

# Proceedings of the British Thoracic Society

The 1985 winter meeting of the British Thoracic Society was held on 11 and 12 December at Kensington Town Hall, London.

## Which patients benefit from long term almitrine?

AJ SUGGETT, A PROCTOR, H SMYLLIE, MD PEAKE, RM CAYTON, P HOWARD *Departments of Medicine, Royal Hallamshire Hospital, Sheffield; Doncaster Royal Infirmary, Doncaster; Pontefract General Infirmary, Pontefract; and East Birmingham Hospital, Birmingham* We have analysed the results of almitrine (up to 200 mg a day) or placebo in a double blind trial of the drug used over twelve months in 50 patients with severe COAD (mean  $\text{PaO}_2 = 57$  mm Hg). The two groups were similar at randomisation and almitrine produced a significant mean rise in  $\text{PaO}_2$  of 6.2 mm Hg ( $p < 0.005$ ) without any effect on  $\text{PaCO}_2$ . Patients increased minute ventilation by increasing respiratory rate. Eleven patients were withdrawn (three died, five became more breathless) in the active group compared with three (one died, one more breathless) on placebo. Analysis of those who withdrew on active drug compared with the 13 who completed the trial on almitrine showed that they were lighter ( $64.7 \pm 7.8$  (S.D.) vs  $74.0 \pm 10.7$  kg,  $p < 0.05$ ), and had a higher haematocrit ( $51.8 \pm 7.4$  vs  $46.0 \pm 3.8\%$ ,  $p < 0.05$ ) although their oxygen tensions were not significantly lower. Residual volume/total lung capacity was the same in both groups. The six minute walking distance was not significantly different between the two groups ( $312 \pm 84$  vs  $242 \pm 134$  m respectively). A number of severely hypoxaemic patients seem to do well on almitrine, showing good improvement in  $\text{PaO}_2$ ; but it was not possible to distinguish them by initial clinical or physiological measurements.

## Rest and exercise pulmonary haemodynamics and right ventricular ejection fraction after oral almitrine in chronic bronchitis

JJ CONNAUGHTON, W MACNEE, GB RHIND, MD HAYHURST, AL MUIR, DC FLENLEY *Departments of Respiratory Medicine and Medicine, University of Edinburgh* Enhanced hypoxic pulmonary vasoconstriction probably contributes to improved arterial gas tensions with almitrine and indeed intravenous almitrine causes a transient rise in pulmonary artery pressure (PAP) in patients with chronic bronchitis and emphysema (CB and E). We have measured the acute effects of oral almitrine (100 mg) on PAP and right ventricular ejection (RVEF) at rest and on supine exercise in 10 patients with CB and E ( $\text{FEV}_{1.0} 0.7 \pm \text{SEM } 0.11$ ,  $\text{PaO}_2 7.7 \pm 0.3$  kPa,  $\text{PaCO}_2 6.1 \pm 0.2$  kPa). The measurements were repeated in five of these patients who had almitrine (50 mg bd) for three months. Almitrine improved arterial gas tensions. Resting PAP rose acutely from  $22 \pm 4$  mm Hg to

$33 \pm 5$  mm Hg ( $p < 0.001$ ) following almitrine. PAP during exercise also rose, being  $38 \pm 5$  mm Hg before and  $49 \pm 7$  mm Hg ( $p < 0.001$ ) after almitrine. RVEF at rest was  $0.38 \pm 0.03$  falling to  $0.32 \pm 0.02$  ( $p < 0.01$ ) after almitrine with no change after exercise. The five patients restudied had mean resting PAP of  $17 \pm 3$  mm Hg before and  $23 \pm 6$  mm Hg after three months' almitrine rising to  $42 \pm 6$  mm Hg ( $p < 0.05$ ) on exercise. RVEF was similar at rest before and after three months' therapy but fell significantly on exercise. We conclude that in these patients with CB and E the changes in arterial gas tensions after a single oral dose of almitrine are accompanied by significant increases in PAP at rest and on exercise with a fall in RVEF. After chronic therapy significant changes in PAP and RVEF were observed with exercise only.

## Neuropathy in patients with COAD and in those on almitrine

AJ SUGGETT, JA JARRETT, A PROCTOR, P HOWARD *Departments of Medicine and Electrophysiology, Royal Hallamshire Hospital, Sheffield* There have been two recent reports of peripheral neuropathy associated with treatment with almitrine (Chedru *et al*, Br Med J 1985;290:896 and Gherandi *et al*, Lancet 1985;1:1247). We have performed electromyograms on 20 patients, eight on almitrine (100-200 mg a day) and 12 on placebo treated for at least a year at the time of the study. All patients suffered from severe COAD and the two groups showed no significant difference in age, arterial gas tensions (mean  $\text{PO}_2 = 60.3 \pm 7.0$  (SD) mm Hg in the almitrine and  $58.8 \pm 5.8$  in the placebo group) or spirometry (mean  $\text{FEV}_{1.0}/\text{FVC} = 32.6 \pm 8.0$  vs  $37.8 \pm 10.2\%$  respectively).

EMG results:	Almitrine	Placebo
Normal	3	4
Ulnar/median nerve lesion	1	5
Mononeuritis multiplex	1	0
Early neuropathy in legs only	2	2
Peripheral neuropathy	1	1

We felt that the ulnar or median nerve lesions were probably incidental. The patient with a mononeuritis multiplex had been treated for a carcinoma five months previously. The patient on almitrine who developed a classical peripheral neuropathy had symptoms and his EMG and symptoms improved over the next six months. None of the other patients with either an early or frank neuropathy had symptoms. Almitrine may merely unmask peripheral nerve symptoms in patients who already have peripheral nerve damage due to their chronic hypoxaemia.

# **The effect of captopril on pulmonary haemodynamics and lung function in patients with chronic airflow obstruction**

AJ PEACOCK, AW MATTHEWS *Queen Alexandra Hospital, Portsmouth, Hampshire* There is animal evidence to suggest that angiotensin II (AII) is involved in the pulmonary vascular response to hypoxia but it is not known if this is true in man. We studied the effect of the angiotensin converting enzyme (ACE) inhibitor captopril on pulmonary vascular resistance (PVR) in nine patients with chronic airflow obstruction (mean FEV<sub>1</sub> = 0.74 l) and arterial hypoxaemia (mean PaO<sub>2</sub> = 8.4 kPa). In each patient pulmonary artery pressure, cardiac output, systemic arterial pressure, arterial and mixed venous blood gas tensions, AII and plasma renin activity (PRA) were measured at rest and at intervals for a total of three hours after 25 mg captopril orally. The patients had moderate pulmonary hypertension (mean = 29 mm Hg), high AII levels (mean = 47.2 pg/ml) and normal plasma renin activity (mean = 2.6 ng AI/ml/h). After captopril the AII levels fell by, on average, 80% (SEM 2%) and the systemic arterial pressure fell by an average 18% (SEM 5%). In seven patients PVR fell (mean = 25%, SEM 6%) and in two patients it rose (mean = 46%). There was no significant change in blood gas tensions. Eight of the patients took captopril 6.25 mg tds for six weeks. At the end of this period there were significant rises in FVC (mean = 27%; SEM 9%; p < 0.02) and TLCO (mean = 15%; SEM 6%; p < 0.05) but no significant change in FEV<sub>1</sub> or arterial blood gases. These findings suggest that ACE inhibition may lead to a fall in PVR in some patients with chronic airflow obstruction without deterioration in gas exchange. The increase in FVC after six weeks' treatment merits further study.

# **The effect of verapamil on secondary polycythaemia**

PE NASH, JS MILLEDGE, TL PRICE *Division of Anaesthesia, Clinical Research Centre, Northwick Park Hospital, Harrow* Following the demonstration by Sheldon *et al* (Clin Sci 1985;68:3p) that verapamil partially reversed the polycythaemia of hypobaric hypoxia in rats, we have observed its effect in patients. Five patients with hypoxic lung disease were treated with verapamil (40-80 mg td) for six weeks. Measurements of red cells mass (RCM), effective renal plasma flow (ERPF), lung function, PCV, Hb concentration and overnight oxygen saturation (SaO<sub>2</sub>) were made before and at the end of treatment. There was a significant reduction in RCM from a mean of 31.1 to 26.2 ml/kg (p = 0.002, paired t test). Hb fell from a mean of 17.5 to 16.9 g/dl (p = 0.035). There was no significant change in ERPF or conventional lung function tests. There was improvement in SaO<sub>2</sub>. From the overnight tapes we calculated the median SaO<sub>2</sub> for each study. The mean values were 84.5% before and 91.7% after six weeks' therapy (p = 0.045, paired t test). We conclude that verapamil partially reverses the polycythaemia of hypoxic lung disease, probably by improving oxygenation.

