in terms of the slope of the linear 'Patlak-plot' tissue to plasma <sup>18</sup>F concentration ratio *v* the plasma integral plasma <sup>18</sup>F, (ratio). Results are tabulated below. All subjects had postsaline FDG uptake within the range previously reported for fasting normal subjects with no substantial increase in the rate of uptake (outside the reference range) at any time point after allergen. It would seem from this pilot study that [<sup>18</sup>F]-FDG/PET does not provide a useful signal for imaging allergen evoked airway inflammation.

Subject	Slope postsaline	Slope postallergen	% Change
SJ (0 min)	0.39	0.49	26
RF (30 min)	0.46	0.50	8.7
PB (4 h)	0.94	1.16	19
AB (18 h)	0.62	0.60	-3.2

*This work was supported by the Medical Research Council*

### Alveolar $\beta$ adrenergic receptor density in asthmatic subjects before and during corticosteroid and $\beta$ agonist therapy: preliminary studies using positron emission tomography (PET) and $^{11}\text{C}$ -S-CGP 12177

F QING, S SRISKANDAN, CG RHODES, J UEKI, PW IND, DJ BROWN, S WATERS, T JONES, JMB HUGHES *MRC Cyclotron Unit and Respiratory Division, Department of Medicine, Royal Postgraduate Medical School, Hammer-smith Hospital, London* Pulmonary  $\beta$  adrenoceptor ( $\beta$ AR) density (B max) has been imaged using PET scanning in five male asthmatic subjects (age 27 to 55) before and after one week of therapy with oral corticosteroids (30 mg prednisolone daily) ( $n = 2$ ) or high dose  $\beta$  agonists (oral 8 mg twice a day salbutamol, inhaled 200  $\mu\text{g}$  salbutamol three times a day, and 50  $\mu\text{g}$  salmeterol twice a day;  $n = 3$ ). One week before the first PET scan, steroids ( $n = 2$ ) or  $\beta$  agonists ( $n = 2$ ) were withdrawn from each group respectively (one subject had very mild asthma and was not on therapy). The four subjects who had asthma of moderate severity (five to six courses of oral steroids in the past eight years) were on maintenance therapy (inhaled 1000–1600  $\mu\text{g}$  beclomethasone/budesonide daily, 50  $\mu\text{g}$  inhaled salmeterol twice a day ( $n = 3$ ), 400–600  $\mu\text{g}$  salbutamol daily ( $n = 3$ ), and 600  $\mu\text{g}$  fenoterol daily ( $n = 1$ )) which was continued, apart from  $\beta$  agonist or steroid withdrawal, but with the addition of 200  $\mu\text{g}$  oxitropium twice a day and 450 mg aminophylline-CR twice a day.  $\beta$ AR (predominantly alveolar in origin) density was measured with the  $\beta$  antagonist radioligand  $^{11}\text{C}$ -S-CGP 12177 in tracer quantities as previously described (Rhodes *et al. Thorax* 1991;46:757P) with two sequential injections of high and low specific activity (3–5  $\mu\text{g}$  and 23–26  $\mu\text{g}$  total ligand respectively) and a graphical approach (Delforge *et al. J Nucl Med*, 1991;32:739). The initial measurement of pulmonary  $\beta$ AR B max was low in all asthmatic subjects (from 5.7 to 11.6 (range) pmol ml gas free tissue $^{-1}$ ) compared with normal subjects (15.4 (0.7) pmol ml $^{-1}$ ; mean (SEM),  $n = 6$ ). After oral prednisolone for seven days, B max rose in both subjects (from 5.7 to 8.9 and from 5.7 to 8.1 pmol ml $^{-1}$ ). After  $\beta$  agonist therapy, B max rose in the two patients (from 9.5 to 13.2 and from 11.6 to 16.4 pmol ml $^{-1}$ ) who had remained on inhaled steroids throughout, but B max fell in the one subject (10.1 to 8.3 pmol ml $^{-1}$ ) not on other treatment.  $\beta$  receptor up regulation with corticosteroid treatment was expected. The low pulmonary B max for  $\beta$ AR in asthma irrespective of treatment and the up regulation with  $\beta$  agonists (while on inhaled steroids) was unexpected and warrants further study.

### Effect of grass pollen immunotherapy on cutaneous mast cell subtypes and immediate sensitivity to allergen and histamine

VA VARNEY, M JACOBSON, M GAGA, AB KAY, SR DURHAM *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London* Grass pollen immunotherapy (Alutard SQ, ALK, Denmark) was effective in reducing seasonal symptoms and medication requirements in adults with summer hay fever (Varney V, *et al. BMJ* 1991;302:265). Immediate cutaneous sensitivity to allergen and to histamine was assessed by performing skin prick tests with 0.5 log incremental concentrations of grass pollen extract (100–100 000 BU/ml) and histamine acid phosphate (0.03–32 ng/ml) in duplicate over the volar aspect of the forearm. Results were expressed as provocation concentrations of allergen (AgPC6) or histamine (HPC6) that caused a 6 mm skin weal. Three mm punch skin biopsies were obtained before and after immunotherapy (IT) and mast cell (MC) subtypes in the dermis were determined by use of a double sequential immunostaining method with monoclonal antibodies G3 (anti-tryptase (T)) and B7 (anti-chymase (C)) (Irani *et al. J Histochem Cytochem* 1989;37:1509). Before IT no significant differences were noted for HPC6 (median 10 mg/ml, 9.5 mg/ml), AgPC6 (500 BU/ml, 500 BU/ml), total MC (counts per field) (5.5, 5.5), or mast cell subtypes (MC<sub>T</sub> 1.5, 2.4; MC<sub>C</sub> 4.0, 3.8) for the Alutard SQ treated compared with placebo treated patients respectively. After IT there was a significant increase in AgPC6 (10 000 BU/ml, 1000 BU/ml ( $p < 0.0002$ )) and significant reductions in total mast cells (1.3, 8.2 ( $p < 0.0001$ )) and mast cell subtypes (MC<sub>T</sub> 0.4, 3.2 ( $p < 0.0001$ ); MC<sub>C</sub> 0.8, 5.5 ( $p < 0.0001$ )) in favour of the Alutard SQ treated compared with placebo treated patients. No change in HPC6 was found. The results indicate that successful IT is accompanied by a reduction in immediate cutaneous allergen sensitivity that may be related to reductions in absolute mast cell numbers in the skin.

### Effect of grass pollen immunotherapy on cytokine mRNA expression during allergen induced late cutaneous responses

VA VARNEY, Q HAMID, M GAGA, SUN YING, AB KAY, SR DURHAM *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London* In a double blind placebo controlled trial we recently showed that grass pollen immunotherapy (Alutard SQ, ALK, Denmark) was successful in reducing symptoms and medication requirements in 40 adult patients with severe summer hay fever. Clinical improvement was accompanied by a decrease in the size of the cutaneous late phase response after intradermal grass pollen (Varney *et al. BMJ* 1991;302:265). Immunohistology of 24 hour late cutaneous biopsies showed a decrease in allergen induced CD3 $^{+}$  and CD4 $^{+}$  lymphocytes and an increase in positive immunostaining for the activation markers CD25 and HLA-DR (Varney *et al. Thorax* 1991;46:750P). We now report in situ hybridisation studies of late cutaneous biopsies after nine months immunotherapy. Ten micron cryostat sections from cutaneous biopsies 24 hours after intradermal grass pollen (and after a control challenge with allergen diluent) were hybridised with a panel of  $^{35}\text{S}$ -labelled riboprobes for cytokine mRNA. Significant allergen induced increases in Th2-type cells expressing mRNA for interleukin-3 (IL-3), IL-4, IL-5, and granulocyte/macrophage colony stimulating factor (GM-CSF) (all  $p < 0.01$ ) were found for both Alutard SQ ( $n = 16$ ) and placebo ( $n = 15$ ) treated patients. By contrast, significant increases in allergen induced cytokine mRNA for IL-2 (eight of 16 biopsies,  $p = 0.02$ ) and for interferon- $\gamma$  (six of 16,  $p = 0.04$ ) were only found in the Alutard SQ treated group. These results suggest that immunotherapy is associated with suppression of allergen induced T lymphocytes, up regulation of CD25 and HLA-DR and the appearance of cells having a TH1-type cytokine profile.

### Web 2086, a platelet activating factor (PAF) antagonist, has no steroid sparing effect in asthmatic patients requiring inhaled corticosteroids

S JOHNSTON, D SPENCE, P CALVERLEY, J WINTER, F DHILLON, A WINNING, E RAMHAMADANY, C HIGGINS, S TURNER, S HOLGATE *Southampton, Liverpool, Dundee and West Middlesex Hospitals, and Boehringer Ingelheim, Bracknell* Platelet activating factor (PAF) has been proposed as a crucial mediator in the pathogenesis of asthma, acting directly and by releasing other mediators such as leukotrienes. WEB 2086 is a potent competitive oral PAF antagonist that inhibits PAF and antigen induced bronchoconstriction in a variety of animal models, as well as PAF induced bronchoconstriction in healthy volunteers. We report a double blind, randomised placebo controlled parallel group study of WEB 2086 as a replacement for inhaled steroids (IS) in clinical asthma. Phase I (up to 12 weeks) involved identification of the minimum acceptable dose (MAD) of IS for symptom free management of asthma, with a protocol to titrate IS according to symptom scores and inhaled salbutamol use. Phase II (12 weeks) involved treatment with 40 mg of oral WEB 2086 three times daily (tds) or placebo, and reduction of IS according to a similar stepwise protocol, including assessment of morning peak flow recordings (PEF). Phase III (four weeks) was for withdrawal of trial treatment and re-establishment of asthma control with IS alone. Primary end point was a reduction in use of IS by at least 50% (or discontinuation of IS) over the last four weeks of the treatment period, compared with the MAD, provided that subjects' asthma remained well controlled. Secondary end points were the IS use, PEF, salbutamol use, and symptom scoring over the last four weeks of the treatment period. Sixty eight (44 male) non-smoking atopic asthmatic patients, mean (range) age 49 (18–69) years, requiring between 400–1500  $\mu\text{g}$  IS daily, entered the treatment phase, only data from the 65 subjects completing at least six weeks of the treatment were analysed. In the WEB and placebo groups, 16/33 (48%) and 19/32 (59%) subjects respectively, responded ( $p = \text{NS}$ ,  $\chi^2 = 0.79$ ). There were no significant differences between groups in the number of exacerbations of asthma, nor in any of the secondary end points. This study conclusively shows that oral WEB 2086 (40 mg tds for 12 weeks) cannot replace IS in clinical asthma.

### Effect of inhalation of the leukotriene D<sub>4</sub> receptor antagonist ICI 204,219 on allergen evoked bronchoconstriction

KM O'SHAUGHNESSY, IK TAYLOR, B O'CONNOR, FB O'CONNELL, CT DOLLERY *Departments of Medicine and Clinical Pharmacology, Royal Postgraduate Medical School, London* In a previous study we have shown that the potent and specific leukotriene D<sub>4</sub> receptor antagonist,

ICI 204, 219, blocks both the early and late responses to allergen challenge when given orally at a dose of 40 mg (*Lancet* 1991;337:690). It also reduced the allergen evoked increase in bronchial reactivity suggesting a disease modifying action. In the study reported here we have looked at the effect of an inhaled preparation of ICI 204, 219 on the bronchoconstrictor response to inhaled allergen. Ten atopic subjects (mean age 25.6 (SEM 4.2); six females; FEV<sub>1</sub> >90% predicted; on inhaled  $\beta_2$  agonists only) were studied on two days two to three weeks apart. They inhaled in a randomised double blind fashion eight puffs of a standard metered dose inhaler containing either ICI 204, 219 (200  $\mu$ g/puff, total dose 1600  $\mu$ g) or propellant alone as control. Thirty minutes later they were given a bronchial allergen challenge with a concentration of allergen that had been previously shown to lower their FEV<sub>1</sub> by at least 15% measured 10 minutes after inhalation. FEV<sub>1</sub> was then monitored hourly for 10 hours. The early and late responses were quantified as the trapezoidal area under the curve (AUC) of the corresponding FEV<sub>1</sub> time profile (zero to two and two to 10 hours respectively). Inhalation of ICI 204, 219 was well tolerated and no adverse clinical or biochemical effects were noted. One subject did, however, fail to complete the study for unrelated reasons. There was no significant effect of ICI 204, 219 inhalation on basal airway calibre (change in FEV<sub>1</sub> 30 minutes after inhalation was -149 (66) ml after placebo *v* 15 (40) ml after ICI 204, 219, *p* > 0.1). The early response to allergen was significantly inhibited by ICI 204, 219 (AUC<sub>0-2</sub> was -761 (426) after ICI 204, 219 *v* -2472 (479) after placebo, *p* < 0.005) although the level of inhibition was less pronounced than after oral administration. There was, however, no significant effect on the late response to allergen challenge (AUC<sub>2-10</sub> was -5864 (2097) after ICI 204, 219 *v* -9018 (1682) after placebo, *p* > 0.1). By the inhaled route, ICI 204, 219 at a dose of 1600  $\mu$ g is unable to significantly modify the late response to inhaled allergen. It is currently unclear whether the differences between the oral and inhaled routes for ICI 204, 219 are a reflection of different pharmacokinetic profiles or not.

This work was supported by MRC and ICI Pharmaceuticals

#### Differential effect of inhaled prostacyclin on airway calibre in hyperresponsive subjects

SA GOMM, AS JUBBER, NAGM HASSAN, SE CHURCH, RW FOSTER, CC HARDY *Departments of Respiratory Medicine, The Royal Infirmary and Department of Physiological Sciences, The University, Manchester* In humans, despite being a smooth muscle relaxant *in vitro*, PGI<sub>2</sub> by inhalation has little effect on airway calibre (Hardy *et al. Am Rev Respir Dis* 1985;131:18). In asthma, PGI<sub>2</sub> protects against bronchoconstriction induced by methacholine (Mch), PGD<sub>2</sub>, exercise and nebulised water (Hardy *et al. J Appl Physiol* 1988;64:1567). Extension of this antagonism to agents causing bronchodilatation would suggest that PGI<sub>2</sub> impairs agent access to the airway smooth muscle. This study compared: (A) the effect of preinhalation of PGI<sub>2</sub> on terbutaline (Terb)-induced bronchodilatation measured as increased specific airway conductance (sGaw) in eight hyperresponsive subjects (geometric mean PC<sub>50</sub> 0.29 mg/ml Mch): (B) the effect of PGI<sub>2</sub> on both Mch and histamine (Hist)-induced bronchoconstriction in six subjects. (A) On four study days, each subject inhaled for 2 minutes: (1) Doubling concentrations of Terb 0.3-5 mg/ml at 15 minute intervals from a Turret 22 nebuliser, flow rate 7 l/min. The PC<sub>50</sub> Terb was determined from the log cumulative concentration log sGaw curves. (2) PC<sub>50</sub> Terb. (3) PGI<sub>2</sub> (250  $\mu$ g/ml for 1 minute). (4) PGI<sub>2</sub> followed immediately by PC<sub>50</sub> Terb, with measurements of sGaw at frequent intervals for 30 minutes (two, three and four). (B) on four study days, each subject inhaled for 2 minutes: (1) PC<sub>50</sub> Mch. (2) PGI<sub>2</sub> followed immediately by PC<sub>50</sub> Mch. (3) PC<sub>50</sub> Hist. (4) PGI<sub>2</sub> followed by PC<sub>50</sub> Hist, with measurements of sGaw at frequent intervals for 30 minutes. The mean peak percentage increase in sGaw for PC<sub>50</sub> Terb = 84% (18%), PGI<sub>2</sub> = 35% (8%) and PGI<sub>2</sub> + PC<sub>50</sub> Terb = 55% (11%). Preinhalation of PGI<sub>2</sub> had no significant effect on Terb induced peak bronchodilatation achieved on study days two and four (*p* = 0.2), or on the difference in the total time course for bronchodilatation (AUC: *p* = 0.1) by paired *t* test. For both Mch and Hist there was a significant antibronchoconstrictor effect of preinhalation of PGI<sub>2</sub>: the peak percentage decrease in sGaw for PC<sub>50</sub> Mch = 54% (5%) and PGI<sub>2</sub> + PC<sub>50</sub> Mch = 23% (5%) (*p* < 0.001) and similarly for PC<sub>50</sub> Hist = 57% (4%) and PGI<sub>2</sub> + PC<sub>50</sub> Hist = 25% (10%) (*p* = 0.01). This was confirmed with AUC (*p* = 0.004 and <0.001 respectively). The differential effect of PGI<sub>2</sub>, causing substantial impairment of Mch and Hist-induced bronchoconstriction but much less impairment of Terb-induced bronchodilatation, suggests that antagonism of these bronchoconstrictor agents occurs by action of PGI<sub>2</sub> on airway smooth muscle rather than by impairment of access of agents to smooth muscle.

#### Effect of amiloride on the airway response to metabisulphite in asthma

KL GRANGE, DR BALDWIN, I PAVORD, AJ KNOX *Respiratory Medicine Unit, City Hospital, Nottingham* Nebulised frusemide has been shown to protect asthmatic subjects against several indirect bronchoconstrictor stimuli but the mechanism of action is unknown. One possibility is that inhibition of sodium transport is responsible. If this is the case then amiloride, an inhibitor of different sodium transport systems to frusemide should also protect against indirect challenges. We therefore studied 10 male asthmatic subjects in a double blind randomised cross over fashion. Subjects were given 10<sup>-2</sup> mol/l amiloride or placebo by nebuliser on two non-consecutive days of the same week, at the same time of day. After each inhalation, FEV<sub>1</sub> was recorded at 10 minute intervals for 30 minutes after which a metabisulphite challenge was performed. Amiloride was well tolerated in all subjects. No significant difference was seen between placebo and amiloride for either serial measurements of FEV<sub>1</sub> or in response to metabisulphite. The mean difference in the provocative dose of sodium metabisulphite required to produce a 20% fall in FEV<sub>1</sub> ( $\Delta$ PD<sub>20</sub>FEV<sub>1</sub>) between placebo and amiloride was 1.015 doubling doses (95% CI -0.201 to 2.231; *p* = 0.09). The lack of effect of amiloride on metabisulphite induced bronchoconstriction suggests that frusemide is unlikely to be acting in asthma by an effect on sodium transport.

#### Effect of frusemide on allergen induced contractions of passively sensitised human bronchi in vitro

I PAVORD, D BALDWIN, E HOLLAND, A TATTERSFIELD, A KNOX *Respiratory Medicine Unit, City Hospital, Nottingham* Inhaled frusemide has been shown to inhibit the bronchoconstrictor response to a number of challenges in asthma. Investigations into the mechanism of action of frusemide have been hampered by the lack of a suitable *in vitro* model. Recently, however, Anderson *et al (N Engl J Med* 1990;324:131) have shown that frusemide inhibits the release of mediators from allergen challenged passively sensitised human lung fragments. We have modified this technique and have examined the effects of frusemide on allergen induced contractions of human bronchial rings. Macroscopically normal human lung tissue was taken from thoracotomy specimens. Bronchial rings were passively sensitised by incubation overnight with diluted serum from an allergic donor (*Dermatophagoides pteronyssinus* specific IgE titre 8.7 KU<sub>A</sub>/l). Sets of four bronchial rings taken from the same thoracotomy specimen were suspended in 15 or 20 ml organ baths in Krebs-Henseleit solution and continuously bubbled with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. After washing, the response to 10<sup>-4</sup> M methacholine was measured and used to standardise the response to allergen (*Dermatophagoides pteronyssinus* (3  $\mu$ g/ml)). Allergen induced contractions were repeatable within, but not between experiments and were inhibited by the leukotriene antagonist ICI 198, 615 and to a lesser extent by the H<sub>1</sub> antagonist terfenadine. Frusemide inhibited contractions, but only when added immediately before allergen. Frusemide (10<sup>-5</sup>, 10<sup>-3</sup> and 10<sup>-4</sup> M) inhibited allergen induced contractions (assessed over 60 minutes as the area under the contraction/time curve) by a mean 23.5% (95% CI -16.6% to 63.6%); 35% (95% CI -5.1% to 75.1%) and 76.4% (95% CI 36.3% to 116.5%; *p* < 0.001) respectively (*n* = 7). Thus frusemide inhibits allergen induced contractions of passively sensitised human bronchial rings *in vitro*. This may prove to be a useful model for the effects of frusemide in asthma.

#### Time course of change in bronchial reactivity to adenosine 5'-monophosphate (AMP) with inhaled loop diuretics in asthma

R POLOSA, K RAJAKULASINGAM, G PROSPERINI, ST HOLTGATE *Institute of Respiratory Diseases, University of Catania, Italy and Medicine 1, University of Southampton* We have recently shown that inhaled frusemide, given 10 minutes before bronchial challenge, produced a significant attenuation of the responsiveness of the asthmatic airways to AMP (R Polosa *et al. Eur Respir J* 1990;3:665). Little is known of the change in bronchial reactivity with time after giving nebulised loop diuretics. We therefore set out to look in more detail at the time course of change in bronchial reactivity to inhaled AMP after treatment with nebulised frusemide (F) (40 mg) and bumetanide (B) (2 mg) in a randomised, double blind placebo controlled study. Eight asthmatic subjects attended the laboratory on nine separate occasions at the same time of day to undertake concentration response studies with AMP. Subjects received nebulised F, B, or matched placebo 10, 30, and 120 minutes before bronchoprovocation tests. Thus on the nine visits

required to complete the study, each subject received (a) placebo solution at 10, 30, and 120 minutes, (b) F at 10, 30 and 120 minutes, and (c) B at 10, 30 and 120 minutes. Changes in airway calibre were followed up as forced expiratory volume in one (FEV<sub>1</sub>) and AMP responsiveness expressed as PC<sub>20</sub>. When compared with placebo, both inhaled F and B reduced significantly the airway responsiveness to AMP at each time, with the exception of 120 minutes for B. After placebo, the PC<sub>20</sub> AMP at 10, 30, and 120 minutes did not differ significantly from each other, their geometric mean values being 57.8, 55.0, and 52.8 mg/ml. After F, the mean PC<sub>20</sub> values for AMP at 10, 30, and 120 minutes were 154.6, 142.6, and 103.9 mg/ml. Similarly the mean PC<sub>20</sub> values for AMP after B pretreatment at 10, 30, and 120 minutes were increased up to 110.2, 92.0, and 71.5 mg/ml. Our study shows that the time course of change in bronchial reactivity to AMP is similar for both inhaled F and B with a peak effect at 10 minutes. As the time course of action of the two drugs is similar, the present findings support the view that it is feasible to draw valid conclusions regarding relative bronchoprotective potencies from comparative studies with frusemide and bumetanide.

### Effects of dexamethasone (DEX) and cyclosporin A (CsA) on T lymphocytes in vitro in chronic severe asthma

AG ALEXANDER, CJ CORRIGAN, NC BARNES, AB KAY *National Heart and Lung Institute, Royal Brompton (London Chest) Hospitals, London* In a randomised placebo controlled double blind crossover trial of oral CsA in steroid dependent chronic severe asthmatic patients, CsA treatment for 12 weeks resulted in a mean increase above placebo of 12.0% in PEF and 17.6% in FEV<sub>1</sub> (Alexander *et al. Lancet* 1992;339:324). Peripheral blood mononuclear cells (PBMC) from 27 patients during both CsA and placebo treatment were cultured for 72 hours in the presence of the T cell mitogen phytohaemagglutinin (PHA) and varying concentrations of DEX and CsA. DEX inhibited cell proliferation in a dose dependent manner over the range 10<sup>-6</sup>–10<sup>-9</sup> M. Inhibitory doses (ID<sub>50</sub>) were distributed bimodally over the range 1.4 × 10<sup>-9</sup> to 10<sup>-6</sup> M with clear separation by at least one log of a group of four patients relatively resistant to DEX in vitro. Two of these four patients had large clinical responses to CsA. CsA inhibited proliferation in a dose dependent manner over the range 25–5000 ng/ml. ID<sub>50</sub>s were distributed continuously over the range 58–1585 ng/ml with no relatively resistant group and no correlation with whole blood CsA concentrations. CsA treatment did not influence inhibition of PBMC proliferation in vitro, there being no difference between the mean ID<sub>50</sub>s of CsA (311.5 v 225.9 ng/ml, p = 0.17) or DEX (4.9 × 10<sup>-8</sup> v 2.8 × 10<sup>-8</sup> M, p = 0.24) on placebo and CsA treatment respectively. ID<sub>50</sub> CsA correlated neither with changes in PEF or FEV<sub>1</sub> nor with ID<sub>50</sub> DEX. These data suggest that (1) in vitro effects of CsA on T cell proliferation do not have predictive value as a determinant of clinical response to CsA; (2) there is no relation between PBMC sensitivity to DEX and CsA in vitro in these patients; and (3) CsA may be an effective pretreatment for chronic asthma even in patients resistant to corticosteroids.

### Alveolar macrophage accessory cell function correlates with bronchoalveolar lavage (BAL) fluid lymphocytosis in asthma

V GANT, M CLUZEL, Z SHAKOOR, PJ REES, TH LEE, AS HAMBLIN *UMDS Departments of Immunology, St Thomas' campus, London, and Allergy and Respiratory Medicine, Guy's campus, London* Normal alveolar macrophages (AM) are unable to stimulate autologous T lymphocytes to proliferate to recall antigens, and this may be relevant to the control of inflammation in the lung. The inflammatory cell infiltrate seen in asthma consists in part of activated T cells. We have compared the ability of AM and peripheral blood monocytes to promote the proliferation of lymphocytes in response to two recall antigens (purified protein derivative of tuberculin, PPD; streptokinase streptodornase, SKSD) in 11 normal and 11 asthmatic patients. We have added AM or monocytes in a 1:10 ratio to autologous peripheral blood lymphocytes completely depleted of monocytes and MHC Class II+ cells by sequential adherence and complement mediated lysis with appropriate monoclonal antibody reagents, and measured lymphoproliferation to 100 µg/ml PPD or SKSD after five days of co-culture by incorporation of tritiated thymidine. No proliferation to either antigen was seen when lymphocytes were cultured alone. By contrast with addition of monocytes, addition of AM from most normal and asthmatic persons failed to promote lymphoproliferation to either antigen. When the results were expressed as the antigen presenting cell ratio (APC) (cpm) (AM + lymphocytes + antigen)/cpm (monocytes + lymphocytes + antigen), we found in the asthmatic group a

close correlation between BAL lymphocyte count and the APC ratio ( $r = 0.95$  for PPD,  $r = 0.90$  for SKSD;  $p < 0.01$  for both). The results suggest a relation between AM accessory cell function and lymphocyte infiltration of the airways in asthma.

### Cross refractoriness between sodium meta-bisulphite and exercise induced asthma

H LAZAROWICZ, D INCHLEY, I PAVORD, D BALDWIN, A KNOX, A TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Exercise and inhaled sodium metabisulphite (MBS) are thought to cause bronchoconstriction in asthma through different mechanisms. The response to both stimuli becomes refractory with repeat challenge. The mechanism of refractoriness is unclear although depletion of mast cell derived mediators or neurotransmitters has been suggested. Recent studies suggest a common mechanism involving inhibitory prostaglandins. We have tested the hypothesis that refractoriness to exercise and MBS induced asthma involves a common pathway by looking for evidence of cross refractoriness. Thirteen subjects with mild asthma were assessed on two days, performing two exercise tests on one occasion and two MBS challenges (a single dose previously shown to cause a 20% fall in FEV<sub>1</sub>) on the other. The second challenge started after recovery (FEV<sub>1</sub> > 95% baseline) from the first. Subjects then attended on two further occasions when an exercise test was performed after MBS and a MBS challenge after exercise. The maximum % fall in FEV<sub>1</sub> after exercise was similar on the two occasions it was given as the first challenge (25.8% before exercise and 22.7% before MBS). The response to exercise given as the second challenge was 13.6% after exercise (mean difference from first exercise challenge 12.2%; 95% CI 8, 16.4%;  $p < 0.001$ ) and 14.3% after MBS (mean difference from response to exercise before MBS 8.4%; 95% CI 4.3, 12.5%;  $p < 0.001$ ). The response to MBS was also similar on the two occasions it was given first (26.7% before MBS and 28.8% before exercise). The response to MBS given as the second challenge was 10.1% after MBS (mean difference 16.6%; 95% CI 12.1, 21.1%;  $p < 0.001$ ) and 19.5% after exercise (mean difference 9.2%; 95% CI 1.8; 16.7%;  $p < 0.02$ ). Thus bronchoconstriction induced by exercise and MBS shows cross refractoriness. This is in keeping with a shared mechanism.

