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The 1988 winter meeting of the British Thoracic Society was held on 8 and 9 December at Kensington Town Hall, London.

Cutaneous and systemic vasculitis in cystic fibrosis (CF)

MJ FINNEGAN, D JAYNE, S NEILL, A WISE, ME HODSON *Brompton Hospital and St Stephen's Hospital, London, and Addenbrooke's Hospital, Cambridge* Vasculitis complicating CF has rarely been reported (*J Pediatr* 1979;**95**:197). Antineutrophil cytoplasmic antibody (ANCA) is associated with systemic vasculitides (Wegener's granulomatosis and microscopic polyarteritis), but an association with CF has not been reported. In a nine month period, four patients with CF developed histologically proved vasculitis. A further eight cases of CF with vasculitis were identified from the CF database: three were histologically proved and in five palpable purpura without thrombocytopenia was present. Markers for connective tissue disease were negative in all cases tested. Five patients had vasculitis only in their last two months of life. Of these, four were localised to the skin but one died of histologically proved cerebral vasculitis. Six patients had skin vasculitis which followed a benign course, remitting and relapsing for up to two years before finally clearing (four spontaneously, one on withdrawal of ranitidine and one with steroid therapy). One patient had systemic vasculitis with typical renal biopsy findings of Henoch-Schoenlein purpura. This responded well to immunosuppressants. Stored serum prior to steroid therapy, available in 10 of these 12 patients, was tested for ANCA. Sera were considered positive only if the indirect immunofluorescence assay was positive (*Lancet* 1988;i:706). Using this criteria four of the patients with vasculitis limited to the skin was positive and the remainder were negative. None of 62 sera from patients with CF but without vasculitis who were matched for age, disease severity and sputum bacteriology were positive. In conclusion: (1) vasculitis is associated with CF; (2) it often follows a benign course, but if there is evidence of systemic vasculitis, treatment with immunosuppressants may be rewarding; (3) ANCA is not a good marker for this type of vasculitis.

Measurement of nasal potential difference in patients with "equivocal" sweat tests

EWFW ALTON, JO WARNER, DM GEDDES *Brompton Hospital, London* We have previously described our experience of the use of nasal potential difference in the diagnosis of patients with cystic fibrosis (CF) (Alton *et al*, *Thorax* 1988;**42**:738). During this study we have been referred 24 patients (mean age 19·6 years, range 6 weeks to 45 years), among whom there has previously been particular difficulty in establishing a final diagnosis. Nasal potentials were measured as part of a prospective work up of this group, and comparison made with the overall diagnosis. Patients fell into two broad categories. The first was a group of 12 subjects whose sweat test result was either equivocal or raised, but suppressed with fludrocortisone. However, the clinical features and in some cases the family history were strongly suggestive of CF. Nasal potentials ranged from −24 to −65 mv with a mean of −42·6 mv. Eleven of the values fell within our CF range with all 12 patients being clinically assigned a definite or most likely diagnosis of CF. The second category comprised 12 patients with either elevated sweat test values or other features suggestive of CF among whom the diagnosis was in doubt. Nasal PD ranged from −5 to −26 mv with a mean of −18·7 mv. Each of these values fell within our normal range and all of the patients were clinically not considered to have CF. We conclude that measurement of nasal potentials may be of diagnostic value in these difficult cases when the sweat test is unhelpful.

Primary ciliary dyskinesia (PCD) and male fertility

NC MUNRO, DC CURRIE, MA GREENSTONE, W HENDRY, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, National Heart and Lung Institute, and Department of Urology, St Bartholomew's Hospital, London* Primary ciliary dyskinesia is thought to lead to chronic bronchial sepsis and sinusitis due to dyskinetic respiratory cilia, and male infertility due to immotile spermatozoa. A proportion of patients also have situs inversus. Isolated case reports have described the presence of motile spermatozoa (Jonsson *et al*, *N Engl J Med* 1982;**307**:1131) or azoospermia (Bashi *et al*, *Br J Dis Chest* 1988;**82**:194–6). We have reviewed the fertility of nine adult male patients with respiratory disease due to PCD. Bronchiectasis was present in eight cases, sinusitis in four cases and situs inversus in two. Five had immotile nasal cilia, and the median (range) ciliary beat frequency of the remainder was 7·2 (4·6–10·8) Hz with ciliary dyskinesia present. Electron microscopy (EM) of nasal cilia showed loss of inner, outer or both sets of dynein arms in eight cases and loss of the central microtubule pair in one. Seminal analysis revealed azoospermia in three patients. Severe oligospermia with only a few motile and immotile sperm was seen after centrifugation in one patient, the number of sperm being insufficient for EM examination. Two patients showed reduced sperm motility (30% and 50%; normal > 60%) but normal sperm ultrastructure. Three patients have not undergone seminal analysis; two of these have fathered children, in one case

twice. We conclude that immotile spermatozoa are not a constant feature of PCD and that patients may have normal or only slightly reduced fertility. The reason for azoospermia in three patients is unclear and may be due to abnormality of the epididymal cilia. We suggest that infertile males with PCD should undergo full urogenital assessment to exclude alternative reasons for their infertility.

Kinetics of cell mediated immune (CMI) response in a rat model of bronchiectasis (BX)

JR LAPA E SILVA, D GUERREIRO, NC MUNRO, B NOBLE, LW POULTER, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, National Heart and Lung Institute, Brompton Hospital, and Department of Immunology, Royal Free Hospital School of Medicine, London* In an experimental model of BX developed in Wistar rats by partial ligation of the apical lobe bronchus and injection of *Pseudomonas aeruginosa* (Ps) the composition and distribution of mononuclear cells (MNC) were analysed at different time intervals. Four groups each of 25 animals were prepared: (1) Partial ligation and injection of Ps (Ps + LIG); (2) injection of Ps without ligation (Ps + NOLIG); (3) sham operated animals (S); (4) age matched normal controls (N). From each group, five animals were killed two, four, eight, 12, and 16 weeks after surgery, and cryostat sections of inflated lobes were stained with monoclonal antibodies against determinants present in rat lymphocytes and macrophages. In the Ps + NOLIG group, peribronchial and perivascular infiltration of neutrophils and MNC, mainly composed of macrophages and dendritic cells with very few helper T-cells, was seen at two weeks but resolved by week 4 without histological evidence of ensuing BX. The Ps + LIG group, however, showed histological evidence of BX after two weeks (in some animals) and in all animals from eight weeks onwards. The pattern of inflammation initially showed many macrophages and some T cells mainly of helper subset, but there was gradual increase in participation of T cells with suppressor cytotoxic phenotype from eight weeks onwards – these often forming follicular aggregates. The expression of MHC-Ia antigen on T cells, macrophages and bronchial epithelium increased with duration and severity of BX. The S and N groups showed no abnormality at any time interval. We conclude that a CMI response occurs during the development of BX following Ps bronchial colonisation. This CMI response may be implicated in the pathogenesis of bronchiectasis.

IgA subclasses in sputum from patients with bronchiectasis

D BURNETT, SL HILL, RA STOCKLEY *Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* IgA is the predominant class of immunoglobulin in external secretions, although little is known about factors that influence its synthesis. We have measured total IgA and its subclasses IgA_1 and IgA_2 in sputum and serum from 27 subjects with bronchiectasis. The total sputum IgA (471·8 mg/l, SD 308; median 541, range 42–1402 mg/l) was 15·8% (SD 12·1%) of the serum level (median 3105, range 1375–10172 mg/l). Sputum IgA levels were therefore higher than expected if derived exclusively from the blood (*Thorax* 1979;**34**:777). On average 31·9% (SD 8%) of the sputum IgA was of the IgA_2 subclass which is higher than the proportion (24%) of IgA_2 plasma cells in the lungs of bronchiectatic patients (*J Clin Pathol* 1987;**40**:1217) and higher than the proportion of IgA_2 in serum (11·7% (4%) of total). IgA_1 concentrations were significantly higher ($p < 0·001$) in mucopurulent (median 398, range 211–926 mg/l; $n = 9$) and purulent (median 414, range 257–566; $n = 9$) than mucoid sputum (median 142, range 22·0–358 mg/l; $n = 9$). IgA_2 concentrations in purulent sputum (median 258, range 150–260) were also higher ($p < 0·001$) than in mucopurulent (median 167, range 105–476) or mucoid samples (median 44, range 17–83 mg/l). The proportion of IgA_2 in purulent sputum (36·2% (4·8%) was significantly higher than in mucopurulent (mean 30·1% (6·6%); $p < 0·02$) or mucoid samples (mean 29·2% (10·5%); $p < 0·05$). The results suggest that bacterial load causes increased synthesis of IgA_1 and IgA_2 in the lung but IgA_2 production is proportionately greater.

Selective bronchography using Iotrolan 240, a non-ionic, iso-osmolar contrast agent

SV BAUDOUIN, R BEEDIE, RW BURY, PB ANDERSON, SK MORCOS *Departments of Radiology and Respiratory Medicine, Lodge Moore Hospital, Sheffield* Selective bronchography via the fibreoptic bronchoscope is a useful technique but the standard contrast agent Dionosil has several disadvantages due to its high viscosity and can significantly reduce lung function (Flower, *Thorax* 1984;**39**:260). Iotrolan 240 is a non-ionic, iso-osmolar dimer with physicochemical properties, making it potentially suitable as a bronchographic agent. Bronchography via the fibrescope was performed in 11 patients (six male, five female; mean age 54 years, range 34–62 years). Indications were possible bronchiectasis in eight, a solitary pulmonary nodule in two and recurrent left upper lobe collapse in one. Spirometry was recorded before the procedure and at four and 24 hours. Oxygen saturations were continuously monitored for four hours by pulse oximetry. The examination was diagnostic in nine patients (five with bronchiectasis, four normal) and unsatisfactory in two. The quality of the examination was good in nine patients and poor in two. Rapid bronchial filling with alveolar overflow was the main technical problem. Significant arterial desaturation ($Sao_2 < 90\%$) occurred in three patients prior to the injection of contrast and in one following injection. This patient was found to have severe bilateral bronchiectasis. Saturations returned to prebronchoscopic levels in all patients by four hours. Four patients had significant falls (> 15%) in spirometry at four hours which returned to baseline levels by 24 hours. Moderate nausea and vomiting was reported by three patients. Iotrolan 240 can be safely used as a bronchographic agent, although rapid bronchial filling with distal overspill can be a problem.

Effect of protein kinase C inhibition on histamine and methacholine induced constriction of airway smooth muscle

AJ KNOX, J CLARK, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Recent evidence suggests a role for the phospholipid derived second messengers inositol triphosphate and diacylglycerol in receptor operated contractile events in airway smooth muscle. Diacylglycerol activates protein kinase C and studies stimulating protein kinase C with phorbol esters have shown that C kinase activation contracts bovine trachea (Rasmussen, *FASEB J* 1987;**1**:177). We have therefore studied the effect of 1-(5-isoquinolinyl-sulphonyl)-2-methylpiperazine (H7, Sigma), a protein kinase C inhibitor, on the contractile responses to histamine and methacholine in bovine trachea. Tissue was obtained immediately after death and bathed in Krebs-Henseleit solution. Paired strips were dissected from each trachea and suspended under 2 g tension in organ baths containing Krebs solution at 37°C, aerated with 95% O_2 and 5% CO_2. Changes in tension were recorded on Grass FTO3 force displacement transducers attached to 2 CR600 two channel flat bed recorders. After the tissue had been allowed to settle for one hour, histamine (eight paired strips) or methacholine (10 paired strips) was added to give cumulative bath concentrations over the range 10^{-8}–10^{-3} M. The tissue was then washed and allowed to settle back to baseline tension. H7 was then added to one of each pair of strips to give a bath concentration of 50 μM, with the second strip acting as a control. After 15 minutes the histamine or methacholine dose response study was repeated as previously. H7 caused a considerable reduction in the response to histamine, the mean response to 10^{-3} M histamine being reduced by 75% ($p = 0.006$). In contrast, H7 caused only a slight effect on the methacholine dose response, which showed a three fold shift to the right ($p = 0.05$). This study suggests that protein kinase C has a major role in histamine induced contraction but only a minor role in methacholine induced contraction.

Identification and characterisation of a mononuclear cell derived peptide in bronchial asthma that enhances granulocyte leukotriene generation

JRW WILKINSON, AEG CREA, TJH CLARK, TH LEE *Department of Allergy and Allied Respiratory Disorders, UMDS, Guy's Hospital, London* Peripheral blood mononuclear cells (MNC) were isolated from seven normal subjects, eight asthmatic subjects clinically sensitive to corticosteroids (CS) and eight asthmatic subjects clinically resistant to corticosteroids (CR). Cells were cultured at 37°C for 24 hours in the absence or presence of 10^{-16}–10^{-4} M hydrocortisone (HC). Calcium ionophore (A23187) activated neutrophils (PMN) primed by supernatants of MNC from asthmatic subjects cultured in the absence of HC generated approximately three fold more leukotriene (LT)B_4 than PMN primed by MNC supernatants from normal subjects. Incubation of MNC derived from CS subjects with 10^{-8} M HC completely inhibited the production of the enhancing activity ($p < 0.01$). In CR subjects there was no inhibition of the release of enhancing activity into MNC culture supernatants by HC at concentrations up to 10^{-4} M. The enhancing activity was destroyed by heating to 60°C for 60 minutes and it was sensitive to pronase but not neuraminidase treatment, suggesting a peptide structure. Characterisation of the active factor revealed a pI of 7·1 and molecular weight 22·5 kd. The peptide enhanced eosinophil (EOS) generation of LTC_4 in response to A23187 under optimal conditions by an average of approximately three fold, and also enhanced the capacity of PMN and EOS to generate LTB_4 and LTC_4 respectively by a mean of two fold when stimulated with unopsonised zymosan.

Histamine and leukotriene antagonists together protect against the late response to inhaled antigen

N EISER, M HAYHURST, W DENMAN *Lewisham Hospital, London* It has been suggested that mediators, such as histamine and leukotrienes, released during the early asthmatic response to antigen may initiate the late response (Durham *et al*, *N Engl J Med* 1984;**311**:398; Delehunt *et al*, *Am Rev Respir Dis* 1984;**130**:748). In this single blind study we have compared on two separate days, two to four weeks apart, the effect of pretreatment with the oral H_1 receptor antagonist terfenadine (120 mg) with nebulised leukotriene C_4, D_4 and E_4 receptor antagonist, SK&F 104353 (1200 μg) with the effects of matched placebo in five asthmatics with previously documented dual bronchial responses to antigen. The same dose of antigen was delivered by a nebuliser dosimeter system on the two days and responses were monitored with FEV_1 and specific airways conductance (sGaw) measured in a body plethysmograph for 7–8 hours. On a third (non-challenge) day, FEV_1 and sGaw were found to vary little within the eight hour period. After placebo, the mean fall in FEV_1 was 28% (range 19–38%) and in sGaw was 42% (36–51%) during the early response and during late response FEV_1 fell by 28% (21–39%) and sGaw 48% (40–59%). After terfenadine with SK&F 104353 together, both early and late responses were prevented in three subjects (FEV_1 falling in early and late responses by 3% and sGaw by 7% and 4% respectively). The other two subjects had maximum falls in FEV_1 of 12 and 8% in the early response and 36 and 14% in the late response with corresponding changes in sGaw of 20% and 17% in the early response and of 51 and 48% in the late response. The results of this pilot study suggest that H_1 and leukotriene antagonists given together can prevent both early and late responses to inhaled antigen and that the late response may be dependent on an early response being manifest. More extensive studies are needed to confirm this.

Effect of CGS 12970, a thromboxane synthetase inhibitor, on the response to inhaled allergen

PN BLACK, BT SALMON, P EWAN, RW FULLER *Departments of Clinical Pharmacology, Royal Postgraduate Medical School, and Clinical Immunology, St Mary's Hospital Medical School, London* It has been suggested that thromboxane A_2 is the mediator responsible for the increase in bronchial reactivity

that occurs when allergen challenge is followed by a late response. We have studied the effect of the long acting thromboxane synthetase inhibitor CGS 12970 on the response to inhaled allergen (*Dermatophagoides pteronyssimus*) in seven male subjects with mild asthma. Two allergen challenges were performed at least three weeks apart. Subjects took 100 mg of CGS or placebo 12 hours and again one hour before allergen challenge. The study was randomised and double blind. The dose of allergen was titrated so that the size of the immediate response was similar on the two occasions. Serial measurements of FEV_1 were made for six hours after the last dose of allergen. Inhaled histamine challenges were performed an hour before and six hours after allergen challenge. Blood was drawn at six hours for measurement of the ex vivo formation of thromboxane B_2 from whole blood. Formation of thromboxane was still inhibited by CGS at this time. There was no significant difference between CGS and placebo in the baseline FEV_1, PC_{20} allergen, or histamine responsiveness before or six hours after allergen challenge.

PC_{20} (95% CI) histamine (mg/ml)	*Before*	*6 h*
Placebo	2·73 (1·09–6·80)	0·57 (0·26–1·24)
CGS	2·45 (0·84–7·11)	0·80 (0·28–2·32)

The area under the FEV_1-time curve (AUC) for 0–90 min and 240–360 min was similar for the two groups. In six of the seven subjects AUC between 90 and 240 min was greater with CGS but the difference between the groups did not reach significance ($p < 0·1$). The findings of this study do not support a role for thromboxane A_2 in allergen induced bronchial hyperreactivity.

Effect of Na-K ATPase inhibition on the contractility of bovine and human airways in vitro

AJ KNOX, J CLARK, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We have previously shown that ouabain (a Na-K ATPase inhibitor) causes a dose related contraction of bovine trachea (*Clin Sci* 1988;**75**:27P), suggesting a role for Na-K ATPase in determining airway smooth muscle contractility. To determine whether inhibition of Na-K ATPase alters airway responsiveness, we looked at the effect of ouabain on histamine responsiveness in bovine trachea and on methacholine responsiveness in human bronchial rings. Fresh bovine tissue from the abattoir and fresh human tissue from thoracotomy specimens were bathed in Krebs-Henseleit solution. Paired strips were dissected from each trachea and paired rings from human bronchi. These were suspended under 1-2 g tension in organ baths containing Krebs at 37°C, aerated with 95% O_2 and 5% CO_2. Changes in tension were recorded on Grass FTO3 force displacement transducers attached to two CR600 two channel flat bed recorders. After the tissue had been allowed to settle for one hour, histamine (eight paired bovine strips) or methacholine (eight paired human bronchial rings) was added to give cumulative bath concentrations over the range 10^{-8}–10^{-3} M. The tissue was then washed and allowed to settle to baseline. Ouabain was then added to a bath concentration of 10^{-5} M to one of each pair of strips/rings, the second acting as a control. After 30 minutes, the histamine or methacholine dose response study was repeated. Ouabain caused a slowly developing contraction of both bovine and human airway preparations, the mean (SD) contraction in bovine trachea being 30(20)% of the maximum histamine response, and in human bronchi 40(18)% of the maximum methacholine response. Ouabain did not affect either histamine EC_{20} ($p = 0·4$) in the bovine preparation or methacholine EC_{20} ($p = 0·2$) in the human preparation. These findings suggest that alteration in Na-K ATPase activity will alter bronchomotor tone in both human and bovine airways but this does not affect histamine or methacholine responsiveness.

Differences in the relative efficiency of nebulisers for delivering pentamidine isethionate

MJ O'DOHERTY, S THOMAS, C PAGE, D BARLOW, C BRADBEER, TO NUNAN, NT BATEMAN *St Thomas' Hospital, London* The study compares the pulmonary deposition of nebulised pentamidine when inhaled via four different nebuliser systems by nine HIV positive patients with a previous history of *Pneumocystis carinii* pneumonia. A 3 ml solution containing 50 mg or 300 mg of pentamidine, mixed with technetium 99m labelled human serum albumin was nebulised using three jet nebulisers—(1) System 22, (2) System 22 Mizer, and (3) Respigard II—operated with a gas flow of 6 l/min and one ultrasonic nebuliser—(4) Pulmosonic. Pulmonary and non-pulmonary isotope deposition was measured for each apparatus using a gamma camera and adverse effects and spirometry recorded. For both doses of pentamidine, the System 22 Mizer resulted in the largest pulmonary isotope deposition and this was completed in the shortest time. Oropharyngeal and gastric deposition were least using the Respigard II which also produced the least adverse effects (coughing and nausea). The adverse effects were greatest with the higher pentamidine dose using the System 22 Mizer and Pulmosonic, which also caused significant reduction in FEV_1, FVC and peak flow. Absolute pulmonary deposition was calculated with a lung phantom (Ruffin *et al*, *Am Rev Respir Dis* 1978;**117**:485). The mean (SD) values in mg for the deposition of pentamidine were:

Pentamidine dose in nebuliser	*Nebuliser system*			
	Sys 22	*Sys 22 Mizer*	*Pulmosonic*	*Respigard*
50 mg	1·2 (1)	2·3 (1)	1·5 (0·7)	1·15 (0·9)
300 mg	4·4 (2)	8·4 (6·7)	4·4 (2·1)	

It is concluded that either the System 22 Mizer or the Respigard II should be chosen to administer nebulised pentamidine. The former produces the best pulmonary drug deposition in the shortest time, but the latter is better tolerated by the patients.

Sputum induction as a reliable method of diagnosing *Pneumocystis carinii* pneumonia in AIDS patients

TR LEIGH, P PARSONS, C HUME, OAN HUSAIN, JV COLLINS *Department of Thoracic Medicine and Department of Cytology, St Stephen's Hospital, London* The use of sputum induction (SI) for the diagnosis of *Pneumocystis carinii* pneumonia (PCP) lessens the need for invasive investigations such as bronchoscopy (*Am Rev Respir Dis* 1986;**133**:515). Thus far most centres have been unable to repeat the success with SI reported originally from San Francisco General, and fibreoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) has remained an essential investigation where PCP is suspected. We report success with SI using nebulised hypertonic saline with special attention to patient preparation, sputum processing and standard silver staining techniques. In a three month period a total of 27 sputum inductions were performed on a total of 24 patients. Where SI was negative for pneumocystis patients underwent bronchoscopy within 48 hours to produce a BAL specimen. In all 20 bronchoscopies were performed. *Pneumocystis carinii* was found in seven of the 27 induced sputum specimens and in three of the 20 BAL specimens. Only one specimen negative on SI was subsequently found to be positive for PCP at bronchoscopy. This represents a sensitivity for SI of 87·5% and a negative predictive value of 95%. We confirm the value of sputum induction as a method for diagnosing PCP. With increasing numbers of patients infected with HIV the provision of bronchoscopies will place an increasing burden on resources. We confirm that SI offers a reliable method of identifying or excluding the presence of PCP, with considerable savings in time, expense and patient discomfort.

Transmission-emission scans in pulmonary oedema and *Pneumocystis carinii* pneumonia correlate with appearance of chest radiograph

DJ SEDDON, BA BRIGGS, PD SNASHALL *Departments of Medicine and Nuclear Medicine, Charing Cross Hospital, London* We have developed a gamma camera scanning technique to measure total thoracic tissue thickness (Tt) by transmission scanning with a flood source containing technetium-99m. Using a combination of transmission and emission scanning with 99m-Tc labelled autologous erythrocytes and ^{99m}Tc diethylenetriaminepenta-acetic acid (^{99m}Tc DTPA), we measure the transthoracic volume per pixel of blood and interstitium. These volumes divided by pixel area give the transthoracic thickness for these compartments (Tbl and Tin respectively). We measure chest wall thickness (Tcw) radiologically and derive lung tissue thickness (Tl) by subtraction. We have previously validated this technique using model experiments, comparison with gravimetric measurements in dogs and also studies in man (Briggs *et al, Clin Sci* 1987;**73**:319). In normal subjects there is a gradient of Tbl from the apex to the base of the lung, while Tin is virtually constant. At the base of the lung Tin is approximately half Tbl. In 11 patients with partially treated cardiogenic pulmonary oedema and in 10 patients with *Pneumocystis carinii* pneumonia (PCP) we related the changes in Tl, Tbl and Tin to the radiographic appearances using numerical scoring methods. The radiographs of pulmonary oedema were assessed using a method of scoring which has been validated against indicator dilution measurements of extravascular lung water (*Radiol Clin N Am* 1978;**16**:551). For PCP we devised a system based on the extent and density of the radiographic shadowing. For both pulmonary oedema and PCP, we found a significant relationship between Tl and Tin, and the numerical assessment of the radiograph ($p = 0{\cdot}05$ for each group). Tbl demonstrated no such correlation. In conclusion, the severity of pulmonary oedema and PCP can be quantified by transmission-emission scanning and this correlates with the appearance of the chest radiograph.

***Pneumocystis carinii* pneumonia (PCP) treated with nebulised pentamidine (NP) using a Respigard II nebuliser (RN)**

RF MILLER, SJG SEMPLE *Department of Medicine, University College and Middlesex School of Medicine, London* At the July 1988 BTS meeting we reported our experience of treating PCP with NP using a conventional nebuliser (Acorn). We now report our experience using NP delivered by a RN (MMAD of aerosol particles = 0·8 μm). Twenty one HIV-1 antibody positive homosexual men with clinical features, arterial blood gases (ABG) and chest radiographs (CXR) suggestive of PCP were given pentamidine isethionate 8 mg/kg nebulised once daily via RN. Subsequently all patients underwent fibreoptic bronchoscopy (FOB). In three patients PCP and a copathogen was identified. PCP and *Haemophilus influenzae* (HI) in two, PCP and *Salmonella typhimium* in one. In these three patients NP would not be effective because of its specific spectrum of activity. In two patients the diagnosis was not PCP; *Mycobacterium avium intracellulare* and HI in one and *Mycobacterium flavescens* in another. In the remaining 16 patients PCP was confirmed at FOB in 14: two patients had negative FOB but had clinical presentations ABG and chest radiograph typical of PCP. None were hypoxaemic (Pao_2 59·2–89·7, mean 73·5 mm Hg). Thirteen patients (75%) responded, including the two with negative FOB, with defervescence of fever, clearing of chest radiograph and a rise in Pao_2 (65·3–104, mean 86·6 mm Hg). Three patients did not respond; one treated with NP for 19 days developed worsening dyspnoea and fever, another became hypoxaemic (Pao_2 42·5 mm Hg) and remained pyrexial after six days of NP, both rapidly responded to intravenous co-trimoxazole (IC), a third patient deteriorated after eight days of NP and responded to IC and methyl prednisolone. Seven patients had cough with NP, abolished in six by pretreatment with nebulised salbutamol, one who continued to smoke had a persistent cough. Five patients had marked contact bleeding at FOB, they had received one to six doses of NP. NP via the RN appears to be as effective as IC for treating mild to moderate PCP. Further controlled studies comparing NP and IC are needed.

Time of development of tuberculosis in contacts

C TEALE, DB CUNDALL, SB PEARSON *Leeds Chest Clinic, Leeds* The British Thoracic Association study of tuberculosis in contacts found that 14% of Asian contacts developing tuberculosis did so late (*Tubercle* 1978;**59**:245). By contrast, recent work in Edinburgh (Selby *et al, Thorax* 1988;**43**:834P) in a mainly white population found no cases of tuberculosis after three months and a high default rate for repeat attendances. In Leeds in the five years 1983–7 there were 555 cases of tuberculosis (135 in Asians). Six thousand six hundred and two contacts were examined and 42 were found to have tuberculosis. In addition, 35 children were given chemoprophylaxis because of positive Heaf tests (grade II or more). Of the patients with tuberculosis, 29 (three Asian) were diagnosed at the first visit. Of the remaining 16 patients, two (one Asian) were diagnosed two months later, one four months later, six six months later, one at 16 months, one (Asian) at 22 months, and two (one Asian) at two years. Of the children given chemoprophylaxis, 32 were started at the first visit but three were started at three months because of Heaf test conversion. Our default rate is less than 5%. We cannot agree with the Edinburgh findings that a single screening of white contacts of infectious tuberculosis at three months is sufficient.

Prediction of the possible effect on tuberculosis notifications of stopping BCG vaccination in 1990 based on published data

PDO DAVIES *South Chest Clinic, Sefton General Hospital, Liverpool* As rates of tuberculosis decline, particularly in the younger half of the population, the usefulness of routine BCG vaccination in teenage children also declines. It is likely that routine BCG will be discontinued by most Authorities within the next few years. Indeed, a few District Health Authorities have already stopped routine BCG. The effect of discontinuing routine BCG in teenage children in 1990 on notification rates in the 15–24 age group has been estimated from OPCS data for England, using a "worst scenario" mathematical model. It has been assumed that 70% of the teenage population receive BCG vaccination and that BCG confers 75% protection (Sutherland and Springett, *Tubercle* 1987;**68**:81). From 1992, 10 000 unvaccinated individuals per 100 000 in this age group would annually "replace" 7000, who had been vaccinated. By 2001, none of the 15–24 year age group would have received BCG. For the purposes of the model the new unvaccinated group is considered to assume the notification rates of the originally unvaccinated group.

Recent corrected data (1982–5) have shown an annual decline of 12% in rates of notification for the 15–24 age group. By 1991 it is estimated that there would be 4·5 notifications per 100 000 a year for those aged 15–24. If BCG were continued this would decline to 1·2 per 100 000 a year by 2001. If BCG were discontinued in 1990 a rate of 2·5 per 100 000 a year by 2001 is predicted. This would be equivalent to 95 "preventable" cases in 2001 or one case per 5400 BCG vaccinations.

Regions with a decline less than 7% may show an overall increase in rates in this age group between 1991 and 2001 if BCG is discontinued. East Anglia, for example, with no decline from 1982–5, on the basis of the same mathematical model would show an increase in rates from 2·1 to 3·5 per 100 000 a year, equivalent to three "preventable" cases in 2001. Mathematical models of this sort may be useful for both regions and districts contemplating the abandonment of routine BCG.

Neutrophil chemotactic activity (NCA) detectable in the serum of patients with acute severe asthma is elaborated spontaneously by cultured peripheral blood mononuclear cells

L NAGY, CJ CORRIGAN, J-J TSAI, AB KAY *Department of Allergy and Clinical Immunology, National Heart and Lung Institute, Brompton Hospital, London* Several studies have demonstrated that cultured peripheral blood mononuclear cells (PBMNC), after activation in vitro, elaborate NCA into the culture medium. We have investigated whether MNC isolated from patients with acute severe asthma (ASA) generate NCA spontaneously in culture. PBMNC and serum were isolated from 14 patients on admission to hospital as an emergency with ASA, and in some cases seven days later. PBMNC and serum were similarly isolated from control subjects (normal, mild asthma, chronic obstructive airways disease). PBMNC (2×10^6 cells/ml) were cultured for 24–72 h (37°C, 5% CO_2) in RPMI 1640 medium buffered with 25 mM HEPES but in the absence of serum. Culture supernatants (SN) were assayed undiluted for NCA using a modified Boyden chamber technique. PBMNC from ASA patients elaborated significantly greater amounts of NCA into the culture SN after 24 h than all control groups ($p < 0{\cdot}01$). There was no further increase in SN NCA after 48 and 72 h. In all ASA patients a reduction was observed in the amount of this PBMNC derived NCA after one week of therapy ($p < 0{\cdot}001$). SN from ASA and normal controls were pooled, concentrated by freeze drying and subjected to Superose-12 size fractionation and Mono P chromatofocusing using FPLC. A peak of NCA corresponding to a molecular size of 16–25 kD and a pI of 6·8 was detectable in the concentrated ASA SN but completely absent from the control SN. An activity with similar physicochemical characteristics was detectable in the serum of patients with ASA but not that of normal controls. This MNC derived NCA may have a role in the genesis of asthmatic bronchial inflammation, and its presence is consistent with the hypothesis that lymphocyte activation is a feature of ASA.

Corticosteroid resistance in chronic asthma: correlation of clinical response with in vitro sensitivity of lymphocytes to anti-inflammatory drugs

CJ CORRIGAN, P BROWN, N BARNES, AJ FREW, J-J TSAI, MB ALLEN, S RAY, GK CROMPTON, AG LEITCH, AB KAY *National Heart and Lung Institute, Brompton Hospital, London; Northern General Hospital, Edinburgh; and City Hospital, Edinburgh* Corticosteroid resistant asthma is well documented (Carmichael *et al, Br Med J* 1981;**282**:1419). We have compared in vivo and in vitro effects of corticosteroids in a group of 33 patients with chronic stable asthma (all non-smokers aged 26 to 68 y, $FEV_1 < 70\%$ predicted, with $\geqslant 20\%$ reversibility in

response to salbutamol). The clinical response was assessed by a formal two week trial of oral prednisolone. Twenty one patients responded with an improvement in FEV_1 > 30% (mean Δ FEV_1 58·3%) while 12 were classified as resistant (mean Δ FEV_1 3·1%). In vitro sensitivity to corticosteroids was assessed by measuring inhibition at 24, 48 and 72 h, of phytohaemagglutinin stimulated peripheral blood mononuclear cell (PBMNC) proliferation. PBMNC from the steroid sensitive asthmatics showed a significantly higher degree of inhibition by dexamethasone 10^{-7} M as compared with steroid resistant patients (mean inhibition 45·8% *v* 9·0%; $p < 0·001$). A similar distinction was observed in vitro with the immunosuppressive drug cyclosporin A (500 ng/ml; mean inhibition 40·6% *v* 8·9%; $p < 0·01$). These results suggest that corticosteroid resistance in chronic asthma may be due to a relative insensitivity of T lymphocytes to these drugs, and are consistent with the hypothesis that lymphocyte activation is important in the pathogenesis of this disease.

Effect of anti-inflammatory agents on neutrophil chemotactic response in vitro and in vivo

M IP, J SHAW, D BURNETT, RA STOCKLEY *Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* Anti-inflammatory agents may alter the neutrophil chemotactic response, although in vivo and in vitro data are often contradictory. We have performed preliminary studies of several agents in order to determine their role in chronic destructive lung diseases. The chemotactic response to 10^{-8} FMLP was assessed using neutrophils from six healthy subjects with or without preincubation (one hour) with dexamethasone, indomethacin or nabumetone. Dexamethasone caused a dose related decrease in chemotaxis from an average control value of 53·7 cells/field (SD 23·4) to 47·3 (19·8) at 10^{-6} M ($p < 0·05$); 37·3 (14·1) at 10^{-4} M ($p < 0·025$) and 24·7 (21·9) at 10^{-3} M ($p < 0·025$). Indomethacin had no effect until a sudden drop from 43·8 (21·7) to 9·4 (8·6) at 10^{-3} M, suggesting cell toxicity. Nabumetone had no effect. Eight healthy subjects received 25 mg indomethacin three times daily or nabumetone 1 g at night for two weeks. Neutrophils were harvested weekly on treatment and for two weeks prior to therapy. The average cell response to FMLP was 51·8 (19·5) and 46·8 (16·1) for the two control weeks. No change occurred after one week's treatment (35·6 (11·4)) but a marked reduction was seen at two weeks (17·9 (9·6); $p < 0·01$). Steroids appear to affect the chemotactic response of mature neutrophils, but NSAID have no effect in vitro or in vivo until two weeks of therapy, suggesting that they act on immature cells prior to their release from bone marrow. These results may explain the disparity between in vitro and in vivo effects of anti-inflammatory agents.

Bronchial T lymphocyte subsets in the late asthmatic reaction in the guinea pig

AJ FREW, R MOQBEL, M AZZAWI, A HARTNELL, J VARLEY, MK CHURCH, ST HOLGATE, AB KAY *Cardiothoracic Institute, Brompton Hospital, London, and Departments of Clinical Pharmacology and Medicine 1, Southampton General Hospital, Southampton* Alterations in T cell subsets were studied in a guinea pig model of the late asthmatic reaction (LAR), in which animals were sensitised and LAR induced by inhalation of ovalbumin. Changes in airways resistance were measured by plethysmography (Hutson *et al, Am Rev Respir Dis* 1988;**137**:548). Cytofluorimetry and immunocytochemistry were used to determine T cell numbers and phenotypes in blood, bronchoalveolar lavage (BAL) fluid and tissue. T cells increased in number in the bronchial submucosa within two hours and showed a biphasic peak at 17 hours (peak of LAR) and 48 hours ($p < 0·01$ at both times). In the lamina propria T cells did not increase at two hours but there was a biphasic peak similar to that seen in the submucosa at 17 and 48 hours. No such changes were observed in the lung parenchyma. These alterations were paralleled by small but non-significant changes in T cell subset numbers in the peripheral blood. No significant changes in T cell profile were seen in BAL fluid. $CD8^+$ cells showed modest increases at 17 hours ($p > 0·05$) but these did not account for the majority of the infiltrate, indicating that $CD3^+$, $CD8^-$ (helper-inducer) T cells were involved. These findings are consistent with previous human studies of the allergic late phase response, and support the view that T lymphocyte subset changes are a feature of the LAR and may contribute to the pathogenesis of allergic inflammation.