# **Clinical and immunological characteristics of asthma in pre-school children**

BG LOFTUS, JF PRICE (SPONSORED BY J COSTELLO) *Departments of Child Health and Thoracic Medicine, King's College Hospital, London* Ninety-two children aged 18 months to six years with moderate to severe asthma were studied. A standardised clinical evaluation was performed. Eighty-two patients were followed for year then reassessed. There was a two to one male predominance. Two were ventilated in the neonatal period and five had a history of bronchiolitis. Eighty-four per cent had their first symptoms of asthma under the age of two years. Common precipitants of attacks were infection, exercise and emotional upset. Allergic triggers were identifiable in only 24%. Half had rhinitis and half had eczema or a history of eczema. One third of parents had a history of atopic disease. Growth was normal. Sixty-three per cent had chest deformity. Skin prick testing was positive in 61 of 77 tested. Half had eosinophilia. Deficiency of IgA or IgG was found in eight. Seventy-four per cent had elevated IgE. Yeast opsonisation was defective in 20%. Over the follow-up period, the level of medication increased in 38, decreased in 25 and remained constant in 19. Clinical course was not related to immunological findings. Persistence of severe asthma was associated with severe chest deformity and repeated hospital admissions.

# **Effect of oesophageal stimulation on asthma in Asian subjects**

N WILSON, N CHUDRY, M SILVERMAN *Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Ingestion of both ice and hydrochloric acid (HCl) can increase bronchial responsiveness particularly in 'Asian' subjects (Wilson *et al*, Eur J Respir Dis 1985;66:25; Wilson *et al*, Thorax 1985;40:592). To determine the site of action nine 'Asian' asthmatics (three adults, six children) with a known positive response to ice or HCl were studied on three days. The response to orally retained or swallowed ice (n = 6) or HCL 0.01N (n = 3) was compared with that to a placebo drink. After baseline measurement of FEV<sub>1</sub> and histamine PC<sub>20</sub> FEV<sub>1</sub>, the challenge was given single-blind and the FEV<sub>1</sub> measured serially for 90 minutes, after which a second histamine test was performed. There was no significant change in FEV<sub>1</sub> or PC<sub>20</sub> after placebo. After the orally retained challenge the mean FEV<sub>1</sub> fell (p < 0.05) but only by < 12% in each subject and there was no change in PC<sub>20</sub>. After the swallowed ice or HCl the mean FEV<sub>1</sub> was progressively reduced (p < 0.01) but only in three subjects by more than 12%. In each of the six remaining subjects the PC<sub>20</sub> fell by at least one dilution (mean (SD) 2.63 g/l (0.37): 0.8 (0.30); p < 0.001). We conclude that stimulation of the upper gastrointestinal tract in 'Asians' can exacerbate asthma and that the response is greater after oesophageal than after oropharyngeal stimulation.

### Respiratory symptoms, atopy and non-specific bronchial responsiveness in children with one asthmatic parent

R CLIFFORD, A PUGSLEY, M RADFORD, S HOLGATE *Faculty of Medicine, University of Southampton* The risk of asthma in children of asthmatics is not known. In contrast to adults, some asthmatic children do not react to inhaled histamine or methacholine. We used a questionnaire, methacholine bronchial provocation tests and allergen skin prick tests in a prospective study of 50 children with one asthmatic parent. Ninety-eight per cent of 50 parents were on current medication with a wide range of severity. Fifty-one per cent had visited their doctor and 20% had had more than five days off work in the previous 12 months; 12% had been admitted to hospital during the preceding 10 years. The current prevalences of wheeze (22%), shortness of breath (16%) and cough (36%) in the 50 index children were high. Of 32 parents and 32 children skin tested, atopy was present in 90% and 39% respectively. Of 28 parents and 29 children tested, bronchial responsiveness to methacholine ( $PD_{20} < 6.4 \mu\text{mol}$ ) was present in 93% and 45% respectively. In the children bronchial responsiveness to methacholine and atopy were correlated ( $p < 0.05$ ). Eleven (50%) symptomatic children did not react to methacholine but none were atopic. Non-allergic children may only display bronchial hyperresponsiveness when exposed to other agents including viral infection. To judge by recent studies in schoolchildren, children with a single asthmatic parent have about double the probability of having asthma symptoms at six years.

### Respiratory compliance and functional residual capacity in young children

A GREENOUGH, J STOCKS, U NOTHEN, P HELMS, J LOFTRUS, J PRICE *Respiratory Unit, Hospital for Sick Children, and King's College Hospital, London* Respiratory problems are a common cause of morbidity in young children; however routine methods of measuring respiratory function are unsuitable in such children as they are too young to actively co-operate. Recently we have adapted the weighted spirometer technique for use in young children. We have measured compliance of the respiratory system (CRS) and helium dilution functional residual capacity (FRC) in 100 children aged from 2 to 7 years. Reliable measurements were obtained in all but eight children (all aged three years). In 57 healthy children significant correlations were found between CRS and height ( $r = 0.73$ ) and age ( $r = 0.83$ ) and FRC and height ( $r = 0.83$ ) and age ( $r = 0.74$ ); no differences were found between males and females. CRS also correlated significantly with FRC ( $r = 0.67$ ). In five children with cystic fibrosis and 30 with asthma CRS, FRC and specific compliance (CRS/FRC) reflected the severity of disease. These techniques are well tolerated in young children and provide a useful means of distinguishing the effects of disease from those of growth.

### Tuberculin sensitivity after neonatal BCG

JW HADFIELD, J ALLEN *Derby Chest Clinic, Green Lane,*

Derby BCG vaccination is recommended for Asian neonates and babies born to families with a history of TB; however the ability of neonates to mount an adequate immunological response has been questioned. In 1984 720 neonates (20% of live births in Derby) were given BCG vaccination within 10 days of birth by one of three TB visiting nurses. Three hundred and sixty-one (50%) were Asian and 278 (39%) had family histories of TB. Vaccination was given by Dermojet posteriorly on the left deltoid and three months later sensitivity assessed by Heaf test. In the same year 198 teenage children were vaccinated by the same nurses and technique. Eight (1.5%) of 517 infants (six Asian, two Caucasian) and four (2.6%) of 153 teenage children tested were Heaf negative on two occasions. Seven infants were Heaf negative on first testing but grade two on retesting one week later. These results show a good rate of tuberculin conversion in these neonates and no complications were seen. However 50% of 149 Asian children given neonatal BCG by intradermal injection were Mantoux negative at 22 months (Grindulis *et al*, Arch Dis Child 1984;59:614-619). This difference may be related to technique or other factors in early childhood.

### Respiratory epithelial permeability, bronchial reactivity, and small airway tests in young smokers and non-smokers

RG TAYLOR, JE AGNEW, RA FRANCIS, D PAVIA, SW CLARKE *Departments of Thoracic Medicine and Medical Physics, Royal Free Hospital and School of Medicine, London; and Department of Medical Physics, Pilgrim Hospital, Boston* We studied 10 healthy young male non-smokers and eight smokers of similar age and lung function, to determine if their respiratory epithelial permeability to radiolabelled diethylenetriamine pentaacetate ( $^{99m}\text{Tc}$ -DTPA) was related to small airway tests or to bronchial reactivity. Histamine was inhaled tidally for two minutes in doubling concentrations from 2 to 64 mg/ml. Bronchial reactivity was expressed as the threshold concentration (reducing  $FEV_1$  by 2SD) and as percentage reduction in  $FEV_1$  with nebulised histamine 16 mg/ml. Permeability was measured as described by Jones *et al* (Lancet 1980;i:66). A small-particle aerosol of  $^{99m}\text{Tc}$ -DTPA was inhaled, and its clearance assessed by gamma camera in inner (containing central airways) and outer lung zones. Lung-to-blood half time ( $LB-T_{1/2}$ ) was derived after correction for blood background measured by a counter over the thigh. Smokers and non-smokers had similar values of  $FEV_1$ , FVC,  $\dot{V}_{\text{max}50}$ ,  $\dot{V}_{\text{max}25}$ , phase III slope of the single breath nitrogen test, and closing volume.  $LB-T_{1/2}$  was shorter in smokers than in non-smokers in both inner (median (range) 21 (5.5-33) vs 63.5 (41-115) min,  $p < 0.004$ ) and outer (20.5 (5.5-30) vs 58.5 (39-105) min,  $p < 0.004$ ) zones. Neither inner nor outer zone  $LB-T_{1/2}$  was significantly related to any index of small airway function or bronchial reactivity. Although bronchial reactivity and small airway tests are more commonly abnormal in middle-aged smokers than in non-smokers, neither is related to the significantly increased respiratory epithelial permeability in young smokers.