### Cross refractoriness between bradykinin and hypertonic saline challenges in asthma

K RAJAKULASINGAM, H MAKKER, MK CHURCH, PH HOWARTH, ST HOLLGATE *Immunopharmacology Group, University of Southampton, England* Repeated inhalation of bradykinin (BK) leads to attenuation of the bronchoconstrictor response in asthma and neural reflexes are thought to have an important role in this. Because hypertonic saline (HS) induced bronchoconstriction may also be in part mediated by neural reflexes, we postulated that repeated BK bronchial challenge might reduce their airway response to subsequent HS challenge. To investigate this, 11 atopic subjects with asthma took part in a double blind and randomised trial. During phase 1, subjects underwent dose-response study with HS and histamine (H) to determine the provocative dose required to produce a fall in FEV<sub>1</sub> (PD<sub>20</sub>). During phase 2, subjects underwent two concentration-response studies separated by one hour with either inhaled H or BK. After recovery, a HS challenge was performed. On the H study day, the geometric mean PC<sub>20</sub> was 1.01 (0.04–8.41) mg/ml for the first test, and 0.91 (0.04–6.78) mg/ml for the second test ( $p > 0.05$ ). On the BK study day, the geometric mean PC<sub>20</sub> was 0.39 (0.01–11.73) mg/ml for the first, and significantly higher at 1.38 (0.01– > 16.0) mg/ml for the second test ( $p = 0.006$ ). The mean (SEM) PD<sub>20</sub> HS for phase 1 was 159.2 (27.3) l. After repeated BK challenge this increased significantly to 377.6 (64.7) l ( $p = 0.003$ ). By contrast, after repeated H challenge the mean PD<sub>20</sub> HS value of 220.7 (42.7) l was not significantly different from that measured at baseline ( $p > 0.05$ ). A significant correlation was found between loss of response to BK and to HS ( $r_s$  0.63;  $p = 0.02$ ). Thus repeated exposure of the airways to bradykinin in addition to producing refractoriness to this mediator also results in loss of responsiveness to hypertonic saline. This finding suggests a shared mechanism for refractoriness produced by these stimuli

### Dose-response relation of nebulised salbutamol against bronchoconstriction induced by methacholine

AS JUBBER, RW FOSTER, NAGM HASSAN *Smooth Muscle Research Group, Department of Physiological Sciences, Manchester University, Manchester* We have previously confirmed (Jubber and Foster. *Thorax*,

1991;47:246P) that the responsiveness to inhaled methacholine (MeCh) in normal subjects is composed of two independent parameters—sensitivity and reactivity. Indices of sensitivity use were (1) the dose causing a half maximal bronchoconstrictor effect ( $ED_{50}$ ); (2) the dose provoking a 35% reduction of specific airway conductance (sGaw) ( $PD_{35}$ ). Indices of reactivity used were (1) the amplitude of the maximal bronchoconstrictor effect ( $E_{max}$ ); (2) the slope of the log dose response curve (LDRC). We have now studied responsiveness to inhaled salbutamol (Salb) and have explored the relations between the responsiveness to MeCh and to Salb. Fourteen normal subjects each underwent three MeCh dosage individualisation experiments (LDRC and offset time effect curve, Foster *et al. Br J Clin Pharmacol* 1991;31:445) and then three cumulative LDRCs of salbutamol. A loading dose and sequence of maintenance doses of MeCh were inhaled over two minutes at 10 minute intervals, aiming to cause a sustained 60–65% reduction in baseline sGaw. After the first maintenance dose, Salb was inhaled over two minutes and at 20 minute intervals in cumulative doses of 7, 37, 255 and 1480  $\mu$ g. Each entire DRC was examined by non-linear curve fitting to a positive rational function. The asymptote response was taken as  $E_{max}$ .  $\log ED_{50}$ , and for MeCh  $\log PC_{35}$  and  $\log PD_{62.5}$ , were derived by interpolation in the LDRCs. All indices were analysed in their normally distributed, logarithmic forms. Within Salb, the two indices of reactivity correlated together ( $r = 0.78$ ,  $p < 0.001$ ), whereas neither correlated with the index of sensitivity ( $r 0.39-0.51$ ,  $p > 0.05$ ). No index of sensitivity or reactivity correlated with either the initial baseline  $\log_{10}$  sGaw ( $r 0.03-0.35$ ,  $p > 0.05$ ) or that at the time of first administration of Salb ( $r 0.11-0.33$ ,  $p > 0.05$ ). Between MeCh and Salb, the indices of reactivity correlated together ( $r 0.58-0.76$ ,  $p 0.03-0.003$ ), the indices of sensitivity correlated together ( $r 0.68-0.75$ ,  $p 0.008-0.004$ ) but sensitivity did not correlate with reactivity ( $r 0.25-0.52$ ,  $p > 0.05$ ). Each index of Salb sensitivity and reactivity correlated with the MeCh  $PD_{62.5}$  and loading dose ( $r 0.59-0.76$ ,  $p 0.03-0.003$ ). We conclude that Salb responsiveness is composed of independent sensitivity and reactivity parameters, each linked to the corresponding MeCh parameter.

#### Comparison of the bronchodilator potencies and effects on bronchial reactivity of nebulised salbutamol and adrenaline in subjects with mild asthma in vivo

Z SIVARIDINE, DR BALDWIN, I PAVORD, AJ KNOX *Respiratory Medicine Unit, City Hospital, Nottingham* We have shown that adrenaline and salbutamol have equivalent airway smooth muscle relaxant potencies in vitro but that adrenaline is more potent at inhibiting histamine induced contraction. We have performed parallel studies to compare their effects in vivo in eight male subjects with mild asthma in a randomised double blind crossover study. After baseline measurements, a histamine challenge test was performed followed one hour later by a dose response curve to either nebulised salbutamol or adrenaline (0.4 to 400  $\mu$ g). A second histamine challenge test was performed after the final dose of each agent. The mean (SEM)  $FEV_1$  rose from 2.96 (0.26) l to 3.41 l (0.25) l after the maximum dose of adrenaline (400  $\mu$ g) and from 2.95 (0.25) l to 3.52 (0.28) l after salbutamol (400  $\mu$ g). Both drugs produced significant bronchodilation at 40  $\mu$ g and 400  $\mu$ g when compared with baseline ( $p < 0.001$ ). Similar to the in vitro experiments, the difference in bronchodilator potencies between the two agents was small: the mean area under the curve for dose *v* change in  $FEV_1$  from baseline was slightly greater for salbutamol than for adrenaline (166.9 l  $\mu$ g and 131.7 l  $\mu$ g respectively;  $p = 0.003$ , paired *t* test). The effect of these two agents on histamine reactivity, however, contrasted greatly with their effects in vitro: Salbutamol produced a rise in mean (SEM)  $PD_{20}$  histamine from 0.49  $\mu$ mol/l (0.15) to 1.98  $\mu$ mol/l (0.57)—that is, 1.84 doubling dilutions, whereas adrenaline caused a rise from 0.44  $\mu$ mol/l (0.09) to 0.57  $\mu$ mol/l (0.18)—that is, only 0.06 doubling dilutions ( $p = 0.008$ , paired *t* test). The contrast between the effect of the two drugs in vitro and in vivo could be explained by adrenaline reducing the clearance of histamine by the bronchial vasculature in vivo thus negating any beneficial airway smooth muscle effect.

#### Pneumonia after stroke

LJ WALSH, JT MACFARLANE, PM FISHER, NC DAVIDSON *Respiratory Medicine, City Hospital, Nottingham* Studies into mortality after stroke (Silver *et al. Stroke* 15;492) have shown a high incidence of non-neurological causes of death, with pneumonia being responsible for up to 20%. There is little information, however, on the incidence of pneumonia after stroke or the risk factors involved. A retrospective

case note review of 151 of patients (mean age 75) admitted with a stroke during six months of 1991 was undertaken to determine incidence, risk factors, and subsequent treatment of patients with pneumonia. In 50 patients (33%), 69 episodes of new lower respiratory tract infection (LRTI) including pneumonia were diagnosed as assessed by symptoms, clinical signs, and other evidence including chest x ray films and neutrophilia. There were 56 hospital deaths; 24 developed LRTI. There was a spectrum of functional disability due to stroke, ranging from mild to severe; only five patients were comatose. LRTI occurred in the first week (peak onset day 2) in 66% (33) of patients with a second smaller peak during the third week (5). This contrasts with the study previously referred to that suggests fatal pneumonia to be a later complication. Many patients are noted to have problems with swallowing in the first few days after stroke and this has been postulated as a possible cause. Swallowing problems were documented in 65 (43%) of our patients at initial clerking or on subsequent speech therapy review. 62% (31) of the patients developing pneumonia had swallowing problems. 48% (31) of those with recorded swallowing problems developed LRTI compared with 22% (19) with no swallowing problems. Of 25 patients with recorded chronic lung disease (CLD), 50% (12) developed a LRTI suggesting that CLD may be another risk factor. 11 patients had 2 or more infections including seven with swallowing difficulties and eight with CLD. Unfortunately few sputum samples were obtained. Seven different antibiotic regimens were prescribed, reflecting the difficulty clinicians have in prescribing; the most commonly prescribed, parenteral ampicillin, is not ideal cover for aspiration. Our pilot study confirms that pneumonia is a problem after stroke, probably related to swallowing problems and CLD but prospective studies are needed for further assessment.

#### A criterion based audit of community acquired pneumonia

TS HARRISON, HM MAY, BDW HARRISON *Department of Respiratory Medicine, West Norwich Hospital, Norwich* For 10 years we have used a protocol for assessing and managing community acquired pneumonia. From 1 February 1991 using a standardised discharge summary we audited the following aspects of patient care in four periods up to 16 March 1992: (1) objective assessment of severity on admission; (2) completeness of microbiological investigation; (3) the rate of positive microbiological diagnoses; (4) mortality. In 33 patients presence or absence of cyanosis was recorded in 32 (97%); confusion in 27 (82%); respiratory rate in 30 (91%) (in seven of whom it was  $\geq 30$ ); heart rate and blood pressure in 31 (94%), (in five diastolic pressure was  $\leq 60$  mmHg). Twenty nine (88%) had arterial blood gases recorded, (in nine (27%)  $P_{aO_2}$  was  $< 8$  kPa.) The white cell count was recorded in 33 (100%); in only one was the count  $> 30\ 000$  or  $< 4000$ . Urea was recorded in 31 (94%); in eight this was  $> 7$ . In the first audit period (1 February 1991–1 May 1991) for 10 patients sputum culture was recorded in three (30%), blood culture in one (10%), and acute serology in 3 (30%). None had the results of pneumococcal antigen tests recorded. A rubber stamp with a checklist of microbiological investigations was introduced for the notes. In the last three audit periods of 23 patients the result of sputum culture was recorded in 15 (65%), blood culture in 21 (91%), sputum pneumococcal antigen in 13 (57%), blood pneumococcal antigen in 18 (78%), urine pneumococcal antigen in 18 (78%), and acute serology in 21 (91%). A positive microbiological diagnosis was made in four (40%) patients in the first period and 10 (43%) in the last three periods. Three patients died. The standard of initial assessment was high in a specialist ward. Of the three patients who died each had had at least two of the above criteria of severity confirming the usefulness of these measurements. A simple change in work practice resulted in a significant improvement in the thoroughness of microbiological investigation. This did not increase the rate of microbiological diagnoses significantly.

#### Induced sputum as a diagnostic tool in community acquired pneumonia

N FRENCH, C PARRY, R WONG, G INKSTER, CRK HIND *Departments of Respiratory Medicine and Microbiology, Royal Liverpool University Hospital, Liverpool* Sputum induction using hypertonic saline solution has found a place in the diagnosis of *Pneumocystis carinii* pneumonia as a first line investigation before bronchoscopy and bronchoalveolar lavage. As it is a simple technique to teach and to perform we are looking at its usefulness in aiding diagnosis and management of community acquired pneumonia. Twenty patients admitted with pneumonia, as defined by an acute illness with new radiographic pulmonary infiltrates, were studied. Patients were taken

at random from the general medical intake. Expecterated samples were collected if available before sputum induction. All samples were collected in the first 24 hours, but after initiation of empirical antibiotic therapy. Of the 20 patients, six were unable to provide expecterated sputum and one was unable to provide an induced sample. Of the 16 patients who provided both expecterated and induced samples, the bacteriological pick up rate on routine Gram staining and plating was similar. Organisms were found in three matched samples while in one patient an induced sample picked up a *Haemophilus* not detected in the expecterated sample. Of those six patients with induced samples alone, a bacteriological diagnosis was made in two (one *Haemophilus*, one *Pneumococcus*). In conclusion sputum induction does not seem to have a part to play in the routine assessment of community pneumonia, but it may be useful for collecting respiratory secretions from those patients unable to provide conventional samples. The information gained in our small study in this sub-group of patients did not affect management, however in areas with high levels of resistant organisms the bacteriological information gained may be more relevant.

**Side effects of anti-tuberculous therapy in the elderly**

C TEALE, JM GOLDMAN, SB PEARSON *St James's Hospital and The Chest Clinic, Leeds* A recent survey of the treatment of tuberculosis in England and Wales reported an overall incidence of side effects of 15% (*Respir Med* 1991;85:319). Isoniazid and rifampicin induced hepatotoxicity is more common in the elderly (*J Am Geriatr Soc* 1983;31:356) but the effects of ageing on the frequency of other side effects of antituberculous drugs has not been studied. To determine the incidence of side effects of antituberculous chemotherapy and to compare them in elderly and younger adults we have reviewed all the cases of tuberculosis notified in adults in Leeds during the five years 1986 to 1990. A total of 93 elderly (65 years and older) and 240 younger adults (age 16 to 64 years) received chemotherapy for tuberculosis. The table shows the number of elderly ( $\geq 65$  years) and younger adults (16 to 64 years) with side effects requiring a drug to be stopped/number receiving each drug (%). There was a highly significant difference between the proportion of elderly (17%) and younger (7%) with side effects ( $p < 0.001 \chi^2$  test). In summary 10% of patients receiving antituberculous therapy developed side effects requiring a change in drug. Side effects were more than twice as common in the elderly (17%) compared with younger adults (7%).

	Elderly	Younger	Total
Rifampicin	5/90 (6)	3/229 (1)	8/319 (3)
Isoniazid	4/89 (5)	5/233 (2)	9/322 (3)
Pyrazinamide	6/61 (10)	7/185 (4)	13/246 (5)
Ethambutol	1/50 (2)	1/138 (1)	2/188 (1)
Total	16/93 (17)	16/240 (7)	32/333 (10)

**Culture positive pulmonary mycobacterial disease in Nottingham 1979-91: an increasing proportion of non-tuberculous infection**

A COLVILLE, M BAKER *Nottingham Public Health Laboratory, University Hospital, Queens Medical Centre, Nottingham* We have reviewed *Mycobacterium tuberculosis*, *M kansasii*, *M malmoense* and *M avium-intracellulare* isolations from pulmonary and pleural sites between 1979 and 1991. Non-tuberculous mycobacteria were considered to be causing infection if isolated from a normally sterile site, or if isolated from other specimens on more than one occasion, with additional evidence (such as radiological study) of infection. *M tuberculosis* was isolated from 690 patients, of whom 571 were white. In white patients the annual rate of new cases fell from 66 in 1979 to 20 in 1991. The rate of new non-tuberculous cases did not change significantly during this period. *M kansasii* was isolated from 53 patients, of whom six did not satisfy criteria of infection. *M malmoense* was isolated from 19 patients, two not satisfying criteria of infection. *M avium-intracellulare* was isolated from 17 patients, eight not fulfilling criteria of infection. All non-tuberculous mycobacteria were isolated from white patients, with the exception of three with *M avium-intracellulare*. Two of these were co-infected with *M tuberculosis*. Two patients with *M avium-intracellulare* and one with *M kansasii* had AIDS. Because of the falling rate of pulmonary tuberculosis in white patients, the proportion of non-tuberculous cases rose from less than 10% in 1979 to more than 30% in 1991. Our results show that *M kansasii* and *M malmoense* isolations usually indicate infection. In white patients the rising proportion of non-tuberculous infections highlight the need to include

these in the differential diagnosis of mycobacterial disease in the chest. This has implications for the choice of therapy, and other management such as notification policy and contact tracing.

**The standardised notification ratio for tuberculosis: a simple way of assessing service needs**

PDO DAVIES, CSD WILLIAMS, J HOTCHKISS, A JONES, Q SYED *Tuberculosis Research Unit, Public Health Observatory and Regional Health Authority, Liverpool* Standardised mortality ratios are available for most diseases and standardised morbidity ratios are available for a number of commoner diseases, particularly cancers. They are derived from the observed to expected numbers of cases based on population data. The same method can be used for assessing standardised ratios for tuberculosis notifications. Ratios by different age groups and sexes separately can be calculated for the nation as a whole using annual notification statistics published by the OPCS. Standardised notification ratios can then be expressed by each age group for any area or local authority. This assessment can be made on a year by year basis, and any deviation from the national standard (100) for any group by age and sex in a given authority can be determined. If there is a sudden increase in a certain area for a given age group such as might arise from immigration or increasing spread of HIV in the community, appropriate services can be alerted and those groups showing an increased ratio screened accordingly. For example, the standardised notification ratio for tuberculosis in 1989 for the following districts (both sexes and all ages combined) was 145 for Liverpool, 182 for Leicestershire, 144 for Newcastle, 154 for North Bedfordshire, and 34 for North Devon. The particularly high ratio for Leicestershire may be explained by the numbers of immigrants of Indian subcontinent ethnic origin resident there. The high ratio for North Bedfordshire is not so easy to explain and further elucidation of notification ratio by age and sex may be appropriate to determine the group or groups where disease incidence is highest.

**Yield from tuberculosis contact tracing: Birmingham 1987-9**

S KUMAR, JA INNES, C SKINNER *Birmingham Chest Clinic, Birmingham* The value of contact tracing beyond six months has been questioned in a study from Edinburgh (Selby *et al. Respir Med* 1989;83:353), whereas a recent study from Blackburn (Ormerod. *BTS winter meeting* 1991;S72) showed a significant yield of cases at one year in white persons and up to two years in the Indian subcontinent (ISC) ethnic group. We reviewed the yield from contact tracing at the Birmingham Chest Clinic for cases notified between 1987-9 inclusive. The contact procedure is broadly similar to the recent BTS guidelines (*BMJ* 1990;300:995). The 788 cases of TB were notified, 484 respiratory (264 ISC; 172 White (WH), 37 West Indian (WI); 11 other (OT). The 7960 contacts were screened, and 75 new cases were identified by contact tracing (46 ISC; 15 WH; 14 WI) being about 1% of contacts examined and about 10% of notified cases. The table shows time of diagnosis and index classification. Cases in contact with non-respiratory disease (all six ISC) were diagnosed at the initial visit. The 254 contacts were given chemoprophylaxis (192 ISC; 42 WH; 16WI; 4 OT). Our results suggest that (for Heaf positive contacts) white contacts of smear positive disease should have a six month follow up; ISC contacts of respiratory disease should have a 12 month follow up; contacts of non-respiratory disease and white contacts of smear negative respiratory disease need not be seen after the initial visit.

	ISC	WH	WI
Diagnosis:			
At initial visit	27 (59%)	13 (87%)	13 (92%)
To 6 months	15 (91%)	2 (100%)	1 (100%)
To 12 months	4 (100%)	—	—
Index case:			
Resp (smear + ve)	33 (24)	11 (11)	7 (7)
Non-resp	6	—	—

**Comparison of the radiographic features of pulmonary infections with *Mycobacterium kansasii* and *Mycobacterium tuberculosis***

AJ EVANS, AJ CRISP, A COLVILLE, SA EVANS, IDA JOHNSTON *University Hospital, Nottingham* The reported incidence of pulmonary infection with *Mycobacterium malmoense* (MM) is increasing. The purpose of this study was to ascertain whether culture positive pulmonary MM infection and pulmonary *Mycobacterium tuberculosis* (MTb) display

differences in their radiological appearances at presentation. As far as we are aware there have been no previous detailed radiological studies of pulmonary MM infection. The chest radiographs of 16 patients with pulmonary MM infection were compared with those of 32 age, sex, and race matched patients with pulmonary MTb. None were known to be HIV positive. Two radiologists viewed the radiographs independently and were blinded to the infecting organism. The radiographs of the MM group more commonly showed the following features than MTb controls; cavities larger than 6 cm (six *v* two,  $p < 0.01$ ), air-fluid levels within cavities (four *v* one,  $p < 0.05$ ), loss of volume (12 *v* 11,  $p < 0.01$ ), and coexistent pneumoconiosis (four *v* none,  $p < 0.01$ ). Airspace shadowing involving more than one bronchopulmonary segment was significantly less common (three *v* 16,  $p < 0.05$ ) in the MM group. Thick walled cavities ( $> 2$  cm) were more common in the MM group, although this was not significant. Radiological evidence of pleural effusions, local pleural disease, cavitory disease, and coexistent emphysema were seen with similar frequency in both groups. The presence of the above features may be useful in alerting the physician to the possibility of infection with MM.

#### Comparison of the radiographic features of pulmonary infections with *Mycobacterium kansasii* and *Mycobacterium tuberculosis*

AJ CRISP, AJ EVANS, A COLVILLE, SA EVANS, IDA JOHNSTON *University Hospital, Nottingham* Non-tuberculous mycobacterial pulmonary infections have become increasingly recognised in recent years. The radiographic features of these infections have been variably reported, but there has been no previous blind study comparing the presenting radiological features of *Mycobacterium kansasii* (MK) and *Mycobacterium tuberculosis* (MTb). Chest radiographs of 28 patients with pulmonary MK infection were compared with those of 56 age, sex, and race matched patients with pulmonary MTb infection. All patients in both groups were culture positive, and none were known to be HIV positive. Two radiologists viewed the radiographs independently and were unaware of the infecting organism. The disease was confined to the upper lobes in all but two patients with MK (26 *v* 27,  $p < 0.01$ ). The following features were less common in the MK group; middle and lower lobe involvement (two *v* 29,  $p < 0.01$ ); airspace shadowing involving more than one bronchopulmonary segment (four *v* 28,  $p < 0.01$ ); cavities larger than 2 cm (6 *v* 24,  $p < 0.01$ ); air-fluid levels within cavities (none *v* five,  $p < 0.05$ ); pleural effusions (none *v* 16,  $p < 0.01$ ). Drainage area disease, contiguous pleural disease, and loss of volume were equally present in both groups. These results show significant differences in the presenting radiological appearances of pulmonary MK and MTb infections, and as some of the above appearances are clearly uncommon in MK infection, their presence may be diagnostically helpful.

#### Comparison of the clinical features of pulmonary infections with *Mycobacterium kansasii* and *Mycobacterium tuberculosis*

SA EVANS, A COLVILLE, AJ EVANS, AJ CRISP, IDA JOHNSTON *University Hospital, Nottingham* The relative importance of pulmonary infections with *Mycobacterium kansasii* (MK) in the United Kingdom is increasing. We have retrospectively reviewed the notes of 47 of the 50 patients (mean age 58 (SD 16) years, 13 women), with culture positive pulmonary MK infection in Nottingham over the past 11 years, and compared them with 47 age, sex, race, and if possible year of diagnosis matched patients with culture positive pulmonary tuberculosis, mean age 58 (16) years. Patients with MK were less likely to have a history of diabetes (none *v* six,  $p < 0.02$ ), but the frequency of a history of previous tuberculosis, other chest disease, and gastrointestinal disease was similar. An alcohol intake of  $> 14$  units/week was less frequent in those with MK (none *v* 15,  $p < 0.001$ ), but there was no difference in drug history, past, and present smoking habit, or occupational exposures. Social class, and marital state were similar. Haemoptysis was commoner in the MK group (15 *v* five,  $p < 0.02$ ), but they were less likely to present as a result of an incidental chest radiograph or symptoms other than those due to mycobacterial infection (one *v* nine,  $p < 0.01$ ), or to have a documented fever (six *v* 15,  $p = 0.05$ ). Erythrocyte sedimentation rate, haemoglobin, and white cell count were similar in the two groups, as was the frequency of smear positive disease. There were no significant differences in clinical response to treatment or in the number of deaths, before, or during treatment. There are group differences in the clinical features of the two infections, but with the probable exception of diabetes and alcohol intake these features are unlikely to be diagnostically helpful.

#### Assessment of PCR amplification of IS6110 DNA in blood as a diagnostic test for tuberculosis

RJ SHAW, IK TAYLOR D WALKER, DM MITCHELL. *Department of Respiratory Medicine, St Mary's Hospital, London* There is a clinical need for a rapid sensitive diagnostic blood test for tuberculosis. The new technique of polymerase chain reaction (PCR) amplification of the DNA sequence IS6110 has been used to identify *Mycobacterium tuberculosis*. This study asked if identification of IS6110 DNA in blood samples from 133 subjects was related to clinical disease. IS6110 DNA was amplified in samples from 28 of 32 patients with active tuberculosis, eight of 15 with past tuberculosis treated by drugs, five of nine with past tuberculosis treated by thoracoplasty over 30 years before, 39 of 44 close contacts of patients with tuberculosis. Six of 11 patients with respiratory disease other than tuberculosis, and one of 22 normal volunteers. There was a statistically greater incidence of IS6110 DNA in blood samples from all disease groups when compared with controls ( $p < 0.01$ ), and a greater incidence in samples from patients with active tuberculosis or contacts, when compared with patients with diseases unrelated to tuberculosis ( $p < 0.05$ ). The location of IS6110 DNA was found to be in the non-adherent mononuclear cell fraction in nine of 10 patients, and in the adherent mononuclear cell fraction in five of 10 patients. IS6110 DNA was not amplified from the granulocyte or plasma fraction of any patient. Thus identification of IS6110 DNA in blood could not differentiate patients with active tuberculosis from close contacts or cases of treated tuberculosis.

#### Why does genitourinary tuberculosis occur proportionately less than expected in the Indian subcontinent ethnic population in the United Kingdom?

LP ORMEROD *Chest Clinic, Blackburn Royal Infirmary, Blackburn, Lancashire* Genitourinary tuberculosis (GUTB) is the only form of non-respiratory TB of which more cases are reported in the white ethnic group compared with the Indian subcontinent (ISC) ethnic group in national surveys. GUTB represented 27%–28% of white, but only 4%–5% of ISC non-respiratory TB in 1983 and 1988. There is thus a considerable difference in the pattern of GUTB between the white and ISC ethnic groups in national surveys where ISC patients make up 36%–38% of cases. Examination of non-respiratory TB notifications from the Blackburn district health authority, which has 70% ISC notifications, shows a striking difference between the ethnic distribution of GUTB and all other forms of non-respiratory TB. The table shows non-respiratory sites in Blackburn from 1978–90. Statistical analysis by  $\chi^2$  shows that there is a highly significant difference in the pattern of non-respiratory sites. There is no difference between miliary, abdominal, CNS, and skin of other sites in ethnic distribution. GUTB accounts for 65/81 of the  $\chi^2$ . The only other difference is that lymph nodes (83%) had a significantly higher ISC percentage than bone or joint disease (69%), the significance being in the opposite direction to GUTB that had only 15% ISC ethnic cases. Possible factors in the difference in the ethnic distribution of GUTB and other non-respiratory forms will be discussed.