Inhibition of airway microvascular leakage by corticosteroids

P BOSCHETTO, DF ROGERS, PJ BARNES *Department of Thoracic Medicine, National Heart and Lung Institute, Brompton Hospital, London* Microvascular leakage of plasma proteins may be an important component of the inflammatory response in asthmatic airways, leading to mucosal oedema and exudation plasma into the airway lumen. Pharmacological modulation of this leakage may therefore be useful therapeutically. Corticosteroids have widespread anti-inflammatory effects and have been shown to inhibit oedema formation due to inflammatory mediators in limb and skin microvasculature. We have now studied the effect of corticosteroids on plasma exudation in rat airways induced by platelet activating factor (PAF), which acts directly on postcapillary venule endothelial cells, and by antigen (ovalbumin) in previously sensitised animals. Microsvascular leakage was quantified by extravasation and extraction of Evans blue dye, which binds to plasma albumin. PAF (500 ng/kg iv) caused significant extravasation of 115% in trachea, 92% main bronchi and 135% in intrapulmonary airways, and ovalbumin leakage of 142% in trachea, 113% in main bronchi and 90% in intrapulmonary airways compared with appropriate control animals. Dexamethasone inhibited PAF induced leakage in a dose related manner: at 2 mg/kg given four hours prior to PAF there was significant inhibition in main bronchi, and at 8 mg/kg complete inhibition in all airways. No significant inhibition was seen two hours after dexamethasone 8 mg/kg. Dexamethasone 8 mg/kg also significantly inhibited antigen induced leakage in all airways of sensitised rats. An inhibitory effect of corticosteroids on airway microvascular leakage and mucosal oedema may contribute to the effectiveness of corticosteroids in prevent-

ing late phase responses to allergen and in reducing bronchial hyperresponsiveness. This work was supported by a grant from the Medical Research Council.

Bronchial hyperreactivity in patients undergoing haemodialysis

MJ WALSHAW, R LIM, L HUMPHREYS, R AHMAD, CRK HIND *Department of Medicine, Royal Liverpool Hospital, University of Liverpool* Bronchial hyperreactivity (BHR) is a characteristic feature of asthma, but its mechanism is not clear. One hypothesis suggests that the neutrophil may have an important role both by causing inflammation within the walls of the airways and perhaps also by the release of circulating humoral factors. Haemodialysis results in a similar array of inflammatory changes both in the lungs and systemically, with neutrophil trapping and increased capillary permeability. Furthermore, some patients undergoing haemodialysis develop wheezing during the procedure (*Dialysis Transplant* 1988;**17**:132). To investigate if there is any change in such patients' bronchial reactivity we performed histamine challenge tests in seven patients (five male; mean age 54, range 36–73 years) who were undergoing hospital haemodialysis for chronic renal failure. No patient gave a history suggestive of asthma (mean FEV_1/FVC 78%, range 58–87) and none was taking bronchodilators or antihistamines. Challenge tests were performed at the same time of day in each patient, both on the preceding day and then immediately (within one hour) after their haemodialysis. Peak expiratory flow rates were also measured half hourly throughout the period of dialysis. We found that one patient was unresponsive to histamine before and after dialysis, even at 64 mg/ml. In the remaining 6 patients there was no significant change in PC_{20} following dialysis (predialysis PC_{20}: mean 18·1 mg/ml, range 2·6–64·0; postdialysis PC_{20}: mean 20·8 mg/ml, range 2·0–64·0). No patient showed a change in peak flow rate during dialysis. These studies suggest that pulmonary neutrophil sequestration per se does not result in BHR or reversible airflow obstruction.

Histological classification of acute lung rejection in heart-lung transplantation

CA CLELLAND, TW HIGENBOTTAM, BA OTULANA, S STEWART, JP SCOTT, J MCGOLDRICK, J WALLWORK *Heart-Lung Transplant Unit, Papworth Hospital, Cambridge* Histology of transbronchial lung biopsies at routine intervals after heart-lung transplantation and during episodes of acute rejection reveals a spectrum of inflammatory changes, as reported for endomyocardial biopsies in heart transplantation. We have therefore developed a grading system. This is scaled 0–3 and is based on the distribution and severity of the typical pyroninophilic lymphocytic infiltrate, which begins around pulmonary venules and arterioles and then extends into lung tissue. 0—No significant inflammation; 1—mild perivascular and/or mucosal inflammation *not* extending into alveolar walls or spaces; 2—perivascular and mucosal inflammation with extension into *both* alveolar walls and spaces. Grade 3 we have associated with the later development of obliterative bronchiolitis (Scott *et al, Trans Proc* (in press)). Forty eight biopsy specimens from 20 patients were received, 18 obtained when patients were well and 30 during rejection episodes, where only two biopsy specimens were inadequate.

	Normal (No (%)) (n = 18)	*Rejection (No (%)) (n = 30)*
Grade 0	12 (66)	6 (20)
1	6 (33)	14 (47)
2	0 (0)	5 (16)
3	0 (0)	3 (10)

We believe that a grading system for lung histology from heart-lung transplant patients would improve clinical management.

Distribution of rejection within the transplanted lung

RL SMYTH, JP SCOTT, G IGBOAKA, C CLELLAND, TW HIGENBOTTAM, J WALLWORK *Papworth Hospital, Cambridge* Transbronchial lung biopsy (TBB) is a powerful aid to the diagnosis of lung rejection following transplantation (HLT) (Higenbottam *et al, Transplant Proc* 1987;**19**:4558). However, it is not known whether the rejection process is diffuse or patchy. Between April and August 1988 45 TBB were performed in 17 HLT recipients, where biopsies were taken from all three lobes of the right lung or from the lingula, upper and lower lobes of the left lung. On average three biopsies were taken from each lobe. Rejection was diagnosed by the presence of perivascular infiltrates (Stewart *et al, Transplant Proc* 1987;**19**:7008). Thirty TBB specimens showed evidence of rejection.

*No of lobes affected**	*Distribution of rejection*	
	Rejection	*Rejection and infection*
3 lobes	8	1
2 lobes	5	5
1 lobe	10	1

*Left lung is taken as three lobes, lingula separate from upper lobe.

In only nine (32%) biopsies were changes to be found in all three lobes. However, in 22 (73%) rejection was present in the lower lobe. In those biopsy specimens in which rejection was found in only one lobe this was in the upper lobe in two (7%), middle lobe or lingula in four (13%) and lower in four (13%) of all cases. Rejection is a patchy process; TBB specimens should therefore be taken from all three lobes.

Pulmonary rejection following transplantation: the value of transbronchial lung biopsy

DT MCLEOD, T ASHCROFT, K GOULD, JH DARK, PA CORRIS The management of patients following lung transplantation has been complicated by the difficulty in distinguishing between

opportunist infection of the lung and rejection. Many centres have relied on confirming rejection by a positive therapeutic trial of augmented immunosuppression following the exclusion of infection by bronchoalveolar lavage (BAL). Recently transbronchial lung biopsy (TBLB) has been proposed as a sensitive and specific method of making a positive diagnosis (Higenbottam TW *et al, Transplant Proc* 1988;**20**:767). We have performed 30 such biopsies in nine patients and report our experience. All biopsies were performed under screening in response to a deterioration in clinical state, chest radiograph or pulmonary function. On each occasion four to six biopsy specimens were taken and there have been no complications. Characteristic features of acute rejection included perivascular lymphocyte infiltrate and mucosal inflammation. Fifteen biopsy specimens showed evidence of rejection with BAL fluid negative for infection and on each occasion patients showed a prompt clinical response to intravenous methyl prednisolone (MP) 10 mg/kg. Five biopsy specimens showed infection (*Cytomegalovirus* (2), *Aspergillus fumigatus* (1), *Herpes simplex virus* (1), *Pneumocystis carinii* (1) and BAL fluid was also positive for infection in each case. Ten specimens showed no evidence of infection or rejection with BAL fluid negative for infection and on six occasions there was a rapid improvement in the patients clinical condition without a change in therapy. On four occasions, however, there was a progressive deterioration in the patients condition and treatment with MP resulted in a prompt response, providing strong evidence that acute rejection had been the problem. On three such occasions patients were receiving antithymocyte globulin (ATG) when biopsied. We conclude that TBLB is a safe procedure providing satisfactory biopsy material to make a positive diagnosis of rejection. A negative biopsy, however, does not exclude acute rejection and patients should be treated on clinical suspicion once infection has been excluded. ATG may prevent typical histological appearances of rejection during the early postoperative period.

Home spirometry: a new approach to monitoring pulmonary allograft function

BA OTULANA. L FERRARI, TW HIGENBOTTAM, J MCGOLDRICH, J WALLWORK *Papworth Hospital, Cambridge* Following combined heart-lung transplantation acute rejection poses a greater problem in the lungs than the heart (Griffith *et al, Ann Thorac Surg* 1985;**40**:488). We have previously reported the usefulness of monitoring of formal lung function in detecting acute rejection and opportunistic infection in heart-lung transplantation (Otulana *et al, Am Rev Respir Dis* 1988;**137**:245). This required patients to undergo routine spirometry every three months and on development of respiratory symptoms. Because daily monitoring provides a continuous record of changes in lung function, we have studied the use of home spirometry for detecting acute lung rejection. Fifteen recipients of heart-lung transplants (seven men) were supplied with a pocket sized turbine spirometer on discharge after their operation. They measured FEV_1 and VC twice daily, recording the best of three attempts each time. These records were retrospectively compared with the histology of specimens from transbronchial biopsies (TBB) carried out either to confirm clinically suspected rejection (Higenbottam *et al, Transplant Proc* 1988;**20**:767) or as part of routine follow up. There were 10 normal TBB and 17 biopsy proved rejection episodes. The mean percentage fall in FEV_1 during rejection in the group was 12·4 (SD 12·3). The fall in FEV_1 with rejection was greater than 3% (the coefficient of variation of the measurement) in 15 out of 17 episodes of rejection, which thus had a sensitivity of 88% for detecting rejection. The fall in FEV_1 preceded presentation in hospital by a mean 3·5 days (range 1–9) in the 15 patients. We conclude that home spirometry is an improvement over scheduled formal PFT, and allows early diagnosis of pulmonary rejection. This should help in reducing the incidence of obliterative bronchiolitis, the chronic sequelae of acute rejection.

Fall in mixed venous oxygen saturation is associated with exercise hyperventilation in heart transplant recipients

BA OTULANA, TW HIGENBOTTAM, JP SCOTT, J WALLWORK *Papworth Hospital, Cambridge* Excessive exercise hyperventilation reported in cardiac transplant recipients (Savin *et al, Circulation* 1980;**62**:55) and in heart-lung transplant (HLT) recipients (Estenne *et al, Thorax* 1987;**42**:629) has remained unexplained. To determine whether the stimulus for this phenomenon is in the systemic or the lesser circulation we have studied four HLT recipients (two male (mean (SD)), age range 24–39 years) with right heart catheterisation carried out during routine endomyocardial biopsy. Haemodynamics and gas exchange were measured at rest and at the peak of 50 watts supine cycle ergometry.

Resting and exercise haemodynamic and gas exchange values

	Resting	*Peak exercise*
$\dot{V}_E$ (l/min)	7·2 (2·3)	24·8 (12·6)
RQ	0·6 (0·2)	0·8 (0·1)
$\dot{V}_Q$ (mmol/mm)	11·0 (3)	40·2 (17·3)
$\dot{Q}_T$ (l/min)	5·3 (1·6)	8·2 (2)
$S\bar{v}O_2$ (%)	67 (4)	49 (8)
Mixed venous $[H^+]$ (mmol/l)	43 (2·5)	47 (3)
SaO_2 (%)	97 (2)	98 (1)
$PaCO_2$ (kPa)	4·9 (0·3)	4·7 (0·5)
$\dot{Q}s/\dot{Q}_T$ (%)	6·2 (2)	0·7 (0·6)
Vd/V_T	0·53 (0·1)	0·42 (0·1)

The $\dot{V}_E$ increased out of proportion with the level of exercise, although neither RQ nor arterial lactic acid levels showed evidence of anaerobic respiration. Both heart rate and $\dot{Q}_T$ rose slowly through exercise with attainment of 92% predicted $\dot{Q}_T$ for the level of exertion. $S\bar{v}O_2$ fell precipitously, reflecting maximal tissue extraction of oxygen. Arterial oxygenation process was, however, satisfactory as SaO_2 remained normal throughout. In the absence of acidosis, arterial desaturation, hypercapnia or abnormal gas exchange, these results suggest that the exercise hyperventilation in HLT recipients may be related to reduced $S\bar{v}O_2$. This supports earlier reports that the lesser circulation may have a role in chemosensitivity (Sheldon *et al, J Appl Physiol* 1982;**52**:1192).

Diurnal variation in FEV_1 following heart-lung transplantation

JFJ MORRISON, TJ HATHAWAY, CA CLELLAND, JP SCOTT, J WALLWORK, TW HIGENBOTTAM *Respiratory Physiology Department, Papworth Hospital, Cambridge* Pulmonary vagal nerve activity may be responsible for diurnal variation in lung function, as intravenous atropine (30 μg/kg) causes significant bronchodilatation in asthmatics with variation of PEF > 20% (Morrison *et al, Br Med J* 1988;**296**:1427). Heart lung transplantation is associated with loss of vagal afferent nerves to the lung, as shown by an absent cough response to inhaled ultrasonically nebulised distilled water (Jackson *et al, Thorax* 1987;**42**:747). Also many heart lung transplantation patients show enhanced methacholine bronchial reactivity, suggesting airway smooth muscle muscarinic responsiveness, which may be associated with lung rejection (Glanville, *Clin Sci* 1987;**73**:299). To exclude vagal reflex mechanisms and pulmonary inflammation associated with lung rejection, as causes of diurnal variation in lung function we have studied 20 heart lung transplantation patients. The best of three FEV_1 measurements was recorded daily at 8am, midday, 4pm, 8pm, and midnight, using a portable mini-spirometer for four weeks. The presence of perivascular lymphocytic infiltrates and airway inflammation was assessed by histology of transbronchial lung biopsies (Higenbottam *et al, Transplant Proc* 1988;**20**:767) during the period of observation in 18 patients and two months earlier in two patients who remained physiologically normal. Patients ranged from 12–51 years and had undergone surgery 1–44 months previously. There were 10 patients studied at times of pulmonary rejection whose biopsy specimens also showed airway inflammation. The median FEV_1 was 2·55 l. A significant ($p < 0·05$) circadian rhythm in FEV_1 was seen in 15 patients, the amplitude of variation being 1·4–22·0%. No relation was found between the variation in FEV_1 and presence of rejection. Also past history of asthma treatment and time since surgery were not related to diurnal variation. The cause of diurnal variation in FEV_1 remains unclear, but its presence in heart lung transplantation patients suggests that a vagal *reflex* mechanism is unlikely and that airway and pulmonary inflammation alone are not the cause.

Tuberculous meningitis in children in England and Wales, 1983

SK MCDONALD, P CULLINAN, JH DARBYSHIRE, AJ NUNN, KM CITRON, WALLACE FOX *MRC Cardiothoracic Epidemiology Group, Department of Clinical Epidemiology, Brompton Hospital, London* In a survey of all new tuberculosis notifications in England and Wales in 1983, there were 20 cases of meningitis in children (< 15 years). Details of treatment and outcome after two years were obtained. There were 11 boys and nine girls; 12 were white, six of Indian or Pakistani ethnic origin, of whom four were born in the UK, and two others; 15 were less than 3 years old. Only two were known to have had BCG vaccination; 12 were found to have had contact with tuberculosis. The mean time from onset of symptoms to admission was 11 days (range three days to three weeks). Two children died before admission or very soon after. Of the remaining 18, the neurological stage on admission (Medical Research Council, *Lancet* 1948;i:582) was: early 7, medium 9 and advanced 2. The tuberculin reaction was positive in all 14 children tested. CSF examination showed a lymphocytic leucocytosis in all 18, protein > 0·5 g/l in 16, glucose < 2·5 mmol/l in 15; five were smear positive and in nine cases *Mycobacterium tuberculosis* was grown in culture. Abnormalities of the chest radiograph were reported in nine cases, five having miliary shadowing. The mean time from admission to start of antituberculosis treatment was 3·2 days (range 0–14 days). All patients received at least three antituberculosis drugs, including rifampicin and isoniazid. Sixteen children had streptomycin, and 13 steroids. Six had surgical treatment for hydrocephalus. The outcome after two years was (*a*) a complete cure in nine cases, (*b*) a residual squint in two, (*c*) moderate handicap in four; (*d*) severe handicap in three, and (*e*) two deaths. Comparison of the 11 children who did well (groups *a* and *b*) with the nine who did badly (groups c, d, e) showed that outcome was related to age, with better results in older children ($p < 0·05$). No relation was found between outcome and length of illness before treatment or neurological stage at admission.

Outbreak of isoniazid resistant tuberculosis in a secondary school

A SHANNON, M COONEY, M LUCEY, P KELLY, L CLANCY, P CORCORAN *North Western Health Board, County Donegal, and Peamount Hospital, Newcastle, County Dublin, Ireland* We present a mini epidemic of tuberculosis which occurred in a large secondary school. This had 1138 students (aged 12–18 y), 78 teachers and 42 other staff; the at risk population also contained 331 family contacts of those with tuberculosis and 30 students who had left school in previous year.

		Heaf results				
	n	*Neg*	*+1*	*+2*	*+3*	*+4*
BCG	895	309	213	301	62	10
No BCG	240	194	10	25	6	5

There were four cases of pulmonary tuberculosis among children with BCG vaccination. Nine cases of tuberculosis among those without BCG vaccination including two cases of miliary tuberculosis (one of whom had meningitis). This shows a statistically significant difference between the attack rates (χ^2 analysis: $p < 0·001$). Two teachers had active tuberculosis, three teachers and six family contacts had evidence of old inactive tuberculosis. Isolates grew *Mycobacterium tuberculosis* fully resistant to isoniazid. Except for miliary/tuberculosis meningitis, treatment was with rifampicin, isoniazid and ethambutol for one year. All therapy is now completed for at least 12 months and there are no relapses. We conclude that BCG protected these teenage students against tuberculosis. Combination of rifampicin, ethambutol for 12 months was effective. This outbreak is unique because of the number of teenage children affected, because the organism was isoniazid resistant, and because it offered an opportunity to assess the protective effect of BCG vaccination among adolescents.

Variations in pattern of tuberculosis in Indian subcontinent (ISC) ethnic patients: effects of age, date of first entry, and ethnic group

LP ORMEROD, AJ NUNN, SP BYFIELD, JH DARBYSHIRE *Chest Clinic, Blackburn Royal Infirmary, Blackburn, Lancashire, MRC Cardiothoracic Epidemiology Group, Brompton Hospital, London* Differences in the distribution of sites of tuberculosis between the Pakistani/Bangladeshi and Indian ethnic groups in Blackburn prompted us to explore the findings for 703 ISC patients registered in Blackburn between 1978–1987 and also 2756 patients in the 1983 Medical Research Council (MRC) notification survey. The site of disease was recorded as (1) parenchymal lung disease (including effusion) with or without mediastinal glands or (2) isolated mediastinal lymphadenopathy or (3) peripheral lymphadenopathy or (4) peripheral plus mediastinal lymphadenopathy or (5) other non-pulmonary sites. Each patient's age, place of birth and, where relevant, date of first entry to the UK were also recorded. The data were analysed using a generalised linear model. For adult (age 15 or more) Blackburn patients parenchymal lesions were more common in Pakistani and Bangladeshi patients and in older age groups. The analysis of the 1983 MRC survey data showed no overall difference between two ethnic groups and no effect of age or year of first entry in the Pakistani and Bangladeshi group. However, for the Indian group parenchymal lesions were significantly more common in those who had been resident in the country for five years or more and in the older patients. Thus there appear to be differences between the Indian subcontinent ethnic groups, although the analyses are based on relatively small numbers in some of the subgroups. There is no obvious explanation for the differences but several factors may be relevant.

Epidemiology of tuberculosis in Ireland: 1986 national survey

J STINSON, F HOWELL, P KELLY, L CLANCY *Peamount Hospital, Newcastle, Co Dublin* We surveyed all directors of community care, hospital clinical consultants and heads of diagnostic laboratories. Four hundred and fifty one (74%) of 617 postal questionnaires were returned. *Community care* Seven hundred and fifty six cases of tuberculosis were notified—pulmonary tuberculosis 71%, pulmonary and extrapulmonary tuberculosis 2·7%, extrapulmonary tuberculosis 15%, primary tuberculosis 6·3%, site unknown 4·7%. The age distribution of patients was: < 15 y 9·4%, 15–35 y 24%, 35–55 y 20%, > 55 y 47%. There was a lack of uniformity in (*a*) method of tuberculin testing and (*b*) BCG policies. *Hospital consultants* Three hundred and fifty six hospital consultants replied but only 127 treated or diagnosed tuberculosis in 1986. On average each consultant treated or diagnosed 2·28 patients (range 1–14); chest specialists average 3·75 (range 1–7). Forty three different treatment protocols were in use and, while the tendency was to prolong treatment, 29% of consultants were using potentially inadequate treatment regimens. *Microbiology laboratories* Twenty two of 40 microbiology laboratories examine specimens for tuberculosis, of whom four do sensitivity tests and identification. Of 58427 specimens, 51461 (89%) were examined in six major laboratories. Sixteen labs examine less than two specimens per day. There is a need for a consensus on treatment, better rationalisation of microbiological services and uniformity of BCG practice. Tuberculosis education must be extended to all clinical consultants.

Should a positive reaction to the tuberculin test in health care workers be an indication for chemoprophylaxis?

P KELLY, P CORCORAN, G SWANWICK, L CLANCY *Peamount Hospital, Newcastle, County Dublin, Ireland* Published guidelines for the prevention of tuberculosis in health care workers indicate that a strongly positive skin test reaction should be regarded as due to infection rather than BCG vaccination and that these workers should be considered for chemoprophylaxis. We present a retrospective review of 2186 *pre-employment* tuberculin skin tests. All medical students and student nurses are offered BCG vaccination if they have a negative response to 10 TU. A strongly positive reaction means in duration of ⩽10 mm in response to a 1 TU Mantoux or Tyne test. *Study population* Medical staff (99); general nurses (253); psychiatric nurses (79); paramedical staff (18); general staff (681); student nurses (531); preclinical medical students (525). All had either a Mantoux skin test or a Tyne test. *A strongly positive skin test reaction* occurred in 47% of all staff: medical staff 78%; general nurses 71%; psychiatric nurses 52%; paramedical staff 44%; general staff 54%; student nurses 34%; preclinical medical students (18%). Two hundred and ninety eight workers with a negative reaction to 10 TU Mantoux were given BCG vaccination. A skin test after vaccination (8–10 weeks) showed that 77% had a strongly positive Mantoux reaction. Our data suggest that a strongly positive skin test response in health care workers may be due to BCG vaccination. A booster effect on exposure to tuberculosis cannot be ruled out. Should these health care workers be offered chemoprophylaxis, given the cost, the clinical work load, and potential drug toxicity? We believe that recommended chemoprophylaxis guidelines in health care workers need to be revised.

Tuberculosis as a cause of pleural effusion, 1980–7

M KIRBY, P KELLY, T HEALY, L CLANCY *Peamount Hospital, Newcastle, County Dublin, Ireland* In the study period we treated 2017 patients for tuberculosis, of whom 144 had a tuberculous pleural effusion.

	% with effusion	*Total %*
n	144	2017
Male	79%	66%
Female	21%	33%
Age (y): < 30	32%	22%
30–60	37%	38%
> 60	31%	40%
Mantoux positive		
1 TU	46%	74%
10 TU	39%	14%
100 TU	10%	4%
Negative	1%	5%
N/A	4%	3%

Microbiology Sputum from patients with effusion was S+C+ 33%; S+C− (4%); S−C+ 9%. Pleural fluid culture for tuberculosis: S+C+ 14; S+C− 39; S−C+ 5. Thirty of 63 pleural biopsies showed granuloma; two without granulomas were positive on direct staining. *Radiography* Pleural effusion only (44%); bilateral parenchymal disease (23%); unilateral parenchymal disease (19%); cavities (24%); calcification (10%); lymphadenopathy (3%). 75 right sided effusions; 66 left sided effusions; 3 bilateral. 22 of 119 pleural fluids show uniform non-traumatic blood staining. All patients received standard chemotherapy (RHE or RHEZ). Comparing patients with effusion to those without there was no difference in terms of radiological or microbacteriological resolution of disease. It is concluded that more younger people had a pleural effusion and that fewer were Mantoux positive. Fifty six per cent of patients with pleural effusion had parenchymal disease. An appreciable proportion had blood stained pleural effusions. The response to therapy is similar to patients without pleural effusion.

Significance of glucose intolerance in pulmonary tuberculosis

PO OLUBOYO, RT ERASMUS *Departments of Medicine and Chemical Pathology, University of Ilorin, Nigeria* A high incidence of glucose intolerance in patients with tuberculosis has long been recognised (Nichols, *Am Rev Respir Dis* 1957;**76**:1016). The significance of this association, however, remains unclear. We performed standard oral glucose tolerance tests (OGTTs) according to the WHO recommendations (*WHO Technical Report Series* 1980;**646**:8) on 54 Nigerian patients with active pulmonary tuberculosis. OGTTs were repeated after three months of effective treatment, and again three months after full therapy in those who had abnormal results during the second series of tests with a view to an evaluation of the risk of development of diabetes mellitus in tuberculous patient with glucose intolerance. Twenty three patients (42·66%) were found to have abnormal results, including three (5·6%) with a diabetic pattern and 20 (37·0%) with impaired glucose tolerance (IGT). Of the 20 with IGT, repeat OGTT after three months' treatment became normal in 75% while the three with the diabetic pattern became respectively diabetic, intolerant of glucose, and normal at the second test. Three months after full antituberculous medication, only one of the eight patients with IGT at the second OGTT remained intolerant of glucose. This patient and the one patient who was frankly diabetic were thus the only two patients (3·7%) out of the initial 54 who remained intolerant of glucose at the end of the study. Our results suggest that the glucose intolerance in active pulmonary tuberculosis represents no more than an acute phase reaction. Only two patients with initially normal OGTT manifested the previously described rifampicin induced early phase hyperglycaemia (Takasu *et al, Am Rev Respir Dis* 1982;**125**:23); this resolved spontaneously. There was no bacteriological relapse three months after the six month treatment regimen.

Levels of antibody to purified antigens of *Mycobacterium tuberculosis* in pulmonary tuberculosis

G BOTHAMLEY, P JACKETT, R RUDD, F FESTENSTEIN, J IVANYI *MRC Tuberculosis and Related Infections Unit, and London Chest Hospital, London* Antibody levels (IgG) were compared in patients with differing contact with tubercle bacilli. Monoclonal antibodies which recognise antigenic determinants largely restricted to tubercle bacilli (TB68, TB23 and TB71: Engers *et al, Infect Immunity* 1986;**51**:718) were used to purify antigens of 14, 19 and 38 kD molecular weight by affinity chromatography; lipoarabinomannan (LAM) was prepared by chemical extraction (Hunter *et al, J Biol Chem* 1985;**261**:12345). Sera from 25 patients with smear negative pulmonary tuberculosis (S–TB), 11 subjects with self healed disease and 24 contacts of infectious cases were compared with sera from 45 patients with smear positive (S+) TB and 39 BCG vaccinated healthy controls. Antibody levels were measured by enzyme immunoassay and positive titres were defined as >log mean +2 SD of control values. Antibody levels to the 14 kD protein were positive in contacts (38%), particularly in those who had been BCG vaccinated (6/11), and in self healed tuberculosis (36%) and S-TB (46%). Patients with S+, S− and self healed tuberculosis had antibody levels positive for the 19 kDA antigen at comparable frequencies (62%, 56%, and 55% respectively), which distinguished them from contacts (25%). Positive antibody titres to the 38 kD protein were most often found in S+TB (82%), but less frequent in S-patients (12%) and contacts (17%). While LAM antibody levels showed a wide variation in control sera, there was a significant correlation between radiographic infiltration and levels of antibody to both LAM and the 38 kD protein in S+ and S–TB ($r = 0{\cdot}50$ (0·10), 0·49 (0·10) respectively) and for low antibody titres to the 14 kD antigen in the self healed group ($r = -0{\cdot}75$ (0·15)). This study suggests that levels of antibody to the 14 kDa antigen may indicate infection with tubercle bacilli, while development of disease is associated with a humoral response to the 19 kD and 38 kD antigens.

Time and cost implications of a uniform policy of infection control in bronchoscopy units

PJV HANSON, S MEAH, D TIPLER, JV COLLINS *Brompton and St Stephen's Hospitals, London* Three infection control policies were implemented consecutively in a bronchoscopy unit; their relative costs and influence on the running of the unit were assessed. Policy 1 had two tiers, extra precautions being taken for designated infectious patients. Policy 2 treated all patients as potentially infected with HIV and hepatitis B (HBV), with 30 minutes disinfection time routinely and 60 minutes, where mycobacteria were suspected; policy 3 differed from policy 2 in routinely disinfecting for 60 minutes, thereby covering all infections in all patients. List sizes, delays between cases and the cost of consumables were recorded for each policy. Patients with HBV and mycobacterial infections at the time of bronchoscopy were identified afterwards from laboratory records and compared with notifications to the bronchoscopy nurse before the

procedure. One hundred and twenty six bronchoscopies were studied. Costs per bronchoscopy were £17·50, £15·50, and £12·90 for policies 1, 2 and 3 respectively. Twenty three percent of booked lists comprised three or more patients. Policies 1 and 2 required two bronchoscopes; policy 3 required three to avoid delays between cases. Compulsory serological screening for HBV before bronchoscopy achieved only 67% compliance; clinical screening for mycobacteria failed to detect two patients with mycobacteria in their sputum at bronchoscopy. It is concluded that screening patients for infection, clinically or serologically, is fallible; implementation of a uniform infection control policy did not increase running costs but will require busy units to use three bronchoscopes to avoid delays between patients.

Evaluation of lung function equipment modified to prevent contamination with HIV and other microorganisms

PJV HANSON, DS CRAMER, JV COLLINS, DM DENISON *Brompton and St Stephen's Hospitals, London* Results from conventional lung function equipment were compared with those obtained using equipment modified to prevent microbial contamination. Paired values for FVC, FEV_1, peak, early, mid, and late expiratory flow rates, peak inspiratory flow rate, TLC, TLCO, VA, and KCO were obtained. The following modifications were made. (1) Spirometry (51 subjects): a rectangular transparent box containing a transparent plastic bag (gauge 120) was placed between patient and spirometer; patients breathed into the bag, displacing air into the spirometer. (2) Gas transfer (56 subjects): a disposable foil bag was filled with test gas to 80% of the patient's FVC; after six timed breaths from RV the gas mixture was analysed by aspiration into a conventional TLCO analyser. (3) Plethysmography (48 subjects): patients exhaled sharply from TLC into a bag in a syringe barrel; expiratory pressure was recorded on a manometer sealing the end of the syringe; change in lung volume was measured plethysmographically. For expiratory spirometry, regressions of modified on conventional measures had slopes between 0·973 and 1·047, intercepts trivially different from zero and correlation coefficients from 0·951 to 0·990. PIFR, being effort dependent, was less reproducible (slope 0·92, r = 0·898). Measurements of absolute lung volume by plethysmography (TLC) and rebreathing (VA) agreed almost as closely as expiratory spirometry. Modified TLCO results (rebreathing) were lower than conventional (single breath) results (slope 0·852) but correlated closely (r = 0·969). It is concluded that with clearly visible, disposable and inexpensive components accurate measurements of lung function can be obtained while contact is avoided between equipment and potentially infected breath and secretions.

Trends in operated non-small cell lung cancer (NSCLC), 1969–85

C JIE, AMJ WEVER, HA HUYSMANS, HCM FRANKEN, J WEVER-HESS, J HERMANS *Departments of Pulmonology, Thoracic Surgery, and Medical Statistics, University Hospital, Leiden, The Netherlands* All patients who underwent surgery for primary NSCLC in the University Hospital, Leiden, between 1969 and 1985 were evaluated (n = 920) by histology, postoperative stage, age group, and surgical procedure. Postoperative TNM classification was established according to AJC (1983) and staged according to UICC (1978). Time trend analyses were carried out by least square regression. the overall descriptive statistics are as follows: histology—adenocarcinoma 21·6%, squamous cell carcinoma 67·7%, and large cell carcinoma 10·7%; postoperative stage—stage I 61·7%, stage II 15·7% and stage III 22·6%; age group—(60 y 35·7%, 60–69 y 46·7%, and >70 y 17·6%; surgical procedure—(bi) lobectomy 64·6%, pneumonectomy 28·5% and exploration 7·0%. The proportion of adenocarcinoma and of age group >70 y increased significantly over time (slope 0·89, p = 0·025 and slope 0·62; p = 0·014), while no significant changes were found with respect to stage and surgical procedure. For the total period the five year survival rates were: adenocarcinoma 36·7%, squamous cell carcinoma 38·9%, and large cell carcinoma 25·9% (p = 0·007); stage I 47·0%, stage II 32·2%, and stage III 12·7% (p = 0·000); age group <60 y 42·2%, 60–69 y 35·9%, and >70 y 29·5% (p = 0·019); (bi)lobectomy 43·5%, pneumonectomy 30·4%, and exploration 2·5% (p = 0·000). No significant changes over time in the five year survival rates of total NSCLC, NSCLC by stage, NSCLC by age group, squamous cell carcinoma, and adenocarcinoma were found. In conclusion, in the operated NSCLC 1969–85 a relative increase in adenocarcinoma and in age group >70 y has been observed. Over this period no significant changes in five year survival rates were found.

Survey of FEV_1 and FVC measurement in respiratory laboratories in the UK

DCS HUTCHISON, *(Department of Thoracic Medicine, King's College Hospital, London)*, R GOOCH, and the Association of Respiratory Technicians and Physiologists (ARTP) Accurate measurement of one second forced expiratory volume (FEV_1) and forced vital capacity (FVC) are required to assist diagnosis, assessment of disability or treatment and for epidemiological purposes. Recommendations on equipment, test procedures and reference values have been made (Quanjer (ed), *Bull Eur Physiopathol Respir* 1983;**19**(suppl 5); American Thoracic Society, *Am Rev Respir Dis* 1987;**136**:1285. A questionnaire was sent to 110 laboratories providing a lung function service; 64 replies were received. Seventy six items of equipment were in use, the types being: plastic bellows spirometer 62%, rolling seal 24%, water filled 7%, pneumotachograph 7% and turbine 1%. The date of manufacture was: before 1971 7% of items; 1971–9 37%, after 1979 57%. An on line computer was used in 45% of laboratories. Calibration of volume measurement was never performed in 20% of laboratories. In the remainder, calibration was performed at various intervals, from daily to annually. Patients were tested sitting in 65% of laboratories and standing in 35%. A noseclip was routinely used in 54%. The number of "blows" ranged from two to six. The "best" result was reported in 97% of laboratories, the mean in 3%. For reference values, 10 of the 64 laboratories (16%) used the ECCS regression equations. The remaining 84% used a total

of 12 other sources, their dates of publication ranging from 1959 to 1981. Five used computer held equations of undetermined source. Fifty six per cent made an allowance for ethnic group. Sixty two per cent reported no reference range; in the remainder the range was given variously as: 1 SD, 1·65 SD, 2 SD or ± 15%. Measurements of FEV_1 and FVC in many UK respiratory laboratories do not accord with the published recommendations and we believe that this should be remedied.

Repeatability of lung function testing using an automated system (Gould 2400) in normal healthy subjects

KF WHYTE, Z ZHANG-ZHONGYI, S MERCHANT, PM WARREN, DC FLENLEY *Department of Respiratory Medicine, Rayne Laboratory, City Hospital, Edinburgh* Conventional "lung function" measurements (lung volumes, transfer factor) requiring skilled manual operators are being replaced by computer driven systems apparently needing less technical skill. We have measured the repeatability (expressed as coefficient of variation: CV%) of such measurements in 10 healthy non-smoking subjects (4M, 6F, aged 21–51 y), at the same time of day each week for 10 consecutive weeks, using the Gould 2400 computerised pulmonary function laboratory, a water sealed spirometer with computerised calibration and reporting systems requiring no manual measurement or calculation. Subjects did not have intercurrent respiratory infection during the 10 week study.

Coefficient of variation (CV) (%) in 10 subjects

	FVC	*FEV_1*	*TLC*	*RV/TLC*	*TLco*	*Kco*
1	1·8	2·3	1·5	6·0	4·1	6·3
2	0·5	1·4	2·0	6·2	4·0	3·1
3	1·1	0·9	1·1	3·7	4·3	4·4
4	1·6	2·6	1·3	2·8	6·0	5·6
5	1·7	1·8	2·2	8·6	5·5	5·5
6	2·0	1·2	2·0	3·2	3·8	5·1
7	4·4	3·6	2·4	4·8	9·0	11·1
8	2·0	2·3	1·1	3·0	4·7	4·9
9	0·7	1·2	1·4	3·9	6·1	5·5
10	1·2	1·4	3·5	5·4	5·0	5·2

CV was lower than that previously reported for manual methods (Cotes, *Lung function,* 4th ed, p 318). This could result from improvement in the measuring device, more accurate reproducible calibration, and/or more uniform test procedures derived from the computer program. In addition to reducing the need for skill and experience in lung function testing, these new computer driven systems appear to improve repeatability, so improving sensitivity for detection of small changes in sequential measurements in the same individual.