Sodium cromoglycate (SCG) pretreatment and clearance of <sup>99m</sup>Tc-DTPA in 'fog' induced bronchoconstriction

M FITZPATRICK, T HIGENBOTTAM *Respiratory Physiology Department, Papworth Hospital, Cambridge* Clearance of inhaled aerosolized <sup>99m</sup>Tc diethylene triamine pentaacetate (DTPA) from lung to blood is enhanced by inhalation of ultrasonically nebulized distilled water (fog) in normals (Borland *et al*, Chest 1985;87:373-376). This rise in clearance rate occurs in asthmatics as well (Higenbottam *et al*, Chest 1985;87:1565-1585) but there is also bronchoconstriction. We report the comparative effects of SCG on the 'fog' induced DTPA clearance and bronchoconstriction. Eight asthmatics on inhaled beta-agonists and/or SCG were challenged with 80 litres of 'fog' on two separate days, one challenge preceded by inhalation of nebulized SCG. DTPA clearance was measured after each challenge and on a separate control day using scintillation probes (Jones *et al*, Br J Anaesth 1982;54:705). FEV<sub>1</sub> was recorded in duplicate immediately before and after each inhalation challenge.

Mean fog DTPA control = 1.73 (± SD 0.20) %/min.

	'Fog'	'Fog' and SCG
ΔDTPA (SD)	- 12.8 (27.2)%	- 7 (10.1)%
ΔDTPA (SD)	- 27.1 (15.0)%	- 8 (7.8)%

This does not support the idea that processes which are inhibited by SCG are involved in the enhanced influx of water and solutes. The 'trigger' for 'fog' induced bronchoconstriction probably lies below the epithelial surface.

Pulmonary permeability in patients with haematological malignancies treated with cytotoxic drugs

MJ O'DOHERTY, J VAN DE PETTE, CJ PAGE, NT BATEMAN *St Thomas's Hospital, London* Pulmonary permeability was assessed using the technique of <sup>99m</sup>Tc- DTPA aerosol transfer to measure a halftime of transfer (T50). Fourteen normal subjects, four untreated patients with chronic lymphatic leukaemia and eleven patients with a variety of haematological malignancies were studied. The treated patients had received a number of different cytotoxic agents over a number of years both orally and intravenously. All had a normal chest radiograph at the time of study. The halftime of transfer for the upper third of the right lung was 59 ± 6 mins (mean ± SEM) in the normal, 42 ± 3 mins in the treated and 115 ± 10 mins in the untreated patients; for the middle third 70.7 ± 6.1 mins, 43 ± 6 mins and 108 ± 7 mins; for the lower third 77 ± 7 mins, 35 ± 6 mins and 66 ± 3 mins respectively. The T50 values in the left lung were similar. We conclude: 1) In untreated stage 0 chronic lymphatic leukaemia, the T50 values were slower at the apices than the bases. This is the reverse of normal subjects and may represent an infiltrative process due to the chronic lymphatic leukaemia at the apices not visible on the chest X-ray. 2) Treatment with cytotoxic agents leads to faster transfer of DTPA (i.e. smaller T50 values) consistent with lung epithelial disruption.

Lung permeability in pigeon fanciers

SW BANHAM, J MCKILLOP, D CARLYLE, G BOYD *Departments of Respiratory Medicine and Nuclear Medicine, Glasgow Royal Infirmary* The half-time clearance of an inhaled aerosol of technetium <sup>99m</sup> labelled diethylene triamine pentacetate from lung to blood (T½ LB) was measured in eight non-smoking pigeon fanciers (mean age 48.2 range 31-66) and seven non-smoking, non-exposed subjects (mean age 32.4 range 28-40). The lower half of both lung fields and the interrenal area were scanned using a gamma camera with the subjects seated. The pigeon fanciers were actively engaged in the pastime although most reported symptoms of pigeon breeder's disease (PBD). Circulating IgG antibody to pigeon gammaglobulin was measured and seven were sensitised (>4ug per ml), with five highly sensitised (>60ug/ml). Mean T½ LB was 26.7 (8.7-63) minutes for pigeon fanciers, significantly less than 72.5 (54.3-97.6) minutes among non-exposed subjects (p<0.001). Furthermore there was a significant negative correlation between antibody response and T½ LB (linear regression, correlation coefficient -0.73, p<0.01). These findings suggest that lung permeability is increased in PBD. Further studies are required to clarify the relationship of lung permeability to exposure and immunological status and to define its relevance regarding the clinical evolution.

DTPA clearance is slower when <sup>113m</sup>indium is the radiolabel

KB NOLOP, DL MAXWELL, S BRAUDE, D ROYSTON, JMB HUGHES *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* The clearance halftime (T½) of inhaled <sup>99m</sup>Tc-DTPA, a popular index of alveolar epithelial permeability, is much slower in non-smokers (mean 60 min) compared to smokers (mean 20 min). In addition, hyperinflation causes increased clearance in non-smokers but not in smokers. To ascertain whether the radiolabel is contributing to these differences, we studied the effects of lung hyperinflation on the clearance of inhaled <sup>113m</sup>In-DTPA in eight non-smokers and eight smokers. After elution, <sup>113m</sup>Indium was added to a DTPA chelating kit, neutralised to pH 7.5, and nebulised in a manner similar to <sup>99m</sup>Tc-DTPA. In a randomised protocol, each subject was studied at both normal and high lung volumes. The level of ventilation was monitored using inductance plethysmography. The mean difference in lung volume was 1.6 liters. The T½ from lung to blood for <sup>113m</sup>In-DTPA was computed from a semilogarithmic plot of chest scintillation counts vs. time and corrected for radioisotopic decay. For the non-smokers, the T½ at normal lung volume was 57.1 ± 6.9 min (mean ± SEM) and declined to 36.8 ± 6.0 min at high lung volume (p<0.05). For the smokers, the T½ was 44.1 ± 8.3 min at normal lung volume and declined to 34.2 ± 7.0 min at high lung volume (p<0.05). The mean T½'s at normal volume for non-smokers and smokers were not significantly different from each other. These data contrast with results previously obtained using <sup>99m</sup>Tc-DTPA and suggest that DTPA clearance is highly label dependent.



### A comparison of clinical and bronchoscopic diagnosis in AIDS related pneumonia

AL POZNIAK, CR SWINBURN, SJG SEMPLE, NMcI JOHNSON *The Middlesex Hospital, London* We have examined data from 20 HTLV-III positive homosexual men presenting with pulmonary symptoms over a two year period. In group one, the first 12 patients underwent fiberoptic bronchoscopy (FOB), bronchoalveolar lavage (BAL) and/or transbronchial biopsy (TBB) prior to treatment decisions. In group two, the subsequent eight patients had treatment decisions made, based upon the clinical radiological and blood gas data only. In group one, three had focal radiological shadows and three had bacterial pathogens isolated. Nine patients had diffuse shadowing on chest radiograph and eight had proved *Pneumocystis carinii* pneumonia (PCP). Overall nine survived the pneumonic episode (seven of eight in the PCP group). In group two all eight patients had suspected PCP, their clinical data being similar to those with proved PCP above. Six survived the pneumonic episode. The two patients who died were in extremis on admission. Complications of drug therapy were similar in the two groups. In suspected PCP, FOB, BAL and TBB may not always be necessary.

### Haemophilus influenzae: A neglected cause of community-acquired pneumonia in previously fit adults?

MA WOODHEAD, JT MACFARLANE *City Hospital, Nottingham* *H influenzae* (HI) is usually regarded as a lower respiratory pathogen only in patients with underlying lung disease. We describe 12 previously fit adults with community acquired pneumonia (CAP) in whom HI was the only pathogen identified. The age was 15-67 (eight less than 40 years), six were female, seven were smokers, but only two had mild airflow obstruction and none had pre-existing lung disease. History length ranged from 2 to 77 days, with six being ill for over a fortnight. Common symptoms were cough (12), fever (eight), dyspnoea (five), pleural pain (six), upper respiratory symptoms (five), weight loss (four), rigors (four) and haemoptysis (two). Crepitations (seven) were the commonest finding on examination, with signs of classical consolidation in only two. Radiographic changes were usually patchy; some collapse was present in four. An elevated leucocyte count (seven) and high ESR ( $>50$  mm/h in six) were common laboratory findings. A heavy, pure growth of HI on sputum culture was found in all but one in whom the organism was isolated from blood cultures. All were sensitive to amoxycillin except one. No evidence of coincident infection was found on culture or paired respiratory serology. Five patients required hospital admission; all recovered, most (seven) taking over two weeks to do so. HI should be considered as a cause of CAP in previously fit adults.