Site	White	ISC	Other	Total
CNS	5 (20%)	19 (76%)	1 (4%)	25
Abdominal	10 (19%)	42 (81%)	—	52
Bone or joint	26 (31%)	57 (69%)	—	83
Skin or other	12 (23%)	40 (75%)	1 (2%)	53
Lymph node	33 (14%)	193 (83%)	6 (3%)	232
Miliary	9 (27%)	23 (70%)	1 (3%)	33
Urogenital	28 (82%)	5 (15%)	1 (3%)	34
Total	123 (24%)	379 (74%)	10 (2%)	512

#### Tuberculosis diagnosed in a contact clinic: Leeds TB survey 1991

JM GOLDMAN, C TEALE, SB PEARSON *Leeds General Infirmary, Leeds* In the five year period beginning in January 1986, 411 cases of tuberculosis were notified in Leeds. We reviewed the notes of 406 patients and in 397 the diagnosis of TB was accepted and data recorded. Thirty six cases (9%) were diagnosed in the contact clinic (CC). The age distribution of these patients was significantly different from that of the remaining population with TB (RP). There were 20 CC patients under 10 years old (56%) compared with eight RP (2%), and 24 (67%) CC under 16 compared with 12 RP (3%). Thus 71% of all patients diagnosed as having TB under the age of 10 and 67% of those under the age of 16 came through the contact clinic. Seven CC

(19%) were from the Indian subcontinent compared with 99 RP (27%). All patients had intrathoracic TB (36 lung, one pleura) with an abnormal chest radiograph. Most had changes compatible with a primary complex, (apical or mid-zone shadowing 21 (58%), mediastinal lymphadenopathy 14 (39%)); two had lower zone shadowing and one pleural effusion. Eight patients had previous BCG immunisation. No symptoms were present in 23 patients (64%). Cough (25%) and malaise (14%) were the most common symptoms reported. Standard regimes, with at least three antituberculous drugs for at least six months were given to 26 patients and eight infants received rifampicin and isoniazid alone. Two patients received unusual regimes, one because of isoniazid induced hepatitis and one because of an isoniazid resistant organism in the index case. All CC patients completed treatment and there were no relapses. In Leeds the contact clinic effectively detects TB in mostly symptom free children, the majority of whom come from the indigenous population of the city. Despite the large number of contacts screened it remains an important service.

**Extrathoracic tuberculosis, presentation and outcome: Leeds TB survey 1991**

JM GOLDMAN, C TEALE, SB PEARSON *Leeds General Infirmary, Leeds*  
 In the five year period beginning in January 1986, 411 cases of tuberculosis were notified in Leeds. We reviewed the notes of 406 patients and in 397 the diagnosis of TB was accepted and data recorded. There was evidence of extrathoracic disease (ETD) in 95 patients (24%). Lymph nodes were the commonest site (38 cases) accounting for 40% of ETD. There were 16 cases involving the kidneys, 10 the bones, nine the gut, five cold abscesses, five gynaecological disease, four liver disease, three meningitis, three peritonitis, and three others. Concurrent thoracic involvement occurred in 23.2% of ETD and this proportion held true for most sites except gastrointestinal and gynaecological TB in which it was uncommon. ETD was more common in women and thoracic disease (TD) less common (53.7%, 37.4%,  $p < 0.01$ ). Patients with ETD were twice as likely to come from the Indian subcontinent (ISC) than patients with TD (43.2%, 21.2%,  $p < 0.001$ ). ISC males made up 24.2% of ETD and 13.2% of TD ( $p < 0.02$ ) whilst ISC females accounted for 20% of ETD and only 7.9% of TD ( $p < 0.001$ ). By contrast TD was three times more common amongst caucasian males than ETD (47.3%, 15.8%,  $p < 0.001$ ). Caucasian females were equally distributed between the two groups (TD 28.1%, ETD 29.5%, NS). Lymph node, renal and gut TB were given a standard six or nine month treatment in about 70% of cases the rest receiving treatment for one year. Bone TB was treated for between nine and 24 months but on average for 18 months. Death from TB occurred in 7.4% of ETD compared to 10.6% of TD (NS). ETD accounted for a quarter of all TB in this survey and a quarter of these patients had concurrent intrathoracic disease. We agree with previous authors (*Thorax* 1991;46:1) that patients with ETD are more likely to be female and from the Indian subcontinent; however, this presentation does not seem to confer an adverse effect on prognosis.

**Extrapulmonary tuberculosis in Lothian, 1980-1989: delay from start of symptoms to diagnosis**

AG LEITCH *Royal Victoria Chest Clinic, Edinburgh*  
 There were 116 notifications of extrapulmonary TB in Lothian from 1980 to 1989. Eighty seven records of bacteriologically or pathologically proved cases were analysed. Forty two cases of lymphatic, 24 of genitourinary, 16 of bone and joint, and five of abdominal TB are described. Twenty three (seven male, 16 female) of the lymph node patients were Caucasian (C) with a mean age of 62 years (range 10-82) compared with a mean age of 29 years (10-60) for the 19 (14 male, five female) non-Caucasian (NC) patients. Only one (male aged 29) of the 24 genitourinary patients was NC and the 23 patients averaged 54 years (24-82) of age. Eleven (five male, six female) patients with bone and joint disease were C with a mean age of 55 years (28-86) compared with a mean age of 36 years (four to 47) for the five (three male, two female) NC. Of the five cases of abdominal TB three were NC (mean 29 years) and two C (mean 74 years). All patients had normal chest radiographs apart from two with mediastinal lymphadenopathy and 11

	Caucasian	Non-Caucasian
Lymphatic (20 C:18 NC)	9 (2-28)	26 (0-156)
Genitourinary (19 C: 1 NC)	20 (0-104)	0
Bone and joint (7 C: 5 NC)	28 (4-104)	27 (4-104)
Abdominal (0 C: 3 NC)	0	8

patients (six lymph node and five genitourinary TB) whose radiographs showed evidence of previous pulmonary TB. All patients, except three, completed a course of standard chemotherapy. The average delay to diagnosis in weeks is shown in the table. This study confirms the earlier age at presentation of NC with TB and records the relative infrequency of genitourinary TB in this group. Delays from start of symptoms to diagnosis were substantial and, for lymphatic TB, significantly longer in the NC group.

**Pre-employment chest x ray films for health service staff: who needs them?**

I MADAN, M MAINLAND, DC SNASHALL *Occupational Health Department, UMDS, St Thomas's Hospital, London*  
 The code of practice suggested by the joint tuberculosis committee of the British Thoracic Society recommends pre-employment Heaf testing of health care workers at risk (*BMJ* 1990;300:995). The report advises that staff who have had BCG vaccination within 25 years and have a scar (group A) should have chest radiography (CR) if the Heaf result is grade 3 or 4. Those without evidence of BCG within 25 years (group B) should have CR if the Heaf result is grade 2, 3, or 4. We followed the guidelines for one year from December 1990 and Heaf tested 640 consecutive new employees including students. The results of the Heaf tests are summarised in the table. (Several employees did not return for reading; group A,  $n = 37$ ; group B,  $n = 15$ .) No cases of active tuberculosis were detected. The proportion with strongly positive Heaf reactions (3 or 4) in groups A and B were not significantly different ( $p > 0.05$ ). These results suggest that a strongly positive Heaf reaction is a common finding in healthy adults and the predictive value of Heaf testing in this population is low. If we were to continue with this policy we would be performing CR on 35% (95% CI 30%-40%) of our staff. In future we will recommend CR only for those who have relevant respiratory symptoms.

Heaf result	Group A (n = 391) mean age 24	Group B (n = 197) mean age 26
0	36	67
1	103	35
2	135	49
3	102	40
4	15	6

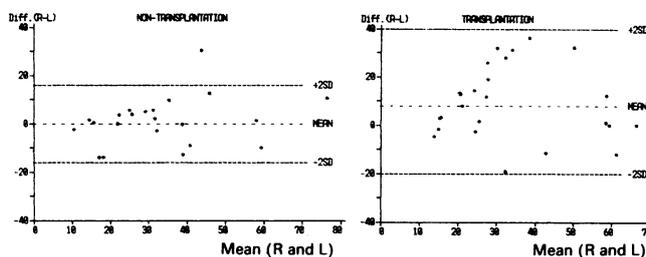
**Tine testing HIV positive patients**

SP HIGGINS, CS BRADBEER, NT BATEMAN *Departments of GU and Thoracic Medicine, St Thomas's Hospital, London*  
 The incidence of tuberculosis (TB) is increased in HIV positive patients. In the United States, where it has been recommended that all HIV positive patients should be tuberculin tested, interpreting the response is simple as BCG vaccination is not practised. In the United Kingdom, there has been no reported increase in TB in the 20-45 age group containing most HIV positive patients; this, and the loss of skin reactivity with deteriorating cellular immunity, leads some to declare tuberculin testing unhelpful in HIV positive patients. St Thomas's Hospital sees a high annual incidence of TB and has many African HIV patients. We routinely Tine test HIV positive patients at presentation. We describe results from the first 127 patients tested. Twenty one patients, seven African, had high grade (2-4) Tine reactions. None had active TB. Six of 21 had CD4+ counts < 200. Two of 21 patients recently treated for pulmonary TB had CD4+ lymphocyte counts of 4 and 60  $\times 10^9/l$  respectively. Four of 19 had CD4+ counts between 20 and 160. Two patients with no previous BCG vaccination, one American (CD4+ count 400), one British (CD4+ count 950) had strongly positive Tine tests. Two patients with *Mycobacterium avium* complex (MAC) infection and CD4+ counts of 50 and 70 respectively had unreactive Tine tests. Although the number of patients is small, we have shown that a positive Tine test (PPD reactivity) may be maintained despite a CD4+ lymphocyte count of < 100, when the patient has tuberculosis or has had BCG. Despite limitations, the Tine test is relatively cheap and a useful way of assessing PPD reactivity in HIV positive patients. Information gained may be useful in the diagnosis of TB in such patients.

**Changes of bronchial mucosal blood flow (BMBF) after lung transplantation (Tx)**

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*Department of Respiratory Physiology, Papworth Hospital, Papworth*

Everard, Cambridge BMBF has been measured by laser Doppler flowmetry in 18 heart-lung transplants, two double lung transplants and 21 non-transplant patients who underwent bronchoscopy. These data were compared with histological and bacteriological results of bronchoscopy. Whereas there were no significant differences in BMBF (mean SD), ml/min/100 g tissue) between the main carina (M) 40.8/14.6 left second carina (L) 33.8 (17.4), and right second carina (R) 34.0 (16.8) in the non-transplant group, there was significant difference between L and R bronchi in the transplant group (M; 37.5 (16.9), L; 29.4 (19.0), and R; 40.0 (17.9)). There was a large difference of BMBF between L and R in four of five patients with chronic rejection or physiological evidence of unreversible severe airway obliteration. Also in three of eight patients with lung infection large differences were seen but not in three transplant patients with normal lung biopsy specimens or in six patients where there was acute rejection. Moreover within the heart-lung transplant group of patients, there were differences in the BMBF of main carina according to diagnosis: acute rejection 22.2 (9.6), chronic rejection 36.6 (9.4), lung infection 51.0 (17.7) and normal lung biopsy specimens 39.7 (12.6). These observations suggest that BMBF may change with complications of lung transplantation. In particular blood flow to the airways may differ between the two sides of the heart-lung transplant. This may have importance for the development of airway obliteration and bronchiectasis seen in the late transplant patients.



### Basal metabolic rate in sleep apnoea

JH GREEN, MB ALLEN *Department of Medicine, St James's University Hospital, Leeds* Obesity is common in patients with obstructive sleep apnoea (OSA) with weight gain frequently preceding the onset of symptoms. Weight loss may be an effective treatment but is often difficult to achieve. To explore the mechanisms of weight problems in OSA we have examined the basal metabolic rate (BMR) and fuel oxidation in such patients. Ten men with symptomatic OSA, confirmed by video-oximetry were studied. BMR was measured using flow through indirect calorimetry and protein oxidation by urinary nitrogen. The results are shown in the table. The BMR of these patients at 8724 (1235) kJ/24 h is within the range predicted by the Harris Benedict equation at 8766 (1476) kJ/24 hours. These results suggest that reductions in basal metabolic rate are not a factor in the development of the obesity found in OSA.

	Mean (SD)
Age (y)	40 (10)
Body mass index (wt/hr <sup>2</sup> )	38.3 (9.4)
Lowest Sa <sub>o</sub> <sub>2</sub> (%)	56.6 (23.6)
4% dips in Sa <sub>o</sub> <sub>2</sub>	25.7 (21.3)
BMR (kJ/24 h)	8724 (1235)
Fuel mix: (% BMR)	
Carbohydrate	36 (28)
Protein	21 (6)
Fat	43 (28)

### Survey of domiciliary nasal continuous positive airway pressure in obstructive sleep apnoea

GM BRAID, CM ROBERTS, JA WEDZICHA *Department of Thoracic Medicine, London Chest Hospital, London* Nasal continuous positive airway pressure (nasal CPAP) is a well established treatment for obstructive sleep apnoea (OSA), and has been shown to reverse symptoms associated with this condition. Although Nasal CPAP is the most effective treatment currently available, it is expensive and may not be initiated if physicians perceive that patient compliance may be poor. We carried out a survey by postal questionnaire of all 30 patients prescribed nasal CPAP at our hospital, who were treated for a mean (SD) of 13.7 (10.1) months. All patients prescribed CPAP presented with symptoms and had multiple episodes of nocturnal oxygen

desaturation. Twenty nine patients (97%), mean age 53 (range 39–63) years, 22 men, seven women, responded to the questionnaire. Twenty four (83%) patients were using nasal CPAP regularly for more than five nights per week, four less regularly, and only one patient was no longer using CPAP. The regular users had CPAP for a mean of 6.9 (1.3) hours a night. The median pressure setting was 7.5 cm H<sub>2</sub>O (range 7.5–12.5). Twenty eight patients thought that they gained from using the CPAP, with one patient reporting no benefit and using the device only once per week. The main advantages patients volunteered were improved quality of sleep (34%), reduced daytime somnolence (24%), and cessation of snoring (21%). Nineteen (66%) patients were in employment, 12 (63%) of these reporting improvement in work performance since commencing nasal CPAP. Ten (34%) patients were unemployed, four due to severity of symptoms thought to be related to OSA, two ascribed dismissal from work as due to daytime somnolence. No patient who was unemployed at time of diagnosis, however, returned to work after commencing CPAP. Twenty four (83%) of patients described some problems using CPAP; these were restriction on travelling (48%), machine noise (38%), mask discomfort (34%), and nasal congestion (31%), social embarrassment (28%), and sleep disturbances (24%). Three of five of the irregular users complained of nasal mask or plug discomfort resulting in a claustrophobic sensation and non-compliance. A total of 97% of patients with OSA reported some symptomatic benefit with nasal CPAP, but the improvement in specific symptoms was lower; 83% of patients prescribed this treatment used it regularly, but there was a high prevalence of equipment related problems. Patients supplied with nasal CPAP require regular review to assess difficulties with its use and to optimise treatment to relieve symptoms.

### Obstructive sleep apnoea in single lung transplant recipients

CM ROBERTS, P ROGERS, DH BRYANT *Department of Thoracic Medicine, St Vincents Hospital, Darlinghurst, Sydney, NSW, Australia* Risk factors for obstructive sleep apnoea (OSA) include increased body weight and neck circumference. We noted these features developing in single lung transplant (SLTP) recipients on long term steroid therapy. We hypothesised that these patients were at increased risk of developing OSA and therefore screened all outpatients attending after successful SLTP. Nine subjects, seven men, median age 46, range 40–56, underwent home sleep monitoring using the MESAM four channel recorder. Oxygen saturation, heart rate, snoring, and body position were monitored. Mean (SD) weight gain since transplantation was 4.4 kg (2.9), four patients reported an increase in collar size. No patient was studied during an acute rejection/infection episode. All patients had periods of loud snoring, mean 25% (7.3%) of recorded time asleep. Seven subjects had > five episodes of desaturation per hour of sleep associated with snoring, mean lowest (Sao<sub>2</sub> 79% (4.3%). One further patient had heat rate fluctuations associated with intermittent snoring and four desaturation episodes per hour suggesting milder OSA. The prevalence of OSA in SLTP patients appears to be much higher than in published control population studies. The reason for this finding is not clear but may be related to steroid usage resulting in increased fat deposition around the neck and possibly localised tissue oedema. The long term significance of these findings is not known but OSA may be a cause of immediate morbidity in such patients.

### Measurement of urinary cyclic GMP in patients with obstructive sleep apnoea (OSA)

A ENGLAND, S EL-GADI, P DIFFLEY, A EVANS, R NEWTON, P EBDEN *Department of Medicine, Prince Philip Hospital, Llanelli and Department of Biochemistry, University College, Swansea* The natriuresis associated with OSA is associated with a rise in plasma atrial natriuretic peptide (ANP), increased overnight urine volumes, and is attenuated by nocturnal continuous positive airway pressure (CPAP). It is uncertain whether the natriuresis is related to the release of ANP from the right atrium by atrial distension or by hypoxic stimulus. We have looked at the overnight urinary breakdown product of ANP, cyclic GMP. We have studied five male patients (mean age 45.2 years) with severe OSA confirmed by sleep studies with a maximum mean fall in oxygen saturation of 38%. We collected overnight urine on three nights: (1) during periods of obstruction; (2) when oxygen levels were normalised by inspired oxygen, and (3) when obstruction was abolished by CPAP. Mean overnight urine volumes (SD) were 0.745 (0.34), 0.78 (0.44), 0.539 (0.32) l. When overnight cyclic GMP was expressed as a ratio of cyclic ANP (to correct for extraction) mean ratios were 0.118 (0.035), 0.134 (0.034), and 0.078 (0.037) and when expressed as a ratio to creatinine the ratios were 3.36 (1.16), 3.56 (1.18), and 2.48 (0.83). The ratios of cGMP/cAMP × 10<sup>2</sup>/creatinine were: 1.46 (0.78), 1.44 (0.56), and 0.64 (0.48). The ratio on the CPAP

night is significantly different from the other nights when compared by *t* test ( $p < 0.001$ ). This study supports the view that ANP release is related to correction of both atrial distension and hypoxia with relief of obstruction with CPAP.

**Do bodybuilders with large necks have sleep apnoea?**

A MUKHERJEE, PA STONE, NCM ATKINS, A WOODCOCK *Department of Respiratory Physiology, Wythenshawe Hospital, Manchester* Previous data suggest that neck circumference is important in defining the risk of sleep apnoea syndrome (for example, 19 of 22 patients with more than 15 >4%  $\text{Sao}_2$  dips/hour had neck circumference >105% predicted; Davies and Stradling 1990). We have investigated a group of non-obese body builders with large necks due to muscle hypertrophy. Twenty male body builders (neck circumference >16.5 inches) were recruited from gymnasia in south Manchester. They completed a screening questionnaire and a full medical examination. Obesity was assessed by body mass index (BMI) calculations and skin fold thickness (Holtain caliper). They were investigated by domiciliary overnight pulse oximetry (Ohmeda Biox 3700) and sleep apnoea quantified by the number of >4%  $\text{Sao}_2$  dips/hour. Eleven of 20 reported loud snoring; five of 20 also reported symptoms of daytime sleepiness. Body mass index measurements were higher than our normal range but % body fat assessments indicated that this was due to muscle rather than fat. None of the subjects desaturated significantly during sleep. Polysomnography performed on the worst reported snorer was also normal. The table summarises the results. We believe that increased neck circumference is an important risk factor for sleep apnoea syndrome but only in relation to obesity.

n = 20	Mean	Range
Age (y)	27.7	24.6 -30.8
Neck circumference (in)	17.1	16.9 -17.3
BMI	27	26.3 -28.5
% Body fat	16.7	14.6 -18.8
>4% $\text{Sao}_2$ dips/hour	0.4	0.22- 0.54

**The frequency content of snores in humans**

NA ISHAQUI, DPS SPENCE, JE EARIS, PMA CALVERLEY *Aintree Chest Centre, Fazakerley Hospital, Liverpool* Heavy snoring is a cardinal symptom of obstructive sleep apnoea and a source of considerable embarrassment in non-apnoeic snorers. There are few objective data, however, about how the pitch of the snore varies between breaths and whether it differs through the night or is influenced by sleep stage or severity of disease. We have considered these problems in a study of seven patients (all men), mean age 50, 17 undergoing standard polysomnography. Upper airways sounds were detected by an air coupled microphone at the manubrium sterni and recorded on video tape. Sleep was staged by using standard criteria with a computer assisted manual system and respiratory variables were verified manually. Snores were identified in each sleep stage (if present) and 30 second periods were digitised and analysed for median frequency by an FFT technique. Sleep quality was variable (TST 334 (55) minutes, sleep efficiency 83 (11)%) with a wide range of apnoea and hypopnoea values (0-50 events an hour). Median frequency of the snores varied in each sleep stage to a similar degree (CV 13%-15%) with no difference between sleep of the same stage whether it occurred early or late in the night. The snores did not differ in frequency with sleep stage but frequency was higher in stage 2 sleep in the four patients with AHI >15 mean 26) (333 (SEM 34 Hz)) than in the other three (mean A + HI 3.1) (219 (SEM 35)). These initial data suggest median frequency is relatively reproducible and may differ with the nature of upper airway obstruction during sleep.

**Can nocturnal hypoxaemia be predicted from daytime respiratory function tests in patients with a thoracoplasty?**

W KINNEAR, L KNOWLES, I JOHNSTON, M WARD *King's Mill Hospital, Mansfield and University Hospital, Nottingham* Respiratory failure is a well recognised late complication of thoracoplasty, often associated with hypoventilation during sleep. We have investigated whether nocturnal hypoxia can be predicted from daytime respiratory function tests in these patients, to see if it is possible to identify which patients should undergo sleep studies to assess the need for assisted ventilation. Ten patients were studied, six women, mean (SD) age 62.6 (7.9). We measured lung volumes by helium dilution (Jaeger), respiratory muscle strength using maximum mouth pressures (Druck) and blood

gases from an arterialised capillary sample (Radiometer). Oxygenation during sleep was recorded with an Ohmeda Biox 3700e oximeter. Daytime measurements showed that  $\text{Paco}_2$  was 5.7 (0.6) kPa, and  $\text{Pao}_2$  was 9.2 (1.8) kPa, with an oxygen saturation ( $\text{Sao}_2$ ), of 93 (3.6) %. Vital capacity (VC) was 49.4 (12.7)% predicted and maximum inspiratory pressure (MIP) was 54.8 (33.1)% predicted. Nocturnal  $\text{Sao}_2$  fell by 4% or more in all 10 patients. Minimum nocturnal  $\text{Sao}_2$  was 77.0 (14.9)%, this being 16.2 (12.8)% below daytime  $\text{Sao}_2$ , and mean nocturnal  $\text{Sao}_2$  was 89.9 (6.3)%. There was no significant correlation between mean or minimum nocturnal  $\text{Sao}_2$  and lung volumes, MIP,  $\text{Pao}_2$ , or  $\text{Paco}_2$ . Nocturnal hypoxia cannot be predicted from daytime parameters in patients with a thoracoplasty, for whom there should be a low threshold for performing a sleep study.

**Phase angle (PA) changes as a measure of paradoxical breathing during sleep related apnoeas/hypopnoeas in patients with the sleep apnoea syndrome (SAS)**

MZ SHAHEEN, NCM ATKINS, PA STONE, V TASKER, A WOODCOCK *North West Lung Centre, Wythenshawe Hospital, Manchester* Ventilatory efforts against occluded upper airway during sleep related apnoea/hypopnoea result in large intrathoracic pressure swings. This causes paradoxical movements of the chest and abdomen the degree of which depends on the extent of ventilatory efforts. Phase angle (DENA Pneumograph DMS100) measures the degree of thoracoabdominal paradox on the basis of the time delay between chest and abdominal movements. We measured the changes in PA during 40 consecutive respiratory events (associated with >4%  $\text{O}_2$  desaturation) in each of the 12 patients with SAS to find its relation with sleep related apnoeas/hypopnoeas. Out of 500 events 364 were apnoeas and 114 were hypopnoeas. PA was uninterpretable in 22 (4.4%). All events were associated with a rise in PA (peak 134 (SD 43.75) degrees). Termination of the event was associated with rapid resolution in PA. There was no significant difference in peak PA and the rate of rise in PA during apnoeas or hypopnoeas; however, resolution of PA was significantly faster with shorter time for complete resolution in apnoeas as compared with the hypopnoeas. Thus phase angle measurements have potential as a screening tool for the detection of sleep related breathing events. It may be complementary to sleep oximetry in screening for SAS.

	T1 (s)	Peak PA (degrees)	T2 (s)*	T3 (s)*	B (degrees)*
Apnoea					
Mean (SD)	24.5 (11.2)	137 (42)	10.7 (4.1)	4.05 (2.3)	72 (40)
Hypopnoea					
Mean (SD)	25.5 (11.7)	128 (48)	12.7 (6.3)	5.9 (4.3)	62 (33)

\*p < 0.05.

T1, time to reach peak PA; T2, time for total resolution in PA; T3, time for 50% resolution in PA; B, PA resolved in 8 s.

**Effect of a subanaesthetic dose of halothane on the ventilatory response to sustained hypoxia in normal subjects**

PM WARREN, C YOUNG, GB DRUMMOND *Rayne Laboratory, Unit of Respiratory Medicine, and Department of Anaesthetics, University of Edinburgh* In humans, sedative concentrations of halothane suppress the ventilatory response to acute hypoxia (Knill and Gelb. *Anesthesiology* 1978;49:244), but the effect on the response to sustained hypoxia is not known. We have therefore measured ventilation in nine normal subjects (8 men, 1 woman; age range 25-43 y) during (A) 15 minutes breathing air, (B) 20 minutes' isocapnic hypoxia ( $\text{Sao}_2$  80%-85%), and (C) five minutes breathing air, both without and with 0.1% halothane (roughly 0.1 minimum alveolar concentration) added to the inspired gas. The order was randomised and the studies separated by 60 minutes breathing room air. Halothan did not affect baseline normoxic  $\dot{V}_E$  (table),  $\dot{V}_{O_2}$ ,  $\dot{V}_{CO_2}$ , or  $\text{PETCO}_2$ . There was a biphasic hypoxic ventilatory response in both studies. In the control study, the initial hypoxic  $\dot{V}_E$  was significantly greater ( $p < 0.05$ ) than at the end of hypoxia, and both baseline and recovery normoxic values. Halo-

	Baseline normoxia	Initial hypoxia	End hypoxia	Recovery normoxia
$\dot{V}_E$ (l/min; mean (SD)):				
Control	7.57 (1.04)	14.54 (2.73)	10.74 (2.59)	7.58 (1.44)
Halothane	7.19 (1.40)	12.08 (2.96)	10.12 (2.20)	7.86 (2.25)

thane significantly reduced the initial rise in ventilation ( $p < 0.05$ ) but did not enhance the subsequent depression. Normoxic  $\dot{V}E$  after hypoxia was similar in both studies, and did not fall below baseline in either.  $PETCO_2$  did not change significantly during either study, but was slightly lower ( $p < 0.05$ ) in the control (5.03 (0.38) kPa) compared with halothane (5.22 (0.24) kPa) study during initial hypoxia. Halothane therefore impairs the initial ventilatory response to hypoxia but does not attenuate that to sustained hypoxia.