ILTARS: an expert system to interpret results of pulmonary function tests

J WYATT, D DENISON *Brompton Hospital, London* The tedium of reporting pulmonary function test (PFT) results and the inconsistency of doctors at this task has led to the development of computer interpretation programs (Pack *et al, Thorax* 1978;**32**:333). However, perhaps because of the difficulties of maintaining these programs and of tailoring them to accommodate known variations in interpretation criteria (Tweedale *et al, Thorax* 1983;**38**:238), they have neither stayed abreast of new developments nor become widely disseminated. "Expert" or "knowledge based" systems are programs written as a series of explicit rules. This allows easier maintenance and tailoring because the expert providing the knowledge can read the program, and the program can provide explanations of its behaviour. The ILTARS system has been written using these techniques; it consists of 39 rules written in pseudo English (see sample below) and runs on a personal computer. Writing it took one third of the time taken by a conventional interpretation program, and the rules can be safely altered by a computer naive physician. It currently processes 13 PFT parameters to build a report consisting of statements selected from a panel of 24. In a "test set" evaluation, its reports were considered adequate by a chest physician in 39 (98%) out of 40 cases. ILTARS takes 20 seconds to report a set of PFTs. The use of rule based techniques has enabled us to build a PFT interpreter with acceptable performance, which runs on inexpensive hardware, and which has the benefit of easier maintenance than using the conventional approach.

ILTARS rule 17

If ratio is low
and rv is high
and dlco is low
then report these results suggest emphysema

PEF/FVC a more sensitive index of both restrictive and obstructive lung disease than FEV_1/FVC

S BLUNT, C DORÉ, M HARRIES *Northwick Park Hospital and Clinical Research Centre, Harrow* The forced expiratory volume/forced vital capacity ratio (FEV_1/FVC) distinguishes airways obstruction but not restriction, from normal lung function. However, in restrictive defects it was our opinion that peak expiratory flow (PEF) is better preserved than is FVC. Therefore the ratio PEF/FVC might separate patients with a restrictive defect from those with normal lung function. To test our observation an independent observer selected 21 patients with restrictive lung defect due either to sarcoid infiltration onto pulmonary fibrosis proved by biopsy. In addition, 35 patients with normal lungs and 32 with a diagnosis of obstructive airways disease based on standard spirometric criteria were selected for comparison. PEF/FVC and FEV_1/FVC were calculated for each patient and expressed as % of the predicted normal for age, sex, height, and race. We then compared % predicted PEF/FVC and FEV_1/FVC in these three groups of patients. Taking the means of each group and looking first at the normals, mean (SD)% predicted PEF/FVC and FEV_1/FVC was 94·8 (11·6) and 99·5 (11·9). In the groups with a restrictive defect, the means were 157·1 (43·2) and 107·4 (17·0) and in the obstructive group were 58·5 (22·5) and 78·1 (18·4) respectively. Welch's test was used to demonstrate how well these two ways of handling spirometric information could separate the

three groups. Both were extremely good at separating normal from obstructive ($p < 0.0001$). But while % predicted PEF/FVC distinguished normal from restrictive ($p < 0.0001$), % predicted FEV_1/FVC failed in this respect ($p = 0.07$). The normal subjects were used to construct reference ranges for % predicted PEF/FVC (71·6–118) and FEV_1/FVC (75·7–123·2). Using these ranges to diagnose abnormality, the specificity of both ratios was high (>0·97). But % predicted FEV_1/FVC was an insensitive measure both of restrictive (0·24) and of obstructive lung disease (0·43) by comparison with PEF/FVC (0·86 and 0·71) respectively. Calculation of % predicted PEF/FVC may therefore prove useful in the computer interpretation of flow volume loops.

Repeatability of FEV_1, FVC and PEF: relation to the size of the measurement

KA GUNAWARDENA, G BUTCHER *Riyadh Military Hospital, Riyadh, Saudi Arabia* Controversy still exists about whether bronchodilator responsiveness should be expressed in terms of percentage change or absolute change (Tweedale *et al Thorax* 1987;**42**:487). Clearly, this question should take into account the relation of the size of the measurements to the variability of repeated measurements (that is, the repeatability) of the indices used. We examined this relation for FEV_1 (Vitalograph, 128 subjects, range 0·35–5·48 l), FVC (Vitalograph, 128 subjects, range 0·57–6·39 l) and PEF (Wright peak flow meter, 167 subjects, range 40–703 l/min) by estimating the Spearman's rank correlation coefficient of the standard deviation of triplicate measurements against the mean of the three measurements. Subjects included both normals and those with lung disease. In all instances the correlation coefficients differed insignificantly from zero ($r = 0.096$ for FEV_1, $r = 0.035$ for FVC, $r = -0.036$ for PEF). The repeatability of these measurements thus showed no relation to the size of the measurements. This supports the contention that to distinguish natural variability from bronchodilator responsiveness the absolute rather than the percentage change should be used.

Exercise rehabilitation in patients with fibrosing lung disease

A SCANE, DT MCLEOD, L COLTMAN, H MOULD, JH DARK, GJ GIBSON, PA CORRIS *Freeman Hospital, Newcastle upon Tyne* Over the last 12 months, nine patients with fibrosing lung disease have been accepted for single lung transplantation. All were housebound, dependent on continuous supplemental oxygen and estimated to have a life expectancy of less than 12 months. In view of the beneficial effects of exercise rehabilitation in patients with severe airflow obstruction we started all patients on a programme of twice daily exercise to try to improve cardiorespiratory fitness prior to surgery. The exercise consisted of a short warm up with light callisthenics, followed by cycling on simple braked pedals, the work load being adjusted for each individual to raise heart rate to 80% of maximum predicted after 10 minutes' cycling. We monitored the response to exercise by monitoring symptom limited progressive exercise on a bicycle ergometer and six minute walking distances (6 MD). The exercise test was performed with 50% oxygen with an initial work load of 10 w increasing every minute by 10 w increments, and the 6 MD was carried out breathing 6 l O_2 via nasal cannulas. Initial (mean (SD)) exercise time and 6 MD were 247 (94) s and 200 (130) m respectively. All patients showed an initial improvement with a maximum exercise time and 6 MD for the group of 299 (107) s and 342 (127) m respectively. The mean time taken for the group to attain maximum performance was 9 (5) weeks. Five patients have been transplanted and three have died awaiting transplantation. The mean time between acceptance and transplantation was 22·6 (12) weeks. Exercise performance deteriorated in all patients after the initial improvement in the rehabilitation programme, exercise time and 6 MD declining to 213 (128) s and 220 (92) m prior to transplantation or death. We conclude that it is possible to improve exercise performance in patients with severe progressive fibrosing lung disease using an exercise rehabilitation programme but that the improvement is not sustained.

Influence of mastication on respiratory activity in man

GA FONTANA, L VIROLI, F BOGIANNI, T PANTALEO, JV COLLINS *Unità di Fisiopatologia Respiratoria and Dipartimento di Scienze Fisiologiche, Università di Firenze, Italy, and Brompton Hospital, London* An attempt was made to investigate the influence of masticatory activity on respiration. In six healthy volunteers tidal volume (VT) and end tidal CO_2 ($PetCO_2$) were recorded by means of a nasal mask connected to a pneumotachograph and to a CO_2 analyser. Surface electrodes were used to record "integrated" electromyographic activity (IEMG) of diaphragm or intercostal muscles and of masseter muscles. Each subject was requested to masticate for one minute a 5 g chewing gum bolus, either at spontaneous rate (SR) or at the maximum possible rate (MPR). Preliminary results show that the onset of SR mastication consistently induced an increase in mean inspiratory flow (that is, the VT/inspiratory time (TI) ratio), which was mainly due to an increase in VT. An increase in the slope of the inspiratory IEMG activity and, to a lesser extent, in mean respiratory frequency (f) was also observed. MPR mastication induced a sudden increase in VT/TI owing to a marked decrease in TI without significant variations in VT accompanied by comparable changes in the slope of inspiratory IEMG activity and a marked increase in f. Minute ventilation, as calculated by excluding breaths affected by swallowing, slightly but significantly increased during SR and MPR mastication. Finally, no changes in $PetCO_2$ were observed with either masticatory patterns. These results indicate that mastication induces significant changes in respiratory "drive" and the pattern of breathing, which may serve to maintain normocapnic conditions despite the frequent respiratory pauses due to swallowing during mastication.

Cough challenge in ACE inhibitor cough

AG MORICE, MJ BROWN, TW HIGENBOTTAM *Respiratory Physiology Department, Papworth Hospital, and Clinical Pharmacology Unit, Addenbrookes Hospital, Cambridge* The widespread use of ACE inhibitors in the treatment of hypertension and heart failure has lead to the recognition that these drugs may cause a dry cough, which is commoner in women and non-smokers. We have investigated with cough challenge six non-smoking patients (four women, three hypertensive) whose sensitivity to ACE inhibitors was demonstrated by withdrawal of captopril and rechallenge with the drug. Cough sensitivity was determined by the construction of dose-response curve to the sequential inhalation of citric acid (10 mM-IM) and capsaicin (1–100 μM) from a dosimeter (Mefar, Italy) activated for one second by inhalation of a single breath. Challenge at each dose was repeated four times. Patients were studied while taking captopril and one and two weeks after stopping the drug. After baseline determination of cough sensitivity subjects received in a randomised, double blind, placebo controlled manner an inhalation of captopril 10 mg followed one hour later by repeat challenge. All subjects showed a normal cough response to citric acid, cough developing at challenge with 100 and 300 mM solutions. In contrast, five out of six subjects showed increased responses to capsaicin, cough developing at 1 and 3 μM challenge. This increased sensitivity was still present one and two weeks post captopril and inhalation of captopril had no significant effect. In four of the six patients enalapril (5 mg) was substituted for captopril, but cough returned. The development of cough in these subjects may be related to abnormalities of the cough reflex, low perineuronal ACE activity leading to an increase in sensitivity to capsaicin.

Timing of sighs during spontaneous breathing in man

CP PATIL, KB SAUNDERS *Department of Medicine I, St George's Hospital Medical School, London* We have used signal analysis to define baseline movement (non-stationarity) in respiratory variables (for example, tidal volume, VT, end tidal P_{CO_2}, P_{ETCO_2}). Random noise is removed by digital filtering, and the resulting variable baseline is resolved into linear segments where peaks and troughs are precisely defined (Patil *et al*, *IRCS Med Sci* 1986;**14**:644). We studied 17 normal subjects at rest and during 50 w exercise, breathing through a mouthpiece, and nine at rest and during 50 w exercise with breathing recorded by Respitrace. At rest large inspirations (sighs) occur significantly ($p < 0.05$) more often in relation to troughs of P_{ETCO_2}, by both recording methods (that is, a deep breath occurs when P_{ETCO_2} is already low). There is no relation to VT. During 50 w exercise sighs occur significantly more often in relation to troughs of VT, by both recording methods, but there is no relation to P_{ETCO_2}. In light exercise therefore sighs are related to mechanical rather than chemical events. Strategies using threshold type control mechanisms may be used to explain findings in both rest and exercise.

Ventilation-perfusion mismatching after methacholine challenge in patients with mild asthma

R RODRIGUEZ-ROISIN, A FERRER, J ROCA, AGN AGUSTI, D NAVAJAS, PD WAGNER *Departments of Medicine, Servei de Pneumologia, Hospital Clinic, Barcelona, Spain, and University of California, San Diego, La Jolla, California, USA* Very little information on ventilation-perfusion ($\dot{V}_A/\dot{Q}$) distributions in models of bronchial challenge is available. We have investigated the effect of a methacholine (Mtc) bronchial challenge on $\dot{V}_A/\dot{Q}$ relationships in seven subjects aged 16–48 years with mild asthma (FEV_1 82 (SD 24) % predicted; Pa_{O_2} 12·7 (0·9) kPa; $AaPo_2$ 1·8 (0·9) kPa). In all but two patients the baseline $\dot{V}_A/\dot{Q}$ distributions were narrow and unimodal with a normal pulmonary bloodflow distribution (log SD Q 0·46 (0·12); normal range 0·3–0·6). Following Mtc challenge FEV_1 decreased by 30 (6·3)% (−780 (352) ml), Pa_{O_2} fell, and $AaPo_2$ increased by the same amount (2·7 (1·7) kPa, $p < 0.03$ each), and there were increases both in the percentage of pulmonary perfusion to low $\dot{V}_A/\dot{Q}$ units (<0·1, including shunt) (from 0·8 (0·1) to 4·0 (3·9) %, $p < 0.05$) and in log SDQ (to 0·9 (0·2), $p < 0.02$), reflecting a moderate worsening in $\dot{V}_A/\dot{Q}$ relationships. Five patients developed a broad unimodal bloodflow distribution pattern and two a small low $\dot{V}_A/\dot{Q}$ mode. Minute ventilation, o_2 consumption and cardiac output remained unchanged. There were significant correlations between changes in Pa_{O_2} and $AaPo_2$ and increases in log SDQ ($r = -0.87$, $p < 0.01$ and $r = 0.98$, $p < 0.0001$ respectively), and between decreases in Pa_{O_2} and FEV_1 ($r = 0.76$, $p < 0.05$). However, there was no relation between severity of induced airway obstruction and degree of $\dot{V}_A/\dot{Q}$ maldistribution. Within two hours all the variables had returned to baseline values. These results show that Mtc challenge produces, parallel to airway obstruction and hypoxaemia, considerable $\dot{V}_A/\dot{Q}$ inequality that is essentially similar to that seen in patients with moderate to severe asthma (work supported by CCA 8309185 and CICYT PA 85-0016).

Differences in the time course of respiratory heat loss in asthma induced by exercise and isocapnic hyperventilation

B ASSOUFI, N ROUTLEDGE, S LOZEWICZ *Brompton and St Bartholomew's Hospitals, London* Respiratory heat exchange (RHE) is regarded as an important determinant of asthma induced by isocapnic hyperventilation (ISH) and exercise. However, the time course of related changes in RHE and airflow limitation during exercise and ISH is not known. We have therefore assessed the time course of changes in RHE and airflow limitation in five male asthmatics (mean age 24 y) during separate periods of provocation by exercise and ISH. On the first visit patients underwent ISH at a ventilation rate of 50–90 litres per minute for nine minutes. On a subsequent day they performed exercise at 2·5–3·75 km/h at an incline of 10–15° for the same period. On each occasion measurement of RHE and FEV_1 was made before, during and for 30 minutes after the challenge. During exercise RHE increased gradually and there was a significant ($p < 0.005$) increase in FEV_1 during the first three minutes.

As RHE continued to rise, reaching a maximum after six to nine minutes, the FEV_1 started to fall. After exercise both FEV_1 and RHE fell until 10 minutes following the end of the challenge, when RHE returned to the baseline value and FEV_1, having reached its lowest value, started to rise. During hyperventilation the highest value for RHE was recorded during the first and second minutes of the test. Following this, both FEV_1 and RHE fell steadily until five minutes after the end of the test, at which point RHE returned to baseline and FEV_1, having reached the lowest value, started to rise. This study demonstrates that the time course of changes in RHE and airflow limitation during exercise is different from that occurring during isocapnic hyperventilation.

Radioisotopic method for measuring pleural fluid drainage

GS BASRAN, WD FLATMAN, T KONTAKIOTIS *Rotherham District General Hospital, Rotherham* Pleural effusions result from either an excessive rate of exudation of fluid into the pleural cavity or a reduced capability for the lymphatic system to drain the fluid. We describe an isotopic method for measuring the rate of drainage. Patients with free flowing pleural effusions were investigated. Effusion volumes were measured by a dilution technique involving the injection of a known amount of ^{125}I albumin directly into the effusion. Fluid drainage was calculated by measuring the rate of appearance of this tracer in the blood. Blood and effusion samples were taken at regular intervals over three hours, and then assayed for ^{125}I. The rate constant (K_{out}), expressed as 10^{-4} h^{-1}, is an index of fluid drainage and was calculated according to a three compartment model. The results are shown in the table.

Case No	*Diagnosis*	*Effusion vol (l)*	*Rate constant (K_{out})*
1	Mesothelioma	1·8	0·0
2	Mesothelioma	2·1	5·5
3	Breast carcinoma	1·1	5·5
4	Carcinoma ?site	2·3	7·9
5	Carcinoma ?site	1·0	11
6	Lung carcinoma	0·8	6·6
7	Lung carcinoma	0·9	8·3
8	Lung carcinoma	1·0	28
9	Lung carcinoma	1·0	32
10	Ovarian carcinoma	1·1	27
11	Pneumothorax	—	210
12	Pneumothorax	—	380

Patients 1–3, in whom impaired lymphatic drainage was suspected as the cause of the effusion, exhibited the lowest K_{out} values. Patients 11 and 12, who would be expected to have normal drainage, exhibited much higher values. The technique offers a potential for evaluating the mechanisms by which pleural effusions accumulate in various pulmonary and extrapulmonary disorders and may provide a method for assessing the effects of therapeutic intervention.

Characterisation of ion transport in the guinea pig trachea

EWFW ALTON, DF ROGERS, DM GEDDES, PJ BARNES *Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* It is likely that abnormalities in the regulation of ion transport underlie the pathophysiology of cystic fibrosis. However, the normal regulation of ion fluxes across human respiratory epithelia is poorly understood, partly because of difficulties in obtaining sufficient tissue. We have therefore characterised ion transport in the guinea pig trachea to establish whether it exhibits similarities to that in man. Tracheas were removed from anaesthetised animals, opened, and mounted in Ussing chambers. Tissues were bathed in oxygenated Krebs solution at 37°C and the potential difference (PD), short circuit current (ISc) and conductance (G) recorded before and following addition of drugs. Basal values from 30 tissues showed the PD to be $-7{\cdot}6$ mv (SE 0·5), ISc 72·6 $\mu A/cm^2$ (3·9) and G 10·3 ms/cm^2 (0·6). Mucosal amiloride produced a dose dependent fall in PD of 44·8% (1·7, n = 8) and ISc of 51·6% (1·7), with an ED_{50} of 3×10^{-7}. Serosal application produced no effect. Addition of isoprenaline to the serosal bath caused a small dose dependent rise in ISc of 33·4% (2·0, n = 8), and PD of 18·6% (2·2) with an ED_{50} of 2×10^{-7} M. Pretreatment of tissues for 30 minutes with propranolol (10^{-6} M on the serosal surface) caused a 0·75 log shift of the dose-response curve to the right. Serosal addition of frusemide had no effect on any parameter up to a concentration of 10^{-3} M. We conclude that the guinea pig trachea demonstrates characteristics typical of a sodium absorbing epithelium, with electrical properties very similar to those reported in human bronchi. This tissue may therefore be useful in investigating the control of ion transport in man.

Differential plasminogen activator and fibronectin degrading activities of leucocytes from acutely and chronically inflamed lung

GM BROWN, K DONALDSON, J SLIGHT *Institute of Occupational Medicine, Edinburgh* The proteolytic activity of inflammatory leucocytes is considered to have a major role in causing pathological change in chronic lung disease. We have measured inflammation in the rat lung in response to particulates causing acute, resolving inflammation (*Corynebacterium parvum* and zymosan) and chronic inflammation (quartz). We assessed the proteolytic activity of the bronchoalveolar leucocytes by measuring plasminogen activator activity and ability to degrade ^{125}I fibronectin. Intratracheal instillation caused an increase in total leucocytes after one day—control cells 4·3 (0·7) $\times 10^6$ (mean (SE)), *C parvum* 26·7 (2·1), zymosan 17·0 (1·0), quartz 17·3 (0·7). Four days later total leucocytes were approximately 50% less, returning to near control levels by 30 days, except in the case of quartz, where they were increased and continued to increase up to 30 days after injection—51·0 (8·3). The plasminogen activator activity of the inflammatory leucocytes did not differ from control leucocytes at any time. In contrast, ability to degrade fibronectin was markedly increased with all inflammogens one day after injection, *C parvum* 222% (fibronectin degraded as a percentage of

control), zymosan 215%, quartz 201%. Thereafter proteolytic activity declined rapidly and reached control levels by 15 days except in the case of quartz, where the activity remaining elevated throughout (239% of control at day 30). Thus the tissue injury which develops in chronic quartz exposed lung is associated with persistence of inflammatory leucocytes whose ability to damage connective tissue is enhanced. Plasminogen activator was not apparently implicated in the development or resolution of inflammation as judged on a cell to cell basis in this study. This research was funded by the Colt Foundation.

Characterisation of the fibronectin degrading activity of inflammatory bronchoalveolar macrophages and neutrophils

GM BROWN, J IRVINE, K DONALDSON *Institute of Occupational Medicine and Moredun Research Institute, Edinburgh*
Fibronectin is a component of lung tissue of major importance in cell:cell and cell:matrix interactions. Proteolytic injury to this and other connective tissue molecules is strongly implicated in tissue derangement arising from chronic inflammatory lung disease. We have therefore evaluated the ability of inflammatory bronchoalveolar macrophages and neutrophils from rat lungs treated with quartz to degrade ^{125}I fibronectin. Inflammatory leucocytes (50% bronchoalveolar macrophages, 50% neutrophils) were retrieved by bronchoalveolar lavage and separated by differential centrifugation. Inflammatory bronchoalveolar macrophages and neutrophils degraded more ^{125}I fibronectin—5220 (1179) (mean (SE) counts of degraded ^{125}I fibronectin released) and 7669 (1768) respectively—than control bronchoalveolar macrophages—3266 (813). Since bronchoalveolar macrophages can sequester and subsequently release active neutrophil elastase, we investigated the source of the bronchoalveolar macrophage enzyme by gel electrophoresis characterisation. Extracts of unseparated inflammatory leucocytes were run on polyacrylamide gels incorporating azocasein gels as a substrate for proteolysis. This showed a major band of proteolytic activity, not present in controls, active at pH 8·3 and of molecular weight $\approx$ 26 000. ^{3}H DFP gel electrophoresis showed that proteolysis was due to serine protease activity, probably neutrophil elastase or cathepsin G. The proteolytic activity of separated leucocytes resided largely in the neutrophil fraction; thus the enhanced ^{125}I fibronectin degrading activity of inflammatory macrophages may be due to de novo synthesis of enzymes. Further work is in progress to verify this. (This research was funded in part by the Colt Foundation.)

Pyocyanin stimulates superoxide generation by human polymorphonuclear leucocytes (PMNL) in vitro

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To investigate possible pathogenic mechanisms of *Pseudomonas aeruginosa* infection we examined the effect of two phenazine pigments, pyocyanin and 1-hydroxyphenazine (1HP), on PMNL superoxide (O_2^-) generation. PMNL were prepared from venous blood by Ficoll-gradient separation and used at a final concentration of 1×10^6/ml. PMNL O_2^- generation was measured by ferricytochrome C (cyt c) reduction in the presence and absence of superoxide dismutase. Different concentrations of pigments (1·5–25 μM) were investigated in the absence (spontaneous) and presence (stimulated) of stimulants such as opsonised zymosan (OZ), calcium ionophore (A23187), phorbol myristate acetate (PMA) and FMLP/cytochalasin B (CB). Results are expressed as reduced cyt c (μ mols/10^6 PMNL) for four separate experiments. Pyocyanin caused a dose dependent enhancement of both spontaneous and stimulated O_2^- generation with optimal effects at a concentration of 12·5 μM ($p < 0.05$). No significant effect of 1HP on O_2^- generation was observed. The results (means (SEM)) for different stimuli were:

	Control	*OZ*	*A23187*	*PMA*	*FMLP/CB*
Stimulant alone	1·3(0·7)	8·1(0·3)	3·8(0·2)	40·4(1·7)	20·8(1·2)
Pyo (12·5 μM) + stimulant	3·2(0·2)	12·4(0·3)	11·1(0·6)	43·1(1·2)	37·1(1·7)

Addition of suboptimal concentrations of 1HP to pyocyanin caused no additional enhancement of O_2^- generation by FMLP/CB stimulated PMNL. We conclude that pyocyanin stimulates enhanced PMNL superoxide generation, which could be tissue damaging in vivo.

***Haemophilus influenzae* attaches exclusively to areas of damaged human respiratory epithelium in vitro**

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Bacterial adherence to respiratory epithelium is accepted as an initial step in colonisation and subsequent infection. We have examined the interaction of *H influenzae* (Hi) and human respiratory epithelium. Adjacent cross sections of inferior nasal turbinates, surgically resected from patients with nasal obstruction, were incubated in either medium alone (control), medium containing a laboratory strain of Hi (RM132) or containing a clinical non-typable isolate of Hi (SH9). The viable count of Hi in each test preparation increased by 2–4 logs to about 10^9/ml over the subsequent 24 hours and controls remained uninfected. Light microscopy showed gradual cell extrusion from the surface of infected turbinates together with slowing of ciliary beat frequency. Using transmission electron microscopy, the ultrastructure of each section was subsequently examined morphometrically for cell surface projection, loss of cilia, cytoplasmic

blebbing, and mitochondrial abnormality. There was a consistent reduction of the proportion of cells bearing cilia in infected preparations compared with controls. Bacteria were only seen in association with damaged areas of epithelium and apposition of bacteria to the epithelial surface was rarely seen. Epithelium in infected preparations that was not associated with bacteria also showed reduction in ciliation but there were no changes in cell ultrastructure, which was indistinguishable from that in control preparations. These provisional observations suggest to us that Hi does not associate with normal epithelium but can itself cause damage to epithelial cells, which may be prerequisite to attachment of the bacterium to that epithelium.

Effect of the antiviral drug ribavirin on human respiratory epithelium in vitro and nasal mucociliary clearance (NMCC) in vivo

LY HAN, R WILSON, S SLATER, A RUTMAN, RC READ, N SNELL, M TURNER-WARWICK, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, National Heart and Lung Institute, Brompton Hospital, London* Ribavirin is given as an aerosol (20 mg/ml) to treat infants with respiratory syncytial virus infection. Recently, benefit has been shown in a patient with cryptogenic fibrosing alveolitis (*Chest* 1988;**93**:446). For safety reasons we have examined the in vitro effect at 37°C of ribavirin on the ciliary beat frequency (CBF) of normal human nasal epithelium obtained by a brushing technique. In separate experiments, sections of human nasal turbinates were immersed in three different concentrations of ribavirin (20, 40 and 80 mg/ml) for 5 h and fixed for transmission electron microscopy (TEM). We have also measured NMCC in three patients before and after nasal inhalation of nebulised ribavirin (240 mg in 4 ml) and have examined nasal brushings following this. Ribavirin (80 mg/ml) in distilled water had physiological osmolality and was further diluted with phosphate buffered saline. pH was adjusted to 7·0–7·5. Slowing of CBF and changes in the epithelial structure of nasal brushings were seen by light microscopy at 40 mg/ml and above. TEM showed dose related changes in epithelial cell ultra-structure after 5 h: at 20 mg/ml these were mild but at 80 mg/ml were gross, consisting of cell blebbing, mitochondrial damage and epithelial disruption. However, NMCC was unaffected by nasal inhalation of ribavirin (60 mg/ml) and epithelial brushings taken after such inhalation were normal under light microscopy and had normal CBF. Drug dilution and protection of the epithelium by mucus may explain the discrepancy between these in vivo and in vitro results and, at least for short term administration, current drug regimens appear safe.

Drug concentration in vitro (mg/ml)	20	40	50	60	80
% of control CBF at 5 h	98	92	67	58	37
n =	3	6	6	3	3

Effect of flurbiprofen on refractoriness following bradykinin induced bronchoconstriction in asthma

R POLOSA, ST HOLGATE *Immunopharmacology Group, Southampton General Hospital, Southampton* Bradykinin is a nonapeptide generated by cleavage of plasma kininogen by tissue kininogenases. This kinin appears to be compatible with a role as a mediator since it is generated on nasal immunological challenge in vivo and it has been shown to induce some asthma like symptoms, such as bronchoconstriction, plasma exudation and mucus secretion. Refractoriness following bradykinin inhalations may be due to release of protective prostaglandins. The aim of this study was to elucidate the contribution of protective cyclo-oxygenase products to tachyphylaxis following repeated bradykinin bronchoprovocation tests in asthmatic subjects. Bradykinin was administered as an aerosol generated from a solution diluted in 10% ethanol in normal saline in order to produce a concentration range of 0·015–4 mg/ml. We examined the effect of pretreatment (150 min) with oral flurbiprofen (150 mg) and matched placebo on two repeated inhalations with bradykinin in a double blind, randomised study of seven asthmatic subjects. The second consecutive concentration-response study was performed 60–75 min apart, once the FEV_1 had recovered spontaneously to within 5% of its baseline value. Test results were assessed as the provocative concentration of agonist needed to produce a 20% fall in FEV_1 (PC_{20}). Tachyphylaxis to bradykinin (Bk) was expressed as the ratio in between PC_{20} Bk test 2 and PC_{20} Bk test 1 (PC20Bk2/PC20Bk1). The change in bradykinin reactivity following the second inhalation test was significant ($p < 0·01$) during both placebo and flurbiprofen study days, there being an increase in PC_{20} bradykinin from 0·07 to 0·47 mg/ml and from 0·10 to 0·57 mg/ml respectively. When the logarithms of the ratios (PC20Bk2/PC20Bk1) obtained after placebo and flurbiprofen were compared by means of the paired *t* test, there was no significant difference. In conclusion, these results suggest that the generation of protective prostaglandins is not involved in mediating the refractoriness following repeated inhalations with bradykinin in asthmatic subjects.

Early cessation of neutrophil migration after localised intrapulmonary instillation of *Streptococcus pneumoniae*

RJ CLARK, C HASLETT *Respiratory Division, Department of Medicine, Royal Postgraduate Medical School, London* Identification of the mechanisms by which inflammation normally resolves may lead to a greater understanding of the pathogenesis of persistent inflammatory states. One prerequisite for resolution to occur is the cessation of neutrophil migration. We have studied this process in localised right upper lobe (RUL) inflammatory lesions induced in rabbits by instillation of agents under direct vision via a neonatal fibreoptic bronchoscope. Intravenous pulses of indium-111 labelled rabbit neutrophils (In-neutrophil) were given at various times after instillation, and neutrophil migration into lung assessed 24 hours later by lung neutrophil associated radioactive counts. We have previously

shown that neutrophil influx persists for up to three weeks after a single instillation of bleomycin, whereas influx ceased within two hours of the instillation of the natural chemotactic peptide C5a des arg. In the present study 17 rabbits received a standardised RUL instillation of *Streptococcus pneumoniae* in saline and a pulse of In-neutrophils was injected intravenously one, two, 16 or 28 hours later. RUL lung migration of In-neutrophils was assessed 24 hours after injection by gamma camera scintigraphy and tissue counting and expressed as a ratio of counts in the unstimulated left upper lobe: 13·2 (7·2) (n = 4, mean (SD)) at one hour, 18·4 (14·8) (n = 4) at two hours, 7·3 (0·54) (n = 4) at 16 hours and 1·67 (0·86) (n = 5) at 28 hours. Similar results were obtained by scintigraphy, and a close correlation was found between these two modes of assessing neutrophil influx (R = 0·72, N = 14, $p < 0·05$). Thus in response to *S pneumoniae* most neutrophil influx is occurring at 1–2 hours, with a reduction at 16 hours and virtual cessation by 28 hours. This early cessation of neutrophil influx in response to *S pneumoniae*, contrasted with bleomycin, may partly explain the resolution and the lack of histological sequelae of inflammatory lesions such as lobar pneumonia.

Effect of cigarette smoke on neutrophil proteolytic activity in vitro

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Recent evidence indicates an increase in active elastase in venous blood during cigarette smoking (Weitz *et al*, *Ann Intern Med* 1987;**107**:680), presumably released from neutrophils (PMNL) sequestered and activated in the pulmonary microcirculation. We studied the effect of in vitro cigarette smoke exposure on the function of PMNL harvested from whole blood (WB), using a discontinuous plasma/percoll density gradient, in six normal subjects. WB and PMNL were exposed in a tonometer to the gas phase of cigarette smoke and compared with control samples. The ability of 1×10^5 PMN to digest ^{125}I fibronectin when unstimulated and when stimulated with 0·1 and 1 mg/ml of phorbol myristate acetate (PMA) or 0·01 and 0·1 mg/ml of zymosan was measured as the counts per minute (cpm) released (Brown *et al*, *Thorax* 1988;**43**:132). Human neutrophil elastase (HNE) was measured by radioimmunoassay in WB and PMNL supernatant. PMNL were also processed for transmission electron microscopy. All results are given as means (SD). The carboxyhaemoglobin of WB rose from 1·4 (0·5) to 8·5 (3·5)% ($p < 0·01$) after four minutes' exposure to cigarette smoke. Unstimulated PMNL, exposed to cigarette smoke degraded less fibronectin ($4·96 (1·36) \times 10^3$ cpm) than control cells ($8·69 (1·70) \times 10^3$ cpm, $p < 0·001$). PMA, but not zymosan, increased the fibronectin degradation by control cells ($10·69 (2·12) \times 10^3$ cpm, $p < 0·005$, and $8·6 (1·7) \times 10^3$ cpm, NS) and restored the activity of smoked cells ($10·4 (5·9) \times 10^3$ cpm, $p < 0·005$). Elastase levels were unchanged in the supernatant of smoke exposed PMNL. Cigarette smoke produced a marked change in PMNL morphology, consistent with cell injury. We conclude that cigarette smoke exposure in vitro reduces the proteolytic activity of PMNL, probably as a result of cell injury, which is reversible when the cells are stimulated with PMA.

Transferrin levels in bronchoalveolar lavage fluid of smokers and non-smokers

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Cigarette smoke associated and phagocyte generated oxidants may contribute to both acute and chronic lung damage both directly through lipid peroxidation and indirectly by inactivation of proteinase inhibitors. Various antioxidants probably play a part in the antioxidant protection of the lung from these oxidants. Antioxidant activity in serum is due, in significant part, to the available iron binding capacity of transferrin (*Am Rev Respir Dis* 1987;**135**:783). Transferrin contains two iron binding sites and binds iron in association with bicarbonate. Partially iron saturated transferrin is reported to inhibit hydroxyl radical (OH) formation. We have measured transferrin concentrations in bronchoalveolar lavage (BAL) fluid from 85 subjects. BAL was performed at diagnostic bronchoscopy in 58 smokers, 17 ex-smokers and 10 non-smokers. Twenty four patients had no active lung disease (controls), 45 had bronchial carcinoma (Br Ca) and 16 had had a recent infection (PI). Unconcentrated BAL fluid was stored at −70°C, until assay. Transferrin was measured by ELISA. There were no differences in concentration (μg/l) between smokers (mean (SEM) 2·15 (0·14)), ex-smokers (2·62 (0·38)) and non-smokers (2·75 (0·28)). Any possible effect of disease was considered by comparison of concentrations for smokers only (too few ex-smokers and non-smokers within each group). There were no differences: controls (n = 15; 2·09 (0·30)); Br Ca (n = 31; 2·26 (0·16)); PI (n = 11; 1·94 (0·38)). We conclude there is no smoking or acute phase induced increase in BAL fluid transferrin concentration.

Inhaled potassium chloride (KCl) induced bronchoconstriction is safe

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Potassium (K+) is intimately concerned in maintenance of transcellular membrane potentials. Smooth muscle contraction results from membrane depolarisation by added KCl in vitro. This may be a mechanism by which mediators produce bronchoconstriction or a possible site of action of bronchodilator drugs in asthma. Inhaled KCl has been reported to be a specific bronchoconstrictor stimulus for asthma (Maygar *et al*, *Schweiz Med Wochemschr* 1984;**114**:910). In order to determine if inhalation of KCl is safe as a bronchoconstrictor challenge six male atopic, non-asthmatic, hyperreactive subjects, with PC_{40} histamine 4·2: 2·5–7·9 mg/ml (geometric mean (GM) and range) were studied on two occasions. On one day subjects received hypertonic KCl (10%) and on the

other NaCl (0·9%), double blind and randomised, by ultrasonic nebuliser (DeVilbiss 65). Measurements were made after one, two, four, eight, 16, 32, 64, 100, and 150 breaths. Partial flow at 40% original vital capacity ($\dot{V}p_{40}$) was measured using a Collingwood spirometer. Breath number for a 40% fall in $\dot{V}p_{40}$ was calculated by interpolation (PBn_{40}). Blood pressure was recorded automatically (Dinamap) after each inhalation. Cardiac output, heart rate, stroke volume, and ventricular ejection time (BoMed NCCOM 3) and oxygen saturation (Sao_2, Kontron) were monitored continuously and recorded after each inhalation as was quantitative ECG (Schiller). Blood was also taken for serum K+ after each inhalation. After KCl, but not after NaCl, all subjects coughed and bronchoconstricted with a greater than 40% fall in $\dot{V}p_{40}$. PBn_{40} KCl was 48 breaths (6–106) (GM: range). No significant change in any cardiovascular parameter, electrophysiological index, Sao_2 or serum K+ occurred on either study day. In conclusion, inhaled KCl produces controlled bronchoconstriction in hyperreactive subjects, with no change in serum K+ or cardiovascular function.