### Comparative clinical and laboratory features of legionella, pneumococcal and mycoplasma pneumonias

MA WOODHEAD, JT MACFARLANE *City Hospital, Nottingham* Early differentiation between community

acquired (CA) pneumonias caused by three pathogens, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*, would be of value in guiding appropriate antibiotic therapy. The features of 79 cases of legionella pneumonia (LP), 83 cases of pneumococcal pneumonia (PP) and 62 cases of mycoplasma pneumonia (MP) have been compared retrospectively. Patients with MP were younger, had a longer history, were less likely to have pre-existing chronic diseases and were more likely to have had antibiotic before hospital referral than those with PP or LP. No symptoms, physical signs or laboratory features were unique to any group. Upper respiratory tract symptoms in MP, confusion in LP and pleural pain and rigors in PP were typical features. Of clinical signs, labial herpes in PP and high fever ( $>39^{\circ}\text{C}$ ) in LP were significantly commoner. Hyponatraemia, abnormal liver function and hypoalbuminaemia were more common in LP than PP. Features of multisystem involvement were seldom noted in MP. In the absence of unique clinical, laboratory or radiographic (Macfarlane JT *et al*, Thorax 1984;30:28-33) features initial antibiotic therapy, particularly in severe CA pneumonia, should probably cover each of the three common pathogens until a specific aetiological diagnosis is made by microbiological methods.

### Gallium 67 lung scans in pulmonary tuberculosis

AJ FRANCE, IC STEWART, CG WATHEN, AJ WIGHTMAN, DC FLENLEY *Departments of Respiratory Medicine and Radiology, Rayne Laboratory, City Hospital, Edinburgh* Gallium 67 citrate ( $\text{Ga}^{67}$ ) is taken up by both tumour cells and macrophages. It has been used to localise neoplasms and to quantitate inflammatory activity in sarcoidosis and interstitial fibrosis. We have investigated whether  $\text{Ga}^{67}$  scanning can be used to assess the activity of pulmonary tuberculosis. We have studied 15 patients with sputum positive pulmonary tuberculosis. In all, a  $\text{Ga}^{67}$  scan was carried out within 4-21 days of starting treatment with rifampicin based triple or quadruple chemotherapy. In every case there was positive  $\text{Ga}^{67}$  uptake in association with the radiological abnormality. Repeat of the  $\text{Ga}^{67}$  scan within 3-16 (mean 7.8) weeks following the start of treatment showed that radiological improvement paralleled reduction in the  $\text{Ga}^{67}$  uptake. In six patients the  $\text{Ga}^{67}$  scan was again repeated 13-24 months after the start of treatment. In all six the  $\text{Ga}^{67}$  scan was negative, despite persisting X-ray abnormality in three patients. We propose that a  $\text{Ga}^{67}$  scan may indicate the activity of radiological opacities which are due to pulmonary tuberculosis.

### Pathogenicity of Mycobacterium tuberculosis during anti-tuberculosis therapy

L CLANCY, P KELLY, L O'REILLY, T HEALY *Peamount Hospital, Newcastle, Co. Dublin, Ireland* It is widely accepted that a patient with open pulmonary tuberculosis quickly becomes non-infectious when treated with appropriate anti-tuberculous drugs. The evidence for this assumption is understandably indirect. To try and give experimental support for this concept we performed the following experiments. Sputum samples from three patients

with open pulmonary tuberculosis were injected subcutaneously into guinea pigs. The guinea pigs were subsequently shown to become tuberculin positive and at post mortem six weeks later had generalised tuberculosis. In the second phase of this experiment sputum from seven patients who had had from four weeks standard chemotherapy (RHE) was injected into guinea pigs. Six of the seven guinea pigs showed TB lesions at post mortem. The guinea pig who did not show lesions had been injected with sputum which was weakly positive and had only three colonies on culture. In a third experiment sputum from three patients who had had eight weeks' chemotherapy was injected into guinea pigs. Two of these patients were culture negative and the guinea pigs were also subsequently negative. One patient had a few colonies on culture and the guinea pigs showed lesions. Two of the patients had been direct smear positive. Our results show that patients who are TB culture positive can infect guinea pigs even after eight weeks' standard anti-TB chemotherapy. We believe these results question the present teaching on this subject.

#### Changes in primary and acquired drug resistance of *Mycobacterium tuberculosis* in Blackburn 1960-84

LP ORMEROD, J HARRISON, PA WRIGHT *Chest Clinic, Blackburn Royal Infirmary, Blackburn* The Blackburn Health Authority (pop. 272000) had an incidence of tuberculosis below the national average in 1960-4. Following substantial immigration from the mid 1960s, the incidence and pattern of tuberculosis changed, with Blackburn consistently in the ten highest incidence areas of England. All isolates of *Myco tuberculosis* during 1960-84 are recorded for the District. Nine hundred and eight-two isolations were made from white patients, and 539 isolates from immigrant patients. Drug resistance when present was recorded as primary (no previous drug treatment) or acquired (previous drug treatment and fully sensitive organisms). Primary resistance in the white population fell from 9.65% in 1960-4 to zero in 1980-4. In immigrant patients primary resistance rose from 2.6% in 1960-4 to 11-15% from 1965 onwards. Acquired resistance in the white population fell from 9.95% in 1965-9 to 1% in 1980-4. In the immigrant population acquired resistance rose from zero in 1960-4 to 1.9% in 1980-4%. During the last 25 years, while the pattern of tuberculosis in Blackburn has changed from low to high incidence with immigration, there is no evidence of cross infection from the immigrant to the white population.

#### A clinicopathological study of bronchial carcinoids

PS HASLETON, S GOMM, B BLAIR, N THATCHER *Department of Pathology, Wythenshawe Hospital, Manchester.* Cases were selected with the SNOP code diagnosis of bronchial carcinoids or "adenoma". Thirty-five cases showed a spectrum of well to poorly differentiated neuroendocrine carcinoma. The clinical and histological data were correlated. There were 21 male patients and 14 females, with a mean age of 42.2 years. The following clinical features were associated with a significantly inferior

survival: age, number of cigarettes smoked per day, lymph node involvement, T and N stage. The following histological features were associated with a poor prognosis: disorganisation of architecture, mitotic count, nuclear pleomorphism, necrosis, vascular invasion and an undifferentiated growth pattern. Lymphatic invasion was of borderline significance. The results of surgical resection for well differentiated bronchial neuroendocrine carcinoma are good and several pathological features give a guide to prognosis.

#### Gallium scanning in small cell lung cancer

R MILROY, ML SMITH, SW BANHAM, J MCKILLOP *Departments of Respiratory Medicine and Nuclear Medicine, Royal Infirmary, Glasgow* In lung cancer, gallium scanning has been extensively investigated as a means of preoperative non-invasive mediastinal staging. However there have been few studies to evaluate the efficacy of gallium scanning as a staging procedure in small cell lung cancer. We report our preliminary findings in such a study of 39 patients. All patients underwent gallium scanning as part of pretreatment staging. Gallium scan was positive for primary tumour in 38 of 39 patients (97%) and indicated mediastinal tumour spread in 31 of 39 patients (79%). In 20 patients (all with positive pretreatment scan) gallium scan was repeated after induction chemotherapy (six complete responders, 11 partial responders, three non-responders). In 13 patients gallium scan returned to normal, in two improved substantially and in five remained unchanged. Of these latter, five patients were non-responders and two partial responders. In five patients gallium scan has been repeated 6-9 months after initial chemotherapy. In two cases the scan indicated relapse confirmed clinically. In three cases the scan remains negative and these patients continue in remission. Gallium scanning is useful in staging small cell lung cancer and in evaluating response to chemotherapy.

#### Prognosis after surgery for lung cancer with and without preoperative CT scans of thorax, abdomen and head

R MILLER, R RUDD *London Chest Hospital, London* We compared prognosis after surgery for lung cancer in patients presenting to services with different policies for preoperative staging. Group one comprised 57 patients whose staging included CT scans of thorax, abdomen and head after a negative isotope bone scan. In 17, CT scans indicated inoperability (11 intrathoracic, four extrathoracic, two combined spread). Of the other 40, surgery was performed in 36 (28M, 8F, mean age 60, SD 7.8), of whom five had thoracic CT scans indicating questionable operability, and was declined by four. Group two comprised 34 patients (27M, 7F, mean age 62, SD 8.6) who underwent surgery after investigations usually including bone scan but excluding CT scans. Distributions of cell type and TNM stage were similar in the two groups undergoing surgery. Macroscopically complete resection was possible in 33 in group one and 29 in group 2. Resection was impossible in three of group one who were questionably operable on thoracic CT scan and five of

group two. There were no significant differences between patients in group one (33) and group two (29) who underwent resection in time to first recurrence or survival. There was no significant difference in survival in patients who underwent surgery between groups one (36) and two (34). Preoperative CT scans save unnecessary surgery in some patients but have little influence on outcome in patients submitted to surgery.