### Effect of breathing strategy on two techniques of incremental threshold loading

PA BARDSLEY, HS HALL, S BENTLEY, SJ SINGH, MDL MORGAN *Department of Respiratory Medicine, Glenfield General Hospital, Leicester* Incremental threshold loading (ITL) is used as a test of inspiratory muscle performance. This is usually performed by breathing through a weighted inspiratory plunger. We have developed a solenoid threshold device which opens to supply air only after a predetermined negative mouth pressure is achieved. Our previous work has shown that ITL with the solenoid device generates a more accurate mouth pressure response and is less variable at higher loads than the weighted plunger (*Thorax* 1991;46:295P). Altering breathing pattern may influence some measures of inspiratory muscle endurance. Little data on this exist for ITL with the plunger and none for the solenoid valve. Six normal subjects (four men and two women aged 23–41 years) were randomised to perform ITL with both systems (10 cm  $H_2O$  or 50 g increments every minute) twice with the breathing pattern fixed and twice when they were free to adopt whatever breathing strategy they chose. Breathing frequency was fixed at 12 breaths a minute and the mouth pressure trace displayed on an oscilloscope to keep inspiratory time constant. The mean final mouth pressure achieved with the solenoid valve was 95 (SEM, 16) cm  $H_2O$  with the breathing pattern regulated compared with 105 (16) cm  $H_2O$  with the breathing pattern free (NS). With the plunger these values were 90 (11) and 86 (15) cm  $H_2O$  respectively (NS). With the solenoid valve work performed or pressure time product (PTP) at completion of the tests was 2822 (734) cm  $H_2O$ .s with breathing pattern fixed compared with 2912 (704) (NS). with the plunger mean PTP was 5532 (1400) cm  $H_2O$ .s with the breathing pattern fixed and 6663 (1653) with the breathing pattern free (NS). We conclude that ITL with both systems is not influenced by breathing pattern. Neither system requires external regulation and thus provide a simple and reproducible test of inspiratory muscle strength and endurance.

### Breath holding time in normal subjects, snorers, and patients with sleep apnoea

V TASKAR, N CLAYTON, M ATKINS, M SHAHEEN, P STONE, A WOODCOCK *North West Lung Centre, Wythenshawe Hospital, Manchester* We have found a paradoxical respiratory pattern before the end of apnoeas that is similar to that seen at the breakpoint of a voluntary breath hold. Arousal that accompanies end of apnoeas may be caused by an unpleasant respiratory sensation similar to that experienced at the end of a voluntary breath hold. We have examined breath hold time (Bht) at increasing levels of end tidal  $CO_2$  ( $EtCO_2$ ) (*Lancet* 1966;2:368) in normal subjects ( $n = 40$ ); sleep apnoea (SAS) ( $n = 30$  (mean apnoea index 46.33 (8.25)), and snorers ( $n = 16$ ). Basal Bht was shorter in SAS compared with normal subjects and snorers. SAS patients started at a higher basal  $EtCO_2$  and tolerated higher levels of  $EtCO_2$  than normal people or snorers. An  $EtCO_2$  of  $> 8\%$  was achieved by 14 of 40 normal subjects (35%), 20 of 30 SAS (66%) and 8 of 16 (S) (50%) ( $\chi^2 p = 0.032$ ). The slope of Bht/ $EtCO_2$  was significantly different between SAS and normal subjects ( $p = 0.008$ ) and snorers ( $p = 0.018$ ). There was no significant difference between subjects and snorers. We conclude that in SAS (1) the basal  $EtCO_2$  is higher; (2) they tolerate higher  $EtCO_2$  at maximal Bht; and (3) as  $EtCO_2$  rises, Bht goes down less in SAS compared with normal subjects and snorers.

Mean (SE)	p Value	SAS	p Value
Basal $EtCO_2$ (%)	5.83 (0.1) ( $p < 0.001$ )	6.72 (0.21)	6.01 (0.12) ( $p = 0.025$ )
Basal Bht (s)	32.38 (2.02) ( $p < 0.001$ )	20.61 (2.25)	33.62 (5.43) ( $p = 0.014$ )
Highest $EtCO_2$ achieved	7.5 (0.12) ( $p < 0.001$ )	8.32 (0.16)	7.74 (0.25) ( $p = 0.052$ )
Bht at highest $EtCO_2$	17.03 (1.23) ( $p < 0.031$ )	13.17 (1.22)	16.44 (2.63) ( $p = 0.204$ )
Slope of Bht $EtCO_2$ (mean (SD))	-10.19 (6.1) ( $p < 0.008$ )	-6.466 (5.05)	-11.93 (10.17) ( $p = 0.018$ )

### Is hypercapnia related to diaphragm fatigue in patients with a thoracoplasty?

W KINNEAR, L KNOWLES, I JOHNSTON, M WARD *King's Mill Hospital, Mansfield, and University Hospital, Nottingham* In patients who have had a thoracoplasty, the diaphragm is subjected to an increased elastic and resistive load. It may also be weak as a consequence of a phrenic nerve crush or avulsion. In normal subjects, the likelihood of developing diaphragmatic fatigue and hypercapnia during loaded breathing can be predicted from the tension time index of the diaphragm (TTIdi). We have investigated whether there is a similar relation between TTIdi and hypercapnia in patients with a thoracoplasty, to see if TTIdi could be used as a screening test to identify patients at risk of developing hypercapnic respiratory failure. Ten patients (six women), mean (SD) age 62.6 (7.9) years, were studied in a clinically stable state. Blood gases were measured from an arterialised capillary sample (Radiometer). Air filled balloons (Morgan) were used to record oesophageal and gastric pressures (Druck). Transdiaphragmatic pressure ( $P_{di}$ ) was measured during tidal breathing and maximal sniffs. The maximum  $P_{di}$  attained during tidal breathing, as a proportion of sniff  $P_{di}$ , was multiplied by the duty cycle of the diaphragm (inspiratory time/total breath time) to obtain TTIdi. The mean  $P_{aCO_2}$  was 5.7 (0.6) kPa and TTIdi was 0.085 (0.047). There was no significant relation between  $P_{aCO_2}$  and TTIdi, with a Spearman rank correlation coefficient of 0.716 (NS). We conclude that hypercapnia in patients with a thoracoplasty is unlikely to be a reflection of diaphragmatic fatigue, and that measurement of TTIdi in these patients is of little clinical value.

### Measurement of attenuation of pseudolung sounds by animal lung and chest wall

SAT STONEMAN, JE EARIS *Department of Mechanical Engineering, University College, Swansea and Aintree Chest Centre, Fazakerley Hospital, Liverpool* The higher frequency components of lung sounds are attenuated as they pass through the lung and chest wall and this is said to be why sounds heard at the chest wall are low pitched with little energy above 500 Hz. This study presents results of the attenuation of pseudolung sounds by specimens of porcine chest wall and bovine lung. These specimens were mounted in a purpose designed two chamber acoustic rig and subjected to white noise from a loud speaker. The difference in sound level from one side of the specimen to the other was detected by matched microphones, spectrally analysed and a transfer function computed. In the 0 to 2000 Hz range pseudolung sound was attenuated on average by 35 dB as it traversed the chest wall and 25 dB as it passed through a similar thickness of lung. The thicker specimens exhibited higher attenuations but this did not comply with numeric prediction of attenuation of 6 dB for doubling of surface mass. Maximum attenuation of between 50 and 60 dB occurred at 3500 Hz. Above this level the attenuation dropped to 45 dB, an observation inconsistent with the behaviour of noise control materials in engineering. The likely explanation is structural resonance within the tissues. From 4000 to 5000 Hz the attenuation remained at roughly 45 dB. This model provides direct evidence of the complex frequency dependent acoustic attenuation occurring in the chest wall and lung and suggests that variation in the thickness of the chest wall and subcutaneous fat needs to be taken into account when interpreting chest wall recordings. The results also indicate that some higher frequency energy may be present at the chest wall.

### The effects of dopaminergic stimulation on airway dynamics and respiratory muscle strength in Parkinson's disease

PF DE BRUIN, VMS DE BRUIN, AJ LEES, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, and Department of Neurology, University College and Middlesex Hospital, School of Medicine, London* Airflow limitation is often present in patients with Parkinson's disease (PD) and is possibly caused by upper airways dysfunction. To further investigate this problem we have studied nine subjects with moderate and severe PD (eight men, mean age 51.4 (SD 5.4) y; stage II ( $n = 1$ ), III ( $n = 3$ ), IV ( $n = 5$ ) Hoehn and Yahr scale) after temporary interruption of antiparkinsonian treatment (OFF) and during continuous subcutaneous infusion of a direct stimulant of dopamine receptors, apomorphine (ON). Maximum inspiratory and expiratory pressures at the mouth (MIP, MEP) were measured at functional residual capacity and total lung capacity, respectively. Respiratory resistance ( $R_{rs}$ ) at 6 Hz was determined during tidal breathing by the forced oscillation technique. Maximum flow volume loops were classified as normal ( $n = 2$ ), type A when flow oscillation and lowered peak flows were present and type B when the

primary aspect was a rounding off or flattening of the expiratory curves together with a shift of the PEF to lower volumes. Results (mean (SD)) are summarised in the table. Apomorphine was effective in increasing MEP and reducing flow oscillation on maximum flow volume loops. MIP were very low and did not improve significantly with treatment. Airflow resistance during tidal breathing was normal even off treatment, suggesting significant upper airway narrowing might be present only during forced manoeuvres.

	Off	On	<i>p</i> Value paired <i>t</i> test
FVC (l)	3.4 (0.8)	3.5 (0.9)	0.638
FEV <sub>1</sub> (l)	2.7 (0.9)	2.9 (0.9)	0.306
PEF (l/s)	4.7 (3.3)	5.7 (2.7)	0.093
MIP (cm H <sub>2</sub> O)	-24.8 (17.1)	-30.8 (16.8)	0.134
MEP (cm H <sub>2</sub> O)	44.9 (26.9)	62.9 (30.5)	0.009
Rrs (cm H <sub>2</sub> O/l/s)	2.3 (0.8)	2.3 (0.8)	0.841
Flow pattern (A/B)	4/3	0/7	

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**Bronchial hyperresponsiveness, airway calibre and atrial natriuretic peptide in chronic heart failure**

SA EVANS, D HETMANSKI, WJ KINNEAR, IDA JOHNSTON *University Hospital, Nottingham* Patients with heart failure may exhibit bronchial hyperresponsiveness (BHR), but the mechanism is unclear. It may in part be due to airway narrowing, but neurohumoral influences could be important. Plasma atrial natriuretic peptide (ANP) concentration is increased in heart failure. ANP is a potent bronchodilator and protects against bronchial challenge in asthma. We have investigated the relations between BHR, plasma ANP concentration, and airway calibre in 37 patients (eight women), mean age 62 years (range 46-79), with chronic heart failure. We measured FEV<sub>1</sub>, PEFR, FEF<sub>50%</sub> and PD<sub>20</sub>-FEV<sub>1</sub> to methacholine with the method of Yan *et al* (*Thorax* 1983;38:760), maximum cumulative dose being 2.8 mg. Resting supine plasma ANP was measured by radioimmunoassay in 28 patients. The 11 patients with a measurable PD<sub>20</sub>-FEV<sub>1</sub> had a lower mean FEV<sub>1</sub> (1.83 (SD 0.5) *v* 2.33 (0.44) l, *p* < 0.01), FEF<sub>50%</sub> (88 (46) *v* 150 (71) l/min, *p* < 0.02), and PEF (375 (92) *v* 442 (93) l/min, *p* = 0.05) than those without BHR. Plasma ANP concentration was not related to % predicted FEV<sub>1</sub> (*r* = -0.3), *p* = 0.1), FEF<sub>50%</sub> (*r* = -0.2, *p* = 0.4), or PEF (*r* = -0.2, *p* = 0.2). ANP concentrations in those with a measurable PD<sub>20</sub>-FEV<sub>1</sub> (*n* = 8) were lower, though not significantly (149 (120) *v* 256 (137) pg/ml, *p* = 0.1) than in eight patients without BHR with similar baseline FEV<sub>1</sub> values (1.9 (0.6) *v* 2.0 (0.4) l). We conclude that in patients with heart failure BHR is seen more commonly in those with narrower airways. Plasma ANP is not related to the degree of airway obstruction, and we have been unable to show any correlation between ANP and BHR.

**Normal range for transdiaphragmatic sniff pressure with catheter mounted pressure transducers**

SA EVANS, WJM KINNEAR, AJ COWLEY, IDA JOHNSTON *University Hospital, Nottingham* Transdiaphragmatic pressure (Pdi) during a maximal sniff is a commonly used test of diaphragm strength. A normal range is available for sniff Pdi with air filled balloons (*Clin Sci* 1985;69:91). Measurement of sniff Pdi with catheter mounted transducers has several potential advantages compared with air filled balloons including the use of a single, more flexible catheter, a faster frequency response, and the ability to make direct repeated measurements with the same equipment. A normal range is not available however. We studied 50 normal subjects, five of each sex, in each of the third to seventh decades. Oesophageal pressure (Poes) and gastric pressure (Pg) were recorded using two microtransducers mounted 15 cm apart on a single catheter (Gaeltec Ltd). Pdi was taken as the best of 10 maximal sniffs from functional residual capacity. Mean (SD) values in cm H<sub>2</sub>O were as in the table. Regression analysis for age, height, and weight showed these factors to have no influence on sniff PDI. Despite differences in the partitioning of sniff Pdi between Pg and Poes our normal range is similar to that published for air filled balloons.

	Present study		Air filled balloons	
	Men	Women	Men	Women
Pdi	149 (32)	127 (22)	148 (24)	122 (25)
Pg	68 (36)	62 (28)	43 (32)	29 (24)
Poes	94 (21)	74 (22)	105 (26)	92 (22)

**Ventilation perfusion (V/Q) scans in cryptogenic fibrosing alveolitis (CFA)**

SJ BOURKE, AD GASCOIGNE, T HAWKINS, P KEAVEY, PA CORRIS *Departments of Respiratory Medicine and Medical Physics, Freeman Hospital, Newcastle upon Tyne* Ventilation perfusion scans are rarely performed in the routine clinical management of CFA but are being increasingly used to assess the V/Q relations of such patients undergoing single lung transplantation so there is now a need to define the full spectrum of V/Q appearances in this disease. We studied 45 consecutive patients (30 men, mean age 53 years) with advanced CFA who were being considered for lung transplantation. All had progressive dyspnoea, lung crackles, hypoxia, and mixed restrictive and diffusion defects (mean TLC 59%, Kco 56% predicted); 18 (40%) were ex-smokers, 36 (76%) were clubbed, and 33 (73%) had undergone lung biopsy. Xenon-133 V scans showed defects in 13 (29%) and washout delay of gas in 15 (33%) patients (seven ex-smokers, four reduced FEV<sub>1</sub>/VC ratio); 10 had asymmetrical distribution of V with one lung receiving >60% V. Q scans using technetium-99m albumin microspheres showed uniform Q in 8 (18%), mild defects in 18 (40%) and major defects in 19 (42%) patients. Q was asymmetrical in 20 (45%) patients. V/Q relations were matched in 15 (33%), mildly mismatched in 15 (33%), and severely mismatched in 15 (33%) patients but this did not correlate with Po<sub>2</sub>, A-a<sub>o</sub> gradient or Kco. V/Q scans showed the typical pattern of pulmonary embolism in eight (18%) patients. In general Q was more severely affected than V. There is a diverse range of V/Q scan appearances in CFA and no particular pattern can be considered as characteristic of the disease. Asymmetrical distribution of V and Q between the two lungs may be severe and this may contribute to the decision as to which side is chosen for single lung transplantation.

**Simultaneous tracheal and oesophageal pH (stop) measurements in patients with gastrooesophageal reflux and asthma: microaspiration does occur**

CIA JACK, J TRAN, G RUSSELL, RJ DONNELLY, PMA CALVERLEY, CRK HIND, CC EVANS *The Cardiothoracic Centre, Liverpool* The association between gastro-oesophageal reflux and asthma is well recognised. Several hypotheses have been proposed including tracheal microaspiration of gastric contents, but it has been difficult to document tracheal microaspiration by radiolabelled isotope techniques. We have recorded the tracheal and oesophageal pH over a 24 hour period and have studied three controls and four patients with gastro-oesophageal reflux and asthma. Patients were admitted for an OGD and rigid bronchoscopy performed under general anaesthesia. At operation a tracheal pH probe was placed 2 cm above the carina and the oesophageal probe positioned 5 cm above the lower oesophageal sphincter. Thereafter simultaneous recordings were obtained for 24 hours and during this time the patient was ambulant and kept an hourly peak flow chart. The procedure was well tolerated. During significant episodes of gastro-oesophageal reflux (oesophageal pH >4.0 for a period of 15 seconds or more) the tracheal pH on some occasions fell. If there was a fall in tracheal pH for more than 30 minutes there was always a fall in the peak flow rate. There was no significant oesophageal aspiration in controls, nor was there any alteration in tracheal pH or peak expiratory flow rate. These preliminary results support the hypothesis that tracheal microaspiration does occur and may be a causative factor in bronchospasm.

**An audit of prolixity, investigation rates and follow up rates in 490 new consultations in a chest clinic**

AG LEITCH *Royal Victoria Chest Clinic, Edinburgh* This study audited 490 new referrals to a chest clinic in 1990 to determine the investigative behaviour of eight consultants and 20 registrars. Twenty two per cent of the referrals were for asthma, 18% chronic bronchitis, and 18% lung cancer. All patients had chest radiography, FEV<sub>1</sub> and urinalysis performed; these investigations did not count in the analysis. Patients with lung cancer were kept in hospital and are excluded from analysis of clinic initiated investigations. Prolixity (letter length in mm), investigations initiated per patient (pp), and follow up rates were measured. On average, consultants (2.3) performed fewer investigations per patient than registrars (3.1) but prolixity was similar (110 *v* 120 mm). For the eight consultants the average number of investigations ranged from 0.1 to 6.1 per patient and there was a positive correlation between prolixity and number of investigations per patient (*r* = 0.85, *p* < 0.01). Favoured consultant investigations were additional pulmonary function tests (0.9 per patient), haematology (0.5 per patient) and biochemistry (0.3 per patient).

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Consultants, on average, followed up fewer patients than registrars (64% v 79%) but the consultant rate varied from 45% to 81%. There was a significant correlation between prolixity and follow up rate ( $r = 0.68, p < 0.05$ ). Contact tracing among registrars identified two prolix subjects with high investigation and follow up rates who are known to have been closely associated in time and space with the two most prolix consultants. This pattern of medical practice may therefore be acquired rather than innate. This study of prolixity, investigation rates, and follow up practices indicates, if patient outcome does not differ between consultants (currently being tested), that there exists potential for saving secretarial, laboratory, and clinic time as well as money.

#### Different methods for calculating diurnal variation in peak expiratory flow (PEF)

FP GANNON, DT NEWTON, A AL-SHATTI, CFA PANTIN, PS BURGE *Occupational Lung Disease Unit, East Birmingham Hospital, Birmingham, Staffordshire Polytechnic, Stafford, City General Hospital, Stoke* Diurnal variation is important in the investigation and management of asthma and non-reversible airflow obstruction. A number of formulas exist for its calculation, but the most appropriate is not apparent. Using 274 PEF records (mean duration 23 days, mean number of readings per day eight) we have compared 10 different measures of diurnal variation against the mean PEF to determine the least correlated. Mean PEF for the group was 480 (range 209–740) l/min. All measures of diurnal variation of PEF were significantly correlated with the mean PEF. Standard deviation of PEF and maximum–minimum PEF were least correlated. Measures containing the predicted in the denominator were generally less correlated. Measures containing the mean or the maximum values as the sole denominator were most correlated. These results are likely to be dependent on the severity of respiratory disease in the group studied.

	Spearman correlation coefficient
Max – min/mean	0.52**
Max – min	0.16*
Max – min/max	0.52**
SD PEF/mean	0.52**
SD PEF	0.14*
SD/predicted (PRD)	0.26**
Max-min/PRD	0.28**
Max-min/PRD-mean	0.26**
Cosinor amplitude/mean	0.51**
Cosinor amplitude/PRD	0.26**

\* $p < 0.01$ ; \*\* $p < 0.001$ .

#### Inhaled formoterol: a comparison of the cardiovascular and metabolic effects with salbutamol and fenoterol

PR BREMNER, K WOODMAN, CD BURGESS, J CRANE, N PEARCE, R BEASLEY *Wellington School of Medicine, Wellington, New Zealand* Important differences in the cardiovascular and metabolic effects of  $\beta_2$  agonists have been identified. These may account for the concerns raised regarding their safety. In this study we have compared the cardiovascular and hypokalaemic effects of a new long acting  $\beta_2$  agonist formoterol (FO) with those of salbutamol (S), fenoterol (FE), and placebo (P) in twelve healthy volunteers using a randomised double blind cross over design. On the study days the subjects inhaled either FO (24  $\mu\text{g}$ ), S (400  $\mu\text{g}$ ), FE (400  $\mu\text{g}$ ), or P at 30 minute intervals for five doses. Heart rate (HR), total electromechanical systole (QS<sub>2</sub>I), a measure of inotropy, the corrected QT interval (QTc) and plasma potassium (K<sup>+</sup>) were measured before drug administration, 10 minutes after each inhalation and at 30 minute intervals for three hours after the last inhalation. Maximum changes for the agents were compared. All the active agents significantly increased HR and QTc and decreased QS<sub>2</sub>I and plasma K<sup>+</sup> compared with P ( $p < 0.001$ —see table). FE had a significantly greater effect on all the cardiovascular parameters compared with S and FO ( $p < 0.001$ ). When compared to

	Mean (SEM) maximum change			
	P	FO	S	FE
HR (bpm)	-2.7 (1.6)	+16.7 (2.7)	+12.8 (3.3)	29.8 (3.9)
QS <sub>2</sub> I (ms)	-7.6 (2.4)	-35.5 (3.9)	-31.5 (2.6)	-53.8 (4.0)
QTc (ms)	+7.1 (3.0)	+40.2 (8.4)	+32.5 (5.2)	+61.4 (7.6)
Plasma K <sup>+</sup> (mmol/l)	+0.08 (0.07)	-0.96 (0.09)	-0.55 (0.06)	-1.13 (0.07)

S, FO, and FE had a greater effect on plasma K<sup>+</sup> ( $p < 0.001$ ). Formoterol is a more selected  $\beta_2$  agonist than fenoterol and has similar cardiovascular effects as salbutamol when inhaled repeatedly by normal volunteers.

#### Partial v full $\beta$ receptor agonism: a clinical study of inhaled salbutamol and fenoterol

J CRANE, PR BREMNER, R SIEBERS, N PEARCE, R BEASLEY, C BURGESS *Department of Medicine, Wellington School of Medicine, Wellington, New Zealand* We investigated the maximum cardiovascular and metabolic effects of repeated inhalations of fenoterol and salbutamol in eight healthy volunteers. The subjects attended the laboratory on two occasions, at least four days apart, in the fasting state. After baseline recordings of heart rate (HR), electromechanical systole (QS<sub>2</sub>I, a sensitive measure of inotropy), plasma potassium (K), and plasma cyclic AMP (cAMP), the subjects inhaled 400  $\mu\text{g}$  (two puffs) of either salbutamol or fenoterol from a metered dose inhaler through a Volumatic spacing device at 10 minute intervals. Recordings were repeated 5 minutes after each dose. Drug inhalation continued until either 48 puffs had been given or until plasma K and QS<sub>2</sub>I had plateaued as assessed by stable recordings of each for at least three consecutive doses over 30 minutes. The treatments were randomised and administered double blind. All subjects reached a plateau. Cumulative log dose-response curves were constructed for each subject and the maximum response (E<sub>max</sub>) for each subject calculated. The E<sub>max</sub> after fenoterol was greater than that after salbutamol for plasma K (-1.4 v -1.03 mmol/l,  $p = 0.0014$ ), QS<sub>2</sub>I (-71.8 v -57.5 ms,  $p = 0.047$ ), cAMP (33.8 v 18.1 nmol/l,  $p = 0.0021$ ) and HR (44.9 v 32.5 bpm,  $p = 0.19$ ). We conclude that in normal volunteers, inhaled salbutamol behaves as a partial agonist at  $\beta$  adrenoceptors when compared with fenoterol.

#### Comparison of the $\beta_2$ adrenoceptor selectivity of inhaled fenoterol and salbutamol

DM NEWNHAM, NM WHEELDON, BJ LIPWORTH, DG MCDEVITT *Department of Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee* Fourteen healthy volunteers were randomised to receive pretreatment with either 25 mg atenolol or placebo, followed by inhaled fenoterol (F) or salbutamol (S) in equal doses by weight (1 mg and 4 mg), in a double blind crossover design. Significant  $\beta_1$  adrenoceptor blockade using 25 mg atenolol was shown by a mean (SEM) reduction in exercise heart rate of 21 (1)% . Measurements of serum K, tremor (Tr), HR, SBP, inotropic response (Doppler stroke distance), and ECG parameters (T wave, Q-Tc) were measured at baseline and 30 minutes after inhaling cumulatively, 1 mg and 3 mg of each  $\beta_2$  agonist. The study was designed to detect a difference in HR of 10 beats/min between F and S with 90% power. Values are means and 95% CI as change from baseline. Plasma concentrations of F and S showed a fourfold rise between 1 mg and 4 mg with peak levels at five minutes after inhalation. A dose response effect occurred for all parameters measured. At 4 mg, F produced greater hypokalaemic (mmol<sup>-1</sup>) and Tr (% change) responses than S: 1.30 (1.19–1.41) v 1.11 (1.00–1.22) and 3498 (2574–4422) v 2551 (1627–3475) respectively. The HR (beats/min) responses to F and S were identical: 44 (39–49) v 45 (40–50) and the attenuation by atenolol was comparable: 14 v 16% (F v S). F produced a greater SBP (mm Hg) response than S: 15 (12–18) v 9 (6–12) with equivalent attenuation by atenolol: 11% v 9%. There were no differences between F and S for the inotropic response or ECG parameters. In summary (1) the effects of F and S on HR were equivalent with no differences between F and S in attenuation of cardiac responses by atenolol; (2) no evidence for any difference in  $\beta_2$  selectivity between F and S was found even at higher than conventional doses; (3) F produced greater  $\beta_2$  mediated effects than S.

#### Sex differences in hypokalaemic, chronotropic, and electrocardiographic effects of inhaled terbutaline

BJ LIPWORTH, ARA RAHMAN, DG MCDEVITT, AD STRUTHERS *Department of Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee, Scotland* Sex differences in the chronotropic effects of infused isoprenaline ( $\beta_1 + \beta_2$  agonist) have been previously described (Johansson *et al. Scand J Clin Lab Invest* 1988;48:183). In the light of recent concerns regarding the safety of inhaled  $\beta_2$  agonists, a study was performed to investigate possible sex differences in hypokalaemic (K), chronotropic (HR) and electrocardiographic effects (T wave and Q-Tc) of inhaled terbutaline, a selective  $\beta_2$  agonist. Twenty healthy volunteers (10 females) were recruited. Mean age was 24 years for

females (F) and 22 years for males (M). The above measurements were made for four hours after inhalation of 5 mg terbutaline or placebo. The effect of terbutaline on serum potassium (K) was chosen as the primary end point, to detect a 0.3 mmol<sup>-1</sup> difference between sexes, with a  $\beta$  error of 0.2, and  $\alpha$  set at 0.05. The hypokalaemic effects of terbutaline were significantly greater in females and were (means and 95% CI): lowest K: F 3.12 mmol<sup>-1</sup> (2.96–3.28) v M 3.65 mmol<sup>-1</sup> (3.49–3.81) ( $p < 0.05$ ), average K throughout four hours: F 3.39 mmol<sup>-1</sup> (3.33–3.46) v M 3.78 mmol<sup>-1</sup> (3.72–3.85) ( $p < 0.0001$ ). There was no significant regression between body weight and K response to terbutaline ( $r = -0.22$ ). There were also significant sex differences for T wave, Q-Tc, and HR responses. Maximum percentage fall in T wave amplitude (delta T wave %) after terbutaline was: F 44.6% (32.1–57.0) v M 22.4% (9.9–34.8) ( $p < 0.05$ ). HR response (delta) was: F 25 beats/min (16–34) v M 14 (7–21) ( $p < 0.01$ ). Thus, females showed greater responsiveness of extrapulmonary  $\beta_2$  adrenoceptors. Further studies are in progress to investigate possible effects of sex hormones on lymphocyte  $\beta_2$  receptor density, affinity, and G-protein coupling at different phases of the menstrual cycle.