Inhaled nitric oxide (NO), a selective pulmonary vasodilator

J PEPKE-ZABA, TW HIGENBOTTAM, P WOOLMAN, JP SCOTT *Department of Respiratory Physiology, Papworth Hospital, Cambridge* Endothelium derived relaxing factor (EDRF) has been demonstrated to be NO (*Nature* 1987;**327**:524). In vivo study is difficult as haemoglobin inactivates EDRF (*Cardiovasc Res* 1986;**20**:549). As NO is of low water solubility, it can be inhaled in low concentration without lung injury (*Int Arch Occup Environ Health* 1980;**47**:71). We have compared the vasodilatory effect of inhaled 40 ppm NO in air with intravenous infusion of prostacyclin (PGI2) in 10 patients with primary pulmonary hypertension (PPH). They were studied using a flow directed pulmonary artery catheter and radial artery cannula. The cardiac index (CI) was measured in triplicate by thermodilution. PGI2 infusion was increased stepwise by 2 ng/kg/min increments every 10 min until systemic arterial pressure fell by 20%. NO or air was inhaled double blind from Douglas bags for two periods each of five min. Comparisons between mean pulmonary artery pressure (PAP), CI, pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were made by paired *t* test, and the results (mean (SEM) values) are shown in the table.

	PAP	*CI*	*PVR*	*SVR*
Air	59·1 (4·2)	2·15 (0·22)	14·5 (2·2)	20·9 (7·0)
NO	53·9 (4·3)**	2·45 (0·24)	13·1 (2·1)**	19·9 (7·1)
Baseline	62·2 (5·7)	2·10 (0·28)	15·5 (2·4)	22·2 (10·1)
PGI2	57·9 (6·3)	2·70 (0·43)**	12·5 (2·5)***	18·1 (12·9)*

*p < 0·05; **p < 0·01; ***p < 0·001.

Inhalation of 40 ppm NO in air causes significant fall in PVR in PPH patients. There was a significantly smaller effect upon SVR. The fall in PVR on NO was smaller than the fall with max dose PGI2, but PGI2 caused a greater fall in SVR. There was no relation between the size of the fall in PVR with PGI2 and NO in those patients. We conclude that inhaled NO causes selective pulmonary vasodilation by separate mechanisms to that of PG12, which is consistent with their different mechanisms of action on relaxing vascular smooth muscle.

Role of histamine and leukotrienes in the early response to inhaled antigen

N EISER, W DENMAN, M HAYHURST, P ANCIC, J RODRIGUEZ *Lewisham Hospital, London* Previous studies suggest that, while released histamine has a role in the production of the early asthmatic response to inhaled antigen, leukotrienes may have little effect (Mann *et al, Thorax* 1986;**41**:746; Chan *et al, Br J Dis Chest* 1986;**80**:375; Britton *et al, J Allergy Clin Immunol* 1987;**79**:811). In the present study of 12 stable asthmatics we compared the effects alone and together of oral terfenadine (H_1 receptor antagonist) and an inhaled novel, selective, potent antagonist of leukotriene C_4, D_4 and E_4 (SK&F104353) in a randomised, double blind, placebo controlled trial. Doubling concentrations of antigen were given cumulatively from a nebuliser-dosimeter system and the responses monitored with FEV_1 and specific airways conductance (sGaw) until FEV_1 fell by 20% baseline or the highest concentration had been given. On four separate days, 2–4 weeks apart, oral terfenadine 120 mg + placebo, placebo + inhaled SK&F104353 1200 μg in 3 ml, terfenadine 120 mg + SK&F104353 1200 μg or double placebo was given to each subject prior to challenge. Within each subject the falls in FEV_1 and sGaw from each dose-response curve on the different days were compared at the dose which had given a 10% fall in baseline FEV_1 and a 20% fall in baseline sGaw on the double placebo day. Median and ranges are given because of the large intersubject differences in sensitivity to antigen. After terfenadine, FEV_1 fell by 4% (range −15 to +6%) and sGaw by 13% (−36 to +16%); after SK&F104353 FEV_1 fell by 3% (−19 to +2%) and sGaw by 16% (−46 to +2%); and with combined treatment FEV_1 fell by only 1% (−36 to +5%) and sGaw rose by 2% (−40 to +28%). Thus the protective effects of terfenadine and SK&F104353 against the early response to inhaled antigen were similar and additive. These results suggest that both histamine and the leukotrienes contribute similar, separate and significant bronchoconstrictive effects in the early response to inhaled antigen.

Effect of nedocromil and sodium cromoglycate on PAF and LTC_4 generation by human eosinophils stimulated by ionophore or unopsonised zymosan

LA BURKE, AEG CREA, TH LEE *Department of Allergy and Allied Respiratory Disorders, UMDS, Guy's Hospital, London* The generation of LTC_4 and PAF from normodense human eosinophils (EOS) stimulated with unopsonised zymosan (ZYM) or calcium ionophore (A23187) has been studied. There was a ZYM time and dose dependent increase in both PAF and LTC_4 production. A plateau of 0·07 (0·03) ng PAF/10^6 EOS (mean (SEM); n = 5) and of 1·38 (0·58) ng LTC_4/10^6 EOS (n = 5) was reached at 5 × 10^8 ZYM particles at

37°C for 30 minutes. Under optimal conditions 93 (6)% of the PAF and 66 (13)% of the LTC_4 remained cell associated. A23187 induced a time and dose dependent increase in the quantities of LTC_4 and of PAF generated by EOS. A plateau of 31 (13) ng $LTC_4/10^6$ EOS (n = 5) was reached at 1 μM A23187 at 37°C for 15 minutes. The dose-response for PAF generation reached 4·2 (0·8) ng/10^6 EOS at 10 μM A23187 at 37°C for 15 minutes and had not plateaued; 90 (5)% of the generated PAF was cell associated. In vitro preincubation of EOS with 10^{-8} M–10^{-4} M nedocromil sodium or sodium cromoglycate for 15 min did not change the subsequent generation or cellular distribution of LTC_4, nor did nedocromil alter PAF production from EOS optimally stimulated with either ZYM or A23187.

Comparative protective effect of inhaled salbutamol on bronchoconstriction provoked by histamine, methacholine and adenosine 5′-monophosphate in asthmatic subjects

GD PHILLIPS, JP FINNERTY, ST HOLGATE *Medicine 1, Southampton General Hospital, Southampton* We have investigated the ability of salbutamol to protect against bronchoconstriction induced by methacholine, histamine and adenosine 5′-monophosphate (AMP) in 15 asthmatic subjects aged 34·1 (SD 2·8) y. In a double blind, placebo controlled study, salbutamol 200 μg administered via a metered dose inhaler to 12 subjected increased the geometric provocation concentrations of methacholine, histamine and AMP required to produce a 20% decrease in FEV_1 from baseline (PC_{20}) from 0·4, 0·8, and 6·7 mg/ml respectively after placebo to 3·4, 5·9 and 53·1 mg/ml after active treatment ($p < 0·01$). Thus this dose of salbutamol produced parallel displacements to the right of the concentration-response curves for methacholine, histamine and AMP of 8·8 (1·2–20·3) 6·8 (2·8–22·9) and 8·0 (1·8–48·9)-fold respectively, there being no significant difference between these values. In nine subjects, salbutamol 2·5 mg administered by nebulisation increased the geometric mean PC_{20} from 0·3 to 2·2, 0·4 to 3·8, and 4·0 to 106·7 mg/ml after placebo and active treatment for methacholine, histamine and AMP respectively ($p < 0·01$). Thus this dose of β_2 adrenoceptor agonist displaced the concentration-response curves for methacholine, histamine and AMP to the right in a parallel fashion by 8·8 (0·6–29·3), 10·3 (1·4–33) and 26·6 (1·5–76·6) fold respectively, the difference between AMP and both histamine and methacholine being statistically significant ($p < 0·01$). In neither part of the study was there any correlation between bronchodilatation and protection against induced bronchoconstriction. We conclude that the lower dose of salbutamol protects against these three agonists by functional antagonism, but that the higher dose has an additional activity possibly in preventing mast cell mediator release.

Impaired bronchoalveolar leucocyte chemotaxis in lungs exposed to pathogenic mineral dust: an important factor in pneumoconiosis?

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Deposition of pneumoconiosis producing dust in the lung causes inflammation as assessed by bronchoalveolar lavage in experimentally exposed animals and also in exposed workers. The ability of bronchoalveolar leucocytes to respond to chemotactic stimuli is a key factor in their accumulation at the inflammatory focus and their subsequent movement within the lung during phagocyte mediated clearance of particles. We therefore assessed the chemotactic activity of bronchoalveolar leucocytes from the lungs of rats inhaling the pneumoconiosis producing dusts—quartz, coalmine dust and chrysotile asbestos; in addition, we used the non-pathogenic particulate titanium dioxide (TiO_2). Rats were exposed to these dusts at 10^2 mg/m^3 airborne mass concentration and chemotaxis assessed in Blindwell chambers with zymosan activated serum as the chemotaxin. Marked impairment of ability to chemotact was seen in the bronchoalveolar leucocytes from rats inhaling the pneumoconiosis producing dusts compared with control rats tested in parallel. The following data are given as migrated cells/high power field (× (SEM) of 10 fields) for rats exposed to dust at 10 mg/m^3 for 75 days: TiO_2—control 68·0 (4·2), dust exposed 58·0 (5·7); chrysotile asbestos—control 62·0 (5·7), dust exposed 17·0 (1·0); anthracite coalmine dust—control 74·5 (0·7), dust exposed 24·0 (0·7); quartz—control 98·5 (0·7), dust exposed 10·5 (0·7). The presence of this impairment of chemotaxis with three different pneumoconiotic dusts makes this a phenomenon of possible general relevance to the development of pneumoconiosis. (This research was funded by the Commission of the European Communities.)

Eosinophils kill spores of *Aspergillus fumigatus*

MAURA ROBERTSON, ANTHONY SEATON *Institute of Occupational Medicine, Edinburgh* *Aspergillus fumigatus* is a filamentous fungus which can cause sensitisation in some asthmatic patients, a proportion of whom may go on to develop allergic bronchopulmonary aspergillosis. A prominent clinical feature of this disease is the presence of peripheral blood and pulmonary eosinophilia. To test the hypothesis that eosinophils may play a part in the eradication of this fungus we have isolated eosinophils by density gradient centrifugation from the peripheral blood of nine asthmatic patients and measured their capacity to kill spores of *A fumigatus*. We have compared these results with those obtained using the patients polymorphonuclear leucocytes (PMN). The spores were opsonised with either autologous serum or serum heat treated to remove heat labile complement components. Eosinophils were slightly more efficient at killing spores of *A fumigatus* than PMN. The following results are expressed as mean % killed (SEM): spores opsonised in autologous serum—eosinophils 58·5 (6·73), PMN 51·52 (3·03). Opsonisation in heat treated serum increased the ability of both cell types to kill *A fumigatus*: eosinophils 66·17 (5·43), PMN 55·72 (8·8). It therefore appears that eosinophils do have a role in the host defences against *A fumigatus*. Further investigations into the mechanisms used for spore killing are warranted. (This work is supported by the Asthma Research Council.)

Production of factors by human polymorphonuclear neutrophils (PMN) capable of stimulating fibroblast replication

A SHOCK, GJ LAURENT *Biochemistry Unit, Cardiothoracic Institute, London* Circulating PMN are usually considered to be end stage cells unable to synthesise proteins. Recent evidence suggests that this may not be true. We have designed experiments to assess whether human PMN, in long term culture, produce factors capable of stimulating human fetal lung (HFL) fibroblast replication. PMN were prepared over density gradients and cultured for 16 hours in the presence or absence of serum treated zymosan, when conditioned media were isolated. Dilutions of such media were then tested in a replication assay based on the uptake of methylene blue by HFL fibroblasts. Media from both challenged and unchallenged PMN were capable of stimulating replication relative to values obtained with media not exposed to PMN (table).

	% stimulation of HFL replication	
Media	*1:8 dilution of media*	*1:16 dilution of media*
Unchallenged PMN	17·3 (7·1)% ($p < 0.05$)	17·6 (4·6)% ($p < 0.01$)
Zymosan challenged	22·4 (5·2)% ($p < 0.01$)	17·5 (2·5)% ($p < 0.001$)

A neutrophil rich alveolitis is often observed in patients with fibrotic lung diseases. The present experiments indicate that, under certain conditions, PMN constitutively release a factor(s) capable of increasing fibroblast proliferation and suggests one way in which these cells might play a part in such disorders.

The respiratory burst of sarcoid neutrophils and blood monocytes is normal

NJ HOUNSLOW, AW SEGAL, NMcI JOHNSON *Department of Medicine, University College and Middlesex School of Medicine, London* Sarcoidosis and chronic granulomatous disease (CGD) are both multisystem granulomatous diseases. CGD is caused by a defect of phagocyte respiratory burst. We have therefore examined the respiratory burst in sarcoidosis, in which the cause of the granulomatous response is unknown. Peripheral blood neutrophils and monocytes were isolated, using standard techniques, from patients with sarcoidosis and controls, who were either healthy volunteers or patients without granulomatous disease. Monocytes were subsequently cultured in RPMI with 10% fetal calf serum for 4–7 days in the presence of mixed lymphokines. The maximum rate of superoxide production was measured by cytochrome C reduction at 37°C in a dual beam spectrophotometer (550 nm wavelength), in the presence and absence of 40 μg superoxide dismutase, after activation of the respiratory burst by 1 μg phorbol myristate acetate. Superoxide production is measured as nmol superoxide/min/10^7 cells. Results are presented as natural log values (SD) to correct for a skewed distribution, which was present in all groups.

	Neutrophils	*Monocytes*
Controls	4·23 (0·43) (n = 8)	4·59 (0·47) (n = 6)
Sarcoidosis	4·41 (0·46) (n = 17)	4·35 (0·81) (n = 13)
	p = 0·6	p = 0·54

No abnormality of respiratory burst activity was demonstrated in sarcoid neutrophils or blood monocytes in this study.

Effect of bronchoalveolar lavage fluid from patients with sarcoidosis on production of tumour necrosis factor by normal human monocytes

NM FOLEY, GAW ROOK, A MEAGER, NMcI JOHNSON *University College and Middlesex School of Medicine and National Institute for Biological Standards and Control, London* We have previously shown that pulmonary alveolar macrophages of patients with sarcoidosis produce a greater amount of tumour necrosis factor (TNF) in vitro than the macrophages of control patients. There is, however, little or no clinical evidence of TNF production in vivo in sarcoidosis. We now report a preliminary study of the effect of cell free bronchoalveolar lavage fluid (BALF) on the ability of normal peripheral blood monocytes to produce TNF in vitro. 60 ml of whole blood was obtained from each of seven healthy volunteers (three female; mean age 27 years). Monocytes were harvested by adherence to plastic and plated at a concentration of 10^5 cells/well in microtitre plates, in the presence of 20% autologous serum. Filtered cell free BALF supernatant was added to cell culture wells. *E coli* lipopolysaccharide (LPS) was used at a concentration of 1 μg/ml in cell culture to induce TNF production by monocytes. Positive (LPS) and negative (no LPS) control wells were used. The monocytes were cultured in the presence of LPS plus a selection of BALFs from patients with sarcoidosis (three acute, five chronic), tuberculosis (2) and controls (2). Cells were cultured for four hours, and the cell supernatants collected and frozen at −20°C. TNF was assayed by ELISA. LPS consistently induced TNF production by monocytes. (mean TNF unstimulated: 83 units/ml, post LPS 260 U/ml, $p < 0.01$). Supernatants from cultures containing BALF of patients with acute sarcoidosis contained (mean) 50% less TNF than supernatants of cells from the same individuals cultured in the presence of LPS only or LPS + control BALF ($p < 0.01$, Student's paired t test). In the case of chronic sarcoidosis, there was a fall in TNF production in four cases and no change in one. BALF from two patients with tuberculosis caused an increase in TNF, while control BALF caused no significant change. These results imply that there is a factor present in cell free BALF of patients with sarcoidosis which inhibits production of TNF by normal monocytes. (This project is supported by the British Lung Foundation.)

Effect of cyclosporin treatment on pulmonary arterial smooth muscle

JP SCOTT, J HUTTER, JP COUETIL, CG GLANVILLE, RL SMYTH, TW HIGENBOTTAM, J WALLWORK *Heart-lung Transplant Research Unit, Papworth Hospital, Cambridge* Cyclosporin (CS) is a highly effective immunosuppressant in organ transplantation but it has vasoconstrictive properties in all patients (Scott *et al, Med Toxicol* 1988;**3**:207). To study whether this is a direct effect on smooth muscle we have used two vasodilators which act on vascular smooth muscle, prostacyclin (PGI2) (Jones *et al, Br Heart J* 1987;**57**:270), and nitric oxide (NO) (Higenbottam *et al, Am Rev Respir Dis* 1988;**137**:107). Thirty clinically well heart transplant recipients (mean age 43 y) were studied using a floated pulmonary artery catheter inserted under fluoroscopic guidance at the time of routine endomyocardial biopsy. Prostacyclin was given in progressively increasing doses up to 6 mg/kg/min and 30 ppm nitric oxide or air were given double blind by inhalation. Immediately prior to the study trough CS blood levels were taken and measured by both specific and non-specific radioimmune assays. Results are given as means (1 SD).

	PVR (Wood units)	*$\overline{PAP}$ (mm Hg)*	*CO (l/min)*
Air	1·33 (0·62)	15·5 (5·9)	7·7 (2·0)
NO	1·36 (0·55)	14·8 (5·5)	7·6 (1·8)
	PNS	PNS	PNS
Baseline	1·22 (0·54)	15·3 (4·9)	9·1 (2·2)
PGI2 max	1·15 (0·49)	16·2 (5·4)	7·9 (2·1)
	NS	NS	$p < 0·01$

PVR—pulmonary vascular resistance; CO—cardiac output; $\overline{PAP}$—mean pulmonary arterial pressure; PGI2 max—maximum PGI2 dose.

Neither PGI2 nor NO significantly reduced PVR. PVR was significantly negatively correlated with CS plasma levels ($p < 0·05$), and as expected SVR was also related to CS levels ($p < 0·005$). CS may act by inhibited smooth muscle relaxation in the pulmonary as well as the systemic circulations.

Effects of a thromboxane receptor antagonist (GR32191) on PAF induced bronchoconstriction and bronchial hyperresponsiveness

SC STENTON, AH HARRIS, JB PALMER, DJ HENDRICK, EH WALTERS *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne, and Glaxo Group Research, Greenford, Middlesex* The effects of inhaled PAF were studied in 12 male non-asthmatic subjects. PAF was inhaled in doubling doses at 5 minute intervals from 0·1 μg to a maximum cumulative dose of 420 μg. Airway calibre was measured as flow rate at 30% of vital capacity ($\dot{V}_{30}$) three and four minutes after each dose. Eleven subjects demonstrated acute bronchoconstriction which increased with increasing PAF dose. Non-specific bronchial responsiveness (NSBR—$PD_{40}.\dot{V}_{30}$ to methacholine) was measured 24 hours before and 24 and 72 h after PAF. Eight subjects had increased NSBR 24 h after PAF and eight at 72 h, six subjects showing increases at both these times. Six subjects who demonstrated acute bronchoconstriction and increased NSBR in response to PAF underwent two further similar challenges, with the PAF inhalation premedicated by either GR32191 80 mg or identical placebo capsules. An interval of at least four weeks was allowed between PAF inhalations. The acute bronchoconstrictor response to PAF, quantified as the area between the $\dot{V}_{30}$ dose-response curve, was not attenuated by premedication with GR32191. Mean (SD) responses were 699 (348) litres with GR32191 and 483 (399) l with placebo ($p = 0·3$). Geometric mean $PD_{40}.\dot{V}_{30}$/s values for methacholine (μg) are shown in the table.

	n	*Before PAF*	*24 h*	*72 h*
Open study	All 12	452	259	258
Open study	6 restudied	1013	462	467
Placebo	6	1377	1660	910
GR32191	6	1002	984	1306

The changes in NSBR following PAF were small and variable and, while no effect of GR32191 was demonstrated, with the number of subjects studied and the variability of the technique it is impossible to exclude a type 2 error. Acute bronchoconstriction induced by PAF is unlikely to be mediated by thromboxane in normal human subjects.

The severity of emphysema, assessed in life by quantitative computed tomography, does not relate to the "blue bloated" or "pink puffing" patterns of chronic bronchitis and emphysema (COPD)

W BIERNACKI, M RYAN, G GOULD, DC FLENLEY *Department of Respiratory Medicine, Rayne Laboratory, City Hospital, Edinburgh* Burrows *et al* (*Lancet* 1966;i:830) contrasted two types of patient with chronic airflow limitation—type A (radiological evidence of emphysema, little sputum, increased TLC, low TLCO) and type B (no radiological emphysema, large sputum volumes, recurrent cor pulmonale, normal TLCO and well preserved DLCO). Type A were later called "pink puffers" and type B "blue bloaters." Quantitative analysis of lung density histogram measured by CT scan numbers can assess the severity of pathological emphysema in life (Gould *et al, Am Rev Respir Dis* 1988;**137**:380). We have used this method to re-examine the relation between the severity of emphysema and the clinical and pulmonary haemodynamic assessment in patients with COPD. We have studied 32 patients (23 M, 9 F) aged 64 (SD 6) y with FEV_1 16–68% pred, Pa_{O_2} (breathing air) 5·1–12·0 kPa, Pa_{CO_2} 4·4–8·4 kPa, Ppa 10–51 mm Hg, cardiac index 1·89–3·6 l/min at rest. We found no correlation between either the sputum volume, cor pulmonale (historical ankle oedema) or TLC% pred and the severity of emphysema CT scan. Furthermore, there was no correlation with CT scan, pulmonary haemodynamic measurements and (Ppa $r = 0·2$), cardiac index ($r = 0·27$), total pulmonary vascular resistance (TPVR: $r = 0·3$) or severity of hypoxaemia (Pa_{O_2} $r = 0·27$). Thus, for example, among patients with severe emphysema by CT scan we could find both "pink puffers" and "blue bloaters," while among the patients with

little CT emphysema we could also distinguish these two clinicophysiological types. These results contradict the widespread impression that the clinicophysiological pattern known as "pink and puffing" relates to severe anatomical emphysema, whereas "blue bloaters" have little anatomical emphysema.

Relation between computed tomography (CT) lung density, lung function, and emphysema

W MACNEE, R HARRISON, S TANCO, P PARÉ, JC HOGG *Pulmonary Research Laboratory, University of British Columbia, St Paul's Hospital, and Medical Physics Department, Cancer Control Agency of British Columbia, Vancouver, Canada* We have previously described a visual scoring system to diagnose emphysema using CT scanning, based on areas of low attenuation and vascular disruption (Bergin, *Am Rev Respir Dis* 1986;**33**:541). Recently, quantitative analysis of CT lung density, measured on a limited (two slices) CT scan of the thorax correlated with pathological measurements of distal airway size in resected lungs, a defining characteristic of emphysema (Gould *et al*, *Am Rev Respir Dis* 1988;**137**:380). We now report the relation between CT lung density, emphysema and lung function in 26 patients (21 M, 5 F, mean age 63·3 (SD 9·7) years), FEV_1 49–119% pred, FEV_1/FVC 43–84% pred, TLCO 51–143% pred) who proceeded to lobar resection for peripheral lung tumours. Analysis of the frequency histograms of CT lung density were obtained preoperatively (Gould *et al*, 1988) and measured as the CT density of the mean or lowest 5th percentile (L 5%) of the cumulative frequency histogram of CT lung density, in a contrast enhanced, full, CT scan of the thorax. Emphysema scored in resected lungs (Paré *et al*, *Am Rev Respir Dis* 1982;**126**:54) was $\geqslant 10$ in only six patients. Regional variations in CT lung density occurred in patients both with and without macroscopic emphysema. CT density was lower in those patients with emphysema (L 5% = 110 (27) than in those without (L 5% = 145 (24), $p < 0{\cdot}01$), CT lung density correlated with FEV_1/FVC % ($r = 0{\cdot}63$, $p < 0{\cdot}001$), TLC and RV % pred ($r = -0{\cdot}42$ and $-0{\cdot}46$ respectively, $p < 0{\cdot}05$), but not with the TLCO or lung elastic recoil. We confirm the results of previous studies, using a different CT scanner (Gould *et al*, 1988), indicating a reduction in CT lung density in patients with mild to moderate emphysema. However, in contrast to Gould *et al* (personal communication), we found that CT density did not correlate with TLCO. Differences in the measurements of TLCO and the use of contrast enhanced CT scanning, undertaken at a different lung volume, may account for the different results found in our study.

Serial measurements of atrial natriuretic peptide (ANP) in acute exacerbations of chronic obstructive pulmonary disease (COPD)

R SANKARAN, K SKWARSKI, S LANNAN, DC FLENLEY, M LEE, W MACNEE *Departments of Respiratory Medicine, Rayne Laboratory, City Hospital, and Clinical Pharmacology, Royal Infirmary, Edinburgh* Plasma concentrations of ANP are elevated in various conditions such as congestive cardiac failure (Raine *et al*, *N Engl J Med* 1986;**315**:533) and in patients with stable COPD (Burghuber *et al*, *Chest* 1988;**92**:31). We measured serial changes in ANP in peripheral blood from patients with COPD presenting with and without peripheral oedema during an acute exacerbation. Patients with ischaemic heart disease, hypertension or renal failure were excluded. We studied 12 patients (8 M, 4 F, aged 70·2 (SD 8·4) y, FEV_1 0·6 (0·2) l, FVC 1·6 (0·5) l Pao_2 6·6 (1·5) kPa, $Paco_2$ 6·9 (1·5) kPa, (H+) 39 (5) nmol/l), nine with and three without oedema. Clinical assessment, arterial blood gas values and plasma ANP concentrations were measured on admission and 6–12 weeks later breathing air, and when breathing oxygen (2 l/min nasal prongs) for one hour on the day of admission and again 24 and 48 hours later. Plasma ANP measured when breathing air was 180 (range 25–525 pg/ml) (normal < 55 pg/ml) and did not change significantly after one hour breathing oxygen (207 (129) pg/ml; $p > 0{\cdot}05$) despite improved Pao_2. The mean ANP concentration did not change significantly on the second and third days (140·9 (83·6) and 192·6 (119·6) pg/ml respectively; $p > 0{\cdot}05$). However, patients with oedema (n = 9) tended to have higher ANP levels (mean 214·7, range 25–525 pg/ml) then those without oedema (n = 3) (mean 77·2, range 64–95 pg/ml). The mean change in body weight over the first three days was 2·5 kg (range 0–6·7 kg), which correlated with the change in ANP ($r = 0{\cdot}68$, $p < 0{\cdot}05$). Plasma ANP was lower at follow up in patients who were clinically stable. We conclude that ANP is elevated during an exacerbation of COPD and is higher in patients with oedema. The ANP level is not influenced by oxygen therapy given over the short term, but correlates with the change in weight during an exacerbation of COPD.

Oxygen concentrators: the patient's view

JP DILWORTH, RJ WHITE, CMB HIGGS, PA JONES *Department of Medicine, Frenchay Hospital, Bristol, and Chest Unit, Royal United Hospital, Bath* Long term oxygen therapy (LTOT) has been established to improve survival in defined patients with hypoxaemia. We investigated patient satisfaction with this form of treatment. Of 91 concentrators installed to 30/4/88 in two health districts, 32 patients remained alive by 15/7/88. A questionnaire was sent to these patients asking about the effect of the concentrator on quality of life, their perception of the aims of treatment, compliance and the details of installation. Thirty questionnaires were completed. Patients seem adequately educated in the aims of treatment, with only five patients (17%) considering that the main objective was immediate or short term benefit. Eighty per cent noted an improvement in their general well being and 76% in their breathing. Sixty per cent found that their mobility was improved. Overall there was a very beneficial response with only two patients (7%) recording a deterioration in any of these parameters. Seventy three per cent said they were using the oxygen for greater than or equal to 15 hours a day and all used the oxygen at night. Seventy per cent had back up or portable cylinders. Nine patients (30%) admitted to continuing smoking, although usually at a reduced rate. The service provided by the nurses and

engineers was considered entirely satisfactory and several patients commented on its excellence. There were seven episodes of machine breakdown in six patients. The principal single complaint was of noise from the concentrator and we note that 53% were sited in the main bedroom or lounge. We conclude that LTOT by concentrator produces significant symptomatic improvement and is well tolerated, refuting objections that it is restricting and unpleasant.

Reversible chronic obstructive pulmonary disease (COPD)—one year on

M NISAR, JE EARIS, MG PEARSON, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* We diagnosed 71 patients as having reversible airflow limitation, defined as an improvement in FEV_1 (by 15% and 200 ml), after either 5 mg nebulised salbutamol or 30 mg oral prednisolone for two weeks (*Am Rev Respir Dis* 1988;**137**:155). Fifty nine patients (40 male, mean age 62 (SD 8) years, FEV_1 1·09 (SD 0·49 l) were restudied one year later with repeated questionnaire and spirometry before and after nebulised salbutamol. Of 34 individuals whose FEV_1 had improved after nebulised salbutamol, but not after steroids, 17 now appeared "irreversible." These 17 included more current smokers ($p < 0·05$) but were otherwise indistinguishable from those still reversible. A year on, these unresponsive patients had a higher mean baseline FEV_1 than did responders (1·01 (0·43) *v* 0·91 (0·29)) but no rise in FEV_1 and a reduced rise in FVC (0·85 (0·37) *v* 0·56 (0·25), $p < 0·05$). Neither subgroup was symptomatically better a year later. Twenty five patients had responded to both salbutamol and steroids. Sixteen still had an FEV_1 response after nebuliser in spite of a 45% increase in baseline FEV_1 (0·87 (0·26) to 1·26 (0·58) l). The FEV_1 and FVC attained after the steroid trial were a good indication of the maximal bronchodilation seen one year later after nebuliser (FEV_1 1·74 (0·71) *v* 1·71 (0·63) l, FVC 3·17 (0·81) *v* 2·92 (0·86) l). Four individuals were apparently irreversible but had a much greater increase in baseline FEV_1, from 0·96 (0·38) to 1·81 (0·46) l, which again is similar to the 1·68 (0·37) l after steroids a year before. Thus their apparent irreversibility may indicate that they were fully bronchodilated. The remaining five patients were unresponsive to the nebuliser now. Their mean increases in FEV_1 and FVC after steroids had been much less than for the other 20 steroid responders (ΔFEV_1 0·35 (0·14) *v* 0·84 (0·49), and Δ FVC 0·56 (0·11) *v* 0·99 (0·41) l; $p < 0·01$). Their baseline FEV_1 was unchanged (0·74 (0·18) to 0·81 (0·22 l)) and they were no better symptomatically. Thus 80% of patients with COPD who had a positive response to a steroid trial had significantly better lung function a year later. In contrast, no individual who responded only to salbutamol improved their FEV_1 by more than 200 ml.

Nebulised fenoterol and ipratropium in severe chronic obstructive airways disease (COAD)

JFJ MORRISON, MF MUERS *Pulmonary Function Laboratory, Killingbeck Hospital, Leeds* Both management of severe COAD and objective assessment of a therapeutic response are difficult. Responses to inhaled bronchodilators in standard doses or to oral steroids are often absent. Nebulised beta agonists or ipratropium, or the combination of the two, may be more effective. We assessed the effect of nebulised Fenoterol 1·25 mg + ipratropium 0·5 mg (F + I) in domiciliary use and assessed whether laboratory tests of airways reversibility could predict long term benefit. Twenty patients, mean age 66, mean FEV_1 0·8 l, were studied in a double blind placebo controlled crossover study. All had less than 20% bronchodilatation after inhaled beta agonists or oral steroids (prednisolone 20 mg for two weeks). Assessments were done weekly for three weeks on normal therapy, after three weeks on F + I or placebo (P) four times daily, after crossover for three weeks, and then after normal therapy for three weeks. At each visit spirometry, lung volumes, specific airways conductance, five minute walking tests and an oxygen cost visual analogue scale (VAS) were performed. Tests were repeated one hour after nebulised salbutamol 5 mg and ipratropium 0·5 mg. At home patients recorded PEF and the number of puffs of rescue inhaler used. Mean home PEF rose from 164 (P) to 196 (F + I) ($p = 0·0001$), mean daily puffs of inhaler used fell from 7·1 (P) to 3·6 (F + I) ($p = 0·0001$) and the VAS measure of exercise capacity at home rose ($p = 0·01$). No significant changes were seen in laboratory tests or walking tests. Laboratory tests of airways reversibility failed to predict subsequent longterm improvement at home. Nebulised F + I appeared to produce an improvement in severe steroid resistant COAD and this was best demonstrated with home PEF monitoring.

Diagnostic mediastinoscopy in superior vena caval obstruction

W PUGSLEY, P KAY, P GOLDSTRAW *Brompton Hospital and Middlesex and University College Hospitals, London* In rapidly progressive superior vena caval obstruction (SVCO) treatment with radiotherapy is often initiated before a tissue diagnosis is established. While such an approach is defended on the basis of an urgent need for treatment versus the risks of obtaining tissue, histological diagnosis prior to therapy is to be preferred. We report on 30 patients (median age 54 years, range 20–83) with SVCO who underwent diagnostic mediastinoscopy, 25 prior to commencement of therapy and 5 after initial radiotherapy. Tissue diagnosis was obtained in all 25 patients investigated before therapy and in 3/5 patients given prior radiotherapy. Histological examination of biopsies obtained from the other two treated patients failed to reveal the pathology. There was no mortality and there were no major complications associated with this procedure. A moderate haemorrhage (< 500 ml) occurred in one patient who had received radiotherapy; this was controlled locally. As a result of diagnostic mediastinoscopy 28/30 (93%) patients were given appropriate therapy (9 (31%) radiotherapy and 19 (62%) chemotherapy) based on the tissue diagnosis. We conclude that mediastinoscopy before therapy is a safe diagnostic procedure in the presence of SVCO and enables appropriate therapy based on tissue diagnosis to be started in all cases. We would recommend its routine use in this condition.

Mediastinal lymph node sizing by computed tomography (CT)

CG WATHEN, KM KERR, W REID, AJA WIGHTMAN, W WALKER, EW CAMERON, NJ DOUGLAS *City Hospital and Royal Infirmary, Edinburgh* CT scanning is widely used in mediastinal staging of lung cancer to assess lymph node size and mediastinal spread of the disease. Different size criteria have been used to imply malignancy of the nodes, often chosen on the basis of small series (Glazer *et al*, *AJR* 1984;**142**:1101). We have prospectively entered 60 patients with lung cancer who had been accepted for surgery into a study to assess the value of CT scanning. All patients had a fast breath hold CT scan with contrast enhancement (GEC 8800) within 10 days of thoracotomy, where all accessible mediastinal lymph nodes were sampled and the site from which they were removed documented. The lymph nodes were measured and examined histologically. Twenty four patients (40%) had mediastinal disease, including three with direct spread of the tumour into the mediastinum. Using histological criteria the sensitivity and specificity of the CT scans have been calculated for different sizes of node. By CT scanning 18 patients had enlarged mediastinal lymph nodes (> 15 mm). Fifteen of those (83%) were involved by tumour, two showing reactive hyperplasia and one sarcoidosis. Of the remaining nine patients with mediastinal disease, three had nodes > 15 mm which were not detected by the CT scan and six had nodes < 15 mm involved by tumour. We conclude that fast breath hold CT scanning with contrast enhancement defining enlarged nodes as >. 15 mm provides the best compromise between sensitivity and specificity in detecting mediastinal node involvement with tumour.

	> 20 mm	*15–19 mm*	*10–15 mm*	*< 10 mm*
Sensitivity (%)	46	58	80	100
Specificity (%)	92	89	55	8

Relevance of intraoperative nodal staging for lung cancer

SJM LEDINGHAM, P GOLDSTRAW *Department of Thoracic Surgery, Brompton Hospital, London* In patients undergoing thoracotomy for lung cancer it is increasingly recognised that careful sampling of apparently normal mediastinal nodes will disclose occult N2 disease. We have reviewed our experience in 303 consecutive thoracotomies in which routine lymph node dissection was undertaken. Preoperatively all patients were thought not to have N2 disease, having been assessed by CT scan or mediastinoscopy and mediastinotomy. A total of 816 node stations were examined. Metastases were identified macroscopically at 53 node stations and microscopically at 10 node stations. Unsuspected N2 disease was found in 15% of cases (45 patients), 18% of normal CT scans, and 12% of normal mediastinoscopies. Comprehensive mediastinal lymph node dissection is important if we are to obtain accurate staging of the patient's disease, truly assess our preoperative evaluation, identify groups with varying prognoses and use adjuvant therapy intelligently.

Randomised trial of planned versus "as required" chemotherapy in small cell lung cancer (SCLC)

SG SPIRO, RL SOUHAMI, CM ASH, DM GEDDES, JS TOBIAS, PG HARPER, H EARL, LE JAMES *University College Hospital, Brompton Hospital, London Chest Hospital, and Guy's Hospital, London* We assessed the value of using chemotherapy according to the rate of progression of disease in the individual patient. Patients were entered into a randomised trial of chemotherapy (cyclophosphamide, vincristine and etoposide) given every three weeks for a total of eight courses; or the same chemotherapy given only when there was disease progression or for symptom control. Patients with responding or stable disease who were asymptomatic were not treated but seen every three weeks for reassessment. Two hundred and seventy eight patients had been randomised up to June 1988. In the "as required" arm the median treatment free intervals did not diminish for those who continued to receive chemotherapy. The median treatment free interval between courses 1 and 2 was 42 days, courses 2 and 3 42 days, courses 3 and 4 43 days, and courses 4 and 5 43 days. To date there is no difference in overall survival between the two treatment strategies, despite the "as required" patient group receiving fewer courses of chemotherapy. Quality of life assessment for the two treatment regimens, however, showed that patients on the "as required" treatment scored less favourably than patients in the regular treatment arm for six of eight variables measured.