### Intensive chemotherapy plus adjuvant surgery in operable small cell carcinoma of the bronchus : a phase II study

G BENFIELD, M CULLEN, H MATTHEWS, D WATSON, F COLLINS, C WOODROFFE, N STUART, T PERREN, C EDWARDS *Queen Elizabeth Hospital and East Birmingham Hospital, Birmingham* Although rare, operable small cell carcinoma (SCC) is potentially curable. In two years, eight such patients, with histologically confirmed SCC (age 58-68, median 63), have been treated with chemotherapy (cyclophosphamide, doxorubicin, etoposide, vincristine, methotrexate) for six weeks, followed by elective surgery. Four patients achieved complete remission on chest radiograph and two partial remission and in two patients the tumour remained static during chemotherapy. All patients had macroscopically complete resections, one which revealed squamous cell cancer only. In two cases no residual tumour was detectable histologically in resected lung or lymph nodes. Five patients remain disease free 24+ to 86+ (median 51+) weeks from diagnosis; one is alive with locally progressive disease (92+ weeks) and two have died with distant metastases (26, 44 weeks) — one in brain, which was the only site of disease at necropsy. Three patients have experienced serious complications. Preoperative, intensive chemotherapy in operable SCC allows for selection of patients with very chemosensitive tumours who may benefit from further chemotherapy postoperatively. The operation performed should be determined by the extent of tumour at diagnosis. Early CNS relapse, mixed histology tumours and the toxicity of combined modality therapy in this age group are complicating factors.

### Breathlessness after surgery for carcinoma of the bronchus

PA CORRIS, BG COOPER, C KELLY, GJ GIBSON *Department of Respiratory Medicine, Freeman Hospital, Newcastle upon Tyne* Changes in maximal exercise performance after surgery for lung cancer are proportional to changes in FEV<sub>1</sub>, while submaximal indices such as ventilation at a given work load are unchanged (Clin Sci 1983;65:39). Exercise in such subjects is usually limited by breathlessness, suggesting that the relationship between severity of dyspnoea and ventilation may be altered by surgery. We have therefore compared changes in the severity of breathlessness (assessed on a visual analogue scale from 0 to 100%) and in ventilation during progressive exercise on a bicycle ergometer before and four months after surgery. Four of ten patients had no change in FEV<sub>1</sub> (<0.2 l) postoperatively and they showed no change in exercise performance or breathlessness. In the other six

patients FEV<sub>1</sub> fell from a mean (SD) of 2.3 (0.6) l to 1.5 (0.3) l, and this was associated with a reduction in maximum exercise ventilation from 54.6 (9.5) to 40.8 (9.8) l min<sup>-1</sup> (p<0.05). The maximum breathlessness score at the end of exercise was, however, unchanged (means 85.2, 82.3%). Although ventilation at a standard workload of 50 w showed no change (means 31.5, 30.7 l min<sup>-1</sup>), there was a significant increase in breathlessness score at 50 w from 34 (16) % to 55.3 (23) % (p<0.05). We conclude that patients cease progressive exercise with similar degrees of breathlessness before and after operation and that removal of functioning lung results in more breathlessness for a given exercise ventilation.

### Abnormalities in gas exchange following oesophageal surgery

RK LAMB, A REDDY, RM CAYTON, HR MATTHEWS *Regional Department of Thoracic Surgery and Medicine, East Birmingham Hospital, Birmingham* Hypoxia remains a significant cause of morbidity following thoracic surgery and yet has been rarely studied. We have therefore measured blood gases hourly for 24 hours in 27 patients breathing oxygen following oesophageal surgery (oesophageal resection 12, other procedures 15). 14 patients were male; ages ranged from 18 to 73 years (mean 52); mean FEV<sub>1</sub>/FVC % was 74 ± 8.5. The alveolar-arterial oxygen tension difference (AaPO<sub>2</sub>) and the arterial/alveolar oxygen tension ratio (a/A PO<sub>2</sub>) were calculated for 25 patients immediately following surgery and at 18 hours. Results were:

	Immediately after surgery	18 hours after surgery
PaO <sub>2</sub> kPa	13.5 ± 5.6	13.1 ± 3.3
a/A PaO <sub>2</sub>	0.50 ± 0.17	0.49 ± 0.14
AaPaO <sub>2</sub> kPa	13.12 ± 4.68	13.9 ± 5.69

Hypoxia (defined by a PaO<sub>2</sub> of less than 10 kPa on oxygen) was found on one or more occasions in 17 of the 27 patients; three patients also had hypercapnia. These findings indicate that all patients had an abnormality of gas exchange which persisted for at least 18 hours following surgery, and was associated with hypoxia in some.

### Fibronectin and collagenase in bronchoalveolar lavage (BAL) fluid from patients with sarcoidosis

CM O'CONNOR, C POWER, A VANBREDA, C ODLUM, MX FITZGERALD *Department of Medicine, University College, Dublin, and St Vincent's Hospital, Dublin* Both fibronectin (Fbn) and collagenase (Coll) have been suggested as biochemical indicators of fibrosis in lung disease. We analysed BAL fluids from 30 biopsy proved, sarcoid patients for Fbn and Coll. Fbn was detected in 30% (n=9) and Coll in 33% (n=10). Only one patient had detectable levels of both markers. Compared with patients with neither marker in BAL fluid, the Fbn +ve group had more active disease as indicated by increased total lavage cells, percentage T lymphocytes, lavage protein and angiotensin converting enzyme (ACE), and increased serum

ACE ( $p<0.05$ ). The Coll +ve group also displayed an increase in the percentage of T lymphocytes in BAL fluid and elevated lavage protein and serum ACE ( $p<0.05$ ). Physiological data indicated that patients with detectable levels of BAL Coll had significantly lower percent predicted FEV<sub>1</sub> and FVC ( $p<0.01$ ) and a significantly higher radiological fibrosis score ( $p<0.05$ ) than those without BAL fluid collagenase. No such changes were seen in the Fbn+ group, but it had more newly diagnosed patients than the other groups ( $p<0.01$ ). These results indicate that the presence of lavage Coll rather than Fbn is associated with pulmonary function impairment in sarcoidosis.

# Inhibition of T cell function by bronchoalveolar lavage fluid

KP JONES, BH DAVIES *Immunology Laboratory, Asthma and Allergy Unit, Sully Hospital, Penarth, South Glamorgan* Bronchoalveolar lavage fluid from six patients with sarcoidosis, six patients with pulmonary fibrosis and four normal controls were concentrated using an Amicon ultrafiltration cell with a YM2 membrane. These lavage fluids were then incorporated into a lymphocyte transformation assay using concanavalin A and lymphocytes from normal healthy individuals. The lavage fluids from the sarcoidosis patients and the pulmonary fibrosis patients had a pronounced inhibitory effect on lymphocyte transformation, whereas those from normal individuals exhibited no such properties. The concentrations of the lavage fluids were quantified to original lung levels by using urea nitrogen determinations of lavage fluid and corresponding sera. Total protein determinations were also performed on the lavage fluids. Heating to 56°C for 30 min did not affect inhibitory activity. These results indicate that bronchoalveolar fluid may have an immunoregulatory role in lung disease.

Inhibition (mean (SD)) of a final concentration of  $\times 4$  of original lavage fluid.

Pulmonary fibrosis	Sarcoidosis	Normals
83.3 (11.2)	90.75 (6.2)	+ 5.62 (7.3) (the + indicates slight stimulation)

# Absence of acute phase response in patients with active pulmonary sarcoidosis

CRK HIND, K FLINT, D FELMINGHAM, BN HUDSMITH, J BROSTOFF, N McI JOHNSON *Departments of Medicine and Immunology, Middlesex Hospital, and Department of Microbiology, University College Hospital, London* Alveolar macrophages from patients with active pulmonary sarcoidosis release greater amounts of interleukin-1 (IL-1) than those with inactive disease. Circulating IL-1 is involved in triggering the hepatic synthesis of the classical acute phase reactant C-reactive protein (CRP). Plasma IL-1 measurement is not well standardised, whereas serum CRP concentration can now

be measured precisely and rapidly. We report here the results of a prospective study of serum CRP measurement in 14 patients with active or inactive pulmonary sarcoidosis, as defined by gallium scan and bronchoalveolar lavage cell counts. The serum CRP level was normal in seven of the nine active cases, and in all four inactive cases (normal range  $<1-10$  mg/l). Both cases of active sarcoidosis with a raised CRP level (14 and 24 mg/l) had anterior uveitis. The absence of a marked CRP response in active pulmonary sarcoidosis suggests either that the IL-1 produced exerts its primary effect locally or that sarcoidosis belongs to the group of inflammatory disorders (eg SLE, ulcerative colitis) in which the serum CRP rises only modestly if at all.