#### A comparison of the cost effectiveness of salmeterol v salbutamol in patients with moderate asthma

JR HALL, ML MIOCEVICH, BA O'NEILL, NEJ WELLS *Glaxo Pharmaceuticals UK Ltd* One hundred and forty seven patients with moderate asthma entered into a double blind, parallel group study to determine the cost effectiveness of salmeterol (SALM;  $n = 80$ , 50  $\mu\text{g}$  twice daily) and salbutamol (SALB;  $n = 67$ , 400  $\mu\text{g}$  twice daily) over seven and a half months. The mean total cost per patient for each treatment group was calculated and included the costs of study drug, relief medication, and additional consultations in primary and secondary care. The mean total cost was £324 in the SALM group and £162 in the SALB group (2:1, SALM:SALB). Effectiveness was measured in terms of: (1) freedom from symptoms. 62% of salmeterol (SALM) and 40% of salbutamol (SALB) treated patients had no symptoms in the final week of the study. (2) an improvement in (A) am or (B) pm PEF from below 90% of predicted value to above this level or for those already above the 90% mark at the start of the study any further increase in PEF. Thirty seven per cent of the SALM and 12% of SALB patients met these criteria for am PEF and 36% and 20% respectively for pm PEF. Cost effectiveness was calculated by dividing the mean total cost by the percentage of effectively treated patients. Thus the cost per effectively treated patient using: (1) freedom from symptoms was £523 on SALM and £405 on SALB (1.29:1). (2a) am PEF was £876 on SALM and £1350 on SALB (1.1:1.54). (2b) pm PEF was £900 on SALM and £810 on SALB (1.11:1). These results indicated that SALM is more effective than SALB in achieving symptom control and improving lung function and this difference leads to cost effectiveness advantages for salmeterol over salbutamol that are not apparent from a simplistic view of drug purchase costs.

#### Salmeterol xinafoate: an extended comparison with salbutamol in patients with moderate asthma receiving prophylactic therapy

EH WALTERS, DJ HENDRICK, TA LOWE *Newcastle General Hospital and Allen and Hanburys Limited* Salmeterol xinafoate (Serevent) is a new, long acting, selective  $\beta_2$  adrenoceptor agonist recommended for the treatment of asthma. This multicentre, double blind, parallel group extension study compared the efficacy and tolerability of salmeterol 50  $\mu\text{g}$  xinafoate twice daily with that of inhaled 400  $\mu\text{g}$  salbutamol twice daily, both via the Diskhaler, with relief salbutamol, over a 29 week treatment period. One hundred and forty seven patients with moderate asthma (FEV<sub>1</sub>, PEF or FVC > 50% predicted; > 15% reversibility to salbutamol on entry to the basic study) were randomised to study medication (salmeterol xinafoate 80, salbutamol 67). All were receiving concurrent prophylactic therapy for asthma. After 29 weeks treatment, both morning and evening PEFs were still substantially higher with salmeterol xinafoate than with salbutamol (mean treatment difference for morning 31.7 l/minute,  $p = 0.002$  and for evening 15.7 l/minute,  $p = 0.079$ ). These improvements were evident after 16 weeks of treatment and were maintained throughout 29 weeks of treatment; 53% of patients receiving salmeterol xinafoate reported less frequent asthma symptoms compared with 24% on salbutamol ( $p = 0.001$ ), and improvement in severity of symptoms was also greater in the salmeterol xinafoate group ( $p = 0.005$ ). At the end of 29 weeks treatment, patients in the salmeterol xinafoate group experienced 57% of days during treatment where no additional relief salbutamol was required compared to zero days in the salbutamol

group ( $p = 0.003$ ). Both treatment groups reported similar numbers of minor and serious adverse events, most of which concerned the respiratory system. This extension study shows that long term inhaled 50  $\mu\text{g}$  salmeterol xinafoate twice daily is well tolerated and offers significant clinical benefits to patients with moderate asthma compared to 400  $\mu\text{g}$  salbutamol twice daily with no loss of efficacy over the treatment period.

#### Salmeterol xinafoate: a comparison with salbutamol in patients with moderate asthma receiving prophylactic therapy

EH WALTERS, DJ HENDRICK, TA LOWE *Newcastle General Hospital and Allen and Hanburys Limited* Salmeterol xinafoate (Serevent) is a new, long acting selective  $\beta_2$  adrenoceptor agonist recommended for the treatment of asthma. This multicentre, double blind, parallel group study compared the efficacy and tolerability of inhaled 50  $\mu\text{g}$  salmeterol xinafoate twice daily with that of inhaled 400  $\mu\text{g}$  salbutamol twice daily, both via the Diskhaler device, with relief salbutamol, over a six week treatment period. Three hundred and eighty three patients with moderate asthma (FEV<sub>1</sub>, PEF, or FVC > 50% predicted; > 15% reversibility to salbutamol) were randomised to study medication (salmeterol xinafoate 189, salbutamol 194). All were receiving concurrent prophylactic therapy for asthma; 97% were taking inhaled corticosteroids. After six weeks' treatment, both morning and evening PEF were significantly higher with salmeterol xinafoate than with salbutamol (mean treatment difference for morning 26 l/min,  $p < 0.0001$  and for evening 16 l/min,  $p = 0.0001$ ). Forty five per cent of patients receiving salmeterol xinafoate reported less frequent asthma symptoms compared with 34% on salbutamol ( $p = 0.009$ ), and improvement in severity of symptoms was also greater in the salmeterol xinafoate group ( $p = 0.003$ ). Patients in the salmeterol xinafoate group gained an extra 18% of days and 10% of nights where no additional relief salbutamol was required compared with the salbutamol group (days  $p < 0.001$ , nights  $p = 0.0011$ ). In a subjective assessment, the chance of a patient finding better control of asthma symptoms with salmeterol xinafoate was highly significant ( $p = 0.003$ ). Both treatment groups reported similar numbers of minor adverse events, but 50% more serious adverse events were reported by patients receiving salbutamol (62 by the salbutamol group, 41 by the salmeterol xinafoate group). This study suggests that 50  $\mu\text{g}$  inhaled salmeterol xinafoate twice daily is well tolerated and offers significant clinical benefit to patients with moderate asthma compared with 400  $\mu\text{g}$  salbutamol twice daily plus relief salbutamol as required when added to existing therapy.

#### Salmeterol xinafoate: a comparison with nedocromil sodium in patients with mild asthma

ME JOHNSON, HC LLOYD *Ashville House Surgery, Barnsley, South Yorkshire and Allen and Hanburys Limited* Salmeterol xinafoate (Serevent) is a long acting, selective  $\beta_2$  agonist used in the treatment of asthma. This open label, multicentre, parallel group study compared the efficacy and tolerability of 50  $\mu\text{g}$  salmeterol xinafoate (SLM) twice daily with 4 mg nedocromil sodium (NED) four times a day both via the metered dose inhaler over a six week treatment period. Two hundred and six patients with mild asthma who had not received any prophylactic medication in the previous year, entered a two week baseline period and were then randomised to receive either SLM or NED. Throughout the study, all patients were provided with salbutamol by a Diskhaler for relief of asthma symptoms. After treatment, both mean morning and evening PEF were significantly higher for patients receiving SLM. (Improvements in morning PEF (l/min) of 360.2 to 397.3 (SLM) and 358.4 to 373.0 (NED),  $p = 0.0002$  and evening PEF (l/min) of 396.3 to 414.8 (SLM) and 395.2 to 404.0 (NED),  $p = 0.06$ ). This resulted in a reduced diurnal variation in PEF for patients receiving SLM. Patients in the SLM group also had a significant reduction in daily relief medication use ( $p = 0.0001$ ) coupled with significantly greater symptom control ( $p = 0.001$ ) than patients on NED. SLM also gave a significant reduction in nocturnal symptoms for patients who had suffered sleep disturbance in the baseline ( $p = 0.009$ ). In a subjective assessment, the chance of a patient finding better control of asthma symptoms with SLM was highly significant ( $p = 0.002$ ). Safety data showed that SLM was well tolerated. Patients receiving NED reported more pharmacologically predictable adverse events (18.5% reported nausea, vomiting or an unpleasant taste). The results of this study therefore show conclusively that salmeterol 50  $\mu\text{g}$  xinafoate twice daily is well tolerated and more effective in patients with mild asthma than 4 mg nedocromil sodium four times a day over a six week period.

### Why uncritical criterion based audit is not enough: analysis of PEF data from a prospective asthma audit

CE BUCKNALL, C ROBERTSON, F MORAN, RD STEVENSON *Royal Infirmary and Strathclyde University, Glasgow* A prospective audit of asthma management showed that substantial improvements in the process of care were not associated with improvements in outcome. One possible reason for this finding is described here. Forty nine patients from the 1991 cohort of acute asthma admissions have data available that describe the lowest PEF during the episode, the variability in PEF in the last 24 hours before discharge and whether or not they were readmitted within two months. For all but seven of this group, details of symptoms of poor asthma control a fortnight after discharge are also known. The mean lowest PEF recorded during the episode was 135 (SD 65) l/min, compared with a mean (SD) highest PEF during the 24 hours before discharge of 336 (104) l/min. The mean variability in the last 24 hours before discharge (maximum-minimum PEF/maximum %) was 30% (SD 14%) compared with the mean increase in PEF throughout the hospital admission of 60% (SD 20%). Subgroups of those whose PEF variability in the 24 hours before discharge was  $\leq 25\%$  and  $> 25\%$  show different outcomes; all those who were subsequently readmitted were having  $> 25\%$  variability in peak flow readings shortly before discharge from hospital; this difference in outcome is not because as a group there were major differences in planned use of oral or inhaled corticosteroids (CS) after discharge from hospital. These observations provide some evidence that peak flow variability immediately before discharge is a useful index that can guide treatment and review planning, but that uncritical recording of a yes/no answer to the audit check list question "PEF measured regularly in hospital" is no guarantee that such recordings are being used effectively.

	PEF variability	
	$\leq 25\%$	$> 25\%$
Symptoms at interview (%)	7/19 (37)	14/23 (61) NS
Readmitted $\leq 2$ months (%)	0/21 (0)	9/28 (25) $p < 0.02$
Mean dose inhaled CS (mg (SD))	0.9 (0.8)	1.3 (0.8) NS

### Audit of maintenance asthma treatment before admission to hospital with acute severe asthma

G INKSTER, N FRENCH, CRK HIND *Royal Liverpool University Hospital, Liverpool* The guidelines for the management of chronic persistent asthma in adults emphasised the importance of inhaled steroid prophylaxis and the use of PEF measurements (*BMJ* 1990;301:651). As part of an ongoing local audit study all patients (aged 18-50) presenting to casualty with acute severe asthma completed a standard questionnaire to determine the duration, severity, and previous management of their asthma before this attack. Forty eight consecutive patients were studied (mean age 34, range 18-50; 29 women; 17 smokers). Twenty two were admitted to a medical ward and 25 received treatment on our observation ward; 37 (77%) had been asthmatic for more than five years, and 31 (65%) had unlimited exercise tolerance when well yet 27 (56%) had persistent nocturnal symptoms. Sixteen (33%) had been admitted with asthma, nine (19%) had received casualty treatment, and nine (19%) had attended a medical clinic in the past 12 months. Forty had seen their GP for asthmatic symptoms over this period (mean number of visits five, range one to 20). All were receiving inhaled  $\beta$  agonists (mean seven puffs/day, range 0-24) at presentation (inhaled 48, nebulised four, oral four, and 24 (50%) inhaled steroids. Other treatments included aminophylline 15 (31%), salmeterol six (13%), and cromoglycate three (6%). There was no correlation between treatment with inhaled steroids and exercise tolerance, nocturnal symptoms, or number of general practitioner visits. Patients admitted to hospital or attending outpatients were, however, significantly more likely to be taking inhaled steroids ( $p = 0.02$ ) and using home peak flow meters ( $p = 0.007$ ). This survey suggests an underusage of inhaled steroids in the management of persistent asthma in the community. These results will now be sent to local general practitioners, with a view to repeating the audit in 1993.

### New HPLC method for the measurement of plasma terbutaline in patients with brittle asthma treated by continuous infusion

PT MCCARTHY, RJ FLANAGAN, A SYKES, JG AYRES *National Poisons Unit, Guy's and Lewisham NHS Trust, London; and Chest Research Institute, East Birmingham Hospital, Birmingham* Some asthmatic patients

with widely variable peak flow despite maximal treatment (brittle asthma) are successfully treated with subcutaneous infusions of terbutaline (CSIT) (O'Driscoll *et al. Br J Dis Chest* 1988;82:360). With this form of treatment, relatively high plasma concentrations are achieved apparently without toxicity. We have developed a new simple, low cost, selective high performance liquid chromatographic assay with fluorometric detection (excitation wavelength 200 nm) to measure plasma terbutaline after CSIT. In summary, plasma (0.5-1.0 ml) was mixed with internal standard solution (1.0 mg/l aqueous atenolol, 100  $\mu$ l). The mixture was applied to a base treated silica column (Bond-Elut 100 mg, 1 ml) and, after washing with distilled water, the analytes were eluted with methanol. The concentrated extracts were analysed on a 250  $\times$  5 mm internal diameter Spherisorb S5SCX column with methanol/acetonitrile/water (2/2/1) containing 60% perchloric acid (0.2% v/v) at a flow rate of 1.5 ml/minute as eluent. The limit of detection was 2  $\mu$ g/l. Plasma concentrations in samples from nine patients with brittle asthma treated for 0.1-5 years by CSIT (2-12 mg/day) ranged from 7-40  $\mu$ g/l and were correlated with daily dose. There was no saturation threshold for terbutaline metabolism as doses up to 0.22 mg/kg. The method can also be used to measure plasma salbutamol in the presence of terbutaline after oral and CSIT dosing.

### Asthma drug and peak flow meter (PFM) prescribing in general practitioner practices

DPS SPENCE, P ROWE, MG PEARSON *Aintree Chest Centre and Sefton FHSA, Liverpool* Each family health service authority (FHSA) monitors every prescription from general practitioners and produces quarterly reports of each drug preparation in each general practitioner practice (PACT). We analysed the first year's data in which PFMs were prescribable for Sefton FHSA (54 practices, pop 302 000). Drugs were aggregated into seven classes expressed as the number of inhaler unit or months of treatment per 1000 patients. Asthma products comprise 11% by value of Sefton FHSA drug budget. Median and range between practices are shown. Inhaled  $\beta_2$  and steroid scrips make up 75% prescriptions by volume, the new salmeterol inhaler less than 1%. Prescribing pattern varied hugely and unpredictably between practices. The smallest range is for  $\beta_2$  inhalers at 5.3-fold that is still 2.2-fold if the top and bottom 10% of practices are excluded. There is a significant positive correlation between use of  $\beta_2$  inhalers, inhaled steroid ( $r = 0.62$ ), anticholinergics ( $r = 0.47$ ), and theophyllines ( $r = 0.43$ ) suggesting that prescribing relates to incidence and recognition of asthma. A stepwise linear regression relates the use of inhaled steroids to use of  $\beta_2$  agonists and lack of theophylline use ( $r = 0.56$ ). Five practices have yet to prescribe a PFM. They prescribe 22% less inhaled steroid, 48% more oral  $\beta_2$  drugs, 39% more theophyllines, and 130% more salmeterol than the rest. By contrast the five practices that gave out the most PFMs prescribed 32% more  $\beta_2$  inhalers, 100% more steroids and 40% less theophylline. These large variations in asthma drug use imply that the asthma guidelines have yet to be widely used in general practice. PACT data analysed in this way may be of value in general practitioner education.

	$\beta_2$ inhaler	Oral $\beta_2$	Xanthines	Salmeterol	Inhaled steroids	PFM
Median	390	73	80	7	290	2
Range	160-830	1-250	10-270	0-50	80-970	0-36
90:10% Ratio	2.2	7	5.2	51.6	2.5	$\infty$

### Postal survey of respiratory symptoms in young adults living in Bergen, Norway

E OMENAAS, R SKJAERVEN, P BURNEY, A GULSVIK *Department of Thoracic Medicine, Section of Information and Statistics, University of Bergen; and Department of Public Health Medicine, United Medical and Dental School of Guy's and St Thomas's Hospitals, London* A questionnaire asking about respiratory symptoms was mailed in October 1991 to a random sample of 4300 subjects aged 20-44. The questionnaire included the EC respiratory health survey screening questionnaire on respiratory symptoms in the past 12 months, as well as other questions on symptoms and smoking habits. The response rate to the questionnaire, after two reminders, was 80% (79% for men and 81% for women). Of the responders, 47% of men were current smokers and 29% ex-smokers, whereas 42% of women were current smokers and 33% ex-smokers. Respiratory symptoms were significantly more frequent in men than in women for "wheezing in the last 12 months" (27% men v 23% women), "morning cough" (26% men v

22% women) and "chronic cough" (10% men *v* 8% women), ( $p < 0.05$ ). There was, however, no significant difference between the sexes reporting "wheezing ever," "wheezing with breathlessness," "waking with chest tightness," "attacks of asthma" or "medication for asthma" (in the last 12 months). Women reported "waking with cough" and "breathlessness after walking up two flights of stairs" more often than men (31% *v* 21% and 13% *v* 8%, respectively). A positive response to at least one of the questions "waking with breathlessness," "attacks of asthma," or "medication for asthma" was given by 6% of men and 5% of women who answered the questionnaire. In conclusion, this survey has provided standardised data on respiratory symptoms for four out of five subjects sampled. It will enable us to make valid comparisons between the prevalence of asthma in Norway and other European countries, including Great Britain, as well as between cohorts six years apart in Bergen.

### Descriptive epidemiology of airway hyperreactivity to methacholine in a random adult population sample

K RICHARDS, I PAVORD, AJ KNOX, I WAHEDNA, A WISNIEWSKI, A JOHNS, A TATTERSFIELD, S WEISS, J BRITTON *Respiratory Medicine Unit, City Hospital, Nottingham; Harvard Medical School, Boston, Massachusetts* We have studied the occurrence of airway hyperreactivity to methacholine in relation to age, sex, atopy, and smoking history in a random sample of adults aged 18–70 drawn from the electoral register of a district of Nottingham. Airway reactivity was assessed by the method of Yan *et al* (*Thorax* 1983;38:760) which gives methacholine to a maximum cumulative dose of 12.25  $\mu\text{mol}$ . Of 2644 subjects who attended for assessment, methacholine inhalation was contraindicated by airflow obstruction ( $\text{FEV}_1 < 60\%$  predicted or  $< 1.5$  l) in 99 (3.7%), and by other illness, pregnancy or breastfeeding in 73 (2.8%). Fifty three subjects refused methacholine. Airway reactivity was therefore measured in 2419 subjects, of whom 1205 were women, 1227 had never smoked and 549 were current smokers, and 1052 had at least one positive skin response to cat fur, *Dermatophagoides pteronyssinus*, or grass pollen. 315 subjects (13%) were hyperreactive to methacholine with a  $\text{PD}_{20}\text{FEV}_1$  of 12.25  $\mu\text{mol}$  or less. Independent odds of being hyperreactive were significantly higher in women (odds ratio (OR) = 1.9, 95% CI 1.5–2.5), atopics (OR = 2.9, 2.2–3.7), current smokers (OR = 1.7, 1.3–2.3), and with increasing age (OR of 60–70 year age group relative to 18–29 years = 1.6, 1.1–2.6). These findings confirm the importance of age, sex, atopy, and current smoking as independent predictors of airway hyperreactivity to methacholine.

### Respiratory effects of air pollution

B STAPLES, J REID, D ASHBY, POD PHAROAH *Halton District Health Authority Department of Public Health, University of Liverpool* The objective was to test the hypothesis that there is an association between air pollution and acute hospital admission for a selected set of respiratory diseases. The analyses of data linked air pollution to acute hospital admissions for the period May 1990 to April 1991 in 143 000 residents of Halton health authority. These people were exposed to sulphur dioxide, nitrogen dioxide, and ozone gas concentrations integrated into a pollution index. Their health was assessed by a transformed hospital admission count derived from acute hospital admissions where a primary diagnosis of International Classification of Disease code 490, 491, 492, 493, 494, or 496 was made. Air pollution was found occasionally to exceed the World Health Organisation guide line recommended maximum exposure, but was generally within current guide line values. Considerable variation in pollution occurred as a result of local weather changes. A weak association between air pollution and acute respiratory hospital admissions over the following week has been shown. It is concluded that these preliminary results show a weak association between respiratory disease and air pollution at gas concentrations below the current World Health Organisation guide line values. If these results are corroborated in ongoing research, the current air quality guide lines should be reviewed.

### Bronchial reactivity and immunoglobulin E concentrations in subjects with respiratory symptoms associated with the flowering of oilseed rape

GE PACKE, A SOUTAR, C HARKER, JAR FRIEND, A SEATON *Department of Thoracic Medicine, Aberdeen Royal Infirmary and Department of Environmental and Occupational Medicine, Aberdeen University* Subjects living in rural areas who develop respiratory symptoms in the early summer commonly attribute their symptoms to the crop oilseed

rape (OSR), which flowers in late April and early May. The nature of this association is unclear. We studied 17 cases, median (range) age 34 (17–51) years, who complained of either cough, wheeze, tightness of the chest, shortness of breath, sneezing and a blocked nose, or sore and itchy eyes at the time that OSR comes into flower. All lived in a rural area of the Grampian region of Scotland where there is intensive cultivation of the crop. We also studied 11 controls, median age 44 (19–51) years, who lived in the same locality but who were symptom free during the OSR season. We measured: total immunoglobulin (Ig) E concentrations; specific IgE concentrations to five varieties of OSR commonly grown in the region; and histamine reactivity before and during the OSR flowering season. There was no significant difference between median total IgE concentrations in the cases, 34 (2–4070) kU/l, and controls, 44.0 (4.0–146) kU/l. Only two cases and no controls showed a significant rise in specific IgE to OSR. Median histamine reactivity ( $\text{PC}_{20}$ ) before the OSR season in the cases was 9.6 (2.7–16.0) mg/ml, falling to 3.9 (0.8–16) mg/ml during the OSR season (Wilcoxon test for matched pairs;  $p < 0.005$ ). There was no significant difference between the preseasonal, 15.7 (4.5–16.0), and seasonal, 7.5 (2.8–16.0), values in the controls. Subjects whose respiratory symptoms coincide with the OSR flowering season simultaneously develop an increase in bronchial reactivity. This increase in reactivity is likely to be mediated by factors other than IgE.

### Effects of dietary fish oil supplementation on seasonal asthma in pollen sensitive asthmatics

FCK THIEN, J-M MENCIA-HUERTA, TH LEE *Department of Allergy and Allied Respiratory Disorders, UMDS, Guy's Hospital, London* Dietary fish oil is rich in eicosapentaenoic acid (EPA), which is an alternative substrate to arachidonic acid in the generation of inflammatory mediators and has anti-inflammatory effects. A 10 week period of fish oil supplementation significantly attenuates the late asthmatic response to inhaled allergen. (Arm JP *et al. Am Rev Respir Dis* 1989;139:1395). We have studied the effects of taking 18 capsules a day of Max-EPA (3.2 g/day EPA) on the clinical symptoms and bronchial hyperresponsiveness in pollen sensitive asthmatic subjects over a pollen season in a double blind, parallel, placebo (olive oil) controlled fashion. The study was conducted over the 1990 and 1991 pollen seasons in London. Thirty seven non-smoking patients were entered into the trial but only 25 completed the six months study period over the two years. The geometric mean  $\text{PD}_{35}\text{sGaw}$  of histamine pre-season for the fish oil ( $n = 12$ ) and placebo ( $n = 9$ ) groups were 0.62  $\mu\text{mol}$  and 0.42  $\mu\text{mol}$  respectively. During the middle of the pollen season histamine  $\text{PD}_{35}\text{sGaw}$  fell significantly for both the fish oil (0.11  $\mu\text{mol}$ ,  $p < 0.0001$ ) and placebo groups (0.10  $\mu\text{mol}$ ,  $p < 0.0074$ ), indicating increased bronchial reactivity compared with pre-season values, but there was no significant difference between the groups. Similarly, morning and evening PEF, diurnal variability, nocturnal cough and wheeze, daytime wheeze, and activity as well as nasal symptoms were not significantly different between the groups. Hence we conclude that dietary fish oil supplementation does not prevent a seasonal increase in bronchial hyperresponsiveness or deterioration in symptoms and clinical variables in pollen sensitive asthmatics during the pollen season.

### Early bacterial and fungal infections in lung transplantation

M TAMM, F CIULLI, C DENNIS, B BIOCINA, P MULLINS, SR LARGE, FC WELLS, TW HIGENBOTTAM, J WALLWORK *Transplant Unit, Papworth Hospital, Cambridge* We have undertaken a retrospective study to analyse the causes and outcome of early bacterial and fungal infections in 150 patients undergoing heart-lung (HLT,  $n = 125$ ), double sequential lung (DLT,  $n = 4$ ) or single lung (SLT,  $n = 21$ ) transplantation between April 1984 and March 1992. In all patients the perioperative antibiotic prophylaxis consisted of flucloxacillin and a third generation cephalosporin given intravenously for 48 hours; also cystic fibrosis patients received nebulised gentamycin and colistin until intermediate discharge. In case of positive donor trachea culture antibiotic prophylaxis was prolonged and modified according to pathogen sensitivity. Out of the 150, 74 donor tracheal cultures were positive (49.3%), 35.2% were Gram positive bacteria, 41.9% were Gram negative, and 22.9% were fungi. *Staphylococcus aureus* was the most common Gram positive organism (81.0%) isolated from the donor cultures, *Haemophilus influenzae* was the most frequent isolate (31.8%) in the Gram negative group followed by *Pseudomonas* (13.6%), *Escherichia coli* (13.6%), *Enterobacter* (11.4%), *Acinetobacter* (11.4%), and others (18.2%). *Candida* was responsible for all positive fungal cultures. Early infection occurred in 23/150 patients (15.3%): nine had pneumonia, six bronchitis, three empyema, two tracheal

dehiscence, one bronchial dehiscence, one aortic rupture, and one cerebrovascular accident or sepsis. The infection rate in the SLT group was 7/21 (33.3%) compared with 15/125 (12.0%) in the HLT series ( $p = 0.047$ ). Early infections were due to *Pseudomonas* in 12 (52.2%), *S aureus* in three (13.0%), *Aspergillus* in three (13.0%) and other isolates in five patients (*Candida*, *Klebsiella*, *Clostridium perfringens*, *H influenzae*, *S epidermidis*). In 2/23 patients (8.7%) the isolate from the donor trachea was the same as the organism responsible for the early infection (*S aureus*, *H influenzae*). Overall early mortality (<30 days) was 12.7% (19/150); nine of these deaths were due to infection. The overall morbidity related to early bacterial and fungal infections in our lung transplant series has been low (15.3%). There was a high early mortality in those patients who developed infection (39.1%). The transmission of infection through the donor lungs seemed to be of minor clinical importance.

### Bronchus associated lymphoid tissue (BALT): a feature of airway immunopathology in smokers

I RICHMOND, GE PRITCHARD, T ASHCROFT, PA CORRIS, EH WALTERS  
*Department of Histopathology and William Leech Centre for Lung Research, Freeman Hospital and Chest Unit, Newcastle General Hospital, Newcastle upon Tyne* Recent studies have questioned whether BALT is a constitutive feature of the human lung (Pabst *et al*, *Immunology Today*, 1992). We have previously shown that presence of human BALT can be shown and that it displays several morphological and anatomical differences from that seen in its mammalian counterparts. This study examines the distribution and extent of BALT in whole lung specimens ( $n = 30$ ) from various sources including pneumonectomies for carcinoma of the bronchus, transplant donated lung where atelectasis or parenchymal contusion prevented their use, and sudden death postmortem cases. Full thickness bronchial wall sections were taken from sites throughout the bronchial tree and four serial sections were examined from each site. In 65% of the lungs BALT was demonstrable in at least one airway site (range 1–5 sites, mean 2.15). BALT foci were typically solitary although up to four foci were seen in occasional sites; BALT was distributed throughout the airway with no predilection for carinae or airway. The specimens were divided into two age and sample size matched groups on the basis of smoking status. Patients with carcinoma were present in both groups. One patient was excluded because of a history of atopy. Group A (Smokers and Ex-smokers < 12 months)  $n = 18$ ; 10 men, eight women; age range 21–72, mean 51.5; sites sampled ( $n = 140$ ) range per case 5–12, mean per case 7.8; total number of BALT foci identified = 42. Group B (never smokers and ex smokers > 12 months)  $n = 11$ ; nine men, two women; age range 14–89, mean 45.3; sites sampled ( $n = 100$ ) range per case 6–15, mean per case 9.1; total number of BALT foci identified = five. BALT was significantly more frequent in Group A than in Group B both in absolute terms ( $\chi^2$  value 6.89,  $p < 0.01$ ) and when expressed as foci per number of sites sampled (Group A 0.3, Group B 0.05). Further work is ongoing to assess whether BALT is associated with smoking alone or with the related carcinomas in these groups.