Malignant pleural mesothelioma (MPM) in Western Glasgow 1980–6

G HULKS, J ST J THOMAS, E WACLAWSKI *Departments of Respiratory Medicine and Pathology, Western Infirmary, Glasgow, and Occupational Health Service, Greater Glasgow Health Board* The Western district of Glasgow has an unusually high incidence of MPM because of its proximity to the shipyards of Clydebank. This study reviews all histologically proved cases which have occurred in our area during the period 1980–6. Potential cases were identified by reviewing the reports of all pleural biopsies and postmortem examinations performed during the study period. Histology was then reviewed by a senior pathologist without prior knowledge of the reported findings. Sixty eight cases were identified (three female) and the age at presentation ranged from 48 to 85 years (mean 68·9). Asbestos exposure was identified in 80% of cases, the overwhelming majority of whom were onetime shipyard workers. Pain and dyspnoea were the most common presentations. Pleural effusion was found in 84% of cases in a ratio of 2·6 right:left. The median survival of our patients was only 30 weeks from the time of presentation, although the prognosis of those presenting with dyspnoea was significantly better than those presenting with pain (median survival 44 and 22 weeks respectively). Postmortem studies were performed in 40/68 cases and metastatic disease found in 80%. Unlike some previous studies, we were unable to identify any significant difference between the incidence of the various histological cell types (sarcomatous, epithelial and mixed); nor was there any correlation between cell type and either survival or the incidence of metastatic

disease. We suggest that MPM should no longer be regarded as having low metastatic potential, and that conventional histological classification would appear to offer little help with respect to disease activity or survival.

Denver shunt in the treatment of recurrent malignant pleural effusion

V TSANG, P GOLDSTRAW *Brompton Hospital, London* The life expectance of patients with malignant pleural effusion is short. Repeated thoracocentesis and attempts at pleurodesis are debilitating and may result in empyema. Pleurodesis cannot succeed if the lung is restricted by cortex preventing apposition of visceral and parietal surfaces. In this difficult situation palliative choices are limited. We report our experience in using Denver pleuroperitoneal shunts in eight patients with this condition, without infection, over a period from October 1986 to August 1988. All shunts were inserted under general anaesthesia, with prophylactic antibiotic cover, using submammary and transverse rectus incisions, with the pumping chamber lodged in a subcutaneous pouch overlying the 6th/7th intercostal cartilages. The average hospital stay was 4·5 days. One shunt occlusion due to blood clot was the only early complication, and the patient had a new shunt inserted which remained functioning until he died of his underlying malignancy one month later. The mean follow up time for the remaining seven shunts was 4·3 months (2–8 months). Late deaths occurred in three patients due to carcinomatosis (2–7 months). Good palliation with minimal morbidity was achieved in these cases, with no operative mortality. Denver shunt should be the treatment of choice for patients with recurrent malignant pleural effusions complicated by thickened restrictive pleura.

Ability of patients with severe airflow limitation to trigger a new breath actuated inhaler

WAH WALLACE, J LENNY, E COOKSEY, AP GREENING, GK CROMPTON *Northern General Hospital, Edinburgh* The conventional metered dose inhaler was introduced in 1956 and is now the most frequently prescribed inhalation device in the UK. Many patients, however, cannot use this device efficiently, the major problem being coordination of dose release with inspiration (Crompton, *Eur J Respir Dis* 1982;**63**:(suppl 119):101). A new breath actuated inhaler (BAI) has been developed to overcome this problem. This device is actuated under laboratory conditions by a flow rate of about 30 l/min. The ability of patients with severe airflow obstruction (FEV_1 less than 1·0 l and/or PEF less than 200 l/min) was assessed and their MIFR was recorded from a flow-volume trace (Vitalograph Compact). Thirty patients (aged 45–81, mean 64·7) were studied. Twenty nine were able to actuate the device (FEV_1 range 0·35–1·08 l, mean 0·69; PEF range 77–251 l/min, mean 154·7 l/min). We conclude that the new BAI, which unlike previous breath actuated devices is virtually silent when triggered, can be used by patients with severe airflow limitation.

Bronchodilator efficacy of salbutamol delivered by breath actuated inhaler compared with conventional aerosol and the "Volumatic" device

NJ ALI, H ARSHAD, S RASTOGI, IA CAMPBELL *Llandough Hospital, Penarth, S Glamorgan* We compared the bronchodilator efficacy of salbutamol sulphate (100 μg/puff) delivered by breath actuated inhaler (BAI) (Riker Laboratories), metered dose inhaler (MDI), and MDI with the "Volumatic" (VI) in an open study of asthmatics (≥15% reversibility) with poor inhaler technique. Twelve patients (6F), mean age 59, range 43–69, took part. Each inhaler was used for two weeks; peak flow (PEF) was recorded before and 20 minutes after two puffs of salbutamol in a diary booklet. Daily symptoms score (1–5: 1 = bad, 5 = good) and any additional bronchodilator use were also recorded. Other medication was unchanged. Recordings from the second week of each period only (mean (SD)) were used in analysis (see table). Preinhaler PEF was significantly lower during VI (paired t $p < 0·05$) than BAI or MDI. There was a trend towards greater bronchodilation after BAI than VI or MDI (paired t NS). Symptoms score was higher during BAI than MDI but not significantly so (Wilcoxon NS), and patients used less additional bronchodilator during BAI than either MDI or VI (Wilcoxon $p < 0·01$). The trend towards greater bronchodilatation after BAI than after MDI or VI suggests that this device may prove a convenient alternative to the cumbersome spacer devices in treating patients with poor inhaler technique.

	Pre-inhaler PEF	*Post-inhaler PEFR*	*Symptom score (max 35/wk)*	*Additional inhaler (puffs/wk)*
BIA	234 (98·1)	52·2 (33·8)	25·9 (6·2)	12·7
VI	229 (97·9)	49·3 (36)	25·2 (7·1)	21·3
MDI	233·9 (105·9)	47·5 (41·8)	23·8 (7·3)	22·4

Is irreversible chronic obstructive pulmonary disease (COPD) irreversible?

M NISAR, JE EARIS, PMA CALVERLEY, MG PEARSON *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* We diagnosed 56 patients as having irreversible airflow limitation, defined as no increase in FEV_1 (by 15% and 200 ml) after either 5 mg nebulised salbutamol or 30 mg oral prednisolone for two weeks (*Am Rev Respir Dis* 1988;**137**:155). Forty five patients (23 male, mean age 62 (SD8) FEV_1 1·01 (0·48 l) were restudied one year later with repeated questionnaire and spirometry before and after nebulised salbutamol. Thirty two patients still had no FEV_1 response to the nebuliser (group 1) but 13 subjects now showed an improvement after salbutamol (group 2) (mean FEV_1 0·84 (0·32) to 1·15 (0·65). Apart from being older (66 (8) *v* 61 (7) years, $p < 0·02$), group 2 patients had similar presenting symptoms, signs and lung function to group 1 (FEV_1 0·98 (0·39) *v* 1·03 (0·51) l). However, group 2 subjects had a lower mean baseline FEV_1 at follow up (0·84 (0·32) *v* 1·12 (0·42) l, $p < 0·02$), which rose after salbutamol to similar values to those of group 1 (1·17 *v*

1·15 l). Group 2 patients also showed a significant rise in FVC after salbutamol (1·78 (0·56) to 2·41 (0·55) l, $p < 0·01$). A similar change in mean FVC after nebuliser had been present at their initial assessment (2·06 (0·69) to 2·47 (0·64) l, $p < 0·02$), whereas group 1 patients did not show any significant change in FVC. The mean FEV_1 in group 1 patients rose over the year (1·01 to 1·12 l) but this was entirely due to a substantially improved baseline FEV_1 in seven subjects (mean increase FEV_1 0·50 l, range 0·24–0·91 l). These seven were younger (55 (6) *v* 61 (7) y, $p < 0·01$) and had better initial lung function (mean FEV_1 1·31 *v* 1·01 l, $p < 0·01$), but were otherwise clinically indistinguishable from the rest of the cohort. The seven did not have a FVC response to salbutamol on either occasion. Only 25 (55%) of our cohort of irreversible COPD patients can still be so classified a year later. In a further 13 (29%) the present reversibility may be due to the downward shift of baseline FEV_1. Seven patients (15%) had significantly better lung function in spite of no evidence of reversibility with acute testing on either occasion. This improvement could not be predicted prospectively.

Anticholinergics in reversibility testing of chronic obstructive pulmonary disease (COPD)

M NISAR, JE EARIS, PMA CALVERLEY, MG PEARSON *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Over half of all patients with COPD improve their FEV_1 after a single dose of salbutamol compared with about 25% with oral steroids (*Thorax* 1988;**43**:231P). The relative merits of ipratropium bromide (IB) were studied in 100 patients with stable COPD (65M, mean age 62 y, FEV_1 0·96 (0·48) l). On day 1 spirometry was recorded before and after nebulised salbutamol (NS). On day 2 this was repeated with nebulised IB. Then all patients received 30 mg prednisolone (PN) for two weeks before being restudied. Reversibility was defined as a 15% and $\geq$200 ml increase in FEV_1. Thirty three patients (group 1) did not respond to either nebuliser. However, as a group they had significant increases in FVC (0·26 (0·37) l to NS, 0·28 (0·31) to IB, 0·16 (0·33) to PN). Over 40% of this group showed a $\geq$300 ml increase in FVC after nebuliser. Two of these patients with severe COPD (FEV_1 0·58 and 0·65L) did improve on PN. Thirty three patients (group 2) patients improved after one nebuliser but not the other. Seventeen responded to IB—partly because of a lower baseline FEV_1 on day 2 (1·01 (0·35) *v* 1·13 (0·44), $p < 0·05$). Only one of these responded to PN. The other 16 responded to NS but not IB and included five PN responders who had better baseline function ($p < 0·01$) and were more responsive to PN than NS (ΔFEV_1 0·81 (0·47) *v* 0·53 (0·26), $p < 0·05$). IB did, however, produce a $\geq$300 ml rise in FVC in 13 of these 16. The remaining 34 patients (group 3) responded to both IB and NS and included 11 who also improved on PN. The size of response to NS and IB was similar (ΔFEV_1 0·42 (0·26) *v* 0·37 (0·20) l). This group had the largest FVC improvement with over 85% having a $\geq$300 ml improvement after each nebuliser. The 11 steroid responders had the largest changes in FEV_1 (0·68 (0·31) to NS, 0·53 (0·30) l to IB and 0·65 (0·39) l to PN), $p > 0·005$. IB and NS produce similar responses in a similar proportion of patients (50 *v* 51). In a third of the cohort the responses to NS and NI are contradictory. An FVC response $\geq$300 ml occurred in 68 patients to NS and 71 to IB. The significance of the FVC changes in the "non-responders" needs to be determined.

Does severity of emphysema as assessed by computed tomography (CT) predict survival in patients with chronic bronchitis and emphysema (COPD)?

W BIERNACKI, M RYAN, W MACNEE, DC FLENLEY *Department of Respiratory Medicine, Rayne Laboratory, City Hospital, Edinburgh* Previous studies (Renzetti *et al, Am J Med* 1966;**41**:115) show that Pao_2, $Paco_2$ and FEV_1 and "cor pulmonale" influence survival in COPD. The quantitative, transthoracic CT scan can measure regional lung density, and we have shown this to correlate with the size of distal airspaces (Gould *et al, Am Rev Respir Dis* 1988;**137**:380), which by definition is increased in emphysema. We have followed 36 patients with COPD (24M, 12F) aged 63 (SD 7) years until death or until 1.8.88 (that is, 18–36 months). They had a wide range of airflow limitation (FEV_1 8–68% pred), hypoxaemia (Pao_2 5·1–12 kPa, hypercapnia ($Paco_2$ 4·4 kPa—8·7 kPa). Ten died during this follow up, but the mean survival from entry to the study was 14·6 (SD), months. Those dying had more severe airways obstruction (FEV_1 20 (7)% pred) compared with 30 (14)% pred in those alive ($p < 0·05$) and they were also more hypoxic when breathing air (Pao_2 7·64 (1·96) kPa compared with 8·53 (1·99) kPa). However, both survivors and those dying within this follow up had similar degrees of emphysema as assessed by CT scan (EMI no defining the lowest 5th percentile 468 (11) in those who died, compared with 463 (14) in those who survived). However, relating the degree of emphysema to the length of survival after entry to the study in those who died did show a significant correlation ($n = 10, r = 0·64, p < 0·05$), whereas in this small group there was no correlation between the length of survival and FEV_1 %pred (Pao_2, or $Paco_2$). These studies suggest that the degree of emphysema, as assessed by CT scan, may be an important determinant of survival in these patients, possibly in association with the already established effects of hypoxaemia, CO_2 retention, and the presence or absence of cor pulmonale; but longer follow up of larger numbers of patients will be needed to establish this role for quantitative CT scan.

Bronchial responsiveness in non-asthmatic chronic airflow obstruction: prognostic implications and changes with time

DC WEIR, P SHERWOOD BURGE *East Birmingham Hospital, Birmingham* We have studied the changes in lung function and bronchial responsiveness to inhaled histamine in 107 of 121 patients who completed a therapeutic trial of oral and inhaled corticosteroids, 12–44 (mean 26·3) months earlier. Seven patients were unavailable for follow up, and seven had died since the original trial. Bronchial responsiveness to

inhaled histamine was measured by the method of Cockroft *et al* (*Clin Allergy* 1977;7:235), if the FEV_1 was > 0·6 litre at recruitment or follow up. The height adjusted decline in FEV_1 was calculated from the follow up level, and that achieved during the inhaled treatment phase (beclomethasone dipropionate 500 μg tds) of the original trial. All PC_{20} values were log transformed before analysis. Eighty four patients had bronchial responsiveness measured at recruitment, but in only 66 of these was it repeated at follow up. On both occasions there was a significant correlation between FEV_2 of PC_{20} values (recruitment: $r = 0·54$, $p < 0·001$; follow up $r = 0·56$, $p < 0·001$). In the 66 patients with two PC_{20} values, bronchial responsiveness improved significantly from recruitment to follow up (geometric mean (range) at recruitment 1·01 (0·03–16), follow up 1·43 (0·03–16); $p < 0·03$). This was despite a significant fall in FEV_1 values from (mean (SD 1·33 (0·45) to 1·15 (0·45) l; $p < 0·02$). The height corrected decline in FEV_1 was not significantly correlated with either the recruitment or the follow up PC_{20} values (recruitment: $r = 0·13$; follow-up: $r = 0·07$). The height corrected change in FEV_1 was not related to the change in the log PC_{20} in individual patients ($r = 0·06$). These results would suggest that factors other than bronchial hyperresponsiveness are responsible for deterioration in lung function in this group of patients.

Salbutamol output from two jet nebulisers

M ALLEN, S LANGFORD *Departments of Respiratory Medicine and Pharmacy, City General Hospital, Stoke on Trent* The physical properties of aerosols produced from jet nebulisers are well known, but little information exists on the crucial aspects of drug delivery. It is assumed that drug output follows fluid output; however, Wood and colleagues, using a 2 ml fill, found no further significant drug delivery beyond four minutes despite continued fluid output (*Br J Dis Chest* 1986;**80**:164). We have investigated the relation between drug and fluid output for two commercially available nebuliser units: Micro-Neb (Life Care) and System 22 (Medicaid). Two millilitres of a stock solution (50% water and 50% Ventolin respirator solution, 5 mg/ml) were nebulised for varying time periods up to a maximum of 12 minutes, using an air flow of 9 l/min from an electric compressor. Fluid output was assessed by weight change and salbutamol concentrations by spectrophotometric methods. One hundred and seventy five samples were analysed for salbutamol concentration from 42 "runs" with the Micro-Neb and 171 samples from 43 "runs" with System 22. Both units showed increasing fluid and salbutamol output as nebulisation proceeded. After 12 minutes the Micro-Neb had stopped "fizzing" with a fluid output of 1·43 ml and salbutamol delivery of 3·3 mg. The System 22 continued to "fizz" beyond 12 minutes, the outputs being 0·98 mls and 1·98 mg respectively. Thus we found considerable differences between the two nebuliser units in the rates of drug and fluid delivery, although drug outputs per ml were similar. In contrast to the previous study, drug output continued beyond four minutes when the more convenient 2 ml fill was used.

How accurate are asthma diary cards?

J LISTER, S BUDIN-JONES, J PALMER, GM COCHRANE *Glaxo Group Research Ltd, Greenford, Middx, and Department of Thoracic Medicine, Guy's Hospital, London* Daily record cards (DRCs) are widely used in asthma clinical studies to record peak expiratory flow (PEF) symptom scores and use of bronchodilator. It is known that compliance with asthma therapy may be poor and compliance in completing DRCs is suspected in some patients to be similarly inaccurate. Electronic data collection devices are now available which can give visual instruction to the patient and can also time/day/date validate the data entered. We have compared such a device (Psion Organiser, PO) with conventional DRCs. Twelve asthmatic patients (age range 16–66 years) entered the study which was of randomised crossover design. Patients were asked to record twice daily PEF, symptom scores and additional bronchodilator using either PO or DRC for two consecutive periods of 14 days. At the end of each study period patient preferences were recorded and compliance checked by measurement of urinary salbutamol levels. Of the 12 patients entering the study, three patients failed to complete the protocol; of these dropouts, one was definitely due to confusion over operation of the PO. Nine patients completed the study; four preferred the PO device and four the DRC, one having no preference. The DRC was considered to be slightly easier to use than the PO. Urinary salbutamol levels in three patients suggested that the time they stated they had last taken bronchodilator was inaccurate. This preliminary study shows that the electronic diary card is preferred as often as the conventional daily record card and has the advantages of being more accurate and having day-date validation, which can prevent falsification of data by the patient.

Characteristics of asthmatics who die and the potentially preventable factors in their deaths

SC WRIGHT, AE EVANS, DG SINNAMON, J MacMAHON *Belfast City Hospital, Coleraine Hospital, and Department of Community Medicine, Queen's University, Belfast* We identified 174 asthma deaths occurring in Northern Ireland during 1981–4 and included all age groups. Death certificates, GP notes, hospital notes, autopsy records, GP questionnaires and physician administered questionnaires to the closest relative of the deceased were assessed before a final decision of death due to asthma was made. One hundred and thirty three deaths occurred outside hospital and the deaths were evenly distributed throughout the province. The mean age at death was 52 years—50·6% female; 47·1% were economically active, of whom 90·4% were employed. There was no statistical difference in distribution of deaths by social class ($p > 0·05$). Asthma had been diagnosed for over 10 years in two thirds, although it was previously undiagnosed in three cases. One third were severely disabled. Thirty of the deceased were still smoking. The GPs felt that 58·8% had their symptoms well controlled, although the relatives stated that 71% awoke with wheeze at least one night each week; 64·5% had wheeze on awakening every morning. One third

had at least weekly episodes of acute wheeze and one third had less than one episode of wheezing monthly. No relation was found between the severity of symptoms and the frequency of GP consultation ($p > 0.5$). One hundred and twenty six (92.4%) had required previous hospital admission, of whom four (2.3%) were mechanically ventilated. The panel felt that 58.6% of the deaths were potentially preventable: 25.4% delayed calling for medical help; the doctor delayed appropriate treatment in 9.8%; poor compliance was found in 13.8%; 10.9% were inadequately managed acutely and 36.8% long term; 19.5% were on medication liable to exacerbate their asthma. Younger asthmatics had a higher percentage of preventable factors ($p < 0.001$).

Occupational asthma in nurses due to chlorhexidine and alcohol aerosol

ER WACLAWSKI, LG McALPINE, NC THOMSON *Occupational Health Service, Greater Glasgow Health Board, and Department of Respiratory Medicine, Western Infirmary, Glasgow*
Chlorhexidine is known to sensitise skin and has been associated with severe allergic reactions but asthmatic reactions have not been reported. We present two cases of occupational asthma in association with the use of chlorhexidine and alcohol aerosol spray (Dispray 2). The first case is of a 54 year old nursing auxiliary who developed attacks of cough and wheeze within minutes of using Dispray 2 to disinfect incubators. There was no previous history of asthma and spirometry was normal with $FEV_1/FVC = 81\%$. Histamine challenge showed borderline airway hyperresponsiveness with PC_{20} 9.2 mg/ml. A bronchial provocation challenge with Dispray 2 demonstrated a 13% fall in FEV_1 when compared with a control day. There was no late response noted. The second case concerns a 43 year old staff midwife with no previous history of asthma who presented with recurrent episodes of chest tightness and wheeze over a six month period after exposure to Dispray 2. Spirometry was normal with $FEV_1/FVC = 86\%$. Histamine airway responsiveness was also normal with $PC_{20} > 16$ mg/ml. Peak expiratory flow recordings demonstrated a 40% variation during periods at work compared with a 10% variation while away from work. A bronchial provocation challenge test with Dispray 2 produced a 22% fall in FEV_1. There was no late response observed. These cases demonstrate that asthmatic reactions can occur with the use of a chlorhexidine and alcohol disinfectant spray in hospital staff with no previous history of asthma. As this form of disinfection is in widespread use, there is potential for a large number of health service employees to be affected.

Infection in exacerbations of asthma: views and practice in the Northern Region

CK CONNOLLY, NK MURTHY, RJ PRESCOTT *Memorial Hospital, Darlington, and Department of Medical Statistics, University of Edinburgh*
Bacterial infection is rarely of importance in exacerbations of asthma, but antibiotics are frequently prescribed, giving rise to concern that corticosteroids might be inappropriately withheld. One hundred and nineteen general practitioners (GPs), 35 (general) physicians, 14 thoracic physicians (TPs) and 31 paediatricians replied to a questionnaire designed to elucidate opinion and practice in the Northern Region of the NHS. In general, GPs agreed with physicians and TPs with paediatricians. A majority stated infection was frequent in exacerbations (paediatricians 84%, GPs 78%, physicians 64%, TPs 64%), but no TP or paediatrician felt that this would be primarily bacterial, while 9% GPs and 29% physicians did ($p < 0.01$). Forty per cent of GPs and physicians but only two TPs and two paediatricians feared secondary bacterial infection ($p < 0.001$). Physicians estimated the highest overall proportion of bacterial infection ($p < 0.0001$). Those fearing secondary infection were more likely to regard green sputum, subacute onset and persistent exacerbations as signs of infection and to prescribe antibiotics on the basis of these factors and of fever and coincidental corticosteroid treatment. They were more likely to claim to prescribe antibiotics frequently ($p < 0.0001$) and to be among the 25% who gave them without corticosteroids ($p < 0.001$). No TP prescribed antibiotics without steroids. Seventy six per cent (85% GPs) of the respondents with juniors or deputies claimed that the latter prescribed antibiotics more often than themselves. Antibiotics appear to be given in asthma because of a perceived risk of secondary infection manifested by green sputum, fever, and prolonged exacerbation. If education aimed at changing prescribers' habits is felt desirable, it should be aimed not only at GPs but also at General Physicians and junior staff.

Improving asthma control in general practice

FRG CROSBY, E WHYTE, S OGSTON, RA CLARK *Carnoustie Health Centre and University of Dundee*
In the context of a busy general practice any improvement in the management of asthma must be within the constraints set by general practice—that is, 6–10 minute consultations and asthma patients presenting at irregular intervals. The Carnoustie asthma project was designed to evaluate the effect of a simple assessment proforma, a management protocol and an education programme on the control of asthma in a practice of 11 500 patients with six principals covering a geographically isolated area. Analysis of the asthmatic population under 55 showed 60% had persistent daily symptoms (group A) and 40% intermittent symptoms of varying intensity (group B). Improvement in control for group A was judged from symptom scores, functional assessment, daily peak flow readings (over 14 days) and time lost off school/work. Improvements were seen in the intervention group, being most significant compared with baseline and controls when both patient and doctors complied with the protocol. For group B days off school/work and the prescription and usage of bronchodilator inhalers were used to assess a significant improvement over baseline and controls. All patients in the intervention group showed a significant improvement in knowledge over baseline and controls. In the light of experience the package has been modified for use in general practices in Tayside.

Atopy and lung function in shipyard workers

DJ CHINN, B KING, IC STEVENSON, JE COTES *Division of Environmental and Occupational Health, Medical School, Newcastle upon Tyne* Smoking can interact with a personal history of allergy to increase the decline in lung function with age of non-asthmatic subjects (Taylor *et al*, *Thorax* 1985;**40**:9). We set out to discover if fumes from shipyard welding can behave similarly. The subjects were redundant welders (but not tack welders), caulker/burners and other tradesmen. Men with a history of asthma were excluded. Dynamic spirometry was performed in 1979 and at follow up, which was on average 7·2 years later. Subsequently in volunteers, atopic status was assessed using skin prick tests to common allergens; serum IgE concentration was measured. Results for 124 men were analysed. Compared with men who refused or did not keep appointments, the participants were older (mean ages 50·1 and 55·7 years) and had mildly impaired lung function (FEV_1 in SD units, $-0{\cdot}21$ and $-0{\cdot}59$ SD). After allowing for age and stature, the forced expiratory volume at follow up was significantly reduced in smokers with a high serum IgE concentration (≥ 250 IU) compared with other smokers. After allowing for age, stature and smoking, the annual declines in FEV_1 and peak expiratory flow were increased in welders and caulker/burners with a raised serum IgE concentration compared with all other tradesmen. For the decline in FEV_1 there was a similar interaction between trade and atopic status, but for most comparisons the proportion of variance which was explained by atopy was less than when IgE concentration was used; the two variables were correlated. Neither was significantly related to smoking history or to trade. Thus welders and caulker/burners were at increased risk of respiratory impairment if they had an atopic constitution. The response could have been mediated by non-specific irritants and/or specific occupationally related antigens in welding fumes.

Occupational airborne pollutants and respiratory symptoms in a general population of Norway

P BAKKE, V BASTE, GE EIDE, A GULSVIK *Department of Thoracic Medicine and Section for Medical Informatics and Statistics, University of Bergen, Bergen, Norway* Information on respiratory symptoms, smoking habits and past or present occupational exposure to airborne pollutants was obtained by a self administered questionnaire from a 1·8% random sample (n = 4992) of the general population aged 15–70 years of the county of Hordaland, Norway. Completed questionnaires were returned by 89·5% of the sample. Past or present occupational exposure to dust or gas was reported by 46% of the men and 12% of the women. A history of occupational asbestos and quartz exposure was given by 10% and 8% of the men respectively and 0·4% of the women. The prevalence of respiratory symptoms (morning cough, chronic cough, phlegm when coughing, breathlessness when climbing two flights of stairs at an ordinary pace (grade II), attacks of breathlessness and occasionally wheezing) were positively associated with occupational exposure to airborne pollutants after adjusting for sex, age, smoking habits, atopy and urban-rural area of residence. The adjusted odds ratio of respiratory symptoms in subjects occupationally exposed to dust or gas compared with those unexposed was approximately 1·8 and did not vary in an obvious way between the symptoms. The adjusted odds ratio of respiratory symptoms in asbestos exposed relative to unexposed subjects varied from 1·5 to 2·3, being lowest for breathlessness grade II and highest for phlegm when coughing. The corresponding figures for quartz exposure varied from 2·0 to 3·4, being lowest for breathlessness grade II and highest for occasionally wheezing. However, no dose-response relationship was noted between asbestos and quartz exposure on the one hand and rates of respiratory symptoms on the other. The population attributable risk of occupational dust or gas exposure for respiratory symptoms varied between from 14% to 21%, being lowest for cough in the morning and highest for occasionally wheezing. These data indicate that occupational airborne exposure gives a contribution to the respiratory symptom load of the general population equal to one third of the contribution made by current cigarette smoking.

Comparison of two methods of expressing the results of bronchial challenge tests with reference to their use in epidemiological surveys

BG HIGGINS, JR BRITTON, S CHINN, P BURNEY, AE TATTERSFIELD *City Hospital, Nottingham, and St Thomas's Hospital, London* Bronchial reactivity measurements are often used in epidemiological studies as objective markers of respiratory function, but conventional means of expressing challenge test results such as the PD_{20} do not provide an estimate in all subjects in a random population sample. O'Connor *et al* recently described the dose response slope (DRS) obtained by performing a standard challenge test and estimating the slope of the dose-response relationship as the maximum % change in FEV_1/μmol bronchoconstrictor (*Am Rev Respir Dis* 1987;**136**:1412). Since a slope can be measured without the necessity for a 20% fall in FEV_1 an estimate of reactivity is obtained in all subjects. To determine whether this advantage of the DRS is offset by poor repeatability we have reanalysed data from 89 sets of repeat challenge tests (45 histamine, 44 methacholine) using the Yan method in subjects selected because of recent wheeze, and calculated a PD_{20} and a DRS. A measurable PD_{20} was obtained on at least one occasion in 58 subjects, and on both occasions in 45 subjects, whereas a DRS could be obtained in all subjects, although the slope was zero or negative in nine subjects on at least one occasion. Correlation between PD_{20} and DRS values was high ($r = -0{\cdot}89$ for histamine, $r = -0{\cdot}91$ for methacholine). The intraclass correlation coefficients for methacholine and histamine PD_{20} results were 0·84 and 0·64 respectively, and for DRS results 0·83 and 0·69 respectively. The intraclass correlation coefficients of the DRS results from subjects in whom a PD_{20} could not be obtained were 0·25 for methacholine and 0·14 for histamine. Thus the DRS gives information comparable to the PD_{20} and provides an estimate in all subjects; however, the extra estimates obtained are of questionable value since they show poor repeatability and discrimination between subjects.

Dose-response effect of terfenadine on resting bronchomotor tone in patients with asthma

S GHOSH, KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow* The mechanism of histamine hyperresponsiveness in patients with asthma remains unclear. Histamine acts on the bronchial smooth muscle by interaction with at least two distinct receptors, H_1 and H_2 receptors, and probably through stimulation of the rapidly adapting irritant receptors also. In single dose studies we have observed that H_1 receptor antagonists clemastine, cetirizine, ketotifen and azelastine produce small but significant bronchodilator effect in patients with extrinsic asthma, suggesting "histamine tone" due to locally released histamine in the lung. In order to examine the dose-response relationship of H_1 antagonists on the bronchomotor tone in asthma we have compared the effect of terfenadine 60, 120 and 180 mg with placebo in 19 patients (age 16–58 y) with mild extrinsic asthma (mean (SEM) predicted FEV_1 88·0 (2·8)%) and seven patients (age 26–62 y) with moderately severe asthma (mean predicted FEV_1 60·2 (4·3)%) up to eight hours in double blind randomised studies. The maximum mean percentage increases in FEV_1 after 60, 120 and 180 mg terfenadine were 7·5%, 12·5% and 9·5% respectively in patients with mild asthma and 21·7%, 26·7% and 29·1% in patients with moderately severe asthma. Terfenadine produced small but significant bronchodilatation in the patients studied and the effect was present up to eight years. Although the bronchodilator response was more marked in patients with moderately severe asthma, no dose-response relationship was observed. These results suggest the presence of histamine tone which is dependent on local endogenous histamine release.

Management of patients with cryptogenic fibrosing alveolitis in the 1980s: experience in three regions

C BLEASDALE, IDA JOHNSON, S KARA, A WOODCOCK, CC EVANS, CRK HIND *Queen's Medical Centre, Nottingham; Wythenshawe Hospital, Manchester; and the Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Liverpool* We are currently developing a case register of patients with crytogenic fibrosing alveolitis (CFA) from the Trent, North West and Mersey regions. This is part of various prospective studies on the epidemiology and natural history of this condition. In order to review how such cases are currently managed in these regions, we have retrospectively analysed the case records of the first 96 patients who have been diagnosed as having CFA (66 male, 30 female; mean age at diagnosis 61·4, range 32–86 years) in the absence of any apparent systemic connective tissue disease. Although all patients had persisting crackles and widespread bilateral chest radiographic shadowing, we found that a detailed history of exposure to fibrogenic agents had not been recorded in 45 cases (47%) for asbestos, and 39 cases (41%) for birds; furthermore avian precipitin tests had only been performed in 21 cases (22%). The transfer factor (TCLO) had not been measured in 15 cases (16%). No attempt at histological confirmation of the diagnosis was made in 56 cases (58%), while the others had transbronchial or drill biopsy (29 cases) with or without bronchoalveolar lavage (8), or open lung biopsy (12). Sixty one patients received treatment (64%), with corticosteroids (59; 61%), and/or cyclophosphamide (7), azathiaprine (6) or penicillamine (1). These results suggest a need for improvement in fulfilling the diagnostic criteria for CFA in an individual patient, and that for a significant proportion of cases the diagnosis remains a clinical one for which the patient receives no specific therapy.

Histopathology of interstitial lung disease in systemic sclerosis (SS): comparison with cryptogenic fibrosing alveolitis and implications for pathogenesis

NK HARRISON, AR MYERS, B CORRIN, CM BLACK, M TURNER-WARWICK *Cardiothoracic Institute, University of London* Despite indirect evidence for an inflammatory-fibrotic pathogenetic sequence in pulmonary SS, there has been no systematic study of antemortem histopathology confirming the concept. Therefore we examined open lung biopsy specimens from 35 patients with well defined SS. Sections from lower and middle lobe biopsies were quantified by a four-point scoring system for indices of inflammation, fibrosis, loss of architecture, vascular involvement and pleural changes. These findings were compared with those in age and sex matched patients with cryptogenic fibrosing alveolitis (CFA). Irrespective of the extent of disease assessed by clinical parameters all cases had evidence of both inflammation and fibrosis, but generally interstitial cellular infiltrates were mild or moderate, whereas fibrosis was moderate or severe. Air spaces usually contained macrophages with only occasional neutrophils or eosinophils. Loss of alveolar architecture correlated with more severe fibrosis. Pulmonary vessels showed medial hypertrophy and fibrous thickening of the intima, particularly when the parenchymal changes were more severe. Pleural abnormalities were very uncommon. In general lower lobes were more severely affected than middle lobes, but all biopsies had both inflammatory and fibrotic components and no "leading edge" of inflammation separated fibrotic areas from normal lung. Our conclusions are: (1) A pathogenetic concept for SS interstitial lung disease must necessarily include an explanation for the presence of fibrosis as well as concomitant inflammation even in early disease. (2) The pathology of SS lung disease is not significantly different from that of CFA, which could suggest a similar pathogenesis.

Isotretinoin given in the treatment of systemic sclerosis may hasten the decline of pulmonary function

CB BUNKER, PDL MAURICE, S LITTLE, NMcI JOHNSON, PM DOWD *Departments of Dermatology and Medicine, University College and Middlesex School of Medicine, London, and Medical Department, Roche Products Ltd, Welwyn Garden City, Herts* The synthetic retinoid isotretinoin (Roaccutane, Roche), has been a significant addition to the dermatological pharmacopeia, specifically for the treatment of severe acne and disorders of keratinisation. Theoretical considerations and one report (Bahmer *et al*, *Arch Dermatol* 1985;**121**:308) have suggested that there may be a place for isotretinoin in the treatment of systemic sclerosis (SS).

During an open prospective study of isotretinoin, at a dose of 1 mg/kg daily in SS, one patient developed an eosinophilic pleural effusion and two patients were noticed to have asymptomatic deterioration in their pulmonary function tests with a marked decline in lung volumes. In view of this, the pulmonary function of all treated patients (n = 10, one male and nine females, mean age 47 years, range 21–62) has been retrospectively compared with that of a similar control group of patients (n = 9, one male and eight females, mean age 57 years, range 24–74) who were not treated with isotretinoin. All patients in both groups satisfied the diagnostic criteria of the American Rheumatism Association (*Arthritis Rheum* 1980;**23**:581). There was a consistent trend of greater decrease in the lung function of patients with SS while being treated with isotretinoin in comparison with both control patients and with pre-isotretinoin treatment data. Statistically significant results were found for the treatment versus control comparisons for FEV_1 ($p = 0.037$) and KCO ($p = 0.011$). The patients are to be followed closely to determine whether these changes are reversible. Studies of lung function in patients treated with isotretinoin for other indications are required.