# Density of HLA-DR antigen on alveolar macrophages obtained by BAL in pulmonary sarcoidosis

DA CAMPBELL, RM DUBOIS, RG BUTCHER, LW POULTER *Departments of Thoracic Medicine and Immunology, Royal Free Hospital, London, and Department of Lung Pathology, Cardiothoracic Institute, Midhurst* In normal bronchoalveolar lavage (BAL) fluid over 90% of alveolar macrophages (AMs) express HLA-DR; this proportion does not appear to be increased in pulmonary sarcoidosis although the total number of AMs is increased. Attention has been drawn to the role of quantitative variation in density of class II major histocompatibility complex (MHC) antigens on individual cells in the induction of immune responses (Unanue ER *et al*, J Immunol 1984;132:1-5, Janeway CR *et al*, Immunol Today 1985;5:99-105). The density of class II MHC antigens on individual AMs has not previously been measured. A Vickers M85 scanning and integrating microdensitometer and a mouse anti-human HLA-DR antibody directly conjugated to fungal glucose oxidase were used to directly quantify the density of HLA-DR antigen expression on AMs in cytospin preparations of BAL fluid from eight patients with pulmonary sarcoidosis and four normal subjects. The mean density of HLA-DR antigen expression on AM's in pulmonary sarcoidosis was significantly increased; this may play a part in the induction of immune responses at sites of disease activity. The advantages of this technique are that the morphology of the cells under scrutiny and the binding of monoclonal antibody can be observed simultaneously, and the method does not suffer from endogenous enzyme activity or non-specific adsorption of second-layer antibody-enzyme conjugate to cells, facilitating the reliable quantification of antigen expression on individual cells in heterogeneous suspensions.

# Lymphocyte and macrophage phenotypes in the lesions of sarcoidosis: are there two pathological processes?

CS MUNRO, DA CAMPBELL, DN MITCHELL, RM DU BOIS, PJ COLE, LW POULTER *Host Defence Unit, Cardiothoracic Institute, and MRC Chest Diseases Unit, Brompton Hospital, and Departments of Thoracic Medicine and Immunology, Royal Free Hospital, London* Sarcoid lesions contain within the centre of the granuloma helper (OKT4+) T-cells



which may be activated (Tac +), while in peripheral areas of the lesions both helper and suppressor type T-cells are found (Semenzato *et al*, New Engl J Med 1982;306:48; Clin Exp Immunol 1984;57:331). Using double immunofluorescence techniques, we have examined in more detail the relative frequencies of T-cell markers in the granuloma centre (C) and the peripheral lymphocytic mantle (P) in sarcoid lesions from lung (four), lymph node (two) and skin (one), and from three positive Kveim test specimens.

Mean frequency (range) relative to 100 OKT4+ cells					
	RFT8 +	Leu8 +	Leu9 +	RFT2 +	Tac +
C	25 (5-50)	<1 (0-3)	5 (1-9)	10 (3-32)	9 (7-14)
P	47 (16-96)	18 (1-50)	12 (4-36)	7 (3-23)	5 (0-16)

The central predominance of T4+ over T8+ was less than in previous reports, but Leu8+ (suppressor-inducer) cells, common outside the granulomas, were virtually absent within them. The mantle varied in extent, but lymphocyte activation markers (Leu9+, RFT2+, Tac+) were found in both regions with comparable frequencies. We also found sharp demarcations of macrophage phenotype (RFD7+ in the mantle; RFD9+ in the granuloma), and different patterns of HLA-DR expression. Together these findings suggest the possibility that the mantle is the site of a separate process, variable in extent, whose expression might determine the outcome of the granulomatous response.

#### Mast cells of bronchoalveolar lavage fluid in interstitial lung disease: comparison with transbronchial biopsy sections and ultrastructural appearance

RM AGIUS, RC GODFREY, E NEVILLE, A HERBERT, R BUCHANAN, C INMAN, ST HOLGATE *Southampton General Hospital, Southampton, and St Mary's Hospital, Portsmouth* Although increased mast cell counts have been reported in bronchoalveolar lavage (BAL) fluid from patients with interstitial lung diseases (ILD) (Agius *et al*, Thorax 1984;39:708), little is known of their pathological significance. We investigated the relationship between BAL mast cell differential counts and mast cell counts in ILD transbronchial biopsy sections (sarcoidosis six, fibrosing alveolitis three, others four) stained with toluidine blue. The mean (SEM) differential mast cell count in BAL fluid from patients with ILD (n=13) was 0.37% (0.15%) and was higher than the mean of 0.08% (0.01%) in 26 controls with carcinoma (p<0.05). In biopsy sections the mean mast cell count was also significantly higher in ILD, being 31.4 (6.2) mast cells/mm<sup>2</sup>, whilst in five controls it was 15.1 (4.5) mast cells/mm<sup>2</sup> (p<0.01). In ILD there was no significant relationship between mast cell counts in BAL fluid and tissue sections (r=0.1). EM ultrastructure of BAL mast cells from ILD (compared with controls from dispersed surgically resected lung) showed that they had a more ruffled membrane, lipid bodies and larger and more amorphous granules, indicating that they are in an activated state. Mast cells may play a part in the pathogenesis of ILD.

#### Edinburgh emergency admission service: Report on 15 years' experience

GK CROMPTON, IWB GRANT, BJ CHAPMAN, SA THOMSON, CF MCDONALD *Respiratory Unit, Northern General Hospital, Ferry Road, Edinburgh* A formal self-admission service for selected patients with asthma was established in 1968. During the first 15 years 195 patients were responsible for 873 admissions. Forty-six per cent did not have to use the Service and their names were removed after they had been free from severe attacks for two or three years. Eighty-two per cent of admissions were arranged by patients. In 11% the general practitioner was involved. Duration of asthma and times of admission were compared during the first and last three years. The duration of severe asthma was significantly less (p<0.001) and more patients were admitted between 1700 and 0900h (p<0.001) during the last three years. Assisted ventilation was necessary on 36 occasions in eight patients. There were three deaths in hospital, one during resuscitation, but in two active resuscitation was electively withheld because of irreversible cardiorespiratory disease. Six patients died out of hospital, one from myocardial infarction and five from asthma. Four of the asthma deaths occurred in Edinburgh but one girl died while on holiday. This Admission Service continues to function efficiently, thanks to Edinburgh general practitioners, the Lothian Area Ambulance Service and the Lothian Health Board.

#### Patterns of <sup>111</sup>In-neutrophil traffic in lung injury

C HASLETT, AS SHEN, GS WORTHEN, RM CHERNIACK, PM HENSON *Royal Postgraduate Medical School (Department of Medicine), London, and National Jewish Hospital, Denver, Colorado* Neutrophils are pathogenetically implicated in some lung diseases, but quantitative study of their traffic in the lung is difficult. Rabbits were treated with intratracheal bleomycin (which causes parenchymal inflammation and late fibrosis), or intravenous endotoxin (E) plus chemotactic peptides (CP), which cause acute microvascular injury. The traffic of an intravenous injection of 5 × 10<sup>7</sup> <sup>111</sup>indium-labelled rabbit neutrophils (<sup>111</sup>In-neutrophils) in a suprahilar lung region-of-interest (ROI) was quantified by external gamma scintigraphy. ROI radioactivity accurately represented actual radioactivity in dissected whole lungs (r>0.98, n=12), and autoradiographs showed radiolabel retained by neutrophils. Minimal lung retention of <sup>111</sup>In-neutrophils was detected in control rabbits (9.4 ± 2% in the ROI at 40 min, and 1.66 ± 0.18% at 24 hours, n=7, ± SD). Intravenous E + CP caused marked initial sequestration of <sup>111</sup>In-neutrophils in the pulmonary vasculature (up to 25% in the ROI at 40 min) but by 4-24 hours sequestration was not significantly above controls. In early bleomycin lung injury, however, marked sequestration continued for up to 24 hours (7.29 ± 0.9% in ROI at 24 hours, n=8; ± SD) and radioactivity in the ROI correlated with numbers of <sup>111</sup>In-neutrophils in bronchoalveolar lavage fluid (r=0.82), which are an index of neutrophil migration. Differing patterns of neutrophil traffic may relate to the type of lung

injury, and the techniques used may be applicable to the assessment of lung disease in man.

### Intracavity drainage of bullous emphysematous lung

GE VENN, PR WILLIAMS, P GOLDSTRAW *Brompton Hospital, London* Dominant bulla formation in the presence of emphysematous lung disease is well recognised. Such bullae frequently produce significant respiratory impairment. A number of approaches have been devised for the surgical ablation of such bullae, none of them entirely satisfactory. We have performed modified 'Monaldi' drainage of dominant bullae in 20 patients. The subjective symptomatic improvement obtained correlated with a mean improvement in the FEV<sub>1</sub> of 20% ( $p < 0.02$ ) and a reduction in total lung capacity ( $p < 0.05$ ) and residual volume ( $p < 0.01$ ). This procedure has the advantage of requiring a small incision, sparing all functioning lung tissue, and permits the drainage of any subsequent bullae under local anaesthetic.