### Nicotine patches v placebo in 234 hospital patients

IA CAMPBELL, RJ PRESCOTT, SM TJEDER-BURTON  
*Llandough Hospital, Cardiff and Medical Statistics Unit, University of Edinburgh* Transdermal nicotine (TNS) was compared with Placebo (P) in a randomised, double blind, between patient trial in cigarette smoking patients attending hospital or in hospital because of smoking related diseases. Patients between 18 and 75 years who agreed to try to stop smoking in response to their doctors' advice and gave informed consent to the study were counselled at entry and at two, four, eight, 12, and 26 weeks. Patches were commenced at entry (dose related to Fagerstrom score) and given for 12 weeks, the dose being altered at two, four and eight weeks according to self reported smoking state. Of 234 patients (115 TNS, 119 P) 69 (29%) were not smoking (CO validated) at 12 weeks (37 TNS v 32 P) this number falling to 51 (22%) at 26 weeks (29 TNS v 22 P). Older and less dependent patients were more likely to succeed. Mild to moderate oedema and erythema were more common with TNS than P, as was nausea and vomiting, these last symptoms usually in association with continued smoking. There was no difference in severe skin reactions (5%). The results show that TNS is reasonably well tolerated and that when combined with counselling in this hard core group of smokers it produces cessation rates comparable with some, and better than other, previous studies of hospital patients. We have been unable to show a statistically significant difference from placebo (according to the power initially chosen) but the suggestions of differences at 12 and 26 weeks are strong enough to warrant a larger study.

### Treatment of tracheobronchial obstruction with bronchoscopic diathermy resection: a cheap and effective technique

M PETROU, D KAPLAN, P GOLDSTRAW  
*The Royal Brompton Hospital, London* Twenty eight patients with tracheobronchial obstruction (23 malignant and five benign) were treated with diathermy resection. Fifteen had received other forms of treatment beforehand including laser resection (Nd:YAG). Five patients required two more treatment sessions for symptom recurrence. There were no intraoperative deaths or complications and the average length of stay was five days (range 2 to 14 days). Twenty seven patients reported immediate symptomatic relief and objective improvement in the results of lung function tests was seen in eight patients (average improvement in the FEV<sub>1</sub> of 33% and FVC of 9%). Bronchoscopic diathermy resection provides an excellent method of treating these patients at a significantly lower cost compared with laser resection. We therefore promote its use as a cheap and effective technique.

Patient	Lung function FEV <sub>1</sub> /FVC	
	Pre-operation	Post-operation
1	1.7/3.2	2.2/3.3
2	1.2/1.5	1.4/2.0
3	0.55/2.2	1.1/2.5
4	0.65/1.2	0.7/1.2
5	2.5/4.4	4.1/4.8
6	1.9/3.5	2.5/3.7
7	0.75/2.6	1.0/2.5
8	0.7/1.75	1.7/3.5

### Bronchography complementing fiberoptic bronchoscopy to evaluate the solitary pulmonary nodule (SPN)

SK MORCOS, PB ANDERSON, A KENNEDY  
*Departments of Diagnostic Imaging, Thoracic Medicine, and Histopathology, Northern General Hospital, Sheffield* The differentiation between the benign and the malignant SPN remains a problem despite advances in imaging techniques. Studying the morphology of the bronchial tree in relation to an SPN may help to determine the nature of the lesion. The feasibility and safety of using Iotrolan 300 in bronchography via the fiberoptic bronchoscope have been recently reported (Morcos *et al*. *Thorax* 1990;45:628). We performed bronchography of the affected lung segment via the fiberoptic bronchoscope in 20 patients (mean age 65.8 years) with an SPN (mean diameter 2.5 cm) using a mean of 14.5 ml Iotrolan 300. The bronchographic features were correlated with the final diagnosis. Bronchial carcinoma in seven cases produced irregular narrowing and underfilling of the air passages within the lesion. Hamartoma (two cases) caused only displacement of the adjacent bronchi. The main air passage within an organised pneumonia (one case) remained patent with normal calibre but no filling of the small side branches. Round atelectasis was diagnosed by the bronchogram in one case. Seven cases with subpleural SPN (three granuloma, two bronchial carcinoma, one lung secondary and one lung infarction) did not display obvious diagnostic bronchographic features. In two cases the bronchial tree of the relevant lung segment was not visualised. In conclusion bronchography can be helpful to evaluate an SPN related to the main subsegmental divisions of the bronchial tree. The more peripheral ones are difficult to assess by this technique.

### Complications following multiple transbronchial lung biopsy

T MARTIN, I OTERO, TW HIGENBOTTAM, J WALLWORK  
*Papworth Hospital, Papworth Everard, Cambridge* A systematic, multiple biopsy of the lung using the transbronchial approach has been successfully used to diagnose rejection and infection in heart-lung and lung transplant patients. The risk of complication has not been estimated for this approach either in patients who had received lung transplants or who had not had lung transplants. A retrospective study over two years of TBB in 129 occasions in non-transplant patients (80 men; 18–85 years old) and 182 occasions in lung transplants, 58 heart-lung and nine single lung transplant patients was undertaken. All underwent a standard TBB procedure (Cielland *et al*. *J Pathol* 1990;161:105–12) but where at least three biopsy specimens were obtained from each lobe of the lung the lingula was considered a separate lobe. Radiological screening was used to position the opened biopsy forceps. No patient died, none required subsequent assisted ventilation, no pneumothorax occurred and only two patients experienced post-procedure fever. There were 2.1% of transplant and

1.8% of non-transplant biopsies where arterial oxygen saturations fell by 10% or more, measured using pulse oximetry. Significant bleeding (> 100 ml) from the lung was recorded in 3.1% of transplant and 1.6% of non-transplant patients. A specific diagnosis was obtained in 78.5% of TBB occasions in the lung transplant patients but only 45.3% of TBBs in the non-lung transplant patients. We conclude that multiple TBB of the lung in both lung transplant and non-lung transplant patients is a safe and effective diagnostic procedure.

#### **Sputum induction in the cytological diagnosis of bronchogenic carcinoma**

TK ROGERS, M LOTT, D SMITH, JR CATTERALL *Respiratory Department, Bristol Royal Infirmary* We have conducted a crossover study to determine whether sputum induction increases the diagnostic yield of sputum cytology in the diagnosis of bronchogenic carcinoma. Eighty four consecutive patients (70 men, 14 women, mean age 69) undergoing elective bronchoscopy or percutaneous needle biopsy for suspected bronchogenic carcinoma were enrolled. On each of the two mornings before bronchoscopy each patient provided a sputum sample, either spontaneously expectorated (control sputum, CS) or induced with an ultrasonically nebulised aerosol of hypertonic saline, in random order. All attended as outpatients, the samples being collected between 8.30 and 9.30 am. One cytologist (ML) examined the samples blind to patient details and to method of collection. Bronchogenic carcinoma was diagnosed in 60 patients by bronchoscopic biopsy or percutaneous needle biopsy. The remaining 24 patients had no evidence of malignancy, including negative bronchoscopy and negative computed tomography of the thorax. The diagnostic sensitivity of CS samples was 16/60 (27%) and of IS was 19/60 (32%) (NS). One false positive occurred in CS and none in IS. Thus in this randomised, single blind crossover study, a single sputum induction was not statistically better than spontaneously expectorated sputum in the cytological diagnosis of bronchogenic carcinoma. These results suggest that sputum induction is unlikely to offer significant advantages over spontaneous expectoration of sputum in the practical management of outpatients being investigated for bronchogenic carcinoma.

#### **How much fluid stays in the lung after bronchoalveolar lavage (BAL)?**

C WARD, J FENWICK, C KELLY, DJ HENDRICK, EH WALTERS *Chest Unit and Department of Medical Physics, Newcastle General Hospital, University of Newcastle upon Tyne* A previous study using magnetic resonance imaging has suggested that fluid remains within the lung several hours after BAL (*Am Rev Respir Dis* 1989;4:A472). We have attempted a quantitative assessment of fluid retention in the lung 24 hours after a 180 ml BAL. The study was performed in five patients attending diagnostic bronchoscopy (four men, median age 55, range 27–68, median FEV<sub>1</sub> 96% predicted, range 83–128%). Two patients had a suspected lung tumour and three were asthmatic. In each patient a 3 × 60 ml BAL was performed with each aliquot of phosphate buffered saline containing 4 MBq of tritiated water (<sup>3</sup>H<sub>2</sub>O). A venous blood sample was taken about 24 hours after BAL and urine collected for the 24 hours between the BAL and blood sample. <sup>3</sup>H counts performed on plasma indicated that a median 79% of the administered <sup>3</sup>H<sub>2</sub>O (range 72–88%) not recovered at BAL, was in equilibrium with the calculated total body water, with a median 2% (range 1–4%), excreted within urine. This left a median 20% (range 7–25%) of the instilled <sup>3</sup>H unaccounted for and, by implication, retained within the lung. This was consistent with the retention of a median 43 ml of fluid (range 20–56 ml) in the lung, 24 hours after BAL. Given the low incidence of sequelae following BAL in our hands, these findings would not imply any adverse clinical implications, but they do underline the complexity of BAL as a sampling process.

#### **Diagnostic value of ACTH, corticotrophin releasing hormone (CRH) and $\beta$ endorphin concentrations as tumoral markers in the bronchial lavage fluid of patients with lung cancer**

R POLOSA, AE CALOGERO, R D'AGATA, E NEVILLE *Institute of Respiratory Diseases, University of Catania, Italy, First Department of Internal Medicine, University of Catania, Italy, Department of Chest Medicine, St Mary's Hospital, Portsmouth* Lung cancers are characterised by their ability to synthesise and release a wide range of peptides and hormones. Among these ACTH and other pro-opio-melanocortin derived peptides have attracted much interest as possible tumour markers. Although the plasma concentrations of these peptides have

been extensively investigated as possible tumour markers that may help in the early diagnosis of the disease, the data collected so far have shown a limited clinical usefulness. Little is known of the amount of these signalling molecules in bronchial lavage fluid of lung cancer patients. We therefore set out to look in more detail at the ACTH, CRH, and  $\beta$  endorphin ( $\beta$  EP) concentrations in the bronchial lavage fluid (BLF) of a group of patients with lung cancer (but with no evidence of ectopic Cushing's syndrome) and compared these with the peptides obtained from the BLF of a control population with no tumoral pathology. After subjects were routinely pretreated with atropine and lidocaine aerosol, a flexible fiberoptic bronchoscope was inserted. Sequential bronchial lavages with prewarmed saline were carried out in 25 subjects with bronchial cancer at the level of the visible tumour and in 18 age and sex matched controls. BLFs were concentrated and extracted using cartridges of SepPak C-18 and ACTH, CRH, and  $\beta$  EP concentrations were measured by RIA. ACTH and CRH concentrations in BLFs from lung cancer patients (251.7 (34.3) and 744.5 (63.3) fg/ml) were not significantly different from those of controls (266.7 (47) and 895.5 (79.6) fg/ml).  $\beta$  EP concentrations in the BLF were about 100-fold higher than those of ACTH and showed a downward trend ( $p = 0.08$ ) in patients with cancer (30.96 (5.38) pg/ml) *v* controls (48.32 (10.9) pg/ml). No specific histological tumour type was associated with particular increases in any of the peptides measured. We conclude that measurements of ACTH, CRH, and  $\beta$  EP in the BLF are of little value in the diagnosis of lung cancer.

#### **Analysis of amylase isoenzyme in the differential diagnosis of amylase rich pleural effusions**

D DEV, J JOSEPH, S VINEY, P BECK, GS BASRAN *Respiratory Unit, District General Hospital, Rotherham South Yorkshire* 200 patients with pleural effusions were prospectively analysed. 25 cases of amylase rich effusions were identified for an overall incidence of 12.4%. Of the 25 patients, 4 (16%) had evidence of pancreatitis. These patients had a higher pleural fluid to serum amylase ratio than patients with a non-pancreatic isoenzyme profile. Bronchogenic carcinoma was found to be the most common associated condition (eight patients) among the remaining 21 patients with high amylase effusions not associated with pancreatic disease. The isoenzyme profile was obtained in 14 patients and all of them were found to have predominant salivary type amylase. We conclude that amylase rich pleural effusions occur frequently and that pleural fluid isoamylase determination is both specific and sensitive for pancreatitis associated effusions. The findings of salivary isoamylase should prompt an evaluation for an occult carcinoma but may also be found in other pleural inflammatory conditions.

#### **Management of spontaneous pneumothoraces: audit of process**

C SELBY, MF SUDLOW *Department of Medicine, Royal Infirmary, Edinburgh* The management of spontaneous pneumothorax (SP) is topical with the planned provision of British Thoracic Society guidelines. Retrospectively, we reviewed case notes of all admissions to this major hospital between 1 October 1991 and 30 September 1992 with pneumothorax as a diagnostic code. Casenotes of all 38 SP events (seven recurrent (RP)) in 36 patients (nine females) aged 15–78 (median 27) years; six with chronic lung disease (CLD)) were then audited. The primary treatment in 21 (55%; including three small (<20%) SP, four RP and four CLD) was intercostal tube drainage (ITD). This decision was taken and performed by accident and emergency senior hospital officers (SHOs) in 11 events, including the four RP, one with CLD and all four SP with mediastinal shift; the balance by physicians (six SHOs). It resulted in five (median, range one to 13) days of ITD, seven (two to 18) inpatient days with six (three to 10) chest radiographs. Two (9.5%) required surgical intervention; five (24%) sustained infections (three wound, two chest) requiring antibiotic treatment and prolonging inpatient stay. Purse-string suturing was universal; tube clamping occurred in at least 17 (81%). Aspiration as primary treatment was performed in only three (none RP, 2 CLD), decided upon by at least a medical registrar. None subsequently required ITD. Inpatient observation was initiated in 14 (37%; three RP, none CLD), exclusively by physicians, of at least registrar grade in 11 (79%). The hospital stay was two (two to four) days with three (two to five) radiographs. Follow up was arranged in only 29 (76%), 7 (3–30) days after discharge, three of the seven RP with surgeons. No SP had recurred radiologically by then. Overall, RP or CLD did not seem to affect the primary treatment decision, and outcome was not determined by age or presence of CLD. This audit has shown undue reliance on ITD to treat SP, a decision taken

predominantly by junior staff, with its concomitant prolonged stay in hospital, radiography, and potential for complications. Aspiration, not an irrevocable decision, was performed infrequently. Follow up was incomplete. There is scope for improvement.

#### Measurement of magnetic particles in the lung by pneumomagnetoimetry

P EBDEN, A ENGLAND, J FARDY, D RASSI *Department of Physics, University College, Swansea; and Department of Medicine, Prince Philip Hospital, Llanelli* Magnetic particles in the lung can be measured non-invasively by pneumomagnetoimetry. This measures the residual magnetism from compounds such as magnetite ( $\text{Fe}_3\text{O}_4$ ) in the lung. We have studied five men (mean age 58.6 years) exposed to asbestos (asbestos contains roughly 0.5% magnetite) two of whom also had exposure to iron in steelmaking. None had a history of welding or had metal prostheses or pacemakers in place. They all had clinical asbestos related disease, either asbestosis or pleural disease. An ADC magnetising field of 0.01 T was applied to the subject's chest for 10 seconds. The remnant magnetic field was measured with a squid magnetometer. Three scans were taken for 5–10 s duration. The measurements were repeated with the direction of the magnetising field reversed. The remnant magnetisation was calibrated with phantom lung results. The total magnetite content of the lungs ranged from 1.0 mg to 31.7 mg. High values were found in both subjects exposed to steel dust but also in one worker who only had exposure to asbestos (mean 9.4 mg magnetite). This technique is capable of measuring magnetic particles non-invasively in the lungs and may give a useful guide in both asbestos and steel exposure.

#### Evaluating $^{99m}\text{Tc}$ DTPA lung clearance: how variable are results?

YATES DH, HAVILL K, CHU J, GLANVILLE A *Respiratory Unit and Department of Nuclear Medicine, Concord Hospital, Sydney, New South Wales, Australia* Clearance of inhaled  $^{99m}\text{Tc}$  DTPA has been used as an index of alveolar epithelial permeability in the serial evaluation of interstitial lung disease. There are, however, few published data regarding the normal range and reproducibility of the test. With a standardised technique on 16 non-smoking healthy volunteers, we evaluated the normal range, within day, and between day reproducibility of the test, as well as the interobserver and intraobserver variability. An ultraviolet nebuliser was used to generate a  $^{99m}\text{Tc}$  DTPA aerosol with a mass median aerodynamic diameter of  $< 2 \mu\text{m}$ . This was inhaled by subjects in the supine position by tidal respiration. Data were acquired continuously over a 35 minute period and two separate regions of interest later selected in an attempt to exclude any gastrointestinal absorption. These were both whole lungs and whole right plus upper two thirds of the left lung. Time activity curves were generated and a  $t_{1/2}$  calculated from the fitted exponential. DTPA scans were repeated 72 hours later. Full lung function was performed before and after each study. A normal range was 76 (18) minutes (95% CI 37–114). The single determinant 95% range was (17) minutes, with a 95% range for change of (25) minutes. Both interobserver and intraobserver correlations were 0.99. Correlation between different ROIs was 0.94. There was no effect of DTPA scanning on any lung function variable. We conclude that the within and between test variability is significant and should be taken into account when interpreting test results.

#### Lung function abnormalities in patients with pulmonary Kaposi's sarcoma

RF MILLER, MC TOMLINSON, CP COTTRILL, MF SPITTLE, SJG SEMPLE *Department of Medicine, UCMSM and The Meyerstein Institute, Middlesex Hospital, London* Twenty nine of 361 consecutive HIV positive patients who had bronchoscopy (FOB) for respiratory symptoms had tracheobronchial Kaposi's sarcoma (KS). Nine patients were excluded (eight had coinfections and one had had earlier chemotherapy for skin KS). Of the remaining 20 patients seven had localised KS (lesions in the trachea or subsegments of one lobe) and 13 had widespread KS (lesions in trachea and one lobe or subsegment of more than one lobe). Nineteen patients had cutaneous and palatal KS. Lung function results are shown in the table. Follow up lung function in seven patients (median interval = three months) showed: (1) in four patients who received no treatment TLCO fell further and two patients also had further reductions in FEV<sub>1</sub> and FVC; Bronchoscopy in three patients showed progressive tracheobronchial KS: (2) in three patients who received chemotherapy, despite palliation of symptoms,

all had further reductions in TLCO and two had falls in FEV<sub>1</sub> and FVC; bronchoscopy showed progressive disease in one, regression in another, and no change in a third. Tracheobronchial KS produces abnormalities of TLCO even in patients with localised disease. If untreated progressive deterioration in lung function occurs, despite treatment palliating symptoms some patients have progressive deterioration in lung function; Bronchoscopy assessment of extent of disease may not reflect response to chemotherapy.

	Localised KS (n = 7)	Widespread KS (n = 13)	p Value Wilcoxon
FEV <sub>1</sub>	88 (13)	61 (19)	<0.05
FVC	89 (9)	70 (21)	<0.05
PEF	82 (22)	50 (16)	<0.02
TLCO	61 (13)	72 (14)	NS
Kco	53 (9)	66 (13)	NS

#### Computerised bronchoscopy reports and audit

BR O'DRISCOLL, RJ TAYLOR *Hope Hospital, Salford* An efficient bronchoscopy service requires the production of clear and legible bronchoscopy reports and the availability of clinical, bronchoscopic, and pathological data for subsequent audit. We have designed a computer program to combine these functions. We used dBASE IV software to produce a user friendly program that allows the bronchoscopist to enter patient data and bronchoscopic results into a cumulative database. Patient data include demographic details, indications for bronchoscopy, clinical laboratory, and x ray findings, details of medications given, and the results of oximetry during the procedure. The bronchoscopy report includes the operator's name, all abnormalities noted and all specimens sent for laboratory analysis. The bronchoscopist may also add comments and recommendations using free text memo fields. The software can run on any IBM-compatible computer system. We use a Phoenix 386SX notebook computer (2.9 kg) and Canon BJ10ex ink jet printer (1.8 kg) which allows easy movement of equipment at a low overall cost (roughly £1200 overall). The system generates a clearly typed bronchoscopy report with patient data on one side of an A4 sheet and the bronchoscopy report on side 2. The computer also generates a supply of preprinted adhesive labels for specimen bottles and pathology request forms. Compared with a manual system, the computerised report takes slightly longer to complete (five to eight minutes) but this extra effort is rewarded by the production of a clear, legible, attractive report and the system may save time when it provides labels for multiple request forms and specimens. A copy of the report also replaces a typed letter to the patient's general practitioner. The hardware and software will be available for inspection together with specimen reports.

#### Relation between breath sounds and airflow obstruction during exacerbations of asthma

DPS SPENCE, C MEAD, J DAWSON, MG PEARSON, PMA CALVERLEY, JE EARIS *Aintree Chest Centre, Fazakerley Hospital, Liverpool* Analysis of the frequency and power content of breath sounds can provide a non-invasive means of monitoring changes in airflow obstruction. This is true in methacholine induced bronchoconstriction but has not been tested in patients with acute asthma. We studied seven asthmatic patients, mean (SE) age 36.4 (4.8) years, over four days while they were recovering from an exacerbation. We measured spirometry, lung volumes, and ventilation when recording breath sounds with an air coupled microphone during forced and tidal breathing. Signals were recorded onto magnetic tape with digitisation of 30 second periods for analysis of power and median frequency by DSP techniques. Although spirometry improved significantly breathing pattern and lung volumes were unchanged. Wheeze was heard during tidal breathing in three and on forced breathing in one further patient and was unrelated to spirometry. Tidal wheeze disappeared as spirometry improved but forced wheeze was unchanged. Changes in median frequency were inconsistent but power normalised for inspiratory flow fell in four of five patients where FEV<sub>1</sub> improved. These data suggest that methacholine induced wheeze may not be representative of that in patients and that the relation of breath sounds to airflow obstruction is not simple.

	FEV <sub>1</sub> (l)	Ti (s)	V <sub>T</sub> (l)	V <sub>T</sub> /Ti (l/s)	Ti/ T <sub>tot</sub>	Median frequency
Start	1.84 (0.2)	1.2 (0.2)	0.72 (0.1)	0.65 (0.12)	0.39 (0.03)	296 (33)
End	2.6 (0.25)	1.3 (0.15)	0.9 (0.12)	0.69 (0.05)	0.4 (0.02)	342 (43)

**Effect of building ventilation on avian antigen concentration in an animal laboratory**

K ANDERSON, G MORRIS, CP MCSHARRY, G BOYD *Departments of Respiratory Medicine, Royal Infirmary; Department of Immunology, Western Infirmary, and Department of Environmental Health, University of Strathclyde, Glasgow* This group has previously shown by field study that airborne pigeon derived antigen concentrations within a pigeon loft do not seem to correlate with dust within the loft, the number of pigeons, or degree of ventilation of the loft (*Thorax* 1990;45:320P). Edwards and colleagues (*Clin Exp Immunol* 1991;21:49) reported similar findings for ventilation, although, by contrast, dust and antigen concentrations seemed related. We re-examined our findings by performing a similar study in the controlled environment of an animal laboratory where powered ventilation had been installed to reduce airborne dust concentration after a technician had developed chest symptoms. A variable number of pigeons were kept (22–63) in linearly arranged cages at shoulder height. The airflow was greatest at the door end of the room where the intake (near floor level) and outflow (near ceiling level) were sited on opposite walls. Simultaneous airborne samples were obtained with low volume samplers at three different heights from each end of the room. The antigenic content of the filter sample was estimated by ELISA. Dust concentration (median 0.14 mg/m<sup>3</sup>, interquartile range 0.09–0.23) was closely correlated with pigeon number ( $r = 0.566, p < 0.001$ ) that also correlated with antigen concentration ( $r = 0.461, p < 0.001$ ). Antigen concentration was lower at the end of the room with higher ventilation (medians 34 v 25 ng/mg<sup>3</sup>,  $p = 0.03$ ) with a trend towards lowest antigen concentration in the line of maximum airflow. Our results suggest that ventilation alone can reduce airborne antigen. Additional measures, such as a positive pressure respirator, might be required to reduce personal dust exposure further.

**Repeatability of histamine bronchial challenge in symptom free textile workers as measured by dose response**

CJ WARBURTON, AM FLETCHER, CAC PICKERING, RM NIVEN, H FRANCIS *North West Lung Centre, Wythenshawe Hospital, Manchester* Fifty nine symptom free cotton spinning operatives underwent histamine bronchial challenge testing (Yan technique) at the beginning and the end of their first and fourth working shifts of the week. Their dose response (DR) to histamine was calculated for each of the four challenge tests as the maximum percentage fall in FEV<sub>1</sub> divided by the total dose of histamine given. The population comprised 40 male and 19 female operatives with a combined age (SD) of 44.3 (12.2) y. Fifteen of the group (25%) showed symptom free bronchial hyperreactivity (PD<sub>20</sub> < 6 μmol). Of these, 14 were current or ex-smokers. The table shows the mean (95% CI) DR for each of the four bronchial challenge tests. When the results were analysed by smoking habit there was a significantly lower mean DR in the non-smokers ( $n = 10$ , mean 0.09 (95% CI 0.07, 0.01)) than in the smokers ( $n = 30$ , mean 0.83 (95% CI 2.16, 0.32)), and the ex-smokers ( $n = 19$ , mean 2.33 (95% CI 7.24, 0.76)). Despite the effect of smoking the DR of FEV<sub>1</sub> to histamine in this population seems to be highly repeatable, especially when the two tests at equivalent times of the day are compared. The trend in DR across the working shift suggests a small effect of cotton dust exposure upon bronchial reactivity in this symptom free population.

	Dose response (%/μmol)
	Mean (95% CI)
Shift 1—beginning:	0.8 (1.67, 0.38)
Shift 1—end:	1.14 (2.26, 0.58)
Shift 4—beginning:	0.8 (1.57, 0.41)
Shift 4—end:	1.31 (2.60, 0.66)

**Technique for double blind inhalation challenge testing with glutaraldehyde**

SC STENTON, J DENNIS, J BEACH, DJ HENDRICK *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne* Considerable concern has recently been expressed about the risks of glutaraldehyde asthma developing in workers in endoscopy units and photographic dark rooms. To date, however, only the results of a small number of unblinded challenge tests have been reported. We therefore investigated an endoscopy nurse who had symptoms suggestive of occupational asthma with a series of double blind glutaraldehyde challenges. A fall in FEV<sub>1</sub> from 3.6 to 1.5 l had already been recorded during an unblinded workplace challenge test. For this series of

challenges, air was pumped through a tower containing glutaraldehyde solutions (0.02%–10%) into a breathing circuit with a 12 l/minute air flow. The relation between the concentration of glutaraldehyde in solution and the vapour concentration was found before the challenges with conventional analytical techniques. The dose range (0.01–0.32 ppm) was based on previous measurements in an endoscopy suite and the occupational exposure standard of 0.2 ppm. Each day the subject inhaled through the circuit for 10 minutes wearing nose clips to disguise the odour. Dose increments of 3.2 (√10) were used and the 3.2 ppm dose was repeated. Four control challenges were administered giving a total of nine challenges. Glutaraldehyde concentrations measured in the circuit during the challenges agreed closely with those expected. FEV<sub>1</sub> was monitored for 24 hours after each challenge but there was no evidence of immediate or late asthmatic reactions on any of the test or control days. The results of these challenges were thus very different from the previous unblinded challenge showing that glutaraldehyde asthma may at times be overdiagnosed.