Circulating concentrations of free radical activity in patients with cryptogenic fibrosing alveolitis

C BLEASDALE, G BUTCHER, MJ JACKSON, CC EVANS, CRK HIND *Regional Adult Cardiothoracic Unit, Broadgreen Hospital, and University Department of Medicine, Royal Liverpool Hospital, Liverpool* Neutrophils are thought to have a central role in the pathogenesis of cryptogenic fibrosing alveolitis (CFA). These cells have the potential to damage the lung parenchyma both by enzyme release and by the generation of toxic free radicals. Such radicals can also cause diene conjugation of native fatty acids (for example, the production of 9,11-linoleic acid [9,11-LA'] from 9,12-linoleic acid [9,12-LA]). This property forms the basis for assay by HPLC for free radical activity, which is best expressed as a molar ratio ([9,11-LA']/[9,12-LA] × 100; normal range in this laboratory 0·5–2·0; intra- and inter-coefficient of variation of assay < 10%). Using this assay the circulating levels of free radical activity were measured in 20 patients with CFA (13 male, seven female; mean age 59 years, range 42–75 years) to look for any correlation with disease activity, as assessed by lung function abnormalities and radiographic changes. Elevated free radical products were found in 11 patients (mean 5·9, range 2·1–8·2). Of these 10 had evidence of active pulmonary disease as defined by a fall in vital capacity (mean 62 ml/month, range 18–200) which correlated significantly with the level of free radical products ($r = 0.90$; $p < 0.05$). The remaining patient had a ratio of 3·8, with no change in pulmonary disease over a six month period. All nine patients with normal circulating levels of free radical activity (mean 1·25, range 0·9–2·0) had apparently quiescent CFA. These preliminary findings suggest that patients with active CFA do have evidence of in vivo free radical production, which may provide an easily measured circulating index of neutrophil activation in this condition. (This work is supported by the British Lung Foundation.)

Growth promoting factors for fibroblasts in bronchoalveolar lavage fluid from patients with systemic sclerosis

NK HARRISON, AR MYERS, RJ MCANULTY, CM BLACK, M TURNER-WARWICK, GJ LAURENT *Biochemistry Unit, Department of Thoracic Medicine, Cardiothoracic Institute, London* Systemic Sclerosis (SS) is frequently associated with pulmonary fibrosis although the pathogenic mechanisms are unknown. The aim of this study was to assess the lower respiratory tract of patients with SS for the presence of factors which may stimulate fibroblast proliferation. Bronchoalveolar lavage fluid (BALF) from patients with SS (n = 7) and healthy non-smokers (n = 5) were concentrated to give a final albumin concentration of 500 μg/ml. Serial dilutions of BALF in culture medium were added to growth arrested human fetal fibroblasts in vitro. At 72 hours the proliferative response was measured by methylene blue elution assay. Concentrated BALF from patients and normal subjects caused clumping of fibroblasts with loss of their typical spindle shaped morphology. Diluted BALF from patients caused a proliferative response of 35·0 (0·3) % (mean (SEM)) above control values, not seen in normal subjects (8 (3) %; $p < 0.05$). Maximum stimulation was seen at dilutions of 1/16–1/32. Growth promoting activity was stable when heated to 60°C for 30 minutes, but activity was lost at 100°C. Our results suggest that fluid lining the lower respiratory tract of patients with SS contains factors which could affect fibroblast numbers. The source of such factors and their role in the regulation of lung collagen production remains to be elucidated.

Influence of cigarette smoking on bronchoalveolar lavage cellular indices in interstitial lung diseases

K WARD, CM O'CONNOR, MX FITZGERALD *St Vincent's Hospital, Dublin* Studies on normal subjects suggest that smoking influences the results of bronchoalveolar lavage (BAL). The effects of cigarette smoking on BAL cellular analysis in different disease states is less well documented. We have performed BAL on 325 occasions in 278 patients (88 current smokers): 97 newly diagnosed sarcoid patients, 141 BAL in 115 chronic sarcoid patients, 28 BAL in rheumatoid patients, 38 BAL in 28 patients with non-sarcoid interstitial lung disease and 21 BAL in 16 patients with fibrosing lung disease. In all groups smokers had a greater total cell recovery than non smokers (mean and 95% confidence limits: 31·9 million (26–38) *v* 17·3 million (16–19) ($p < 0.001$). Macrophage numbers and BAL macrophage % were increased in smokers

	*Macrophages**	*T lymphocytes**
New sarcoid		
Smoker (33)	29·6 (20–39)	4·6 (2–8)
Non-smoker (64)	9·3 (8–11)***	7·6 (5–10)
Rheumatoid		
Smoker (12)	24·5 (9–40)	0·9 (−4–6)
Non-smoker (16)	8·3 (5–12)**	1·4 (−3–6)
Non-sarcoid interstitial disease		
Smoker (9)	20·4 (7–34)	11·5 (6–17)
Non-smoker (29)	9·6 (7–12)**	10·6 (7–14)

*No cells × 10^6, mean (95% confidence limits).
**$p < 0.01$; ***$p < 0.001$.

in each disease category (table). In both the sarcoid groups T lymphocyte helper cells were increased in both number and percentage in non-smoking patients. T suppressor cells were not different between smoking and non-smoking groups. Cigarette smoking has a major influence on BAL cellular analysis. This observation has important implications for any serial BAL studies during which patients change their smoking habits.

Cellular source of collagenase in bronchoalveolar lavage (BAL) fluid from patients with sarcoidosis

C POWER, CM O'CONNOR, C ODLUM, MX FITZGERALD *Department of Medicine, University College Dublin, and St Vincent's Hospital, Dublin* The neutrophil (NP) has been implicated as the source of BAL collagenase in patients with interstitial lung disease. We have demonstrated the presence of collagenase in BAL fluid from sarcoid patients, a disease where elevated lung NPs are not commonly seen (O'Connor *et al*, *Thorax* 1988;**43**:393). The aim of the present study was to compare the characteristics of collagenase from BAL fluid of sarcoid patients with collagenase from NPs and alveolar macrophages (AMs). Collagenase from homogeneous preparations of AMs and NPs were characterised with respect to substrate specificities on type I and type III collagens. Both cell types produced collagenase that degraded type I in preference to type III collagen. However, the relative rates of type I to type III digestion (table) indicated that NP collagenase exhibited a higher specificity for type I collagen than did AM collagenase. To examine the substrate specificity of BAL fluid collagenase two groups of sarcoid patients were assessed: (i) patients with normal BAL NP counts (<2·0%) and (ii) patients with elevated BAL NP counts (>2·0%). The relative rate of type I to type III collagen digestion in BAL fluids from patients with elevated NPs was similar to that observed for NP collagenase (table). However, patients with normal NP levels displayed a relative digestion rate intermediate between that observed for NP and AM collagenase. These results indicate that (i) both AMs and NPs can contribute to the collagenase observed in BAL fluid from sarcoid patients and (ii) even relatively small numbers of neutrophils may be the source of a significant proportion of BAL collagenase.

	*BAL collagenase**			
	AM collagenase	*NP collagenase*	*NPs <2%*	*NPs >2%*
Type I	0·09*	2·81	0·55	3·81
Type III	0·02	0·014	0·013	0·03
Type I/III	4·5:1	200:1	42:1	127:1
% NP	0	>95%	1·1	8·5

*Activity is expressed as m units/ml.

Bronchoalveolar lavage (BAL) fluid fibronectin and procollagen peptide reflect inflammation and not early fibrosis in sarcoidosis

CM O'CONNOR, K WARD, C ODLUM, G CHADWICK, A MCILGORM, MX FITZGERALD *Department of Medicine, University College Dublin, and St Vincent's Hospital, Dublin* Fibronectin (Fbn) and procollagen peptide (PCP) are elevated in bronchoalveolar lavage (BAL) fluid of sarcoid patients. It is suggested that these proteins reflect an early stage of fibrosis and may serve as prognostic indicators of disease. In this study we examined BAL levels of PCP and Fbn with respect to disease stage and presentation in 110 sarcoid patients. *Disease stage*: Patients were classified as having stage 0 (n=5), stage 1 (n=29), stage 2 (n=36), and stage 3 (n=40) disease (Siltzbach). Both Fbn and PCP levels were elevated above those of controls (n=14) in stage 1, 2 and 3 disease ($p < 0·01$), stage 2 disease patients displaying highest level of both proteins. Thus neither BAL Fbn or PCP reflect the extent of radiological lung involvement in sarcoidosis. *Disease presentation*: Newly diagnosed patients (n=62) were divided into two groups—those presenting with acute inflammatory onset disease (EN and uveitis) and those presenting with respiratory or radiographic evidence of disease. Although BAL levels of Fbn and PCP were elevated above those of controls in both groups ($p < 0·05$), highest levels were observed in the acute onset group (table). As such acute onset disease generally heralds a good prognosis, the high levels of both proteins seen in this group suggests that neither protein will serve as an indicator of poor prognosis. These results suggest that elevated BAL Fbn and PCP may reflect a reversible inflammatory process rather than the early stages of fibrosis.

	Sarcoid disease presentation (mean (SD) [n])		
	Acute onset	*Insidious onset*	*Controls*
Fbn μg/ml	1·03 (0·19) [30]	0·7 (0·12) [32]	0·23 (0·06) [14]
PCP ng/ml	3·69 (1·95) [30]	0·59 (0·25) [23]	0·01 (0·03) [10]

Functional effects of exposure to dust in wool textile mills

RG LOVE, M MUIRHEAD, HPR COLLINS, CA SOUTAR *Institute of Occupational Medicine, Edinburgh* Following our previous observations that respiratory symptoms are strongly associated with exposure to inspirable dust in wool textile mills (Love *et al*, *Thorax* 1987;**42**:208) we have examined the lung function, chest radiographs and intracutaneous response to wool extracts and common allergens in 634 wool textile workers. Only 5·9% of these workers had recognisable small opacities (category 0/1 or more) on their radiographs. FEV_1/FVC ratio was inversely related to current dust levels in European women ($p < 0·05$) and a similar relationship was suggestive for FVC in Asian men. Transfer factor was unrelated to dust levels or other occupational factors in any group, nor was any spirometric variable associated with dust levels in European men. Twenty four per cent of the workforce responded (weal diameter > 4 mm) to one or more allergens but only 12 of these (7·9%) responded to wool extracts. Atopics in general were younger, had spent less time in their current job and had significantly more respiratory symptoms than non-atopics but did not demonstrate an increased susceptibility to the effects of wool dust on symptoms. Dye workers and wool scourers (relatively non-dusty jobs) on average experienced an FEV_1 251 ml lower than other workers once age, height, smoking habit and

occupational factors had been taken into account. These studies indicate that exposure to wool mill dust not only is associated with the presence of respiratory symptoms but also can cause functional impairment in certain workers. Although these functional effects appear to be fairly mild, better estimates of cumulative dust exposure might show stronger associations with lung function.

Pulmonary manifestations of rheumatoid arthritis

D GILLIGAN, CM O'CONNOR, K WARD, M BARRY, B BRESNIHAN, MX FITZGERALD *Departments of Medicine and Rheumatology, St Vincent's Hospital, Dublin, and University College Dublin* Previous studies on the association between interstitial lung disease (ILD) and rheumatoid arthritis (RA) have reported a prevalence of ILD which varies from 5% to 50%, depending on the criteria used to (i) select patients and (ii) assess lung involvement. The aim of the present study was to examine the prevalence of ILD in an unselected RA population by pulmonary function testing and chest radiography. In addition, the influence of RA disease characteristics, drug therapy and smoking on the prevalence of lung involvement in RA was assessed. Lung function tests (FEV_1, FVC, TLCO) and chest radiography were performed on 90 RA patients (59 female, 31 male, age 23–74 y). Details of RA disease severity, therapy and smoking status were also obtained for each patient. Thirteen (14%) of the patients studied were found to have evidence of lung disease as indicated by an FEV_1, FVC, or TLCO of $<80\%$ predicted or an abnormal chest radiograph. There was no difference between these patients and those without evidence of lung involvement with respect to age, sex or duration of RA disease. However, a higher proportion of patients with lung involvement had erosive disease associated with rheumatoid factor (62%) than patients without lung involvement (31%, $p < 0.05$). In addition, 62% of these patients were current smokers compared to 27% of patients without evidence of lung disease ($p < 0.05$). These results suggest that lung involvement in RA may be associated with RA disease severity and smoking. (This work was supported by the Arthritis Foundation of Ireland.)

Impairment of lung mucociliary clearance in pigeon fanciers

A HASANI, MA JOHNSON, D PAVIA, JE AGNEW, LW POULTER, SW CLARKE *Departments of Thoracic Medicine, Medical Physics and Computing, and Immunology, Royal Free Hospital and School of Medicine, London* Lung mucociliary clearance was measured in 15 (14 M; 1 F) pigeon fanciers. The study group was subdivided into two; group A (n = 9, mean (SD) age 44 (15) y and % pred FEV_1 88 (22)) with circulating blood precipitins and group B (n = 6, mean (SD) age 46 (15) y and % pred FEV_1 98 (18)) with no circulating precipitins. Clearance was measured using an objective, non-invasive radioaerosol technique. The data for both subgroups were compared with those of two control groups of healthy subjects with similar physical characteristics, smoking habits and initial topographical radioaerosol lung deposition as those of the two study groups. The mean (SEM) area under the tracheobronchial retention curves (AUC) over the six hour observation period were 262 (28) % h for group A compared with 179 (18) % h for its control group ($p < 0.05$) and that for group B was 257 (30) % h compared to 176 (20) % h for its control group ($p < 0.05$). Thus both groups showed a similar (46%) reduction in tracheobronchial clearance (increase in AUC) compared with their respective control groups. In pigeon fanciers inflammation of the distal portions of the lung (extrinsic allergic alveolitis) is a frequent occurrence. Our study illustrates involvement of the conducting airways in as much as one of the host defence mechanisms—namely, mucociliary clearance—appears to be compromised. This finding indicates that (1) airways are involved as well as the alveoli and (2) the presence or absence of precipitins is not related to defective mucociliary clearance.

Airways manifestations of pigeon fancier's lung (PFL)

S BOURKE, R CARTER, K ANDERSON, J BOYD, S KING, B DOUGLAS, G BOYD *Respiratory Medicine Department, Glasgow Royal Infirmary, Glasgow* Classic concepts of PFL focus upon the alveoli as the main site of inflammation and the disease is characterised by a restrictive ventilatory defect with impaired gas diffusion. However, bronchiolitis is an important feature of the pathology of the disease and chronic bronchitis is common in these patients (*Thorax* 1988;**43**:238). To further assess the airways component of PFL, 280 fanciers completed a questionnaire of respiratory symptoms, performed spirometry on a Vitalograph Compact spirometer and had IgG antibody to pigeon gammaglobulin measured. A restrictive defect was defined as FVC < 80% predicted in the absence of large airways obstruction. Large airways obstruction was defined as $FEV_1/FVC < 80\%$ predicted and distal airways obstruction as $FEF_{25-75} < 70\%$ predicted. Eighty (28·5%) met the criteria (*Thorax* 1986;**41**:274) for PFL and these patients had a lower prevalence of current smoking ($p < 0.001$). Smokers had more large ($p = 0.019$) and distal ($p < 0.001$) airways obstruction than non-smokers and were therefore excluded from further analysis, as were 22 patients with asthma. Abnormal spirometric results were more common in those with PFL: a restrictive defect was present in 14 (25%), $p = 0.015$; large airways obstruction in 13 (23·2%), $p = 0.014$; and distal airways obstruction in 24 (42·8%), $p = 0.001$. Distal obstruction increased in prevalence as sensitisation to pigeon gammaglobulin rose ($p = 0.037$). Thirty one (55·4%) with PFL had chronic bronchitis compared with 12 (16%) without PFL ($p < 0.001$). Obstructive defects were more common in those with chronic bronchitis but this did not reach statistical significance, suggesting that they are different but overlapping entities. Although alveolitis is the hallmark of PFL, the airways are also involved in the disease with a resultant hypersecretory disorder as chronic bronchitis and an obstructive defect which predominantly affects the distal airways.

Oral high frequency oscillation (OHFO) as an aid to physiotherapy in chronic bronchitis with airflow limitation

JA PRYOR, J WIGGINS, BA WEBBER, DM GEDDES *Brompton Hospital, London* Oral high frequency oscillation (OHFO) may be a useful aid to physiotherapy because it has been shown to enhance mucociliary clearance and reduce minute ventilation, relieving dyspnoea. Oscillator devices are under development for commercial use. We assessed OHFO generated by a Medic Aid Ltd IMP oscillator (stroke volume 48 ml, frequency 12·6 Hz) as an aid to physiotherapy in 16 patients (14 males; mean age (SD) = 65·9 (5·6) years) with exacerbations of chronic bronchitis and airflow limitation (mean FEV_1 % (SD) = 38 (12)). The study, which compared chest physiotherapy with (treatment A) and without (treatment B) OHFO, lasted for two consecutive days, with two 20 minute physiotherapy sessions in each day. One treatment (A or B) was given in both sessions on the first day and the alternative was given on the other, the order being randomised on entry. Ten patients (all males) completed the study; six withdrew, four because of dislike of the sensation of the oscillator (two on first use of the device); one could not cooperate with the protocol and a sixth developed cardiac failure. Use of the oscillator had no effect on sputum weight, visual analogue scale score (VAS) of breathlessness, spirometry, oxygen saturation or exercise tolerance in comparison with chest physiotherapy alone. However, the latter was associated with significant falls in breathlessness VAS (for example, mean (SD): pre-physio 4·8 (3·0), post-physio 3·0 (1·9); $p < 0.05$). No complications or side effects were recorded. Despite theoretical attractions, this study suggests that routine use of OHFO is not indicated for this group of patients.

Limits to bronchial narrowing in normal subjects

J PERTUZE, A WATSON, J THOMPSON, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* In recent years several studies have shown that normal subjects differ from subjects with asthma by showing limited bronchoconstriction (bc) in response to increasing doses of inhaled bronchoconstrictor drugs. In a pilot study comparing never-smokers with smokers, we noted that some non-asthmatic never-smokers did not show convincing plateaux of expiratory flow. To investigate this further we studied the response of 20 healthy non-asthmatic subjects (nine men, mean age 28·9, SD 8·7 y) to increasing concentrations of inhaled methacholine (Mech) up to 256 mg/ml. As we suspected that any limits to airway narrowing might initially be present only at extreme lung volumes, in 10 of the subjects we examined sequential changes in complete maximum (m) and partial (p) flow-volume ($\dot{V}/V$) curves; and in the remaining 10, sequential changes in expiratory and inspiratory V/Vm curves and in respiratory resistance (Rrs) measured by an oscillatory technique during tidal breathing. FEV_1 was derived from $\dot{V}/Vm$ curves. A plateau of maximum expiratory flow at increasing Mech doubling concentrations (dc) was defined by (*a*) complete superimposition of $\dot{V}/Vm$ curves, by (*b*) < 5% change in FEV_1, in maximum flow at 40% initial VC in maximum ($\dot{V}_{40}m$) and in partial ($\dot{V}_{40}p$) $\dot{V}/V$ curves, and by (*c*) < 15% change in Rrs. Mean % fall from baseline and number of subjects presenting a plateau (pl) of 2 or more dc were: FEV_1 27·4 SD 19·4%; pl: 15/20 subjects, $\dot{V}_{40}m$ 62 SD 24·2%; pl: 11/20 subjects, $\dot{V}_{40}p$ 82 SD 17·6%; pl 6/10 subjects. Plateaux of Rrs over 1 dc were observed in 7/10 subjects. FVC at the highest dc fell by a mean of 17·5% (range 0–71%), and reductions in inspiratory flow largely paralleled reductions in FVC. Complete superimposition of the whole $\dot{V}/Vm$ curve at > 1 Mech dc was observed in 12/20 subjects at all lung volumes. This technique improves the poor signal to noise ratios inherent in taking single measurements from the curves. Using this more rigorous criterion of curve superimposition limited bc appears to be a less consistent feature in normal subjects than previously described.

Altering baseline airway calibre does not affect airway responsiveness in asthmatic subjects

SK HOOD, OP TWENTYMAN, ST HOLGATE *Medicine I, University of Southampton* Measurements of non-specific airway responsiveness are a widely used research tool. Despite theoretical reasons for believing that baseline airway calibre may influence the result of these measurements it is not known how altering baseline airway calibre in asthmatic subjects influences the results of tests for non-specific hyperresponsiveness. Several mechanisms may alter the response to inhaled bronchoconstrictor agents, including (1) altered deposition within the lung, (2) the limits imposed by maximal airway narrowing, and (3) the inverse relationship between flow and the fourth power of the radius that applies to non-turbulent gas flow through tubes. We have studied 17 asthmatic subjects with baseline PC_{20} histamine varying from 0·06 to 16 mg/ml. The concentration of inhaled nebulised histamine (five deep breaths) to produce a 15–20% fall in FEV_1 was determined for each individual. This concentration of histamine was then administered on separate days at baseline FEV_1 (100%) and following bronchoconstriction to 85%, 75% and 65% of the original baseline FEV_1 by inhaled methacholine. The results of each histamine challenge were recorded as percentage fall in FEV_1 from the immediately preceding baseline. The mean (SEM) fall of FEV_1 from the respective baselines on the first and second histamine challenges were 17·6% (4·4%) at 100% baseline and 21·6% (11·6%) at 85% baseline (day 1), 18·0% (7·9%) at 100% baseline and 19·6% (12·4%) at 75% baseline (day 2), and 18·9% (5·9%) at 100% baseline and 19·5% (9·7%) at 65% baseline (day 3). Varying baseline airway calibre over this range does not affect the measurement of bronchial responsiveness.

Effect of inhaled budesonide on bronchial reactivity in asthma

AS VATHENEN, AJ KNOX, A WISNIEWSKI, S COOPER, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We have investigated the time course of change in FEV_1 and bronchial reactivity in patients with asthma during

six weeks' treatment with inhaled budesonide and for two weeks following cessation of treatment. Forty subjects, aged 18–45 y (mean (SD) FEV_1 3·46 (0·7) l) were randomly allocated to receive inhaled budesonide 800 μg or placebo bd via a Nebuhaler in a double blind non-crossover study. Following a baseline histamine PD_{20} measurement at 0830 on day 1 and the first dose of drug at 0900 subjects were asked to take the allocated drug at 0900 and 2200 daily, starting on day 2 at 0900 and stopping on day 41 at 2200. Further histamine challenge tests were carried out at 0830 on days 21, 42, 49 and 56, and at 1, 6, 12 and 24 h after the first dose of drug (days 1 and 2) and at 1, 6, 12, 24 and 36 h after the last dose of drug (days 41 and 42). Thirty two subjects (18 budesonide, 14 placebo) completed the study. The first dose of budesonide caused an increase in FEV_1 and PD_{20} within 24 h with the maximum increase of 0·40 l and 1·1 doubling doses (DD) occurring after 6 h. There was a further increase in FEV_1 and PD_{20} over the six weeks in the budesonide group, the maximum increases (0·55 l, 3·4 DD) being recorded 6 h after the last dose on day 42. Following this peak FEV_1 and PD_{20} declined slowly being higher than placebo at 36 h but near to pretreatment values at one week. Mean am and pm PEF increased by 64 and 55 l/min with budesonide treatment and decreased following cessation of treatment. Symptom scores and $beta_2$ inhaler use were lower in the budesonide group than the placebo group during treatment but were higher in the two weeks following treatment. Thus inhaled budesonide caused an increase in FEV_1 and PD_{20} over six weeks with 73% of the increase in FEV_1 and 32% of the increase in PD_{20} occurring within 6 h of treatment. PD_{20} and FEV_1 had returned to baseline values within one week of cessation of treatment.

Effect of inhaled budesonide on bronchial responsiveness to histamine, eucapnic dry air hyperventilation (EVH) and exercise in asthma

AS VATHENEN, AJ KNOX, A WISNIEWSKI, DJ SHALE, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We have compared the effect of six weeks' treatment with budesonide (B) on bronchial responsiveness to histamine (H), EVH and exercise (Ex) in a double blind non-crossover study. Forty subjects with asthma, aged 18–45 y (mean FEV_1 3·46 l), were randomly allocated to receive inhaled B (800 μg) or placebo via a Nebuhaler at 0900 and 2200 daily for six weeks starting at 0900 on day 1 and stopping at 2200 on day 41. Bronchial responsiveness to H (Yan *et al* method), EVH (modified from Phillips *et al*) and Ex (treadmill running for 6 min at 90% pred max heart rate) were measured at 0830 on days −2, −1 and 1 respectively at the beginning of treatment and on days 40, 41 and 42 (same order) at the end of treatment. Log cumulative H dose and log cumulative volume of dry air breathed were plotted against FEV_1 to obtain the PD_{20} H and PV_{20}. The response to Ex was recorded as the maximum % fall in FEV_1 from pre-Ex baseline. To allow the three challenge tests to be compared by a similar method we also calculated the max % fall in FEV_1 for the H and EVH tests for the highest common dose used in each subject before and after treatment. Thirty four subjects (18 B, 16 placebo) were eligible for full analysis. Following B treatment there was an increase in FEV_1 (0·40 l), PD_{20} H (2·6 doubling doses), and PV_{20} (1·0 doubling doses). When max % fall was used to assess the effect of B treatment there was a similar decrease in H % fall (Δ H), EVH % fall (Δ EVH) and Ex % fall (Δ Ex) from 23·6% to 8·1%, 26·0% to 10·2% and 26·7% to 8·7% respectively. Δ H correlated with Δ EVH ($r = 0·5$) and with Δ Ex ($r = 0·5$), as did Δ EVH with Δ Ex ($r = 0·6$) (all p values at least 0·05, log transformations used). Thus inhaled B at 1600 μg a day for six weeks caused a reduction in bronchial reactivity, and the reductions in bronchial responsiveness to histamine, EVH and exercise were similar when equivalent methods of measuring response were used.

Exercise tests in chronic obstructive pulmonary disease (COPD): which test and how many?

JG HAY, P STONE, J CARTER, S CHURCH, A EYRE-BROOK, MG PEARSON, AA WOODCOCK, PMA CALVERLEY *Fazakerley Hospital, Liverpool; Wythenshawe Hospital, Manchester; and Boehringer Ingelheim UK* Corridor walking tests are simple, inexpensive and widely used to assess the effects of COPD therapy on exercise performance. The relative importance of training effects on six minute walk distance (6MD) and how 6MD compares with cycle exercise in detecting drug responders are not known. We studied 32 COPD patients (age 66SEM (1·6) y, FEV_1 0·69 (0·05) l) on four days. On days 1 and 2 patients performed two walks receiving 200 μg salbutamol or 40 μg ipratropium either before (group A) or between (group B) the walks. There was no significant within day training effect in group A (increase between walks day 1 12 m, day 2 3 m), but a between day training effect of 32 m (8·3%) in group B. On days 3 and 4, patients performed two walks before and after oxitropium bromide or placebo (double blind), followed by a symptom limited cycle exercise test. After each, dyspnoea was scored using a modified Borg scale. Group B showed no further training effect on 6MD (day 3 406 (19), day 4 420 (19) but 6MD did increase after oxitropium in both groups (393 (17) to 420 (16) ($p < 0·001$). 6MD and distance cycled were highly correlated (placebo day $r = 0·75$ *v* $r = 0·68$ after drug). Oxivent resulted in significant increases in peak $\dot{V}o_2$ (775 (281) to 831 (262); $p < 0·05$) and ventilation (23·0 (6·8) to 24·6 (6·8); $p < 0·05$). However, the improvements in 6MD and any of the cycle variables after drug did not correlate. Ten of the 32 patients walked further without cycling better while 6/32 cycled better but walked no further. Borg scores were consistently higher for cycle exercise than walks (4·8 (0·7) *v* 4·1 (2·1); $p < 0·02$) but the reduction in Borg scores after oxitropium were consistent after both types of exercise and well correlated ($r = 0·45$). Between day training effects on 6MD are important and can be equivalent to the effect of a drug. Although 6MD and cycle exercise variables do correlate well, they do not respond consistently to drug treatment. In contrast, subjective Borg score assessment of drug response was the most consistent variable.

Analysis of the effects of subject motivation and intercurrent illness on the outcome of rehabilitation programmes for asthmatics

LM COCHRANE, CJ CLARK *Department of Respiratory Medicine, Hairmyres Hospital, East Kilbride, Glasgow, and University of Glasgow* Subject compliance is crucial to the effectiveness of physical activity programmes. Normal adults typically show adherence rates of 40–65%. This study analyses the effects of asthma severity and variability, subject anthropometric characteristics and attitude to exercise (five point motivation score during run in period) on outcome of a six month programme of aerobic exercise performed three times per week under medical supervision. Of the 26 trainers, six defaulted during the first three weeks. Twenty fulfilled the training criteria in the initial three month period and $\dot{V}O_2$ max (% pred) increased from 62 (9·7)% to 76 (12·7)% ($p < 0·001$) with no change in control asthmatics continuing normal daily activities during this time. A further six subjects defaulted in the second three month period and no significant difference was found between trainers and defaulters in terms of asthma severity (prestudy FEV_1) or variability (diurnal peak flow). The motivation score was significantly lower in defaulters ($p < 0·05$). The trainers failed to make significant improvements in mean $\dot{V}O_2$ max between three and six months but could be divided into: nine subjects who fulfilled the training criteria consistently with a significant increase in mean $\dot{V}O_2$ max to 81·9 (10·9) % ($p < 0·05$) and five subjects who "detrained" because of exacerbations of asthma. There are therefore two reasons for failure to achieve physiological targets during rehabilitation: (1) a negative attitude to exercise, which can be identified early, and (2) the effects of asthma variability on continuity of training. Different approaches to the medical supervision of such subjects would be required to improve outcome of rehabilitation programmes for asthmatics.

Control of ventilation and perception of effort in dystrophia myotonica

J CLAGUE, J COAKLEY, RHT EDWARDS, J CARTER, MG PEARSON, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, and University Department of Medicine, Liverpool* Patients with dystrophia myotonica (DM) show a reduced ventilatory response to CO_2 (Siriser, *Q J Med* 1982), which may reflect a defective central drive to breathing. The sensation of inspiratory effort (IES) is closely related to the mouth occlusion pressure ($P_{0.1}$) in normals and index of respiratory centre output (Clague, *Clin Sci*, 1988). We wondered whether $P_{0.1}$ was altered in DM and how the relationship between IES and $P_{0.1}$ would be affected by respiratory muscle weakness. We studied 10 normal subjects (mean age 30 (SD 4) y, P_{ETCO_2} 5·4 (0·5) kPa) and nine patients with DM (age 40 (12) y, VC 3·3 (1·3) l, P_{aCO_2} 5·54 (0·7) kPa). The ventilatory response to CO_2 ($\dot{V}e/P_{CO_2}$) was measured (Read rebreathing method); $P_{0.1}$ and IES (modified Borg scale) were recorded every 30 s. Although mean $\dot{V}e/P_{CO_2}$ tended to be lower in DM (16·1 (7·5) *v* 21·9 (9·4) l/kPa in normals) the difference was not statistically significant and neither was the mean $P_{0.1}/P_{CO_2}$ response (2·3 (1·1) cm/kPa DM; 2·8 (1·2) cm/kPa normals). IES rose at the same rate with $\uparrow CO_2$ in normals and DM. The IES/$P_{0.1}$ relationship was no different. The mean inspiratory drive per litre of ventilation, a measure of the impedance of the respiratory system, was 0·13 (0·04) cm H_2O/l in normals and 0·16 (0·07) cm H_2O/l in the DM group. However, DM patients had weak muscles with mean maximum inspiratory pressures (MIP) of 47 (13) cm H_2O compared with 135 (16) cm H_2O in the normals. Thus $P_{0.1}$/MIP/l, the amount of this inspiratory capacity used per litre of ventilation, is greater in the DM group (0·37 (0·16) in DM *v* 0·1 (0·04) in normals, $p < 0·01$), although IES is no greater. We found no relationship between MIP, $\dot{V}e/P_{CO_2}$ or $P_{0.1}$/MIP/Ve and tendency to CO_2 retention in DM patients. These data do not support a central defect of ventilatory control in DM. The CO_2 response is relatively well preserved, although more of the inspiratory capacity is used. Moreover, inspiratory effort perception appears to be related to the absolute pressure developed and not the proportion of the inspiratory capacity used.

Automated assessment of sleep disturbance from video recordings

G THOMAS, A RAHMEN, R BELCHER, J STRADLING *Osler Chest Unit, Churchill Hospital, Oxford* Breathing disorders during sleep produce daytime hypersomnolence through sleep disturbance. This is usually measured via recordings of EEG, eye movements and chin muscle tone, but is very time consuming. The simpler technique of logging movement with a wrist worn device adequately defines sleep/wake periods but such devices are still expensive. Because we use eight hour video recordings as part of our assessment of children and adults with sleep disordered breathing, we have devised a technique for analysing these recordings for movement. This allows a totally non-invasive, automated assessment of sleep and sleep disturbance, which is particularly useful in small children. During fast playback of the eight hour overnight recordings six light sensors, temporarily stuck on the screen over the area occupied by the patient in bed, register light intensity. A computer differentiates this signal over 12 second epochs. Any movement of the subject registers as a change in light intensity and this is logged. The system is sensitive enough to register normal breathing movements and thus a threshold is introduced during analysis. Overnight movement tracings with this new technique have been compared with wrist actigraphic tracings in seven subjects (ranging from normal to gross sleep apnoea). In all subjects the majority of body movements were logged by both devices. Discordance was usually explicable following inspection of the video recording—when, for example, an arousal provoked head movement (which registered on the new device) but no arm movement to activate the actigraph. Thus this technique should allow cheaper analysis of sleep quality from overnight video recordings and identify areas on the videotape that need inspection, without having to review the whole eight hours.

Effect of tonsillectomy and adenoidectomy on overnight hypoxaemia, sleep disturbance, and growth in young children who snore

G THOMAS, J STRADLING, P WILLIAMS, A FREELAND, A WARLEY *Osler Chest Unit, Churchill Hospital, Oxford* We have studied at home, prospectively over a 10 month period, 48 snoring children (aged 2–14, majority < 7 y) referred from the ENT department following their booking for tonsillectomy (with or without adenoidectomy). Only one had been referred initially by his GP for suspected sleep apnoea. Overnight oximetry (Ohmeda 3700) was performed in all children before and six months after operation and in 15 children overnight video recordings were also made. We also measured height and weight and asked questions about general health and behaviour. The average number/h of Sao_2 dips (in excess of 4% below baseline) was measured. The video recordings were objectively processed with a new device to log body movement during sleep and this was expressed as % time spent moving to indicate the degree of sleep disturbance. The same measurements have also been made once in 17 normal matched controls. Twenty of the 48 children had more than 5/h of >4% Sao_2 dips before their operation, but only 1/48 had this postoperatively (dip rates 6·5 (SD 7·1), 1·7 (1·3), 1·0 (0·5)/h before and after operation and controls respectively). The video recordings showed noisy and obstructed breathing as the cause of these dips in Sao_2. Twelve out of 15 spent more than 8% of the sleep period moving before their operation, whereas this level of sleep disturbance occurred in none of the children postoperatively ($p < 0·001$) or the control children (% time spent moving 10·7 (SD 3·9), 5·2 (1·3), 4·7 (1·7) % before and after operation and controls respectively). Postoperatively the average weight and height centiles rose from 45% to 65% ($p < 0·001$) and from 44% to 57% ($p < 0·001$) respectively. Nocturnal hypoxaemia and sleep disturbance are common in snoring children going for tonsillectomy and these resolve postoperatively in association with improved growth.

Sleep hypoxaemia and its correlates in 480 men aged 35–65 years

J CROSBY, A WARLEY, J STRADLING *Osler Chest Unit, Churchill Hospital, Oxford* We are currently surveying men aged 35–65 years, drawn randomly from a group practice register in a village outside Oxford, for nocturnal hypoxaemia and related factors. Five hundred and thirty three men have been approached and 480 (90%) agreed to be interviewed at home by JC, and have an unattended arterial oxygen saturation recording made overnight (Ohmeda 3700, finger oximeter). Measurements of height, weight, neck circumference, resting oxygen saturation and spirometry were also made. Nineteen subjects showed more than 5/h of >4% dips in Sao_2. Sixteen agreed to full polysomnography in hospital and, in the 13 who slept adequately, the Sao_2 dipping was due mainly to obstructive sleep apnoea when supine. The level of 5 dips/h was an arbitrary cut off and was on the tail of a skewed unimodal smooth distribution of dip rates ranging from 0 to 11/h (with one subject over 30/h, not included in the subsequent analysis). When the group was analysed together by linear regression the following variables correlated significantly ($p < 0·001$) with the rate of >4% Sao_2 dipping overnight (correlation coefficient): age (0·34); neck circumference corrected for height (0·33); obesity index; Wt/Ht^2 (0·25); awake Sao_2 (−0·23); % predicted normal FEV_1 (−0·15). Multiple linear regression to remove related variables showed that only age (0·34), neck circumference (0·25), and awake Sao_2 (0·15) were independently correlated and together explained 20% of the interindividual variability of >4% Sao_2 dipping overnight. Sleep hypoxaemia in the general male population is a continuous variable and related mainly to age and neck obesity.