### Effect of interferon on the activity of cytotoxic agents in human lung cancer xenografts

RJ FERGUSSON, LE ANDERSON, JF SMYTH *Imperial Cancer Research Fund Medical Oncology Unit, Western General Hospital, Edinburgh* Interferon has been shown to be inactive as single agent treatment in lung cancer. We have studied the effect of recombinant  $\alpha_2$  interferon (IFN) on the activity of cis-platinum (CP) and ifosfamide (IFOS) in human non-small cell lung cancer xenografts grown in CBA mice rendered immunodeficient by neonatal thymectomy and total body irradiation. Groups of 6-9 tumours were randomised to single agent treatment, combination therapy (CP + IFN or IFOS + IFN) or a control group. IFN was injected s.c. in a dose of  $2 \times 10^4$  IU daily for 35 days. Drugs were given i.p. weekly  $\times 5$  at 20% of MTD. Tumour volume was estimated assuming an ellipsoid shape. The median doubling time was calculated for each group and the activity of each agent or combination was expressed in terms of the specific growth delay (SGD) compared with controls. IFN showed no activity as a single agent (SGD 0.2). In a squamous carcinoma the activity of CP and IFOS alone (SGD = 0.77 and 0.27) was increased by combination with IFN (SGD = 1.44 and 0.66). A similar effect was seen in an adenocarcinoma (SGD for CP = 0.12, CP + IFN = 0.48, IFOS = 0.04, IFOS + IFN = 0.28), showing that IFN given in a dose which produces no cytotoxic effect alone is able to potentiate the effects of CP and IFOS in non-small cell xenografts.

### The role of cryoanalgesia in control of postthoracotomy pain

JC ROXBURGH, CG MARKLAND, BA ROSS, WF KERR *Department of Thoracic Surgery, Norfolk and Norwich Hospital, Norwich, Norfolk* Thoracotomy causes severe postoperative pain, management of which is difficult, the use of systemic analgesics often causing

respiratory depression. Cryoanalgesia of the intercostal nerves has been advocated as an effective means of local analgesia without serious side effects. A prospective randomised blind trial to investigate the efficacy of the technique was therefore carried out. A total of 53 patients undergoing thoracotomy were allocated to either a trial or a control group. At thoracotomy the surgeon was informed of the patient's allocation. The trial group received one minute of direct cryotherapy to at least five intercostal nerves related to the incision. All patients received methadone via the lumbar epidural route in a dose calculated according to their weight. A linear analogue assessment of postoperative pain was made by patients as soon as they were able to give an assessment. An independent record of all postoperative analgesia was kept. After discharge further assessments were made at least six weeks after operation. There is no statistical difference between the two inpatient populations. However, there is an increase in longterm morbidity in the cryoanalgesia group. We conclude that cryoanalgesia has no role in the control of postthoracotomy pain.

### Distribution of bronchial reactivity to histamine in an adult population

P BURNEY, J BRITTON, S CHINN, A TATTERSFIELD, AO PAPACOSTA, M KELSON, F ANDERSON, D CORFIELD *Department of Community Medicine, United Medical and Dental Schools (St Thomas's), London* *Department of Respiratory Medicine, Nottingham;* *Department of Medicine, Southampton* Although bronchial reactivity has been widely used in the study of asthma, and has been suggested as a standardised test for use in epidemiological surveys, little is known of its distribution in the general population. All adults aged 18-64 living in two villages in Hampshire and a market town in Dorset were asked to complete a questionnaire which sought information on respiratory symptoms and other variables including age and smoking history. A random 20% sample of these were asked to come for bronchial reactivity tests and skin prick tests for three common allergens. Of 873 individuals invited for tests 522 (60%) came and of these 511 were tested. Positive bronchial challenge tests were associated independently with positive skin tests and with current smoking. Both of these associations were however strongly associated with age, reactivity being more closely related to skin sensitivity in the young and to smoking in the older age groups. No independent effect on reactivity could be shown from sex, social class or area of residence, and no significant effect could be shown from recent upper respiratory tract symptoms. The relationship with initial lung function was significant but this only partially explains the relationship with smoking.

### Should serial records of peak expiratory flow (PEF) be plotted on a logarithmic scale?

S SHAUNAK, AJ FRANCE, A ROSIE, GJR MCHARDY, MF SUDLOW *Chest Unit and Department of Respiratory*

**Medicine, City Hospital, Edinburgh** Serial measurements of PEF are used to monitor airway obstruction over the range 60-600 l/min. Clinical improvement often accompanies small increases in PEF from low initial values. To model this, we measured PEF in four healthy blindfolded subjects with tubes of diameter 3.5-19 mm and length 10-60 cm interposed in random order between the mouth and the PEF meter. Baseline PEF did not change during the experiments. PEF was linearly related to the logarithm of tube cross sectional area ( $r = 0.98$ ). Alterations in tube length had little effect. A given diameter change in small tubes produced larger percentage changes in PEF than the same change in large tubes, in accord with predictions of the influence of diameter changes on resistance in long straight pipes. A similar dependence of airflow resistance on diameter would be expected in the more complex flow regimes in branching systems like the bronchial tree. (TJ Pedley, RC Schroter, MF Sudlow, J Fluid Mech 1971;46:365-383). These results suggest that non-linear plots of serial PEFR measurements could be clinically useful because of the greater visual emphasis on small absolute changes at low values of PEF and this is borne out by initial clinical experience with a logarithmic chart.

#### **Pulmonary complications associated with the Manchester air disaster**

S O'HICKEY, E CROWNE, CAC PICKERING *Wythenshawe Hospital, Manchester* On the 22 August 1985 a Boeing 737 jet airliner burst into flames at take off at Manchester Airport. Of 137 people on board 52 died on the aeroplane. Of the remainder who escaped most had minor or trivial injuries. Fifteen were admitted to hospital, of whom all had evidence of smoke inhalation; in addition two had burns. At presentation only one required ventilation (for "shock lung") but within 12 hours a further five were ventilated. Indications for ventilation included laryngeal oedema, hypoxia despite 100% O<sub>2</sub> and severe airways obstruction in a previously diagnosed asthmatic. The other received nebulised and IV bronchodilators, high dose oxygen therapy, antibiotics and intensive physiotherapy. Lung function was assessed as soon as possible until discharge in all but two patients. This revealed a marked reduction in FEV<sub>1</sub>, FVC and PEFR with normal gas exchange. A pronounced improvement in these parameters occurred between the fourth and fifth days. One patient died (shock lung and 24% burns on arrival), the remainder were discharged by 15 days. Although at presentation patients with smoke inhalation may seem relatively well, lung function may deteriorate rapidly in the first 24 hours. In our group, however, all but one made a good recovery.

#### **Rapid diagnosis of cytomegalovirus pneumonitis by bronchoalveolar lavage**

HJ MILBURN, PR STIRK, AG DAVISON, RM DU BOIS *Departments of Thoracic Medicine and Virology, Royal Free Hospital, London* Cytomegalovirus (CMV)

pneumonitis occurs in approximately 13% of patients receiving bone marrow or kidney transplants and is fatal in 90% of these. Establishing a diagnosis may take several weeks when routine culture methods are used. Material obtained by bronchoalveolar lavage (BAL), however, may provide a diagnosis within 27 hours. We have used monoclonal antibodies to identify CMV infected cells in BAL fluid and for the detection of early antigenic fluorescent foci (DEAFF) in fibroblast cultures inoculated with lavage fluid; (Griffiths *et al*, Lancet 1984;i:1242-4). BAL with 180 ml of normal saline was performed on 19 immunosuppressed patients who developed evidence of pneumonitis over the past year. A positive diagnosis of CMV pneumonitis was made in ten patients. Nine of these were positive by DEAFF and the tenth by conventional cell culture. Five of the DEAFF positive samples were also positive in cell culture but three of the remaining four were unevaluable in conventional culture owing to bacterial contamination. Two were positive by direct staining. These early positive results enabled eight patients to receive CMV hyperimmune serum and five of these survived. Using these techniques we have been able to improve the survival of patients with CMV pneumonitis.

#### **Comparison of the PEF and spirometric response to corticosteroids in chronic airflow obstruction**

RI GOVE, AS ROBERTSON, GA WIELAND, PS BURGE *East Birmingham Hospital, Birmingham* The change in the mean PEF was compared with the change in FEV<sub>1</sub> and FVC in measuring the response to corticosteroids in 92 patients with adult onset chronic airflow obstruction (CAO). All patients measured their PEF four hourly for two weeks before and throughout a double blind randomised trial of prednisolone 40 mg a day and a placebo inhaler, beclomethasone dipropionate (BDP) 50 µg tds and placebo tablets, and both preparations as placebo. Each treatment was given for two weeks with a two week washout in between. Spirometry, six minute walks and visual analogue scales of respiratory symptoms (VAS) were recorded at the beginning and after each treatment. Patients with clinical asthma were excluded. A response was defined as >20% improvement in FEV<sub>1</sub>, FVC or mean PEF during the second week of treatment, as compared with baseline. Thirty-six patients (39%) had a response, eight in terms of their PEF only, 14 in spirometry only, and 14 in both. The only significant treatment effect on the VAS and walk results was seen in the responders whose six minute walks improved significantly on both active treatments. There was, however, no significant correlation with the physiological data. Spirometry is the commonest indicator of a response to steroids but the PEF is an important adjunct. PEF is less likely to be affected by single bad days and may be easier for some patients to perform. Failure to include measurements of PEF may cause some steroid responders with CAO to be missed.