**Caffeine decreases histamine induced bronchoconstriction in mild asthma**

JC HENDERSON, F O'CONNELL, RW FULLER *Departments of Clinical Pharmacology and Respiratory Medicine, Royal Postgraduate Medical School, London* Whereas there is evidence that theophylline is an effective bronchodilator and has inhibitory effects in asthma against various challenge agents, it is unclear whether related methylxanthines such as caffeine have these properties. Several studies in moderate to severe asthma indicate that at a dose equivalent to three cups of coffee (roughly 5 mg/kg body weight) the bronchodilator effects of caffeine are significant. In mild asthma, however, a similar effect is seen only with higher doses of caffeine. In bronchoprovocation testing with various substances the results indicate that in mild asthma there is some protection at higher doses but not at lower doses although the pattern is not clear. Our study aimed to clarify the effect of caffeine on histamine induced bronchoconstriction. We measured FEV<sub>1</sub> and PC<sub>20</sub> histamine in eight mild asthmatics before and 1, 2.5, and 4 hours after a single oral dose of caffeine (5 mg/kg) or matched placebo. Baseline FEV<sub>1</sub> was 91% (SEM 5.5%) of predicted on the placebo study day and 91% (4.7%) on the caffeine day. FEV<sub>1</sub> did not change significantly after giving either caffeine or placebo. PC<sub>20</sub> values, however, were significantly higher 2.5 and four hours after caffeine compared with placebo (see table). We conclude that caffeine does not have a bronchodilator effect as assessed by FEV<sub>1</sub> measurements in mild asthma. Caffeine, however, decreases the bronchoconstrictor response to histamine challenge and to exclude variability attributable to caffeine, its consumption should be excluded for a period greater than four h before testing.

Time (h)	0	1	2.5	4
Placebo	3.8 (0.5)	6.3 (1.9)	5.1 (1.9)	3.7 (1.1)
Caffeine	4.6 (0.6)	12.4 (3.9)	12.1 (3.2)*	10.5 (3.4)**

PC<sub>20</sub> values in mg/ml expressed as mean (SEM); \* $p = 0.014$  v placebo; \*\* $p = 0.042$  v placebo

**A new device to determine which patients can use a turbobalher efficiently**

P AGARWAL, M SAUNDERS, R RICHARDS *Department of Thoracic Medicine, Llandough Hospital, Wales* Powder inhalers are often prescribed, and their use is likely to increase. The inspiratory flow rate (IFR) at which a turbobalher is used is an important factor in determining its efficacy; values below 28 l/min give poor performance (Pedersen *et al. Arch Dis Child* 1990;65:308). Prediction of IFR using standard spirometry is poor (Engel *et al. Eur Respir J* 1990;3:1037). We have designed a simple device to predict a patient's suitability for the turbobalher. This device consists of a tube with a 4 mm internal diameter attached to a Youtlen Peak Nasal Inspiratory Flow Meter (Clement Clark Int Ltd). Twenty six patients with obstructive airways disease aged 12–73 were studied. The patients were asked to inhale as fast and as hard as possible through the turbobalher and the resistor in random order. Three readings of each were taken. There was a high degree of agreement between the IFR generated in both the devices ( $r = 0.96; p < 0.001$ ). The coefficient of repeatability (95% CI) was ±12.1 l/min. This simple device can be used to assess and train a patient in the use of a turbobalher. With minor modifications other powder devices can be similarly assessed.

### Screening for asthma in the British army

DG SINCLAIR, AN WILSHIRE, NA HOAD, CR WINFIELD *Army Chest Unit, Cambridge Military Hospital, Aldershot* To improve our screening of potential recruits with a history of asthma in childhood (HAC) we have performed a study to determine whether our standard exercise challenge could be made more sensitive. We have studied two groups, both made up of recruits with HAC and soldiers with symptoms of mild asthma. Group A (n = 24) underwent a standard exercise challenge, running for six minutes on a treadmill at a speed of 3.5 mph and a slope of 18%, and on another day, at increasing workloads on a treadmill aimed at achieving their maximum heart rate (MHR) within four to six minutes and maintaining it for two minutes. Group B (n = 44) underwent exercise challenge to MHR as detailed above on separate days breathing room air for one and cold air (-5°C to -10°C) for the other in randomised order. Fall index (FI) and exercise liability index (ELI) were calculated for each challenge. Previous work has shown that an FI or ELI of greater than 15% is abnormal for this population (Carson and Winfield *J R Army Med Corps* 1983;129:14). We have compared mean FI and ELI in those subjects who were positive to either test within their group and the table shows the results. These results suggest that the addition of cold air to MHR exercise does not improve the sensitivity of exercise challenge in this population.

	Standard	MHR	p Value
		<i>Group A positives</i>	
Mean FI% (SEM)	6.2 (0.91)	17.6 (3.1)	< 0.01
Mean ELI% (SEM)	10.6 (1.1)	19.2 (2.25)	< 0.01
% Positive	4.1	41.6	
		<i>Group B positives</i>	
Mean FI% (SEM)	11.7 (2.3)*	15.4 (2.7)†	NS
Mean ELI% (SEM)	19.2 (2.25)*	22.7 (2.5)†	NS
% Positive	29.5	38.6	

\*Room air; †cold air.

### Self management of asthma-like symptoms in a Scottish community

A DA COSTA PEREIRA, R CLARK, C DU V FLOREY *Ninewells Hospital and Medical School, University of Dundee* To determine the frequency, severity, and management of asthma-like symptoms in the community, two consecutive self administered postal surveys were undertaken in Kirkcaldy, Scotland (total population = 150 000). In the first survey, the prevalence of asthma-like symptoms was assessed in a random sample of 6000 adults (age range 20 to 44 years) stratified by sex (1:1) drawn from the Community Health Index. The response rate was 77%. Six months later a follow up questionnaire, asking about frequency, severity and management of asthma-like symptoms, was sent to the 28% originally reporting wheezing within the previous year. The response rate was 78%: 70% continued to report wheezing (recurrent wheezers); in this group 80% experienced associated breathlessness and 73% had wheezing in the absence of a cold. Two thirds of recurrent wheezers had had symptoms for > five years, 67% reported nocturnal symptoms and 27% disruption to daily life in the past 12 months, yet only 17% considered their symptoms severe. Forty per cent of recurrent wheezers had never sought medical advice. Of these, 19% reported wheezing with breathlessness for > 30 days a year or disruption to daily life in the past 12 months. Only < 30% of recurrent wheezers had taken asthma medication, whereas 44% had taken no medication at all in the past 12 months. Illness behaviour was associated with self perceived severity: 35% reporting mild symptoms compared with 87% reporting severe symptoms had sought medical help and 9% mild compared to 65% severe reported taking regular medication. This study suggests that there are an appreciable number of people with asthma-like symptoms in the community unknown to health care providers in whom a change in the perception of their illness and possibly a greater awareness of the potential benefits of medical contact might reduce avoidable morbidity.

### Trial of a "credit card" asthma self management plan in a Maori community

R BEASLEY, W D'SOUZA, J CRANE, C BURGESS, H TE KARU, C FOX, M HARPER, B ROBSON, L CROSSLAND, N PEARCE, E POMARE *Department of Medicine, Wellington School of Medicine, Wellington, Wairarapa Maori Executive/Taiwhenua, Masterton, and Choice Health, Masterton, New Zealand* Although asthma self management plans are now widely

recommended as being essential in the long term treatment of adult asthma, there are few studies which have examined their use. In this study, the effect of a "credit card" asthma self management plan, which uses guidelines based on the self assessment of asthma severity, was assessed in a Maori community. Self management guidelines based on the interpretation of peak expiratory flow recordings (PEF) were printed on one side of the plastic card, and those on the interpretation of symptoms on the reverse side. Sixty nine Maori asthmatic subjects kept asthma diaries for an initial period of eight weeks. After this, the plan was introduced through a series of clinics held in Maori community centres, with the participants keeping diaries for a further 15 weeks. After the introduction of the plan, the mean PEF increased significantly by 12% (from 340 to 385 l/min) and the percentage of nights woken fell significantly from 30% to 18%. Other indicators of asthma morbidity also improved. In the situation of worsening asthma, 28% of subjects found the peak flow side of the card most helpful, 7% the symptoms side, and 48% found both sides equally helpful. We conclude that the credit card asthma plan is an effective system for self managing asthma, when introduced in a formal programme of community based clinics.

### Asthma policy in state schools of 14 education authorities in the UK

EC SMITH, AH KENDRICK *Respiratory Department, Bristol Royal Infirmary, Bristol* We have previously reported the policy towards asthmatic children in schools in the County of Avon (Smith and Kendrick *J R Coll Physicians* 1992;47:65) and of Education Authorities in the United Kingdom (Kendrick and Smith *Thorax* 1992;47:759P). We concluded that simple guidelines were needed to help teachers to deal with an asthmatic child in school. In September 1991, the National Asthma Campaign (NAC) released such guidelines. A questionnaire was sent to all head teachers of state schools (n = 2010) in 14 Education Authorities in the United Kingdom to determine their policy and potential influence of the NAC guidelines. Nine hundred and four schools replied, of which 108 were secondary schools. The number of pupils was 221 091. The number of registered asthmatic patients in each school range from 0% to 31.0% (mean 6.6%). Four hundred and thirty seven schools had no formal register of their asthmatic patients. The designated person responsible if a child became ill with asthma was the head teacher (36%), class teacher (25%), first aider (14%), office staff (6%), and the school nurse (3%). Only 194 (21%) of schools had arranged any form of training; 471 (52%) schools allowed pupils to carry their own medication, principally on the basis of age. In many schools, the medication was either centrally located or kept by the class teacher. Generally pupils were allowed access as required, although some schools (7%) stated that this depended on parental instructions; 543 (60%) of schools had some form of procedure to deal with an asthma attack; 90% of schools wanted more information about asthma and 71% wanted a short course on asthma. The NAC guidelines had been obtained by only 269 (30%) of schools; 39% (104/269) of these schools had either altered their schools' asthma policy or simply become more aware of the problems of asthmatic children. We conclude that (1) much more needs to be done to provide guidance to schools and teachers in the care of asthmatic children and (2) the NAC guidelines have so far had only a modest impact on this problem.

### Changes in Mini-Wright peak flow meter performance after prolonged use

JF MILES, P BRIGHT, MR MILLER *The Chest Research Institute, East Birmingham Hospital, and the Department of Medicine, University of Birmingham* The accuracy of 26 Mini-Wright meters that had been in constant use for more than one year (max 13 years) was tested on a computer driven pump whose slewing rate was > 1300 l/minute. These results were compared with those from 40 new meters. Each meter showed the error profile we have previously reported (*Am Rev Respir Dis* 1991;143:29A) with on average an over-reading by up to 70 l/min around 400 l/min and under-reading at each end of the scale. Eight (30%) of the old meters had readings outside the 95% confidence limits derived from the 40 new meters ( $\pm 15$  l/min from the mean reading), with two of these being above the limit. The precise age of 14 of the old meters was known and six of these were in the abnormal group of eight. The average age of these six abnormal meters was slightly higher than but not significantly different from the others (5.1 years v 4.2 years, p = 0.64); however, two of them were under two years old. Cleaning five of these meters led to significant changes in only two. We conclude that some meters can retain their performance unaltered for up to 12 years but for others significant changes can occur within two years of constant use.

**Influence of peak flow meter non-linearity on recorded PEF variability**

JF MILES, MR MILLER *The Chest Research Institute, East Birmingham Hospital and the Department of Medicine, University of Birmingham* In 20 asthmatic patients (7 male, 13 female, age range 15 to 58 years) the peak expiratory flow (PEF) was recorded using Mini-Wright meters at least twice daily for two weeks. Twelve of these subjects were known to have large diurnal variation in PEF. The accuracy of the meters was determined by testing on a computer driven pump and a polynomial equation derived to correct the 280 patient days of raw data for the non-linearity of PEF meter response. The within day amplitude % mean (A%M) PEF was determined from the raw and corrected data. The mean PEF (SD) for the study period was significantly reduced by correction from 358 (140) to 315 (150) l/min ( $p < 0.001$ ). This correction changed the A%M by more than 5% on 110 patient days and by >10% on 32 days. With the raw data the A%M was >15% in 17 patients and was >50% in nine. This increased to 19 and 12 patients respectively when using the corrected data. Significantly more patient days had the A%M increased by correction than decreased, 192 v 63 ( $p < 0.0001$ ), and this was determined by the magnitude of the subject's mean PEF. We have shown that correcting for the non-linearity of PEF meters will influence their clinical application in diagnosing asthma and its severity.

**Non-linearity of the Mini-Wright peak expiratory flow (PEF) meter and its effect on calculation of diurnal variation**

PFG GANNON, DT NEWTON, A AL-SHATTI, CFA PANTIN, PS BURGE, SA DICKINSON, MR MILLER *Occupational Lung Disease Unit, East Birmingham Hospital, Birmingham; Staffordshire Polytechnic, Stafford; City General Hospital, Stoke; University of Birmingham, Birmingham* Mini-Wright meters exhibit non-linearity in the measurement of PEF (Dickinson *et al. Thorax* 1991;46:289P). The clinical effect of this is unknown but it is postulated that this may be an effect of diurnal variation. We have investigated this using 274 PEF records (mean duration: 23 days, mean number of readings: eight per day) and a polynomial allowing correction of readings taken from the Mini-Wright meter. Non-parametric tests were used in the analysis. After correction the mean PEF is decreased and range of PEF was increased. All measures of diurnal variation were increased. If a max-min/mean >20% was used to define significant variability 25(9%) patients would have changed groups after correction was applied. The results are likely to be dependent on the position of this group on the non-linear curve.

	Median (range)	
	Measured	Corrected
Mean daily PEF	480 (209-740)	435 (153-799)
Max - min/mean	13 (2-60)	17 (2-58)
Max - min	56 (8-264)	66 (7-281)
Max - min/max	12 (2-49)	15 (2-48)
SD PEF/mean	5 (1-21)	6 (1-20)
SD PEF	20 (4-93)	24 (3-91)
SD/predicted	4 (1-23)	5 (1-17)
Max - min/PRD	11 (1-66)	14 (1-53)
Max - min/PRD - mean	0.4 (-19-38)	0.4 (-34-44)
Cosinor amplitude/mean	11 (1-49)	14 (2-51)
Cosinor amplitude/predicted (PRD)	9 (1-46)	11 (1-46)

**Ipratropium bromide delivered orally by metered dose inhaler does not decrease salivary flow in normal subjects**

VE THOMAS, F O'CONNELL, AJ HARRISON, RW FULLER *Departments of Clinical Pharmacology and Respiratory Medicine, Royal Postgraduate Medical School, London and Boehringer Ingelheim (UK) Ltd., Berkshire* Ipratropium bromide (IPB) is an anticholinergic agent widely used in the treatment of asthma and obstructive airways disease. Xerostomia has been reported with inhaled and nasal IPB suggesting that IPB delivered into the oral cavity might be a simple and effective treatment for hypersalivation or drooling. We carried out a randomised placebo controlled crossover group study to ascertain the occurrence and duration of xerostomia induced by 240 µg (high dose) and 120 µg (low dose) of IPB delivered by metered dose inhaler (MDI) into the mouth in normal healthy subjects. Salivary output was measured at intervals over a four hour period after drug administration using preweighed dental rolls. There was no significant difference between baseline salivary outputs on the three study days (mean 0.74 (SEM 0.11) g/minute after placebo, 0.84 (0.11) g/minute after low,

and 0.82 (0.11) g/minute after high dose IPB). Change in salivary output from baseline was not significantly higher with either dose of IPB compared with placebo (mean area under the curve was -1.51 (10.62) g after placebo, 4.84 (15.9) g after low, and 25.0 (12.42) g after high dose IPB,  $p = 0.43$ ). There was also no significant difference between VAS scores for dryness of mouth on any day either before or after drug administration. VAS scores for palatability did, however, show that both low dose and high dose IPB were more unpleasant than placebo (placebo 49.3 (4.0), low dose 69.4 (4.2), and high dose IPB 71.9 (4.2),  $p = 0.003$ ). The taste of the drug may have caused a reflex increase in salivary output from the major salivary glands that would have masked any possible local effect of the drug on the smaller submucosal glands of the mouth. We conclude that IPB delivered into the oral cavity by MDI is therefore not a suitable treatment for hypersalivation.

*This work was supported by Boehringer Ingelheim (UK) Ltd*

**Difference in systemic absorption produced by inhaling corticosteroid by different devices**

K KRISHNAN, DJ WOOD, MJ WARD *King's Mill Hospital, Mansfield, Notts* Twelve healthy volunteers (seven male) received two doses of 2000 µg of each of the inhaled steroids budesonide and beclomethasone. One dose was administered using a multidose inhaler with a spacer device, volumatic for beclomethasone and nebulizer for budesonide, the other dose was administered using a dry powder administration system, diskhaler for beclomethasone and turbobalher for budesonide. Mouth rinsing was not carried out. Assays of cortisol were performed with a Famos radioimmunoassay kit with a sensitivity of 5 nmol/l according to the manufacturer's data. Data were analysed with the Wilcoxon signed rank matched pairs test for non-parametric data. The results showed that both of the dry powder devices produced a greater mean percentage fall in serum cortisol than the same drug dose administered via a multidose inhaler with spacer device ( $p < 0.05$ ). This study did not show any significant difference between the two agents when administered via the same type of device. Mean serum cortisol was 481 before and 317 nmol/l after beclomethasone by MDI and 464 and 233 nmol/l after diskhaler. Mean serum cortisol was 450 before and 408 nmol/l after budesonide by MDI and 471 and 279 nmol/l after turbobalher.

**Fluticasone propionate: a comparison with budesonide in adult asthmatic patients**

CG LANGDON, J THOMPSON *Maidenhead, Berkshire and Allen and Hanburys Limited, on behalf of a United Kingdom Study Group* Fluticasone propionate (FP) is a new generation, synthetic glucocorticosteroid currently in clinical development as an inhaled preparation for the treatment of asthma. In early clinical studies, doses of 200 µg FP daily have been shown to be equivalent to 400 µg beclomethasone dipropionate (BDP) daily, showing a 2:1 potency for the two drugs. To determine whether this same ratio exists between FP and budesonide, a multicentre, open, eight week parallel group study compared the efficacy and tolerability of 100 µg FP twice daily with 200 µg budesonide twice daily in 157 adult patients with mild to moderate asthma. Both medications were administered via a metered dose inhaler (MDI) and throughout the study all patients were provided with a salbutamol MDI for relief of asthma symptoms. Mean morning PEF was higher in the FP group although the difference did not reach statistical significance. Other lung function variables; evening PEF, clinic PEF, FEV<sub>1</sub> and FVC showed the two treatments to be equivalent. All other variables measured—that is, reversibility, use of relief medication, and symptoms showed no significant differences between the two treatments. Four patients from the FP group and nine patients from the budesonide group reported at least one serious adverse event. The pattern of minor adverse events was similar for the two groups. The results of this study, therefore, show that FP (100 µg twice daily) is equivalent in terms of efficacy and safety to budesonide (200 µg twice daily) in adult patients with mild to moderate asthma.

**Vascular effects of chronic treatment of both normoxic and chronically hypoxic rats with L-NAME, an inhibitor of nitric oxide release**

CELIA EMERY, GUO QI TENG *Department of Medicine and Pharmacology, Sheffield University* The role of nitric oxide (NO), an endothelial derived relaxant factor, in the control of low pulmonary vascular tone was investigated by studying the effects of chronic

treatment of rats with the L-arginine analogue L-NAME. Systemic blood pressure (BP), pulmonary artery pressure (Ppa), pulmonary vascular resistance (PVR), and heart weights were measured. Wistar male rats, both normoxic (C) and during exposure to chronic hypoxia (CH: 10% O<sub>2</sub>), were treated with L-NAME ad libitum in the drinking water; matched controls drank water. In this pilot study three dosages were tested; daily dosages of roughly 25 mg (n = 4), 7.5 mg (n = 8) and 2.5 mg (n = 6) were given for 10–14 days. BP (mm Hg) was raised (p < 0.01) in all C-L-NAME treated rats (C-LN) (153 SD 10) (n = 3) v 115 (10) n = 8 in water treated rats (C-W) and CH rats (CH-LN 146 (10) n = 8 v CH-W 128 (12) n = 9). Ppa measured by cardiac catheter in six CH-W and four CH-LN rats was high in both groups (30–40 mm Hg) but not significantly altered by L-NAME. Pressure flow lines were studied in isolated blood perfused lungs; results were variable but showed some increase in PVR with L-NAME. Heart weights showed similar right ventricular hypertrophy (RVH) in CH-W and CH-LN rats with no evidence of RVH in C-LN rats. L-NAME did not produce left ventricular hypertrophy. In this pilot study, production of systemic hypertension suggests NO blockade by L-NAME. Little evidence of a controlling, dilator role of NO in the pulmonary vasculature was found. Our earlier studies suggest that under certain circumstances NO may be released when Ppa is raised, including chronic hypoxia. This point requires further investigation.

### Inhibition of hypoxic vasoconstriction in isolated small pulmonary arteries by ANP

TK ROGERS, AH MORICE *Department of Medicine and Pharmacology, Royal Hallamshire Hospital, University of Sheffield* We have studied the inhibition of the contractile response to acute hypoxia by atrial natriuretic peptide (ANP) of isolated pulmonary resistance vessels (PRVs) from chronically hypoxic (H) and control (C) rats. Litters were separated at five weeks of age: half were placed in a normobaric hypoxic chamber and half breathed room air. After at least 17 days C and H littermate pairs (nine of each) were anaesthetised, lungs were removed and PRVs dissected. C and H vessels were mounted as isometric ring preparations in the same bath of an automated, small

After 90 minutes exposure (time to plateau response), 100 nM amlodipine caused a mean relaxation of 45 (SD 11.8)% compared with 84.5 (8.7)% in six control vessels. The same protocol was applied to 13 large pulmonary vessels of mean internal diameter 1.07 mm (range 0.77–1.50) and 13 resistance vessels of 0.33 mm (0.20–0.47). After 90 minutes, seven control vessels of mean 1.07 mm (0.81–1.35) and six of 0.29 (0.21–0.47) had relaxed to 99.7% (0.7) and 95.7% (5.2) respectively (NS). Amlodipine 100 nM relaxed resistance vessels to a mean of 44.6% (SD 9.9). This effect was much greater than was found with the larger arteries, which were relaxed to 68.9 (10.4)% (p < 0.01). The relaxation seen in the aortic sections was similar to that found previously (Burgess *et al. J Cardiovasc Physiol* 1987;9:110). This study shows that amlodipine relaxes isolated pulmonary arteries, and may therefore be of value as a pulmonary vasodilator in humans.

### Hypobaric and normobaric hypoxia in rats

W SHEEDY, JS THOMPSON, AH MORICE *Department of Medicine and Pharmacology, University of Sheffield* Exposure to chronic hypoxia is a well established experimental model of pulmonary hypertension (PH) in rats. We have compared the physiological effects normally seen in rats exposed to normobaric hypoxia with those seen in animals exposed to hypobaric hypoxia. Male Wistar rats aged 28 days were either kept in a normobaric, hypoxic (NB) chamber at 10% O<sub>2</sub> or in a hypobaric (HB) chamber at 500 mbar. Littermate controls (C) were kept in air. Animals were weighed daily. At 10 and 14 days, rats (n = 8 per group) were anaesthetised, and exsanguinated via the pulmonary artery for measurement of haematocrit (Hct) and plasma ANP, and the heart was dissected for determination of ventricular ratios (RV/[LV + S]). Lungs were perfused with 10% formol saline and fixed for histological examination. The table summarises the results. After 10 days, both hypoxic groups (NB and HB) had developed significant RV hypertrophy and gained significantly less weight, compared with controls. These changes were greater after 14 days. The results suggest that a hypobaric chamber may provide an equally efficient yet more convenient model of experimental pulmonary hypertension.

	C		NB		HB	
	10 days	14 days	10 days	14 days	10 days	14 days
BW/g	178.2 (12.2)	218.9 (14.7)	150.1 (9.2)	174.8 (11.3)	144.7 (10.2)	163.2 (6.9)
RV/[LV + S]	0.31 (0.04)	0.30 (0.02)	0.51 (0.05)	0.50 (0.06)	0.54 (0.05)	0.51 (0.02)
Hct/%	34.0 (3.5)	32.9 (2.2)	43.3 (3.4)	48.9 (2.4)	45.2 (3.4)	52.3 (3.7)

BW = body weight; results are mean (SD).

vessel myograph (Cambustion Ltd, UK). The bath was bubbled with 95% N<sub>2</sub> and 5% CO<sub>2</sub>, producing a resting PaO<sub>2</sub> of 10–12 KPa in the physiological saline solution (PSS) bathing the vessels. Gentle precontraction with 10 μm prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) was found greatly to enhance hypoxic contraction (HC), and this was performed before each hypoxic challenge: the PaO<sub>2</sub> was reduced by covering the organ bath. The average of four baseline HCs was 3.92 (1.54) mN/mm for C vessels and 1.79 (0.21) mN/mm for H (p = 0.19). After increasing concentrations of ANP had been added to the bath further HCs were performed. Hypoxic contraction of both C and H vessels showed dose dependent inhibition by ANP, being virtually completely abrogated by 170 nM. We have previously found that vasodilatation of PGF<sub>2α</sub> precontracted vessels by ANP is increased appreciably after chronic hypoxia. By contrast there were no significant differences between the hypoxic responses of C and H vessels to ANP, with greater inhibition occurring in the C vessels. This may be a result either of methodological differences or of the different ways in which chronic hypoxia modifies the response of the PRV to receptor mediated agonists and acute hypoxia.

### The calcium antagonist amlodipine preferentially inhibits the contraction of isolated rat pulmonary resistance arteries

PA WOODMANSEY, F ZHANG, KS CHANNER, AH MORICE *University of Sheffield* Calcium antagonists are pulmonary vasodilators found to be of benefit in primary pulmonary hypertension. We investigated the effect of amlodipine, a long acting dihydropyridine calcium antagonist on rat pulmonary arteries in vitro. A time relaxation curve with amlodipine was measured in vessels maximally precontracted with KCl. Results are expressed as the percentage of maximal contraction. Statistics were by unpaired t test comparison of areas under curves. In an initial experiment, 10 sections of rat thoracic aorta were mounted on a myograph (Cambustion) in a bath of physiological saline solution.