Reproducibility of home oximeter tracings

J CROSBY, J STRADLING *Osler Chest Unit, Churchill Hospital, Oxford* Overnight recordings at home of Sao_2 with an oximeter have been advocated as an adequate screening technique for disorders of sleep and breathing. It has already been shown that there is no "first night" effect during overnight home recordings (*Sleep* 1988;**11**:273) and in severe cases of obstructive sleep apnoea there is little night to night variation that might disguise diagnosis. But at mild levels of sleep apnoea does the rate of hypoxic dipping vary significantly from night to night? Seventy male volunteers aged 35–65 years had two overnight oximetry studies (Ohmeda 3700) separated by one to 26 months. The Sao_2 dip rates (>4% Sao_2) ranged from 0 to 17·5/h of study. Sixteen of these subjects were studied with full polysomnography because they had the highest Sao_2 dip rates. Thirteen had supine obstructive sleep apnoea as the main explanation for these dips; three slept too poorly for diagnosis. The r^2 of the Sao_2 dip rate between studies was only 0·48 ($r = 0·69$). The difference between the studies was not related to the length of time elapsing between them and the mean dip rate of study 1 was the same as study 2 (4·3/h). Forty four of the 70 had less than 5 dips/h on both studies, 11/70 had more than 5 dips/h on both studies, whereas 9/70 went from more than to less than, and 6/70 went from less than to more than 5 dips/h. Thus between the studies 21% crossed this arbitrary level of dipping. This between study variability is likely to be due to different lengths of time spent supine during sleep. This means that only about 50% of the interindividual variation in >4% Sao_2 dip rates is ever likely to be accountable for by other factors, such as age and obesity.

Resolution of nocturnal postoperative hypoxia following thoracotomy

S PATERSON, MDL MORGAN, HR MATHEWS *Departments of Thoracic Surgery and Respiratory Medicine, East Birmingham Hospital, Birmingham* Hypoxia resulting from atelectasis or respiratory depression is well known to persist for several days following abdominal or thoracic surgery (Cateley *et al*, *Anesthesiology* 1985;**63**:20). Since the risk is

greater during sleep, we have determined to identify the time course of recovery of postoperative hypoxia and the need for nocturnal supplementary oxygenation. We have studied oxygen saturation (Sao_2) in five patients (age 57–72, 1 F) over seven nights following thoracotomy for oesophageal surgery without pulmonary resection. The patients had no symptomatic respiratory disease and normal spirometry FEV_1 (73–103% pred), but no patient was hypoxic (Pao_2 9·5–12·2 kPa, Sao_2 95·8 (SD 1·3) %). In each patient Sao_2 was studied on consecutive nights between 22·00 and 06.00 hours. Both supplementary oxygen (Fio_2 0·35) and analgesia by infusion were only given on night 1. The mean Sao_2 was defended on night 1 (95·30 (2·3) %) and remained > 90% on each night. However, long periods of desaturation (< 90%) occurred on each night between 2 and 6 (mean period Sao_2 < 90%, 178, 150, 170, 111, 65 minutes). The minimum Sao_2 (73–85%) occurred on night 2 (one case), 3 (three cases) and night 5 (one case). Even in cases of thoracotomy without pulmonary resection it may be necessary to consider nocturnal supplementary oxygen therapy for at least five days postoperatively.

Is an acclimatisation night necessary in the investigation of sleep apnoea?

M ALLEN, K PROWSE *Department of Respiratory Medicine, City General Hospital, Stoke on Trent* Overnight polysomnography is important in the diagnosis and management of patients with sleep apnoea. It is suggested that an acclimatisation night is performed for most studies to overcome the effects of sleeping in a strange environment. This additional night may not be required for patients with sleep apnoea who are often hypersomnolent. Seven patients (five male) aged between 37 and 58 years (mean 47) with sleep apnoea underwent full polysomnography on two consecutive nights in a sleep laboratory. Only one patient was receiving specific therapy (protriptyline). Sleep was staged by one scorer (MBA) according to standard criteria and the two nights compared. Recurrent episodes of apnoea and arterial desaturation were found in all seven patients. As expected, there was a short latency to sleep onset on both nights (5·6 *v* 4·5 min). On the first night marginally more time was spent awake and in stage 2 sleep, with less time in REM sleep, although the differences were not significant. Thus, in contrast to normal individuals, patients with sleep apnoea do not appear to have a different sleep architecture between two consecutive studies, suggesting that an acclimatisation night is unnecessary for patients being investigated for sleep apnoea.

Treatment of hyperventilation syndrome

J HARVEY, JG WILLIAMS *Department of Respiratory Physiotherapy and Medicine, Halton General Hospital, Runcorn* Hyperventilation syndrome is easily dismissed as a non-treatable cause of dyspnoea. We wish to present our experiences in the last two years of patients with this condition. Twenty nine patients (17 women and 12 men, age range 18–71 years) diagnosed on either clinical observation or exercise testing were treated. Ten had underlying existing cardiac/pulmonary disease. Each underwent a six stage programme by the respiratory physiotherapist, which established diaphragmatic breathing control in static and then dynamic positions, during speech, exercise, then vigorous exercise combined with speech. The end point of the programme was achieved when the patient was symptomless and the physiotherapist felt that the patient had diaphragmatic breathing control during movement, normal tidal volume and no breath holding. All were told to refer themselves directly back to the respiratory physiotherapist if they had a troublesome recurrence of symptoms. Twenty two out of 29 patients (76%) completed the programme in a mean number of 6·8 (SEM 0·6) visits, 20/22 patients (91%) had complete relief of symptoms, while the remainder had partial relief. Those who had partial relief felt able to cope with more activities than before. None of the 29 patients who completed the programme referred themselves back. Seven patients did not complete the programme, even though five of them seemed to be improving. Two of these subsequently have been seen again only to drop out for the second time. The mean number of visits of the seven patients was less than those who completed the programme (4·9 (0·85) visits) but the difference between the groups did not reach statistical significance. We believe that our six stage treatment programme is a simple and effective treatment for the hyperventilation syndrome provided the patient is motivated.

The cough threshold after abdominal surgery

JP DILWORTH, JC POUNSFORD, RJ WHITE *Department of Medicine, Frenchay Hospital, Bristol* It is frequently suggested that abdominal surgery suppresses cough. We have assessed the effect of surgery on the cough threshold (the concentration at which cough occurs) to inhaled citric acid and capsaicin. Of 49 consecutive patients undergoing elective upper abdominal surgery, 26 consented to being studied. Clinical details including chronic respiratory symptoms and smoking habit were recorded. Cough was stimulated by doubling doses of irritants (capsaicin and citric acid) using a single vital capacity inhalation (Pounsford *et al*, *Thorax* 1985;**40**:657). Threshold was recorded on the immediate preoperative day and on the first and fourth days postoperatively. Anaesthetic and postoperative analgesic regimens were controlled. On the first postoperative day five patients refused further testing. The remaining 21 patients demonstrated a fall in sensitivity to capsaicin and to citric acid ($p < 0·01$). On the fourth postoperative day 17 had further tests and there was a significant increase in sensitivity to both capsaicin and citric acid compared with the first postoperative day ($p < 0·01$). Sensitivity on the fourth postoperative day was still depressed in comparison to the preoperative values ($p < 0·05$). All patients received opiate analgesia on the first postoperative day and there was no significant correlation between the interval from opiate

administration and the threshold to both agents. In most patients the depression of sensitivity to citric acid and capsaicin was similar. The results show that the sensitivity to inhaled irritants is significantly depressed in the immediate postoperative period and this is not fully explained by opiate administration. By the fourth postoperative day the threshold has partially recovered. The relevance to the development of postoperative chest infection requires further study.

The antitussive properties of inhaled local anaesthetics

NB CHOUDRY, RW FULLER, N ANDERSON, J-A KARLSSON *Departments of Medicine and Clinical Pharmacology, Royal Postgraduate Medical School, London, and A B Draco, Lund, Sweden* Cough presents difficult therapeutic problems as most antitussive therapies have minimal benefit. In 10 normal volunteers (6 F, age range 23–34) we investigated the antitussive properties of low dose nebulised lignocaine (L) and dyclonine (D) (which is about five times more potent than L as a topical anaesthetic) on capsaicin induced dose cough response (DCR). The effect of these drugs on capsaicin induced reflex bronchoconstriction was also assessed. DCR was tested by recording the number of coughs after inhaling single breaths of saline or capsaicin (0·4–100 nmol) in random order from a PK Morgan dosimeter. Total respiratory resistance (Rrs) was measured using a forced oscillation technique. Rrs was measured before and immediately after the subjects inhaled a dose of capsaicin using <2 coughs. Rrs and level of oropharyngeal anaesthesia (on a 0–4 scale) response was then measured 2 min post 1 ml saline (S), 40 mg lignocaine (L) and 8 mg diclonine (D) given in a randomised double blind manner. DCR was repeated 10 min after treatment. Median (range) anaesthetic scores after L (3·0 (1–4)) and after D (2·5 (1–4)) were significantly greater than after S (0 (0–3)); $p > 0·01$). Only L reduced the sensitivity of the cough reflex. Geometric mean (95% CI) dose causing three or more coughs (D_3) was 7·8 (4·8–12·6) nmol after S; 12·6 (7·8–20·8) after L ($p < 0·05$); 6·8 (3·0–12·0) after D. Neither treatment altered baseline Rrs or the change in Rrs after capsaicin inhalation, mean change in Rrs being 20·5 (4·0)% after S; 18·5 (4·0)% after L; 23·8 (6·9)% after D. This dose of lignocaine, which caused mild oropharyngeal anaesthesia and no inhibition of reflex bronchoconstriction, reduced the sensitivity of the cough reflex. The lack of antitussive effect of inhaled D, despite producing the same degree of subjective anaesthesia as L, suggests different potencies for local anaesthetics as inhibitors of different sensory nerves. This data supports the view that separate afferent pathways are involved in cough and reflex bronchoconstriction and that they have different sensitivities to local anaesthetics.

Breathlessness in the accident and emergency department: a management problem?

MA HALEPOTA, SP HANLEY *Department of Medicine, North Manchester General Hospital, Manchester* During a three month period, from March to June 1988, the casualty records of all patients (n = 200) indexed in the casualty register as suffering from shortness of breath, breathlessness, difficulty in breathing, and asthma, were examined. Data on diagnostic category, investigations, treatment, outcome, disposal and GP communication were obtained. All patients discharged were sent a questionnaire 4–6 weeks later to assess the outcome of the problem for which they were seen in casualty, and further contact with their GP. Of the 200 patients studied 2·5% (n = 5) died in casualty, 54% (n = 108) were admitted to hospital (A), and 43·5% (n = 87) were discharged from hospital (D). Twenty three percent (n = 20) of patients discharged returned to casualty within 4–6 weeks, of whom 40% (n = 8) were admitted; in addition 5% (n = 4) were seen in outpatients. The five commonest diagnoses were: no diagnosis 46% of all patients, (A = 45%, D = 47%), asthma 12% (A = 13%, D = 12%), COAD/COPD 10% (A = 17%, D = 2%), chest infection 6% (A = 6%, D = 5%), hyperventilation/anxiety 4% (A = 1%, D = 6%). ECG was performed in 37% of all patients (A = 48%, D = 22%), PEF in 33% (A = 26%, D = 43%), chest radiography in 17% (A = 12%, D = 23%), arterial blood gas determination in 13% (A = 22%, D = 1%). In only 8% of those discharged was the GP informed of their attendance at casualty. Fifty four per cent of those discharged replied to the questionnaire, of whom 60% had consulted their GP for the same problem. Of those who consulted their GP 46% had no diagnosis in casualty as opposed to 31% in those who sought no further consultation. We conclude that breathlessness is a diagnostic problem in casualty, for which relatively few simple investigations are undertaken at the time of the acute event. In addition, a substantial proportion of patients seek further advice from their GP, who is unaware of information obtained during the presenting event.

Prospective study of the value of direct general practitioner referral for spirometry and reversibility studies

W KINNEAR, P DENNIS, S REVILL, J WYATT, J MACFARLANE *City Hospital, Nottingham, and Westminster Hospital, London* The value of direct referral of patients by GPs for spirometry and reversibility testing was studied over a six month period. Seventy six patients were referred by the 24 GPs participating in the study. Spirometric results were normal in 27 patients and showed a restrictive defect in six patients. Of the 43 patients with an obstructive defect, the degree of obstruction was severe ($FEV_1 < 50\%$ of predicted) in 17 patients, moderate (FEV_1 50–75% predicted) in 13 patients and mild ($FEV_1 > 75\%$ of predicted) in the remainder. Fifteen of the patients with an obstructive defect showed improvement ($>15\%$ change in FEV_1, FVC or PEF) after two puffs of terbutaline from a metered dose inhaler. After a further six puffs of terbutaline through a nebuhaler, four of the 15 patients who responded to the simple inhaler showed further improvement. Seven patients responded to the higher dose of terbutaline through the nebuhaler, but did not respond to the simple inhaler. Nine patients showed additional reversibility in response to four puffs of ipratropium from a metered dose inhaler. The GPs predicted an obstructive defect in 38 of the

43 patients with airflow obstruction, but their assessment of its severity was in agreement with the spirometry in only 22 patients. Only 16 of the 31 patients predicted to have a reversible defect showed reversibility, compared with five of the 10 patients predicted to be irreversible. In reply to questionnaires sent one month after the tests, the GPs said they had found the tests helpful in the management of 67 of the patients, prompting a change of medication in 35 patients and preventing referral of 21 patients to hospital. Direct referral of patients for spirometry and reversibility studies appears to be useful for GPs in assessing the severity of airflow obstruction and reversibility to inhaled therapy.

Acceptability of direct referral of patients by a general practitioner to a bronchoscopy clinic

W KINNEAR, P GASKIN, J MACFARLANE *City Hospital, Nottingham* We have evaluated direct referral of patients to a clinic where history and examination were followed by fibreoptic bronchoscopy. Twenty five patients were referred on account of an abnormal chest radiograph, while five had haemoptysis with a normal chest radiograph. These patients were compared with 55 patients who were seen in an outpatient clinic before attending for bronchoscopy as a day case on a subsequent day. After a normal bronchoscopy, seven of the 30 patients were referred back to their general practitioner. Two patients with endobronchial malignancy were referred from the bronchoscopy clinic directly for treatment. The remaining 21 patients were given a further outpatient appointment. The median interval between the date the patient was referred and bronchoscopy was 10 days for the patients attending the bronchoscopy clinic and 21 days for those seen in a separate clinic beforehand ($p < 0.01$). In reply to questionnaires on the day after the bronchoscopy, there was no difference between these two groups of patients in the inconvenience of attending for the bronchoscopy or in anxiety before or discomfort during the procedure. Direct referral to a bronchoscopy clinic is acceptable for patients and reduces both the delay between referral and bronchoscopy, and the number of hospital attendances.

Arterial blood sampling with a modified standard plastic syringe

JH CAMPBELL, R CARTER, R MILROY, SW BANHAM *Department of Respiratory Medicine, Glasgow Royal Infirmary, Glasgow* When a standard plastic syringe is used for arterial blood gas sampling a venous sample may be taken in error. Although several manufacturers have developed syringes specifically for arterial blood gas sampling these are not always available. However, the standard syringe can be readily converted into a self filling system. The plunger of a preheparinised 5 ml polypropylene plastic syringe is withdrawn to a predetermined volume and a 21 gauge needle introduced beside the rear of the plunger, so that the needle point lies within the syringe cavity just proximal to the rubber tip of the plunger. On connecting this to an artery, filling of the syringe will take place, displacing the air from it via the needle vent. We studied the accuracy and reliability of this technique by comparison with the standard glass syringe. Twenty paired samples were taken (10 venous, 10 arterial via preinserted arterial lines). No significant differences were seen in any of the measured values between the modified plastic and glass syringes. This is a simple, effective and inexpensive means of reliably obtaining an arterial sample for blood gas analysis.

Lung cancer in young patients

S CAPEWELL AND R SANKARAN on behalf of the Edinburgh Lung Cancer Group *Department of Respiratory Medicine, City Hospital, Edinburgh* The diagnosis of primary lung cancer in patients aged 45 or less is particularly tragic. Do they differ from older patients? During 1981–6 the Edinburgh Lung Cancer Group prospectively registered 3070 new patients, of whom only 45 (1·5%) were aged 45 or less. When compared with 3025 older patients aged >45, a similar proportion of young patients were female (16/45, 35% *v* 28%) and they had equally advanced disease (62% *v* 58% in stage III). Slightly more were in better Karnofsky performance status groups (59% *v* 45%, ⩾80) and symptom duration was shorter (median 45 *v* 93 days). A pathological diagnosis was obtained more often in young patients (98% *v* 81%). The commonest cell type was small cell (34% *v* 24%), with 20% *v* 13% adenocarcinoma and significantly less squamous carcinoma (23% *v* 48%; $p < 0.001$). Although only 11/45 (24% *v* 19%) underwent surgical resection, 8/11 were still alive after three years (73% *v* 40% in older patients). Nine received radiotherapy alone, and one patient was given symptomatic treatment only. Far more young patients received chemotheraphy either alone (16) or with radiotherapy (5)—46% *v* 15% in older patients: There was only one long term survivor and the median survival was eight months in 12 patients with small cell and only four months in nine with non-small cell carcinoma. Lung cancer in young patients, aged 45 and under, is therefore uncommon. Only 24% tumours are surgically resectable and prolonged survival after chemotherapy is rare. Only one of these 45 patients was a non-smoker.

Expandable metallic stents in the treatment of bronchial obstruction

AK SIMONDS, JD IRVING, SW CLARKE, R DICK *Royal Free Hospital, London* An expendable metallic stent designed for intravascular placement has been used in modified form (Wallace *et al*, *Radiology* 1986;**158**:309) to treat symptomatic bronchial obstruction. Patient 1 presented with complete right main bronchial collapse due to probable polychondritis, and patient 2 was treated for extrinsic compression of right and left main bronchus secondary to bronchogenic tumour. A single 2·5 cm length stent was placed in the right main bronchus in patient 1, and two 2·5 cm stents in the right

main bronchus and a single 2·5 cm stent in the left main bronchus in patient 2. The stents comprise 0·018 inch stainless steel wire arranged in zig zag fashion to form cylinders (Cook Inc.) Patients underwent general anaesthesia and fibreoptic bronchoscopy was carried out via an endotracheal tube to ascertain the site and extent of the airway obstruction. Following dilatation of the lesion using an iliac angioplasty balloon, a skin marker was placed over the area of maximal obstruction and the delivery catheter containing the compressed stent introduced under fluoroscopic control. The stent was released once aligned with the skin marker. Hooks on the outer aspect of the stent are designed to embed in the bronchial wall and hence secure position. Symptomatic improvement was immediate. The right main bronchus diameter increased from 0 to 1·9 cm in patient 1 and from 0·7 to 2·0 cm in patient 2. Left main bronchus diameter in patient 2 increased from 0·5 to 1·2 cm. FEV_1/FVC increased from 1·5/3·0 to 2·4/4·0 litres post stent in patient 1 and from 2·0/2·5 to 2·6/3·5 litres in patient 2, with corresponding improvement in the flow-volume loop. No adverse side effects or displacement of stents was observed during 2–12 months of follow up.

Sputum eosinophilia and bronchogenic carcinoma: an 11 year review

P WRIGHT, J YAZBECK, P KELLY, L CLANCY, T HEALY *Peamount Hospital, Newcastle, Co Dublin* Only sputum specimens graded as moderate or numerous were considered in the analysis. All patients with sputum eosinophilia were followed until a definitive diagnosis was made. Fifteen thousand two hundred samples of sputum from 4 479 patients were studied. Two hundred and sixty five patients had sputum eosinophilia and 83 of these had blood eosinophilia. Of the 68 patients who had bronchogenic carcinoma, 27 had both malignant cells and eosinophils in sputum. A further six patients had other malignancies. It is concluded that in the absence of known cause of sputum eosinophilia a moderate or large amount of eosinophils in sputum raises the question of an underlying carcinoma. Patients with unexplained sputum eosinophilia should be assessed for underlying bronchogenic carcinoma.

Diagnosis	*Sputum eosinophilia*	*Blood eosinophilia*
Lung cancer	68	23
Tuberculosis	55	12
Respiratory infection*	46	9
Asthma	37	8
Pulmonary eosinophilia	21	21
No definite diagnosis	13	3
Other cancer	6	2
Other diagnosis*†	19	5
Total	265	83

*Respiratory infection other than tuberculosis.
†Three pneumothoraces, 3 sarcoidosis, 3 aspergilloma, 2 farmer's lung, 2 pulmonary embolus, 2 supraventricular tachycardia, 2 angina; 1 each of bronchiectasis and cryptogenic fibrosing alveolitis.

Nucleolar organiser regions and histological differentiation in squamous cell carcinoma of the bronchus

DAR BOLDY, JG AYRES, JJ CROCKER *Departments of Respiratory Medicine and Histopathology, East Birmingham Hospital, Birmingham* Nucleolar organiser regions (NORs) are loops of DNA which transcribe to ribosomal RNA. NORs can be visualised using a silver staining technique which demonstrates proteins associated with the NORs (AgNORs). The AgNOR method can be used to distinguish benign from malignant tissue, low grade from high grade non-Hodgkin's lymphoma (Crocker and Nar, *J Pathol* 1987;**151**:111) and is useful in many other neoplasms. We have applied the AgNOR method to a series of squamous cell carcinomas of the bronchus to determine whether there is a positive relationship between AgNOR numbers and tumour differentiation. The AgNOR method was applied to 118 paraffin embedded specimens of surgically resected squamous cell carcinomas of the bronchus. The number of AgNOR dots per nucleus were counted for 50 tumour cells per specimen at a magnification of × 1000. AgNOR dots in pseudo stratified columnar epithelium were counted in a similar manner (n = 11). Subsequently a routine H and E section from the same paraffin block was classified histologically into well (W, n = 13), moderately (M, n = 60) or poorly differentiated (P, n = 45) malignancy. In 10 cases it proved impossible to obtain suitable AgNOR staining (4M, 6P) and these specimens are not considered in the analysis. The mean (SD) AgNOR scores were: columnar epithelium 2·3 (0·78), W 10·5 (2·6), M 10·7 (3·2) and P 12·7 (4·5). All grades of tumour had significantly higher scores than normal columnar epithelium ($p = 0·0001$). There was a trend towards higher AgNOR scores in less well differentiated tumours (W *v* MNS, W *v* P = 0·063, M *v* p = 0·009) but there was a considerable spread within the histological group (W 5·9–15·0, M 4·6–18·9, P 5·5–24·0). Further investigation is required to determine whether the AgNOR method may be useful as a prognostic indicator (taking account of tumour staging) and whether higher AgNOR scores reflect an increase in cell proliferation or in cellular DNA content.

Resistance modification in small cell lung cancer (SCLC) cell lines in vitro

R MILROY, J PLUMB, S KAYE *Department of Respiratory Medicine, Royal Infirmary, Glasgow, and CRC Department of Medical Oncology, University of Glasgow* It has been suggested that resistance modifiers such as verapamil (V) may be used to overcome drug resistance in SCLS. Since this suggestion is based on laboratory studies of cell lines where drug resistance has been induced in vitro little is known of the value of such agents when drug resistance is developed in vivo. We have therefore compared the efficacy of resistance modifiers on SCLC cell lines made resistant to doxorubicin (D) in vitro with that on newly established small cell lines. H69LX10 is about 100 fold more resistant to D (ID_{50} = 6·1 μM) than the parent cell line, H69, from which it was derived (ID_{50} = 86 nM).Both lines become more sensitive to D in the presence of V (6·6 μM) but the change is much

greater for H69LX10 (10 fold) than for H69 (two fold). Similarly, three newly established small-cell lines also show a two to three fold increase in sensitivity in the presence of V (6·6 μM). The effect of V on the drug sensitivity of H69LX10 is dose dependent and at clinically achievable doses (2 μM) the effect is much smaller (four fold). In contrast, quinidine (6·6 μM) increases the sensitivity of H69LX10 to D by 10 fold and this concentration can be achieved in patients. The D isomer of V is less cardiotoxic than the racemic mixture but is equally effective at increasing drug sensitivity. Thus the effects of resistance modifiers appear to be much greater in cell lines that have been exposed to cytotoxic drugs in vitro. None the less, there is clear evidence of significant resistance modification in newly established small cell lines and this should encourage further clinical studies using such agents.

Increased levels of vaccenic acid in bronchogenic carcinoma tissue

N LAWSON, D HUSBAND, J MCGUIGAN, DCT WATSON, FJ COLLINS, HI PANDOV *Departments of Clinical Chemistry and Regional Thoracic Surgery, East Birmingham Hospital, Birmingham* The fatty acid profiles in bronchogenic carcinoma tissue (BCT) were compared with those in normal tissue (NT) employing a previously described capillary gas liquid chromatography method (Taylor *et al, Ann Clin Biochem* 1987;**24**:293). Tumourous and normal tissue was collected into liquid nitrogen from 28 patients undergoing surgery. The tumours were classified as squamous cell carcinoma (n = 20), adenocarcinoma (n = 4) or other (n = 4). The most consistent changes observed were an increase in the level of vaccenic acid: 0·025 (SD 0·008) *v* 0·054 (0·025), NT *v* BCT (results expressed relatively where the sum of all the fatty acids measured = 1); $p < 0·001$ (Wilcoxan signed ranks test) and a decrease in palmitic acid: 0·312 (0·028) *v* 0·259 (0·036), NT *v* BCT ($p < 0·001$). When the results were expressed as a vaccenic:palmitic acid ratio (VPR), it was found that 90% of the patients had a higher VPR in BCT compared with NT (21·93 (10·95) *v* 8·24 (2·97), the biggest differences (up to 10 fold) being seen in the patients with squamous cell carcinoma. This change in the VPR has given some insight into changes in lipid metabolism that are occurring during tumourgenesis and development. Vaccenic acid (C18:1,11 *cis*) is synthesised by the direct desaturation of palmitic acid (C16:0) followed by elongation, as opposed the 10 fold more abundant isomer, oleic acid (C18:1,9 *cis*), which is produced by direct desaturation of stearic acid (C18:0). It is possible that specific changes in the activity of the Δ-9 desaturase is occurring in tumour tissue, which leads to an increase in vaccenic acid.

DNA heterogeneity in lung cancer and its relevance to studies of prognosis

FA CAREY, D LAMB *Department of Pathology, University Medical School, Edinburgh* Flow cytometric studies of lung cancer have shown great variation in the percentage of aneuploidy detected, ranging from 45% to 96% in different series. Many authors have claimed that abnormal DNA content is associated with a poor prognosis but not all have found this to be the case. In these studies little attempt has been made to assess the effects of sampling methods on the results of ploidy estimation. The aim of the present study was to determine the degree of heterogeneity of DNA content within lung carcinomas, to attempt a correlation with histological appearances and to assess the implications for prognostic studies. Twenty consecutive resection specimens for lung cancer were systematically sampled, an average of 10 different tissue samples from different tumour areas being taken in each case. Of the carcinomas 90% showed intra-tumour variation in ploidy when analysed by flow cytometry. Ninety five per cent of cases were aneuploid in at least some areas but, if only one sample were taken for each case, the incidence of aneuploidy could be as low as 45%. It was also found that, in many cases, DNA heterogeneity could be related to differences in histological pattern. The findings suggest that sampling methods are of primary importance in assessing the ploidy status of lung cancer. Adequacy of sampling is essential if DNA status is to be used in prediction of prognosis in patients with lung cancer.

Injury to pulmonary epithelial cells grown on different extracellular matrices caused by rat mast cell protease

K DONALDSON, GM BROWN, GFJ NEWLANDS, J SLIGHT, HRP MILLER *Institute of Occupational Medicine and Moredun Research Institute, Edinburgh* Mast cells are present within the lung and they release a range of mediators including proteases during inflammatory and immune events at epithelial surfaces. We assessed the ability of highly purified protease (*Immunology* 1948;**58**:101), derived from rat mast cells, to cause injury to an alveolar epithelial cell line in vitro (*Br J Exp Pathol* 1988;**69**:327) and degrade a fibronectin matrix (*Thorax* 1988;**43**:132). Rat mast cell protease 1 (RMCP1) caused dose dependent detachment injury (detachment of live cells from the substratum) to epithelial cells cultured on uncoated (plastic), or fibronectin coated surfaces (results given as × (SD) cpm of ^{51}Cr in cells detached from fibronectin coated surfaces): background 636 (280), 100 ng/ml RMCP1 1375 (399), 500 ng/nl RMCP1 5702 (1550) ($p < 0·001$). In contrast, there was substantially less detachment injury caused to epithelial cells cultured on type IV collagen: background 809 (240), 100 ng/ml RMCP1 1691 (855), 500 ng/ml RMCP1 1778 (808) (NSD). RMCP1 also had the ability to attack the extracellular matrix component fibronectin (results given as × (SD) cpm of ^{125}I fibronectin degradation products): spontaneous 1800 (208), 100 ng/ml RMCP1 5068 (30) ($p < 0·001$). These in vitro results may reflect the ability of mast cell proteases to cause epithelial permeability changes during degranulation at epithelial surfaces within the lung.

Bleomycin induced lung injury in the rat: effects of the platelet activating factor (PAF) receptor antagonist BN 52021 and platelet depletion

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don Bloemycin is a highly effective antitumour agent, but pulmonary toxicity, characterised by an acute inflammatory reaction and associated pulmonary oedema, limits the dosage and applications of the drug. Platelet activating factor (PAF) is a membrane derived phospholipid that can mediate pulmonary microvascular injury, possibly through platelet activation. We sought to investigate the role of PAF in bleomycin induced lung injury in the rat, using the PAF receptor antagonist BN 52021; and the role of platelets through the use of an antiplatelet antibody. Lung injury was induced by intratracheal bleomycin and assessed by measurements of lung wet weight and total pulmonary extravascular albumin space (TPEAS). Bleomycin caused a significant increase in both indices after 48 hours compared with control animals ($p < 0.05$). A single dose of BN 52021 (20 mg/kg orally) caused a significant reduction in lung weight ($p < 0.05$) but not TPEAS after 48 hours. BN 52021 20 mg/kg 12 hourly postoperatively again resulted in a significant reduction in lung weight alone after 48 hours ($p < 0.05$). Reducing circulating platelet number by approximately 75% had no effect on either lung weight or TPEAS 48 hours after bleomycin ($p > 0.05$). We conclude that PAF has an important role in bleomycin induced lung injury, but that its effects are probably not mediated via platelets.

A mechanism for the role of steroids in the treatment of asthma?

AB MILLAR, BN HUDSPITH, A LAU, F PEARCE, NMcI JOHNSON *Departments of Immunology and Medicine, University College and Middlesex School of Medicine, and Department of Chemistry, University College London* Bronchoalveolar mast cells have been proposed as important in the pathogenesis of airflow obstruction in asthma (*Br Med J* 1985;**291**:923) and the role of steroids in the treatment of asthma is universally accepted. We have studied the effects of a course of steroid treatment on the number and behaviour of mast cells obtained by bronchoalveolar lavage (BAL) in seven patients with chronic stable asthma. All the patients studied exhibited a change in FEV_1 of greater than 20% in response to inhaled salbutamol. Each patient underwent full lung function tests, fibreoptic bronchoscopy and BAL before and after a two week course of prednisolone (30 mg/day). Any baseline treatment remained unchanged. Their mean (SD) FEV_1 before and after treatment was 70 (22) l and 81 (23) l respectively. Before and after steroid therapy a total cell count $\times 10^6$ obtained from BAL fluid was 13 (2·4) and 16 (2·0) respectively, whereas the percentage of mast cells was 0·18 (0·04) and 0·11 (0·03) respectively. The total histamine content of the BAL fluid was 6·6 (2·9) and 3·3 (0·7) (ng/ml) before and after therapy and the spontaneous release of histamine as a percentage of the total was 17·1 (2·7) and 8·5 (3·6) respectively. This suggests that the mechanism of action for steroids in the treatment of asthma may be related to mast cell numbers and action.

Effect of *N*-acetyl cysteine on the release of oxygen radicals from neutrophils and alveolar macrophages

E DROST, S LANNAN, K DONALDSON, M BRIDGEMAN, DC FLENLEY, W MACNEE *Department of Respiratory Medicine, Rayne Laboratory, City Hospital; Institute of Occupational Medicine; and University Department of Biochemistry, Edinburgh* Glutathione (GSH) is an antioxidant in cells and body fluids. The thiol containing drug *N*-acetyl cysteine (NAC) when deacetylated to cysteine is a precursor of GSH synthesis and hence may be effective as a scavenger of active oxygen species. We measured the spontaneous and phorbol myristate acetate (PMA) stimulated release of hydrogen peroxide (H_2O_2), and superoxide anion (O_2^-) using standard assays from: (1) alveolar macrophages ($2·5 \times 10^5$ cells) obtained at bronchoalveolar lavage (BAL) in six control rats and six rats given NAC for one week; (2) neutrophils (PMNL) ($2·5 \times 10^5$ cells), harvested from whole blood in five normal, non-smoking subjects before and after five days' NAC (600 mg/day). Spontaneous release of O_2^- was higher (mean (SEM) 1·9 (0·1) nmol) and PMN stimulated release was similar (9·5 (0·5) nmol) in NAC treated rats than control animals (1·1 (0·1) nmol, $p > 0.01$; 9·0 (1·2) nmol, $p > 0.05$ respectively), without significant change in H_2O_2 release. Thus the fold increase in O_2^-, but not in H_2O_2 release, following PMA stimulation was less in NAC treated rats (4·9 (0·3)) than control animals (8·6 (0·8), $p < 0.01$). PMNL from normal subjects after treatment with NAC also showed a reduction in the fold increase in O_2^- release when stimulated with PMA (2·7 (2·4)) compared with pretreatment values (20·1 (8·8), $p < 0.02$), as a result of both an increase in spontaneous and a decrease in PMA stimulated O_2^- release from PMNL ($p > 0.05$). NAC did not change H_2O_2 release significantly. These results were associated with an increase in cysteine in rat BAL fluid (control 0·8 (0·7) μmol, NAC 1·4 (1·1) μmol, $p < 0.05$) and in both plasma cysteine and GSH in man ($n = 3$) (pre-NAC, cysteine 6·0 (1·0), GSH 2·0 (0·4) μmol; post-NAC, cysteine 11·4 (3·6), GSH 2·8 (0·3) μmol). We conclude that NAC enhances the spontaneous release of O_2^- from rat AM and human PMNL, but reduces the change in O_2^- release from cells stimulated with PMA.

Flow cytometric analysis of pulmonary lymphocytes recovered from mice infected with human respiratory syncytial virus (RSV)

PJM OPENSHAW, BA ASKONAS *Immunology Division, National Institute for Medical Research, London* RSV is an important respiratory pathogen, especially in infancy. Vaccines have been ineffective or worsened subsequent disease, and require testing in animals. Passive transfer of RSV specific $CD8^+$ cytotoxic T cells into RSV infected mice clears virus from the lung but induces haemorrhagic pneumonitis, which may be fatal (Cannon *et al*, *J Exp Med*, in press). Such studies have been hampered by difficulties of quantifying the pulmonary response to RSV. Lymphocytes appear in bronchoalveolar lavage (BAL) fluid of RSV infected mice (Openshaw and Askonas, *Clin Sci* 1987;**72**(suppl 16):35P); we now describe phenotypic studies of these cells. Groups of BALB/c mice aged 10–16 weeks were infected intranasally with 10^5 pfu of A2 strain RSV, and subjected to BAL at six time points up to 12 days after infection. Multiple two colour immunofluorescent stains were performed using antibodies to CD4 (L3 T4), CD8 (Lyt 2), CD3 (Mouse T3), Thy 1·2 and surface immunoglobulin (SIg); and an EPICS V flow cytometer was used to quantify size, scatter and staining. Cytospin prepara-

tions showed >95% of cells recovered from uninfected or sham infected mice to be macrophages. Following infection, lymphocytes increased between days 5 and 10, and declined towards baseline after day 14. Total viable cell recovery increased from 2×10^5 to 6×10^5 per mouse by day 10, of which 40% were lymphocytes. Flow cytometry showed: (1) On days 3–6, 30–60% of recovered lymphocytes were Thy 1^- Sig^- ("null cells") but this proportion fell to <20% later during infection. (2) $CD8^+$ cells outnumbered $CD4^+$ cells from day 6 onwards by 2–4 fold. (3) SIg^+ (B) cells never exceeded 4% and were typically <2% of recovered lymphocytes. We conclude that $CD8^+$ T cells constitute the major lymphocyte subset recovered from the lungs of mice recovering from RSV infection.

Characterisation of phenotypically distinct macrophage subsets found in human bronchoalveolar lavage (BAL) fluid

MONICA A SPITERI, J TUCKLEY, SW CLARKE, LW POULTER *Royal Free Hospital and School of Medicine, London* Three phenotypically distinct macrophage subsets have been isolated from human BAL fluid (Spiteri *et al*, 1988). These subsets exhibit different functional capacities in allogeneic mixed lymphocyte reactions. Their fundamental characteristics were thus investigated by using a panel of monoclonal antibodies (RFDR1 identifies a framework epitope on the HLA-DR molecule and LEU 11b human NK cell and neutrophil antigens associated with Fc receptor for IgG; anti-C_3b reacts with receptor for third component of human complement) by analysing their lyzosomal enzyme content (acid phosphatase reaction) and physiological activity (hexose monophosphate shunt). The non-adherent $RFD1^+$ $D7^-$ cells (strong MLR stimulators) were Fc receptor negative, with reduced expression of C_3b receptors (<1%) and poor lyzosomal activity. In contrast the adherent $RFD7^+$ $D1^-$ and $RFD1^+$ $D7^+$ macrophages (poor MLR stimulators) were Fc receptor positive with increased C_3b receptor expression (60% and 35% respectively) and high acid phosphatase content. All three subsets showed marked expression of RFDR1 (>95%). Hexose monophosphate shunt activity was found to be high in both $RFD7^+$ $D7^-$ and $RFD1^+$ $D7^+$ macrophages, while the $RFD7^+$ $D1^-$ subset had minimal activity. These findings support the heterogeneity of the alveolar macrophage population. Further evaluation of these subsets (which appear to change in disease states: Ainslie *et al*, 1988; Johnson *et al*, 1988) should provide a useful tool in understanding their individual roles in modulating disease processes.

Mediators and cells of bronchoalveolar lavage fluid during compensatory lung growth

RJ MCANULTY, LH STAPLE, D GUERREIRO, GJ LAURENT *Biochemistry Unit, Department of Thoracic Medicine, Cardiothoracic Institute, University of London, London* After unilateral pneumonectomy in many species a rapid compensatory growth of the remaining lung tissue occurs. The mechanism of this compensatory growth is unknown. To investigate this process, we have examined the effects of bronchoalveolar lavage (BAL) fluid on fibroblast replication as well as changes in vascular permeability and BAL cell profiles at various times after partial pneumonectomy in the rat. Left unilateral pneumonectomy was performed in rats under halothane anaesthesia. BAL was carried out in situ via a cannula in the right main bronchus. Cytocentrifuge preparation of BAL cells were stained with May-Grünwald-Giemsa or non specific esterase for differential cell counts. BAL fluid was tested for its effect on fibroblast replication in a colorimetric assay, based on methylene blue uptake into cell cultured in 96 well plates. Animals were injected 24 hours prior to death with 1 μCi of ^{125}I human serum albumin. Vascular permeability was assessed by calculating the ratio of radioactivity in 1 g of lung to that in 1 ml of plasma. Vascular permeability increased by about 50% six days after pneumonectomy ($p < 0.05$). The total number of BAL cells increased, with more than double control values. Differential cell counts showed a marked influx of neutrophils at two days with increased proportions of lymphocytes and eosinophils later. BAL fluid from pneumonectomised animals were more active than control in stimulating fibroblasts. The results demonstrate the presence of stimulatory activity for fibroblast replication in BAL fluid and suggest a potential role for cells and/or mediators from the circulation during compensatory lung growth.

Effect of theophylline and adenosine on guinea pig and human eosinophil activation

T YUKAWA, C KROEGEL, P CHANEZ, G DENT, KF CHUNG, PJ BARNES *Department of Thoracic Medicine, Cardiothoracic Institute, London* Theophylline is an effective bronchodilator; in addition, it may possess anti-inflammatory activity in the treatment of asthma as illustrated by its inhibition of the late phase response to inhaled antigen. Because eosinophils may have a critical role in asthma, we have examined the effects of theophylline on opsonised zymosan induced superoxide anion (O_2^-) release from guinea pig eosinophils harvested from the peritoneal cavity. High concentrations of theophylline (10^{-3} M) inhibited O_2^- release (mean (SEM) by 27·6 (9·4) % ($p < 0.05$), but therapeutic concentrations (10^{-6}–10^{-5} M) caused potentiation (26·8 (9·9) % ($p < 0.05$) to 36·9 (6·3) % ($p < 0.01$)). 8-Phenyltheophylline, an adenosine antagonist with no phosphodiesterase activity, produced potentiation from 10^{-7} M to 10^{-3} M. Adenosine deaminase (0·1 U/ml), which inactivates endogenous adenosine, enhanced O_2^- release (72·4 (15·2) %, $p < 0.01$) and adenosine (3×10^{-8} to 10^{-6} M) reversed the potentiation induced by 10^{-5} M theophylline in a concentration dependent manner. The adenosine A_2 selective analogue *N*-ethylcarboxamide adenosine (NECA) was a more effective inhibitor than the A_1 analogue phenylisopropyl adenosine (PIA), suggesting that A_2 receptors are involved. A similar effect of theophylline and adenosine on O_2^- release was observed on human eosinophils obtained by differential centrifugation of blood from patients with peripheral eosinophilia. Thus, at therapeutic concentra-

tions, theophylline may potentiate eosinophil activation by inhibition of endogenous activation of adenosine A_2 receptors; this effect would be consistent with the lack of effect of theophylline on the bronchial hyperresponsiveness of asthma.

Optimal time for nebulisation of beta agonists in asthma

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Previous dose response studies have reported various "optimal" doses for nebulised beta agonists obtained by varying the dose of drug in a standard volume of solution for nebulisation. In this study the dose of drug was varied by altering the time of nebulisation of a standard solution of 5 mg terbutaline in a total volume of 4 ml normal saline, from a standardised nebuliser (Medic-Aid Portaneb 50 compressor, Acorn nebuliser and mouthpiece). We expected to find that a shorter time of nebulisation would be as satisfactory as the currently recommended nebulisation to "dryness." Eight asthmatic patients (two male and six female) were studied, each on five separate occasions. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured at baseline, immediately after nebulisation and thereafter at 5, 10, 15, 30, and 60 minutes. Nebuliser time was varied at 2, 4, 6, 8, and 10 minutes on different days. As expected, in this group of asthmatics there was marked variability in the baseline measurements for each individual and therefore results were expressed as a percentage of the maximum FEV_1 achieved on any of the five attendances measured at 60 minutes after nebulisation. In each case > 90% of the maximum FEV_1 was achieved after either four or six minutes' nebulisation. This suggests an optimal time for nebulisation of six minutes when the above concentration of terbutaline is used.

Comparative assessment of enprofylline and theophylline for chronic obstructive airways disease in the elderly

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Enprofylline is a recently developed xanthine derivative which is five times more potent than theophylline in its bronchodilatory effect. We report the first study comparing the use of oral enprofylline with theophylline for chronic obstructive airways disease in elderly subjects. The study was of a randomised double blind parallel design and commenced with a reference period lasting one week when any oral bronchodilators were withdrawn. Patients were then treated with either enprofylline or theophylline 150 mg bd for two weeks (period 1) followed by 300 mg bd for a further three weeks (period 2). Throughout the study patients recorded peak expiratory flow (PEF) and adverse experiences in a diary. Plasma concentrations of enprofylline and theophylline were measured 4–6 hours after tablet intake at the end of periods 1 and 2. Of 111 patients recruited for the study, 85 entered active treatment (theophylline n = 44, enprofylline n = 41). Mean age was 72 years and their mean bronchodilatory reversibility was 22%. Enprofylline increased morning PEF by 11% (period 1) and 19% (period 2) whereas theophylline increased PEF by 13% and 19% respectively. The most common adverse experiences (29%) with enprofylline were headache and nausea/vomiting. With theophylline, nausea/vomiting was the most common experience (7%). Mean plasma concentrations of enprofylline were 2·0 mg/l and 3·4 mg/l, and with theophylline 5·4 mg/l and 10·0 mg/l for periods 1 and 2 respectively. Enprofylline and theophylline produced similar improvements in lung function and asthma symptoms but enprofylline was less well tolerated than theophylline.

Salbutamol and ipratropium bromide responses in patients with partially reversible airflow obstruction

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We have performed a retrospective survey of patients attending the respiratory function laboratory to have their bronchodilator response tested. Patients were routinely given both salbutamol (S) and ipratropium bromide (IB) sequentially by inhalation. We selected 206 consecutive patients who had an FEV_1 response of more than 200 ml to at least one drug and whose FEV_1 post salbutamol was less than 80% predicted. The median dose of S was 800 mcg and of IB was 108 μg. The age range was 24–84 years. Eighty six patients had responses to both drugs, 92 to S only and 28 to IB having failed to respond to S. FEV_1 increase with S was correlated with age ($r = -0{\cdot}32$, $p < 0{\cdot}01$) and with baseline % predicted FEV_1 ($r = 0{\cdot}17$, $p < 0{\cdot}05$). Subjects who responded to IB alone were significantly older. There was no difference between the groups in smoking habits or in the doses received. Those responding to both bronchodilators had a significantly lower starting FEV_1 and FVC (% predicted) than those responding to S alone. The results demonstrate that 14% of these patients responded to IB after failing to respond to S, and 48% did so when incomplete reversibility occurred with standard doses of S. They also confirm the relationship between age and the response to beta adrenergic agents.

Efficacy and side effects of sublingual salbutamol in asthma

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The sublingual route of administration provides rapid drug absorption and avoids first pass metabolism. Sublingual isoprenaline was used in the past as bronchodilator therapy for asthma, but fell into disrepute because of dose limiting adverse effects (tachycardia and tremor). Salbutamol is a more selective $beta_2$ adrenoceptor agonist with a longer duration of action, and might therefore be of potential value given sublingually. Seven asthmatic patients (five males, mean (SEM) 45 (8) y, FEV_1 76 (7) % predicted) were given either sublingual salbutamol tablet 2

mg (SL), swallowed tablet 2 mg (O), metered dose inhaler 200 μg (INH) or placebo (Pl: by all three routes), in a randomised cross over design. Airways parameters (FEV_1, FVC, PEF), finger tremor (Tr), heart rate (HR) and plasma potassium (K) were measured at 15, 30, 60 min and then hourly up to six hours past treatment. Baseline values were unchanged on all four days for all variables measured. Maximum ΔFEV_1 (1) were: 0·393 (0·053) (INH), 0·300 (0·119) (O), 0·271 (0·024) (SL); and time to peak response: 30 min, 2 h and 2 h respectively. These changes in FEV_1 were highly significant ($p < 0.001$) in comparison to Pl. Maximum ΔFEV_1 was greater with INH than with O and SL ($p < 0.001$). Similar changes were found with FVC and PEF. Tr was unchanged with INH, whereas O and SL produced significant increases in Tr (as % change) with a peak at 3 h: 281·3 (106·2) ($p < 0.05$ *v* Pl) and 308·7 (52·9) ($p < 0.001$). There were no differences in Tr between O and SL. The oral route was associated with a ΔHR of 4·1 (2·3) beats/min at 2 h ($p < 0.05$ *v* Pl) and ΔK of −0·25 (0·09) mmol/l at 4 h ($p < 0.05$). In conclusion, the pharmacodynamic profile of sublingual salbutamol is similar to that of the oral route. However, inhaled salbutamol produced a more rapid and larger airway response than sublingual or oral administration, without systemic adverse effects.

Nedocromil sodium and sodium cromoglycate in patients over 50 years of age with reversible airflow obstruction

D BOLDY, JG AYRES *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* Inhaled non-steroidal prophylaxis is rarely used in older patients with reversible airflow obstruction (RAO). A randomised double blind study compared nedocromil sodium (NS) with sodium cromoglycate (SC) in the treatment of patients over 50 years of age with RAO. All patients were taking inhaled $beta_2$ agonist and inhaled steroid, demonstrating either a $\geq$ 15% reversibility in response to an inhaled $beta_2$ agonist or a PEF diurnal variation (DV) of $\geq$ 15%. In patients with stable RAO inhaled steroids were reduced during a run in period; they were entered if inhaled $beta_2$ agonist use rose by > 25% or PEF DV exceeded 15%. Seventy seven patients entered the 16 week study period, 38 receiving 4 mg qds of NS (mean age 62·9 years, mean duration of RAO 12·1 years, 21 M: 17 F) and 39, 10 mg qds of SC (mean age 63·6 years, mean duration of RAO 12·5 years, 19 M: 20 F). The mean PEF, FEV_1 and FEV_1/FVC (%) were similar in the two groups (NS 288, 1·54 and 57; SC 298, 1·55 and 59 respectively). Sixty nine patients completed the study. Both groups showed a reduction in inhaled bronchodilator usage (NS from 9·5 to 7·90, SC from 8·7 to 7·2) but the difference between the groups was not significant. Mean PEF increased slightly in both groups (morning: 4·8% NS, 6·0% SC; evening: 0·4% NS, 4·0% SC). Symptoms and clinic FEV_1 and FVC showed no overall changes during the study. Seventeen out of 29 (59%) NS patients and 19/38 (50%) SC patients considered the treatment to be very or moderately effective. Sixteen out of 77 (23%) (6 NS; 10 SC) showed considerable improvement in $beta_2$ inhaler use (reduction > 25%) and PEF (increased by > 30% or DV reduced to < 10%). The commonest side effect was an unpleasant taste (10 in each group); 28/77 (36%) reported blocking of the inhaler. Therefore both NS and SC may be useful additional treatments in the management of the older patient with RAO.

Increased airway reactivity to histamine after smoke inhalation injury

J KINSELLA, R CARTER, WH REID, D CAMPBELL, CJ CLARK *Burns Unit, University Department of Anaesthesia; and Departments of Respiratory Medicine, Glasgow Royal Infirmary and Hairmyres Hospital, Glasgow* Airways obstruction is a feature of smoke inhalation injury. The degree of obstruction is related to the severity of inhalation injury (Clark *et al*, *Thorax* 1988;**43**:828). This study assesses the role of altered airways reactivity in this process. Eighteen fire victims with proven smoke inhalation had histamine challenge performed within one week of injury. Three had normal reactivity (PC_{20} > 8 mg/ml), 10 had mildly increased reactivity (PC_{20} 1–8 mg/ml), three had moderately increased reactivity (PC_{20} 0·125–1·0 mg/ml) and two had markedly increased reactivity ($PC_{20} < 0.125$ mg/ml) (Cockcroft *et al*, *Clin Allergy* 1977;7:235). The PC_{20} did not correlate with the severity of smoke inhalation as measured by the exposure carboxyhaemoglobin (eCOHb). There was no correlation between the PC_{20} and FEV_1 (absolute or predicted). Nine of these patients with increased reactivity have now had repeat testing at three months. The mean PC_{20} has improved from 1·41 (SEM 0·34) to 4·14 (1·48) mg/ml ($p = 0.038$, Wilcoxon matched pairs). The FEV_1 change from 2·40 (0·28) to 2·55 (0·25) l, not significantly different. A high incidence of increased airway reactivity to histamine has been shown in a group of smoke inhalation patients. The reactivity has decreased when repeat tests are performed three months after the acute incident, which suggests that the results are not due to pre-existing disease. Since the PC_{20} does not correlate with eCOHb the response does not appear smoke dose related. The presence of increased reactivity suggests that airways obstruction following acute smoke inhalation injury should be treated with suitable anti-inflammatory medication, such as inhaled corticosteroids, and the duration of treatment should be determined by sequential respiratory function assessment, including bronchoprovocation testing.

Circumstances of death in asthma

SC WRIGHT, AE EVANS, DG SINNAMON, J MACMAHON *Belfast City Hospital, Coleraine Hospital, and Department Community Medicine, Queens University, Belfast* We have investigated asthma deaths in Northern Ireland for 1981–4. As previously described, information was obtained from death certificates, GP case notes and questionnaires, interviews with a relative of the deceased, hospital charts and autopsy reports. One hundred and seventy four deaths were confirmed. Seventy per cent of the patients had consulted their GP

within two weeks of death. Of the 144 cases where details were obtained, 26 (18%) had felt worse for over one month. Fifty nine (41·3%) suddenly deteriorated and of these 29 (49·1%) were dead within 15 minutes and a further 10 (16·9%) within one hour. Only one quarter of the deceased were thought by their relatives to have felt the fatal asthma attack was initially more severe than usual. The GP was called during the fatal episode in 90 cases. The patient had already died when they arrived in 51 cases (56·7%). Twelve (13·3%) were treated and left at home. Of the other 84 cases, 37 (44·1%) were found dead and 18 (21·4%) dialled 999. The majority of deaths (62·6%) occurred at home but 11 (6·3%) died en route to hospital. The length of the fatal attack was known in 130 cases. In 69 cases (53·1%) the acute attack was rapidly fatal—26 (20%) died within five minutes of the onset. Death was more common in the early morning hours but was evenly distributed throughout the week days. We conclude: (1) Many deaths occurred in previously "healthy" individuals. (2) Action taken by patients in the fatal attack varied widely and was often delayed. (3) Better transport to hospital is required for the acutely ill asthmatic. (4) Asthma patients should have a clear plan of action in the event of a severe attack.

Formoterol inhibits exercise-induced bronchospasm for longer than salbutamol

LG McALPINE, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow* Formoterol is a new potent beta$_2$ agonist bronchodilator; there is evidence to suggest that it has a more prolonged duration of action than currently available agonists. We have compared the protective effect of formoterol 12 μg with salbutamol 200 μg and placebo against exercise induced bronchoconstriction; these doses of beta agonist have previously been shown to be equipotent. Twelve patients with asthma were studied, five male and seven female, mean age 28·2 years (range 19–41 years). All had normal resting lung function with mean FEV_1 92·2% (range 69–113%) predicted and all had demonstrated a fall in FEV_1 of > 20% after treadmill exercise. On each of three study days formoterol 12 μg, salbutamol 200 μg or placebo was administered from a metered dose inhaler, double blind and in random order. Treadmill exercise challenge was performed two hours and four hours later and FEV_1 was recorded over the 30 minutes following exercise. Pre-exercise FEV_1 was increased equally by the two active drugs: formoterol 11·5%, salbutamol 10·0%; there was no significant change after placebo (−1%). At two hours the maximum fall in FEV_1 after formoterol (7·7%) and salbutamol (14·1%) was significantly less than after placebo (32·7%), ($p < 0·01$); there was no difference between the active drugs. At four hours, formoterol (6·7%) was significantly more effective than salbutamol (21·2%) and placebo (22·3%), ($p < 0·01$). Similarly, by analysis of the area under the curve of percentage change in FEV_1, formoterol and salbutamol were equally effective compared with placebo ($p < 0·01$) at two hours whereas at four hours formoterol was more effective than either salbutamol or placebo ($p < 0·01$), salbutamol being no more effective than placebo. Formoterol 12 μg and salbutamol 200 μg produce similar degrees of bronchodilation and provide equal protection against exercise induced bronchoconstriction two hours after administration; formoterol gives continuing protection four hours after administration while salbutamol is no more effective than placebo at that time.

Prospective study of pneumonia developing in surgical wards

WJM KINNEAR, RG FINCH, R PILKINGTON, JT MACFARLANE *City Hospital, Nottingham* Studies from North America have suggested that pneumonia developing in hospital is not uncommon, and often associated with Gram negative and *Legionella* infection. We have studied the incidence, pathogenesis, morbidity and mortality of pneumonia in patients on surgical wards. Over a six month period, daily visits to five surgical wards identified 38 patients who developed pneumonia more than 48 hours after admission. The median age of the patients was 70 years, range 37–90 years and 19 were smokers. Thirty three patients (17 smokers) developed their pneumonia postoperatively, the median duration of anaesthesia for the 32 patients who had a general anaesthetic being 95 minutes, range 15–360 minutes. Twenty eight patients had an abdominal incision, upper midline in 22. The median time after surgery that pneumonia developed was two days, range 1–12 days. Two patients were ventilated and six (18%) died. A pathogen was identified in 50% of cases. Sputum from 34 patients was cultured and grew *Strep pneumoniae* in two patients, *H influenzae* in four patients, and *Staph aureus* in two patients, one of whom also grew *H influenzae*. *Pseudomonas species* and coliform bacilli were each grown from one patient. Pneumococcal antigen was detected in the sputum from 10 patients, including both of those who grew *S pneumoniae* and one who grew *H influenzae*. All blood cultures were negative. Respiratory serology was diagnostic in only two cases, one with *Chlamydia psittacii* and one with respiratory syncytial virus. No change in mycoplasma or legionella titres was seen in any patient. Nosocomial pneumonia is rare on our surgical wards. Although a pathogen was identified in only 50% of cases, the pattern of infection is similar to that seen in community acquired pneumonia.

Inspiratory and expiratory chest films in the diagnosis of pneumothorax

M BRADLEY, C WILLIAMS, MJ WILSHAW *Departments of Medicine and Radiodiagnosis, Royal Liverpool Hospital, University of Liverpool* It is common clinical practice in some hospitals to request paired inspiratory and expiratory chest films when there is the suspicion of a pneumothorax, thus doubling the radiation dose to the patient and the cost of the investigation. It was our impression that little extra information is gained from an expiratory over the routine inspiratory film. To study this further, a review of paired inspiratory and expiratory erect chest radiographs demon-

strating a pneumothorax in our hospital between January 1985 and April 1988 was carried out. All the films were reviewed by two radiologists independently. A pneumothorax was classed as "small" if it occupied less than 25% of the hemithorax as measured by the average intrapleural diameter. We found that 79 patients with pneumothoraces had had paired chest films at presentation (mean age 42 years, range 16–84; 59 males). Thirty nine cases (49%) were spontaneous, 16 (20%) were associated with an exacerbation of airways disease, and 24 (30%) were due to trauma. Twenty nine patients (41%) were aged over 50 years. Forty two pneumothoraces (53%) were classed as small, and 52 (66%) required some form of drainage (9 aspiration, 43 intubation). At presentation, all pneumothoraces were plainly visible on both inspiratory and expiratory films. On follow up in only one case was the resolving pneumothorax visible on an expiratory film when it was not visible on the inspiratory film also. However, in two patients with traumatic pneumothoraces, a lung contusion was visible at presentation on the inspiratory film only, suggesting that a routine expiratory film alone would be inadequate. Our review shows that all the pneumothoraces could reasonably be diagnosed on an inspiratory film alone, and suggests that expiratory films should not routinely be performed in this condition.

Investigation and treatment of pulmonary arteriovenous malformations

MKB WHYTE, ER CHILVERS, J JACKSON, AM PETERS, JMB HUGHES, DJ ALLISON *Departments of Medicine and Diagnostic Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London* This report deals with the investigation and treatment of 18 patients (nine male, age range 13–59 y) with pulmonary arteriovenous malformation (AVM) seen in the last 18 months. Nine had Osler-Weber-Rendu (OWR) hereditary haemorrhagic telangectasia. Pulmonary angiograms with digital subtraction (DSA) demonstrated single (n = 2) or multiple AVMs (n = 12) of varying sizes. All patients had anatomic shunts (range 12–48%) demonstrated by 100% oxygen breathing and renal accumulation of ^{99m}Tc microspheres (Chilvers *et al*, *Clin Radiol* in press) even in the four cases (one OWR, two portal hypertension, one cryptogenic) where the shunts were microvascular and not visible on DSA. Six patients had had previous lobectomies (two multiple). Embolisation of the larger abnormal channels under angiographic control was carried out in 12 cases (seven OWR, five others) using steel coils (n = 3–24 per patient on 1–5 occasions). Morbidity was slight but femoral vein thrombosis and pulmonary infarction occurred rarely (one occasion for each). Following embolisation there was a considerable improvement in oxygen saturation at rest (mean increase 7%, n = 10) and on maximal exercise (mean increase 13% n = 9) and in the anatomic shunt (mean absolute decrease 18%, n = 9). The most dramatic cases (n = 3) have shown absolute decreases in shunt of 30–40%, with resolution of polycythaemia in two of these. There were no significant changes in lung function following embolisation. The follow up period is still short but at 12–18 months post embolisation there has been no recrudescence of the shunts (n = 9). Embolisation is a relatively non-invasive method for treatment of large channel pulmonary AVMs and preferable to lobectomy.

Effects of social class, sex, and region of residence on age at death from cystic fibrosis in England and Wales

JR BRITTON *Respiratory Medicine Unit, City Hospital, Nottingham* Evidence that cystic fibrosis survival is greater in patients managed in specialist clinics than in those receiving local care has led to increasing pressure to establish regional cystic fibrosis centres in the UK. The effect of specialist clinic management is likely, however, to be confounded by the effects of social class, yet few comparisons of specialist and local care have allowed for this possibility and the independent effect of social class on cystic fibrosis survival is unknown. In this study cystic fibrosis mortality data from 1959 to 1986 in England and Wales have been used to determine time trends in age at death, and to estimate the independent effects on age at death of social class, and of sex and regional health authority (RHA) area of residence. Median age at death increased from six months in 1959 to 17 years in 1986. In most years since 1970 median age at death was higher in males by one to six years, and in non-manual social class by one to 12 years. Since the introduction of RHA coding of region of residence in 1974 independent odds ratios for death above the median age for the year of death in males relative to females, and non-manual relative to manual social class were 1·47 (95% confidence interval 1·16–1·87, $p < 0·005$) and 2·75 (2·16–3·52, $p < 0·0001$) respectively. After allowing for these effects there were also significant ($p < 0·005$) variations in the odds of death at above median age between RHA areas of usual residence, the odds ratio between the extremes of the distribution being 2·67. Thus social class, sex and region of residence are all determinants of age at death from cystic fibrosis. Confounding by these factors should be considered when comparing survival data from different forms of cystic fibrosis health care.

Role of limited thoracoplasty in the management of complicated pulmonary aspergilloma

M AL-ZEERAH, K JEYASINGHAM *Frenchay Hospital, Bristol* Complicated pulmonary apergilloma is a life threatening condition which results from colonisation with *Aspergillus fumigatus* of thick walled cavities with substantial surrounding parenchymal disease. Indications for surgery are few and the procedures conservative—for example, resection, drainage and collapse therapy, or a combination of these. We report our experience with three recent patients treated with limited thoracoplasty as the common denominator. The first presented with massive haemoptysis and a right upper lobe aspergilloma in a treated tuberculous cavity. She had previously undergone a right pleurectomy for recurrent pneumothoraces. She underwent a right upper lobectomy and an apical thoracoplasty. The second patient, with

bullous cysts and chronic respiratory inadequacy, known to have an aspergilloma in the right apex, presented with superimposed infection leading to a lung abscess. He was treated with cavernostomy and apical thoracoplasty. The third patient had undergone right upper lobectomy in childhood for a congenital cyst. This was complicated by a bronchopleural fistula and an aspergilloma in a residual apical space. She had aspergillosis and bilateral pulmonary infiltration. Cavernostomy combined with an apical thoracoplasty was employed in controlling deteriorating lung function. We believe that limited thoracoplasty in combination with one or more conservative measures can provide effective palliation in selected cases. This requires a bold physician, an expert anaesthetist, a willing surgeon, and an informed patient!

Prospective hospital based study of community acquired pneumonia (CAP) in the elderly

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Previous studies have suggested that CP in the elderly is caused by a somewhat different spectrum of pathogens than in younger adults, with a higher incidence of Gram negative infections. Over a six month period, we studied 73 consecutive patients over the age of 64 years who were admitted to the City Hospital with CAP. The mean age was 80·5 years and 38 were male, with 20 current smokers and 27 ex-smokers. Forty four had had a previous hospital admission, 54 had a history of prior respiratory disease, and other chronic disease was present in 53. Sixty nine patients presented with respiratory symptoms and 31 were confused. On admission, only 44 were pyrexial, 19 had a raised respiratory rate and 48 an elevated white blood count. C reactive protein was elevated in 57 of 62 patients and nine patients had low immunoglobulins. Two patients received assisted ventilation and 25 patients (34%) died. Thirty five pathogens were identified in 31 (43%) patients, including *Streptoccus pneumoniae* in 22, *Haemophilus influenzae* in five, legionella infection in two, influenza B infection in five and respiratory syncytial virus in one. Coliforms isolated from 12 sputum samples were not thought to be pathogenic by BTS criteria. The 12 patients concerned had had prior antibiotics and five had evidence of pneumococcal infection. CAP has a high mortality in the elderly, but the spectrum of pathogens identified is similar to those in younger adults and antibiotic therapy should be similar.

Mortality and morbidity from asthma and chronic obstructive lung diseases in The Netherlands, 1980–6

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National mortality and hospital discharge (morbidity) data were analysed for asthma (ICD 493) and for chronic obstructive lung diseases (ICD 490+491+492+496) for the total population and according to age-group (0–4, 5–34, 35–64, and ⩾65 y) and sex from 1980 onwards since the ninth revision of the ICD was finally introduced in the Netherlands in 1980. Rates per million per year were calculated and time trend analyses were performed by least square regression. The overall asthma mortality rate was 14·3 per 10^6 of the total population in 1980 and remained almost steady during the period of observation (slope +0·28 ($/10^6$/y), p = 0·237). No significant trends were found in males and females within a particular age group. The overall asthma morbidity rate showed a significant decrease (slope −10·7, p = 0·010), as was the case in all age groups apart from the age group 0–4 y, in which the asthma morbidity rate increased significantly (slope +106·6, p = 0·001) in both males and females. For the chronic obstructive lung diseases a significant increase was observed in the overall mortality rate (slope +17·66, p = 0·000) and the overall mortality rate (slope +63·9, p = 0·000), mostly due to the trends in the age group ⩾ 65 y and to a lesser extent the age group 35–64 y. There were no discrepant trends in the rates within the age groups between males and females. In conclusion, in The Netherlands asthma mortality is not a major issue but the significant increases observed in the period 1980–6 in morbidity from asthma in the age group 0–4 y and in mortality and morbidity from chronic obstructive lung diseases in the older age groups are cause for concern and deserve further attention.

Underestimation of the rise in asthma over the last decade: evidence from general practice in the UK

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The prevalence of asthma is increasing as assessed by patient consulting rates in the second and third National Morbidity Surveys (1970–1, 1981–2). A labelling shift might partly explain this, but patient consulting rates for acute bronchitis (AB) have changed little in the last decade, rising only slightly in the older age groups (Fleming and Crombie, 1987;**294**:279). We have used the weekly returns service (WRS) of the research unit of the Royal College of General Practitioners to examine trends in acute asthmatic episodes (AAE), acute attacks of bronchitis (AB) and the other "infective" respiratory diseases on the WRS from 1976 to 1987. Rates are expressed as the average attack rate/100 000/wk for each year for all ages. AAE rates have increased from 10·2 in 1976 to 20·2 in 1987 (+98%) while AB rates in the same period have risen from 80·3 to 111·8 (+39%). Conversely, other respiratory illnesses have fallen, notably "influenza like illness" (a more prevalent condition than AB in 1976), whose rates have reduced slowly to 40 (1987). Coryza showed a stepwise increase in 1980–1 from around 130 to 160, but have remained steady since. The possibility that the rise in AAE might be due to increasing viral infections is therefore not supported by these data. The rise in AB attack rates with a relatively unchanging patient consulting rate suggests that a fairly static pool of patients are suffering more attacks of AB per year. This points to patients

with asthma as yet undiagnosed being coded as AB during an exacerbation. Therefore the 98% rise in AAE over the last decade may be an underestimate. If 10% of attacks of AB occur in undiagnosed asthmatics this would represent, in 1987, a 50% underestimation of the numbers of exacerbations of asthma.

Drug prescribing in fatal asthma

SC WRIGHT, AE EVANS, DG SINNAMON, J MACMAHON *Belfast City Hospital, Coleraine Hospital, Department Community Medicine, Queen's University, Belfast* In the course of a previously described study on asthma deaths in Northern Ireland from 1981 to 1984 information was obtained in 174 cases on the drugs used during the week before the fatal attack. Eighty one per cent were taking inhaled beta agonists, 5·7% nebulised beta agonists, 32·8% oral beta agonists, 58·6% theophyllines, 13·2% ipratropium bromide, 29·3% inhaled corticosteroids, 34·5% oral corticosteroids and 2·3% ACTH. There was no relationship between prescribing these drugs and the severity of asthma. The duration of asthma was associated with oral theophyllines and inhaled steroids. Poor control was associated with oral beta agonists and inhaled ipratropium. Hospital outpatients were more often presribed theophyllines, ipratropium and oral steroids. Thirty four (20·8%) were prescribed medication which might have been inappropriate: Benzodiasepines—26, beta blockers—five, tricyclics—two, phenothiazine—one, aspirin—one, barbiturate—one. During the fatal attack the GP administered treatment in 50 cases: intravenous aminophylline 17 (34%), intravenous corticosteroids 10 (20%), oral steroids four (8%), injected beta agonists five (10%), nebulised beta agonists four (8%), oral bronchodilators four (8%), and "other" eight (16%). We conclude: (1) Many patients dying from asthma may be undertreated. (2) Some patients were given inappropriate drug therapy. (3) Compliance with medication was reasonably good. (4) Peak flow monitoring was noticeable for its absence. (5) Many patients died despite appropriate management.

Changes in hospital management of acute severe asthma by thoracic and general physicians in Birmingham and Manchester during 1978 and 1985

DR BALDWIN, LP ORMEROD, AD MACKAY, DE STABLEFORTH *Departments of Respiratory Medicine, Sandwell District General Hospital, Blackburn Royal Infirmary, and East Birmingham Hospital* Hospital management of acute asthma in Birmingham and Manchester was audited in a random 20% sample of 1156 admissions for the year 1985 (*Br J Dis Chest* 1987;**81**:232). This enabled a comparison to be made with a previous study for the year 1978, in which the same hospitals and methods were used. The clinical characteristics of patients in 1978 and 1985 were similar in age, sex, smoking history, duration of asthma and hospital attendance, but there was a highly significant reduction in 1985 in patients presenting with symptoms of over seven days' duration (1978 = 26%, 1985 = 7·5%; confidence limits 10·0, 26·5). The inpatient management of asthma improved significantly in both "thoracic" and "general" units, with less difference found in 1985 between those units with a "thoracic" interest and those without such an interest. There remained in 1985, as in 1978, differences in the monitoring of inpatients (peak flow measurements, blood gas analysis), outpatient prescribing and follow up arrangements. Inhaled preventative medication and oral steroids were prescribed more often in 1985 than in 1978. In 1985 there was a 50% increase in admissions for asthma. The proportion of severely ill patients was similar to 1978, but significantly more patients were ventilated in 1985 (1978 = 0, 1985 = 9, $p = 0·013$) and in the most severe functional grade the mean $Paco_2$ was higher in 1985 (1978 = 6·5 kPa, 1985 = 9·9 kPa; $p < 0·02$). We have shown an improvement in hospital management in the face of increasing incidence of all grades of asthma severity and earlier presentation.

Acute preventable asthma: the cost of hospital admission

AD BLAINEY, A BEALE, D LOMAS, MR PARTRIDGE *Chest Clinic, Whipps Cross Hospital, London* Recent surveys have indicated that many patients admitted to hospital have been inadequately treated before admission. We have assessed the cost implications of this in a prospective study of patients admitted to a district general hospital (DGH) with acute asthma. Seventy five patients (28 male, 47 female, aged 16–76) with asthma presenting in a 14 week period in 1988 were studied. Asthma was self assessed as moderate to severe in 65% of patients and 53% were waking at least five nights per week in the week before admission. Thirty five per cent had been waking this often for a month before peak flow on admission was 22·1 of predicted. Only 37% were taking adequate doses of inhaled steroids before admission. Sixteen per cent had sudden attacks which gave them no time to consult a doctor before admission. Of the remainder 54% had received medical advice in the week before admission, but only five patients (15%) had appropriate changes in treatment. A total of 406 hospital inpatient days were used by these patients, and mean peak flow on discharge was 70·9% predicted. Twenty seven patients admitted under one author (MRP) were seen 7–14 days after discharge. All these patients were significantly improved and mean peak flow was maintained at 74·8% predicted. Only one subject reported waking at night with asthma. There was scope for improved education and management in 53/75 (73%) of patients admitted to a DGH with asthma. The significance of sleep disturbance remains under-recognised by patients and doctors. If three-quarters of hospital admissions for asthma could be prevented, this DGH would save 1100 hospital inpatient days per year, and if the same situation applies throughout England the saving could be up to £27 million per annum. The cost of preventable asthma is likely to be even greater to the individual patient. The 27 patients followed up after discharge from hospital reported a total of 244 days off work because of their asthma.

Effect of controlled release salbutamol in severe nocturnal asthma

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Respiratory Unit, Northern General Hospital, Edinburgh In patients with asthma nocturnal symptoms are commonplace. In any therapeutic trials, however, overnight falls in peak expiratory flow (PEF) alone are called "nocturnal asthma." We have examined the efficacy of controlled release (CR) salbutamol (Volmax) 16 mg nocte, in a double blind, placebo controlled, cross over trial in the management of true nocturnal asthma (patients had to awaken with asthma on a minimum of five nights during a 14 night run in period). Nineteen patients (13 women: ages 21–66 y (mean 41)) were studied. While none was using oral steroids all but two required 800 μg or more/day of inhaled beclomethasone/budesonide. Four patients failed to complete the study (in each limb one due to an exacerbation of asthma and one to unwanted drug effects). During the 14 night run in period the mean (SEM) nocturnal awakenings were 12·4 (2·2). These were substantially decreased by CR salbutamol (7·3 (2·2); $p < 0·001$) and reduced by placebo (9·0 (2·7); $p < 0·05$). During the run in period the PEF at times of nocturnal awakening (197 (23) l/min) was markedly lower than that on morning awakening (267 (26)), which was significantly reduced compared with the evening PEF (305 (27)), $p < 0·02$). For only seven patients were there sufficient nocturnal awakening events to compare the nocturnal PEF during placebo and active limbs. On CR salbutamol the PEF was greater ($0·05 > p > 0·02$) than on placebo (263 (38) *v* 237 (41)). The fall in PEF from evening (pm) to morning (am) during the placebo period, while less than during the run in, remained significant (pm 323 (28); am 300 (28); $0·05 > p > 0·02$) There was no significant fall during the active period (pm 333 (28); am 317 (28); $p > 0·05$). We conclude that CR salbutamol can reduce the frequency of nocturnal awakening, improve the nocturnal PEF, and abolish the overnight fall in PEF in patients who have moderately severe asthma with marked nocturnal symptoms.