### Effect of hyperinflation on pulmonary artery pressure (Ppa) in chronically hypoxic rats

P RUSSELL, K KAPPELER, G BARER *Department of Medicine and Pharmacology, Royal Hallamshire Hospital, Sheffield S10 3HJ* Pulmonary vessels of chronically hypoxic (CH) rats respond differently to many stimuli including inflation. CH rats, like many humans with lung disease, have a high thoracic gas volume. We compared inflation in control (C) rats with rats exposed two weeks to 10% O<sub>2</sub>. Isolated blood perfused lungs (constant flow) were ventilated with air (normoxia) or 2% O<sub>2</sub> (hypoxia), both +5% CO<sub>2</sub>. Inflation by high alveolar pressure (PALV; 10, 15, or 20 mm Hg) caused larger rises in Ppa in CH than C rats. In normoxia ΔPalv (10 mm Hg) raised Ppa 8.3 (SEM 0.7) mm Hg in 10 C rats and 16.6 (1.4) in 10 CH rats. In hypoxia ΔPalv (10 mm Hg) raised Ppa 3.3 (0.6) in 10 C and 15.9 (2) in 10 CH rats; differences between C and CH rats were also seen during vasoconstriction caused by almitrine (5 mg) or PGF<sub>2α</sub> (20 mg). One possibility is that constriction in CH rats takes place in small newly muscularised vessels compressible by alveolar pressure, whereas constriction in C rats is in larger extra-alveolar vessels pulled open by inflation. At high Palv during hypoxic vasoconstriction, Ppa often rose and then adapted in C rats (32.3 (1.4) to 29.8 (1.1) mm Hg; p < 0.001 n = 10) whereas it often rose further in CH rats (58.8 (3.9) to 64.4 (3.4) mm Hg; p < 0.001, n = 10). Radial tension might attenuate vasoconstriction in extra-alveolar vessels in C rats. In CH rats constriction in smaller vessels might be enhanced by external compression, or reduced vascular compliance might prevent expansion of larger vessels. Hypoxic vasoconstriction was reduced in C but not CH rats after inflation tests and recovered slowly. The adaptation of Ppa and attenuation of constriction during inflation in C rats was not due to release of NO, since they persisted after blockade of NO synthesis with L-NAME (n = 6). We suggest that hyperinflation and airway obstruction might contribute to pulmonary hypertension in lung disease, especially on exercise.

**Effects of intravenous prostacyclin on haemodynamics and pulmonary gas exchange in severe chronic obstructive pulmonary disease**

AY BUTT, TW HIGENBOTTAM, G CREMONA, M TAKAO, BA OTULANA, AT DINH-XUAN *Respiratory Physiology Department, Papworth Hospital, Papworth Everard, Cambridge* Pulmonary gas exchange and haemodynamics were studied in 11 patients with advanced chronic obstructive pulmonary disease (COPD). Right heart catheterisation was performed on all of these patients and measurements were made at baseline and on acute vasodilatation with intravenous prostacyclin (PGI<sub>2</sub>). We have found that prostacyclin caused a small but significant drop in arterial oxygen tension (Pao<sub>2</sub>) but did not change mixed venous oxygen tension (PvO<sub>2</sub>) significantly (from 4.64 (0.22) to 4.8 (0.25) kPa; NS). The physiological shunt (Q<sub>s</sub>/Q<sub>t</sub>) was raised at baseline and sustained a further significant rise with PGI<sub>2</sub>. Mean pulmonary artery pressure remained unchanged from 29.38 (4.63) to 29.82 (3.72) mm Hg; NS); however, there was an appreciable improvement in cardiac index (CI) and oxygen tissue delivery (To<sub>2</sub>). The table summarises the effects of acute vasodilatation with PGI<sub>2</sub> on gas exchange and haemodynamics. These data suggest that vasodilator treatment could be of value in the management of selected patients with COPD. It would be desirable first to evaluate their response carefully to acute vasodilator challenge during right heart catheterization. It also opens up the possibility of using local pulmonary vasodilators such as inhaled nitric oxide in the management of this condition.

	Pao <sub>2</sub>	Q <sub>s</sub> /Q <sub>t</sub>	CI	To <sub>2</sub>
Baseline	7.61 (0.57) kPa	30.28 (6.85)%	2.93 (0.21) l	26.87 (1.31) mmol/min
After PGI <sub>2</sub>	7.16 (0.37) kPa*	38.5 (7.38)%*	4 (0.31) l**	35.85 (1.5) mmol/min**

\*p < 0.05; \*\*p < 0.001.

**A three probe portable system for assessment of pulmonary endothelial permeability**

CM DRYDEN, AA BOLSTER, TE HILDITCH, KR PATEL *Intensive Care Unit, Department of Clinical Physics and Bioengineering and Department of Respiratory Medicine, Western Infirmary, Glasgow* A double radionuclide technique using a single scintillation probe has been used to quantify pulmonary endothelial permeability (*J Thorac Imag* 1988;3:28). We have developed a portable, three probe system and assessed its use. Transferrin was labelled in vivo by intravenous injection of 10 MBq of 133<sup>m</sup>-indium (133<sup>m</sup> In). Red blood cells were labelled using 10 MBq of 99<sup>m</sup> technetium. The pulmonary accumulation of transferrin was monitored simultaneously by three scintillation probes linked to an IBM PC based multichannel analyser. The probes were positioned over the mid-zones of each lung and over the heart and radioactivity at each site was monitored for one hour. Analysis of the data produced a protein accumulation index (PAI) with estimates of standard error (SE). Patients were categorised clinically by the lung injury score (LIS) described by Murray (*Am Rev Respir Dis* 1988;138:720). Mean PAI × 10<sup>-3</sup> (mean SE × 10<sup>-3</sup>) in three healthy volunteers (all non-smokers, mean age 30) was 0.03 (0.5). In four studies performed in two patients with established adult respiratory distress syndrome (ARDS) LIS > 2.5, mean PAI was 4.6 (0.8). In seven studies carried out in six patients at risk of ARDS (LIS 0.1-2.5), mean PAI was 1.3 (0.5). In seven studies, PAI was significantly different for each lung and the higher value was used to calculate mean PAI. Blood kinetics of the two radionuclides were also quantified, showing one study significantly affected by extravasation of the injectate, and giving potentially useful information on binding of the isotopes in the circulation. We conclude that the three probe system offers significant practical and clinical advantages over the single probe system.

*This study was supported by the Chest, Heart and Stroke Association, Scotland*

**Hypoxic pulmonary vasoconstriction (HPV) of isolated porcine lungs is not dependent on changes in endogenous nitric oxide (NO) release**

G CREMONA, TW HIGENBOTTAM, A WOOD, L HALL *Department of Respiratory Physiology, Papworth Hospital and Department of Anaesthesiology, School of Veterinary Medicine, Cambridge* Acute hypoxia can cause release of NO from pulmonary artery endothelium (Pepke-

Zaba *et al. Thorax* 1991;46:746P). Yet it has been argued that acute hypoxic pulmonary vasoconstriction (HPV) results from a reduction of endothelial NO production. Both lungs, obtained from seven anaesthetised pigs undergoing cardiopulmonary bypass, were mounted for perfusion and ventilation in a temperature control isolated rig. Pressure flow (P-Q) curves for the pulmonary vasculature were recorded over a range of pulmonary flows of 0.5-6 l min<sup>-1</sup> using a Krebs-dextran perfusate or Krebs-blood perfusate (haematocrit 16-20%). The lungs were ventilated with air, normoxia or hypoxia (2% F<sub>O2</sub>) and were treated with the inhibitor of NO synthase N<sup>w</sup>-nitro-L-arginine methyl ester (L-NAME) (10<sup>-5</sup>). With regression analysis the slope and intercept of the P-Q curves were calculated and means presented (see table). Despite inhibition of NO production by L-NAME hypoxia can still cause a significant change (p < 0.5) in slope and intercept of the P-Q curve, both in the presence and in the absence of blood. We argue that acute HPV is not dependent on changes in NO production by the pulmonary endothelium.

	Blood (P-Q)		Krebs-dextran (P-Q)	
	Slope	Intercept	Slope	Intercept
Baseline	3.6	4.8	3.4	0.8
Hypoxia	5.3	8.4	3.3	2.2
Normoxia L-NAME	9.1	10.3	7.1	2.5
Hypoxia L-NAME	11.4	15.0	10.2	7.3
Nitroprusside (10 <sup>-4</sup> M)	4.0	6.6	2.6	1.0

**Anti-inflammatory drugs increase mRNA of platelet derived growth factor-B in alveolar macrophages**

RJ SHAW, AR HAYNES, SP SUTCLIFFE, A WANGOO *Department of Respiratory Medicine, St Mary's Hospital Medical School, London* Alveolar macrophages in the setting of chronic lung inflammation are thought to produce growth factors for fibroblasts, and thus promote the development of lung fibrosis. Anti-inflammatory agents may exert a beneficial action by decreasing the level of inflammation but it is not known how these agents specifically affect the production of growth factors by macrophages. This study measured the effect of two anti-inflammatory agents, dexamethasone and colchicine, on the mRNA of two important growth factors, platelet derived growth factor-B (PDGF(B)) and transforming growth factor-β (TGF-β), in both alveolar macrophages and in vitro derived macrophages. Both dexamethasone and colchicine caused a marked increase in the abundance of PDGF(B) mRNA but not TGF-β mRNA. When the macrophages were cultured in the presence of interferon-γ, which may be present in the chronically inflamed lung, the addition of dexamethasone or colchicine resulted in a further marked increase in PDGF(B) but not TGF-β mRNA. These data lead to the speculation that both corticosteroids and colchicine increase PDGF(B) mRNA in macrophages, this may in part explain the lack of clinical efficacy of these anti-inflammatory agents in established lung fibrosis.

**Effects of intranasal challenge with interleukin-8 (IL-8)**

CE GURR, J DOUGLASS, J SHUTE, ST HOLGATE, MK CHURCH *Department of Immunopharmacology, Southampton General Hospital, Southampton* Interleukin-8 is a chemotactic cytokine that is important in several respiratory pathologies. We have investigated the effects of intranasal instillation of human recombinant IL-8 in eight atopic (four male) and eight non-atopic (one male) donors in a double blind placebo controlled study. Changes in nasal resistance were monitored by posterior rhinomanometry for four hours after challenge. Symptom scores were recorded on a visual analogue scale. Nasal scrapings were taken and stained with Haema-Gurr for differential cell counts. Nasal resistance data in the whole group showed an increase in nasal resistance 10 minutes after challenge compared with placebo (p < 0.01 t test). There was no significant difference between atopic and non-atopic subjects. Symptoms scores were significantly increased in all 16 subjects with IL-8 compared with placebo. Nasal scrapings from both

groups showed a significant increase in the proportion of neutrophils compared with the placebo control ( $p < 0.001$ ). There was no significant difference between atopic and non-atopic groups. Whereas there was no significant difference in eosinophil infiltration in the non-atopic group a pronounced eosinophil infiltrate was found in three atopic subjects. Interleukin-8 therefore causes a significant increase in nasal obstruction, symptoms, and cellular infiltrate in the nasal challenge model of respiratory disease.

*This study was supported by the Sandox Research Institute, Vienna*

### Changes in mucosal blood flow and airways resistance after nasal challenge with bradykinin and histamine

K RAJAKULASINGAM, R MANI, MK CHURCH, ST HOLGATE, PH HOWARTH *Departments of Immunopharmacology and Medical Physics, University of Southampton, England* Nasal challenges with histamine (H) and bradykinin (B) have been shown to induce many of the features of rhinitis including nasal blockage and microvascular leakage. The mechanisms of nasal blockage and microvascular leakage may reflect involvement of two different vascular compartments, the deep venous sinusoids and the superficial mucosal capillaries respectively. To investigate this eight non-rhinitic subjects took part in a study to assess the changes in blood flow in venous sinusoids and mucosal blood vessels by undertaking rhinomanometry to measure changes in nasal airways resistance and laser doppler flowmetry to measure changes in mucosal blood flow. The subjects attended on three occasions to undergo nasal challenge with incremental doses of B (200, 1000, 2000  $\mu\text{g}$ ), H (520, 1040, 2080  $\mu\text{g}$ ) and vehicle placebo (V). The nasal challenges were undertaken at 15 minute intervals. Nasal challenges with B and H induced dose-related increase in NAR and V was without effect. The median maximal increases for each dose were 29.4, 80.6, and 109.7% for B and 40.9, 113.6 and 122.7% for H. B and H also induced significant 9.5 and 12.0% increases in mucosal blood flow after the first dose challenge. There was no further dose-related increase in mucosal blood flow. Nasal challenge with V failed to induce significant changes in nasal mucosal blood flow. This study shows that changes in nasal airways resistance do not reflect changes in nasal mucosal blood flow. It is thus possible that obstructive response and microvascular leakage could be differentially affected within the respiratory tract.

### The role of histamine and cholinergic pathways in bradykinin induced nasal responses

K RAJAKULASINGAM, R POLOSA, LCK LAU, MK CHURCH, ST HOLGATE, PH HOWARTH *Immunopharmacology Group, University of Southampton, England* Nasal instillation of bradykinin elicits many of the characteristic features of rhinitis. To assess the relevance of histamine release from metachromatic cells and the activation of cholinergic pathways, we investigated the effects of terfenadine (T), a histamine  $H_1$ -receptor antagonist, and ipratropium bromide (IB), a selective antimuscarinic agent, on bradykinin induced rhinorrhoea, nasal airways resistance (NAR), nasal pain, and plasma protein leakage. Oral T (120 mg) or matched placebo and nasal IB (80  $\mu\text{g}$ ) or matched placebo were administered at four hours and 30 minutes respectively before bradykinin nasal challenge in two randomised, double blind and crossover studies on eight non-rhinitic subjects. Thus subjects received either double placebo, oral T and nasal placebo, oral placebo and nasal IB, or oral T and nasal IB, as pretreatment. Bradykinin challenge induced mean maximal increases of 57%, 59%, 77%, and 72% in NAR on the placebo, T, IB, and T plus IB pretreatment days respectively. These increments were not significantly different. Similarly rhinorrhoea and nasal pain induced by bradykinin nasal challenge were not significantly different on the four challenge days. Bradykinin nasal challenge caused a mean maximal increase in albumin levels in recovered nasal lavages of 11.5, 13.0, 12.2, and 12.3 times baseline levels on the placebo, T, IB, and T plus IB pretreatment days respectively. Similarly total protein achieved a mean maximal increase of 8.0, 8.2, 7.9, and 8.8 times of baseline on these challenge days. The increments in both albumin and total protein did not significantly differ on the four challenge days. This study, therefore shows that cholinergic pathways and mast cell release of histamine do not contribute to increase in NAR, rhinorrhoea, and plasma protein extravasation induced by bradykinin.

### Patients with sarcoidosis express increased concentrations of leucam adhesion proteins (CD11/CD18) on their peripheral blood leucocytes

AS HAMBLIN, Z SHAKOOR, N BATEMAN *Departments of Immunology and Thoracic Medicine, UMDS, St Thomas's Campus* The LeuCAM adhesion proteins (CD11a, CD11b, CD11c, and CD18) found on all leucocytes, are cell-surface proteins that mediate the adhesion between leucocytes themselves and between leucocytes and vascular endothelium. Their expression is increased on cell activation. Using a method of preparation of peripheral blood leucocytes for the quantitative analysis of LeuCAMs by flow cytometry (Hamblin *et al. J Immunol Methods* 146, 219, 1992) we have shown increased mean fluorescence intensities (MFIs) of expression of these molecules on the monocytes, polymorphs (PMNs), and lymphocytes from 11 Caucasian (Ca) and 10 Afro-Caribbean (AC) patients compared with age, sex, and race matched controls. CD18 was significantly increased (paired Student  $t$  test) on all cell types ( $p < 0.01$ ). CD11 was also increased on all cell types achieving statistical significance for CD11a on Ca monocytes ( $p < 0.01$ ) and AC lymphocytes ( $p < 0.05$ ); CD11b on Ca ( $p < 0.05$ ) and AC ( $p < 0.01$ ) monocytes, AC PMNs and lymphocytes ( $p < 0.05$ ), and CD11c on AC ( $p < 0.001$ ) and Ca monocytes ( $p < 0.05$ ). There were no significant differences in the percentages of the cells expressing the molecules. Significant correlations (Spearman's rank test) were found between monocyte CD11b and 11c, and PMN CD11b and SACE concentrations and between a fall in SVC and monocyte CD11a and 11b and PMN CD11a and CD11b. No correlation was found between CD11/CD18 expression and other lung function tests, ESR, or duration of symptoms. We suggest that in sarcoidosis there is systemic leucocyte activation, that increased LeuCAM expression may play a part in cellular extravasation and granuloma formation and that LeuCAM expression could be investigated as a marker of disease activity.

### Corticosteroid improves bacterial clearance and reduces bronchial inflammation in experimental bronchiectasis (EBX)

NC MUNRO, MN SHEPPARD, HC TODD, J ROHDE, D GUERREIRO, AND PJ COLE *Host Defence Unit, Royal Brompton National Heart and Lung Institute, Manresa Road, London* Non-steroidal anti-inflammatory agents have been shown to modify the inflammatory response to *Pseudomonas aeruginosa* (*P aer*) in murine lungs (*J Infect Dis* 1989; 179:232). We have examined the corticosteroid methylprednisolone for its ability to reduce bronchial inflammation associated with EBX. Partial ligation of the apical lobe bronchus followed by intrabronchial injection of *P aer* was carried out in two groups of rats, a procedure producing EBX. (Lapa e Silva *et al. Am J Molec Cell Biol* 1988;1:297). One group then received methylprednisolone 30 mg/kg daily by intraperitoneal route, the other group received vehicle alone. Rats from each group were killed at intervals up to three months and quantitative bacteriological cultures of the apical lobes carried out. Bronchial histology was also assessed after three months. The tables summarise the results. Rats treated with methylprednisolone cleared intrabronchial bacteria after one month and their bronchial inflammation and intraluminal secretions were reduced at three months.

Treatment	Days post-surgery				
	2	7	14	28	90
Vehicle only	7.14 (5)*	7.34 (6)	2.95 (5)	3.42 (5)	2.93 (4)
Methylprednisolone	8.08 (2)	6.70 (5)	4.19 (5)	0.65 (4)	0.00 (4)

\*Mean number of *P aer* ( $\log_{10}$  in apical lobe (No of cultures).

Treatment	Bronchial inflammation	Intrabronchial secretions
Vehicle only	5/10*	4/10
Methylprednisolone	0/9	2/9

\*Number of rats with feature/total rats.

### Use of nebulised immunoglobulin as adjunctive therapy for severe pulmonary infection in bronchiectasis

MF BONE, V NAGENDRAN *Russells Hall Hospital, Dudley, West Midlands* Although colonisation of the respiratory tract is common in bronchiectasis, the advent of deep seated infection and the subsequent

inflammatory response leads to an appreciable deterioration in well-being and lung function. Eradication of the infection with resolution of the inflammatory markers of disease activity is difficult, often requiring prolonged parenteral antibiotics and inpatient supportive care. The use of nebulised polyvalent IgG has been shown to reduce infection in experimental animals inoculated with *Streptococcus pneumoniae*. We describe the use of nebulised immunoglobulin in seven patients with severe bronchiectasis and deep seated infection with a variety of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas*, *Proteus*, *Coliform*, and *Aspergillus*, despite physiotherapy, high dose antibiotics and nebulised colomycin. All patients were unwell with weight loss, chest pain, falling lung function, and global ill health. A variety of inflammatory markers such as C reactive protein, complement breakdown products C3d, serum  $\beta_2$  microglobulins, and serum immunoglobulins were increased. Only two patients exhibited a deficiency of immunoglobulin subclasses. These patients were treated with additional nebulised immunoglobulin diluted 1:5 with saline, either once or twice daily. Six patients showed considerable improvements in wellbeing, weight gain, better lung function, a reduction in sputum volume and purulence and reduction in the level of raised inflammatory markers. Side effects in one patient consisted of chest tightness and a fall in peak flow with the more concentrated immunoglobulin mixture. Thus nebulised immunoglobulin may well prove useful adjunctive therapy for severe deep seated infection in bronchiectasis, even when there is no obvious immunoglobulin deficiency.

**5-Hydroxytryptamine and sensitivity of the human cough reflex**

RA STONE, Y-M WORSDELL, RW FULLER, PJ BARNES *National Heart and Lung Institute, London* To investigate whether serotonergic mechanisms influence the cough reflex, we induced cough during infusions of 5-hydroxytryptamine (5-HT), 5-hydroxytryptophan (5-HTP) which crosses the blood brain barrier (BBB), and saline control. Eight normal men (21–28 years old) were screened for sensitivity to 5-HT (2–3  $\mu\text{g}/\text{kg}/\text{min}$ ); this was manifest as an increase in heart rate (HR). They received baseline cough challenge with a low chloride solution (1.26% sodium bicarbonate) and a single breath of capsaicin during sham infusion. After three hours subjects received repeat cough challenge during infusion of either 5-HT, 5-HTP, or saline, dispensed randomised and single blind. Cough challenge was given when increased HR occurred, or at the time point when it had occurred during the screening infusion. HR and respiratory rate (RR) were noted every 15 seconds before, during, and after infusions. Blood pressure (Bp) was measured every two minutes. 5-HT and 5-HTP reduced cough responses to the low chloride solution ( $p < 0.05$ ,  $p < 0.01$ ) but not to capsaicin. 5-HT caused a transient increase in HR ( $p < 0.01$ ). Respiratory rate and Bp were unchanged. Median cough responses are shown during sham and real infusions; group mean HR is shown at baseline, immediately before and immediately after cough challenge (tables). As 5-HTP but not 5-HT crosses the BBB, we conclude that the inhibitory influence of 5-HT may be peripheral and that of 5-HTP peripheral, or central, or both.

	Chloride deficient		Capsaicin		p Value Wilcoxon
	Sham	Real	Sham	Real	
5-HT	23.5	11.5	6.5	6	<0.05
5-HTP	26.5	15.5	7	6.5	<0.01
Saline	20	17.5	6	5.5	

	HR		
	Baseline	Before	After
5-HT	63.4	75.4**	74.3*
5-HTP	73.3	73.3	75.5
Saline	64.7	65.9	67.7

\* $p < 0.05$ ; \*\* $p < 0.01$ : paired *t* test.

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**Allergen evoked urinary leukotriene E<sub>4</sub> excretion, bronchoconstriction, and airway hyperreactivity after inhalation of a topically potent glucocorticoid, fluticasone propionate**

KM O'SHAUGHNESSY, B WELLINGS, B GILLIES, RW FULLER *Department of Clinical Pharmacology, Royal Postgraduate Medical School, London and Glaxo Group Research, Greenford, Middlesex* We have previously shown that acute dosing with either short or long acting  $\beta_2$  agonists does not alter the increased urinary leukotriene E<sub>4</sub> (LTE<sub>4</sub>) excretion that follows bronchial allergen challenge (*J Allergy Clin Immunol* 1992;89:575). In the study reported here, we have extended these observations with a new and topically potent inhaled glucocorticoid, fluticasone propionate (FP). Ten patients with mild asthma (six male; FEV<sub>1</sub> >60% predicted; PC<sub>20</sub> histamine  $\leq 8$  mg/ml; on inhaled  $\beta_2$  agonists only) were studied before and after a two week period of FP (800  $\mu\text{g}/\text{day}$ ) or placebo administered by identical metered dose inhalers as two puffs twice daily through a Volumatic spacer. Treatments were assigned in a double blind crossover fashion separated by a three week washout period. The PC<sub>20</sub> histamine was measured at the start and end of each treatment when subjects also received a bronchial allergen challenge. Urine was collected for four hours after challenge for determination of LTE<sub>4</sub> using HPLC-RIA and two hours later the PC<sub>20</sub> histamine measurement repeated. Bronchial reactivity was significantly reduced after two weeks of treatment with FP but not placebo (median (range) change in PC<sub>20</sub> histamine was 1.28 (0.49 to 3.88) and 0.1 (-0.52 to 0.68) doubling dilutions respectively,  $p < 0.01$ ). The early and late responses to allergen challenge were also significantly inhibited; the maximum fall in FEV<sub>1</sub> during the early (0–two hours) and late response (two to six hours) was 32.6 (SEM 3.4)% and 19.6 (5.2)% after placebo *v* 19.5 (4.5)% and 3.6 (2.6)% after FP (both  $p < 0.02$  FP *v* placebo). The allergen induced hyperreactivity was completely abolished on the FP limb (median change in PC<sub>20</sub> histamine after allergen -1.59 (-0.40 to -2.59) doubling dilutions after placebo *v* -0.10 (-0.92 to 1.36) after FDP,  $p < 0.01$ ). Despite this, FP had no significant effect on the increased urinary LTE<sub>4</sub> excretion following allergen challenge; 18.4 (3.4–104.1) ng. mmol creatinine<sup>-1</sup>, geometric mean (95% CI), after placebo and 18.7 (3.2–109.5) after FP ( $p > 0.5$ ). Thus FP behaves like other inhaled glucocorticoids administered chronically with decreased bronchial reactivity and inhibition of both early and late responses to inhaled allergen. Its lack of effect on allergen evoked urinary LTE<sub>4</sub> excretion suggests that the second represents systemic and not pulmonary cysteinyl leukotriene production.

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**Frusemide and allergen induced contractions of passively sensitised human bronchi: evidence of a role for prostaglandin E<sub>2</sub>**

I PAVORD, E HOLLAND, D BALDWIN, A TATTERSFIELD, A KNOW *Respiratory Medicine Unit, City Hospital, Nottingham* We have previously shown that frusemide (10<sup>-6</sup> to 10<sup>-4</sup> M) dose dependently inhibits allergen induced contractions of passively sensitised human bronchi in vitro. In this study we have tested the hypothesis that this effect is related to enhanced synthesis of inhibitory prostaglandins (PGs) such as PGE<sub>2</sub>. Macroscopically normal human lung tissue was obtained from thoracotomy specimens. Bronchial rings were passively sensitised by incubation overnight with diluted serum from an allergic donor (*Dermatophagoides pteronyssinus* specific IgE titre 8.7 KU<sub>A</sub>/l). Sets of four bronchial rings obtained from the same thoracotomy specimen were suspended in 15 or 20 ml organ baths in Krebs-Henseleit solution and continuously bubbled with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. After washing the response to 10<sup>-4</sup> M methacholine was measured and used to standardise the response to allergen (*Dermatophagoides pteronyssinus* 3  $\mu\text{g}/\text{ml}$ ). Eight sets of four bronchial rings were preincubated with indomethacin (3  $\times$  10<sup>-6</sup> M) or vehicle for 20 minutes, washed, and retreated with indomethacin or vehicle immediately before allergen challenge. Frusemide (10<sup>-4</sup> M) or vehicle were added immediately before allergen. Organ bath PGE<sub>2</sub> concentration was measured over a 20 minute period before and after allergen. Frusemide inhibited allergen induced contractions (assessed over 60 minutes as the area under the contraction/time curve) by a mean 67.8% when given alone and by 34.7% when given with indomethacin (mean difference 33.1%; 95% CI 9.6, 56.6%;  $p < 0.01$ ). Indomethacin alone inhibited the response to allergen by 2.4%. Immunoreactive PGE<sub>2</sub> production increased 2.3, 1.2, 0.9, and 0.7-fold ( $p < 0.05$ ) with frusemide alone, vehicle alone, indomethacin alone, and indomethacin and frusemide respectively. These data would support a role for PGE<sub>2</sub> in the protective effects of frusemide against allergen-induced contractions in vitro.

**Cytokine immunoreactivity in the normal human nasal mucosa**

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*Medicine 1, Southampton General Hospital* Several cytokines have been implicated in the pathogenesis of allergic inflammation, particularly IL-4 that regulates IgE synthesis, IL-5 that promotes eosinophil growth, survival, and chemotaxis, IL-3 that stimulates mast cell growth, IL-6 that synergises with IL-4 in IgE production, and IL-8 that is chemoattractant for neutrophils; TNF $\alpha$  upregulates adhesion molecules; IFN- $\alpha$  antagonises the activities of IL-4 and may downregulate allergic type responses. To investigate the presence of these cytokines in normal nasal mucosa, nasal biopsies from 10 normal

subjects were taken under local anaesthesia (six non-atopic, four atopic), embedded in glycol methacrylate and stained immunohistochemically with specific mouse monoclonal IgG<sub>1</sub> antibodies to the relevant cytokine. Adjacent 2  $\mu$ m sections were stained with AA1 to mast cell tryptase and CD3 for pan T cells to identify the cellular localisation of each cytokine. Immunoreactivity for IL-4, IL-5, IL-6, and TNF was present in all biopsies and colocalised with AA1 immunostaining but not with CD3 positive cells, therefore identifying cytokine product localised to mast cells but not T cells. IL-8 was localised to the epithelium. No immunoreactivity was present for IL-3 or IFN- $\gamma$ . These findings suggest that mast cells have a potential role in the pathogenesis of allergic inflammation through the release of IL-4, IL-5, IL-6, and TNF $\alpha$ .