**Survival of patients with hypoxic cor pulmonale given domiciliary oxygen therapy**

CB COOPER, J WATERHOUSE, JP NICHOLL, AJ SUGGETT, P HOWARD *University Department of Medicine, University of Sheffield, Royal Hallamshire Hospital, Sheffield*

In the past 12 years, 72 patients aged 60.5 (7.5) years mean (SD) with severe chronic obstructive airways disease, hypoxaemia and at least one illness with peripheral oedema were studied whilst receiving long term domiciliary oxygen therapy. Fifty-three were male and 19 female. In a stable phase before O<sub>2</sub> therapy, FEV<sub>1</sub> was 0.78 (0.32) litres, % predicted FEV<sub>1.0</sub> 28.7% (9.9%), Pao<sub>2</sub> (air) 6.1 (1.0) kPa and Pao<sub>2</sub> (air) 6.9 (1.2) kPa. All patients had a Pao<sub>2</sub> < 8.0 kPa but only 59 were initially hypercapnic (Pao<sub>2</sub> > 6.0 kPa). Oxygen was delivered for at least 15 hours within the 24 hour day. Forty-five patients underwent right heart catheterisation using a floating catheter technique. Mean PAP initially was 28.3 (10.2) mmHg, cardiac output 5.9 (1.8) l min<sup>-1</sup> and TPVR 403 (172) dynes s cm<sup>-5</sup>. Overall survival was similar to that previously reported for continuous oxygen therapy (24 hours) (Arch Int Med 1980;93:391-398) and better than the MRC control patients (Lancet 1981;i:681-685). Previous sex differences were not seen. Survival was found to be associated with impairment of FEV<sub>1</sub> (p<0.02) and FVC (p<0.02) but surprisingly not with Pao<sub>2</sub> (p=0.27), PaO<sub>2</sub> (p=0.53) or PAP (p=0.21). Pulmonary haemodynamics did not change in 38 patients after at least one year of therapy. PAP was 26.1 (11.0) mmHg, and cardiac output 6.7 (2.8) l min<sup>-1</sup>. Total pulmonary vascular resistance fell to 348 (168) dynes s cm<sup>-5</sup> but the change was not significant owing to enormous variability between patients.

**Problems with staphylococcal infection in patients with transtracheal micro-catheters**

NR BANNER, A HAIGH, T BUSHNELL, JR GOVAN *Harefield Hospital, Harefield, Middlesex*

The use of transtracheal micro-catheters has been shown to be an effective method of oxygen delivery (Heimlich, Ann Otol Rhinol Laryngol 1982;91:643-7). Thirteen transtracheal oxygen (TTO) patients were studied over six months (56 patient months). TTO micro-catheters were changed every two months and during infections. The catheter tips were cultured and nasal swabs obtained. Thirteen cultures were sterile, eight (from five patients) grew *Staph aureus*, two *Pseudomonas*, one *Proteus* and one *Enterobacter*. Four patients with *Staph aureus* also had the organisms with identical antibiotic sensitivities in cultures from nasal swabs. Three episodes of chest infection were treated by general practitioners and five in hospital. In three hospital cases no pathogens were isolated. One patient developed severe respiratory failure requiring mechanical ventilation. In this patient *Staphylococcus aureus* was grown from both the sputum and the micro-catheter. One patient with a resistant *Staphylococcus aureus* in the nasal swab subsequently developed chest infection due to *Haemophilus influenzae* which responded to treatment but the catheter site became colonised with the resistant *Staphylococcus* and the system was removed. *Staphylococcus* infections are a complication

of TTO therapy and treatment of serious chest infections should include an anti-staphylococcal agent.

**An assessment of nebulised saline and terbutaline as an adjunct to chest physiotherapy**

PP SUTTON, HG GEMMELL, J DAVIDSON, N LAWTRIE, JS LEGGE, JAR FRIEND *Departments of Thoracic Medicine, Nuclear Medicine, and Physiotherapy, Aberdeen Royal Infirmary, Foresterhill, Aberdeen*

Nebulised saline and terbutaline were examined as an aid to increase the clearance of tracheobronchial secretions during chest physiotherapy using the inhaled radioaerosol technique. Seven patients with bronchiectasis and copious sputum production (mean 24 h sputum wt 39 g) were studied on four separate occasions. Each patient inhaled a nebulised suspension of HSA millimicrospheres labelled with <sup>99m</sup>Tc and underwent gamma camera imaging before and after a 30 minute treatment period. These were in a randomised order: a) control b) physiotherapy alone c) physiotherapy following nebulised saline d) physiotherapy following terbutaline. The physiotherapy regime included postural drainage and forced expiration, which are the most effective components available (Sutton *et al*, Eur J Respir Dis 1983;64:62-89 and 1985;66:147-152). Both sputum yield and radioaerosol clearance increased above the means for physiotherapy alone following the additional use of nebulised saline (p<0.05) and terbutaline (p<0.01). Mean (SE) of radioaerosol clearance during physiotherapy alone was 14.9% (1.7) and during nebulised terbutaline and physiotherapy was 24.7% (3.7). Terbutaline was associated with a greater clearance of radioaerosol than nebulised saline (p<0.05) and this effect was seen in both central and peripheral regions. The action may be due to increased hydration of the periciliary fluid and subsequent enhanced tracheobronchial clearance. We suggest the use of nebulised bronchodilators to increase sputum mobilisation during chest physiotherapy.

**Oral high frequency oscillation (OHFO) as an adjunct to physiotherapy (PHYSIO) in cystic fibrosis (CF)**

RJD GEORGE, D PAVIA, G. WOODMAN, MT LOPEZ-VIDRIERO, R FRANCIS, JE AGNEW, SW CLARKE, DM GEDDES *The London Chest and Royal Free Hospitals*

OHFO improves tracheobronchial clearance in normal subjects (Thorax 1985;40:433). We have compared this technique, using a portable, hand held oscillator, with PHYSIO (postural drainage percussion and forced expiration) in seven adults with CF. The study had four limbs: 30 min OHFO with instructed cough, 30 min self-administered PHYSIO, OHFO with postural drainage and forced expiration (OHFO + PHYSIO) and control (instructed cough). These were randomised and where possible performed in consecutive weeks. Tracheobronchial clearance was measured by clearance of inhaled radioaerosol and expectorated sputum was weighed. The control wet weight of sputum produced during and 30 minutes after treatment, expressed as a percentage of 24 hour production, was



10.6% (range 0-23%). All three interventions were more effective than control: OHFO 23.3% (range 3-76  $p < 0.05$ ), PHYSIO + OHFO 38% (range 17-73,  $p < 0.05$   $n = 6$ ) and PHYSIO 47.7 % (range 12.4-68  $p < 0.01$ ). Tracheobronchial clearance showed a trend of improvement with all three interventions but only OHFO + PHYSIO enhanced clearance significantly ( $p < 0.05$ ). In patients requiring daily bronchial toilet, OHFO is a useful adjunct to PHYSIO and is a practical and simple way of increasing expectoration of sputum.

### The effects of postural drainage incorporating the forced expiration technique on pulmonary function in cystic fibrosis (CF)

ME HODSON, BA WEBBER, JL HOFMEYER, MDL MORGAN *Brompton Hospital, London* The clearance of excess bronchial secretions by postural drainage (PD) is a widely accepted form of treatment but studies of its effect on pulmonary function are limited. The forced expiration technique (FET) used as a part of a PD treatment has been shown to be a more efficient means of clearance of bronchial secretions than conventional PD (Pryor *et al*, Br Med J 1979;2:417). A pilot study on the effects of PD incorporating the FET on pulmonary function was carried out in our unit but statistically significant changes were not seen after a single treatment session. It was therefore decided to study a longer period of treatment. Twelve patients, mean age 19.3 years, with CF were studied. The patients were newly referred and although they had been performing some form of physiotherapy, they had not previously performed PD using the FET. Detailed pulmonary function tests were performed before and after three days' treatment with PD incorporating the FET. No other changes in treatment were made. The results following treatment showed a statistically significant improvement in FEV<sub>1</sub> ( $p < 0.001$ ), FVC ( $p < 0.001$ ), PEF ( $p < 0.001$ ), PIF ( $p < 0.001$ ) and the  $\dot{V}_{Emax50}$  ( $p < 0.025$ ). This form of physiotherapy improves pulmonary function in patients with CF.

### Which nebuliser and compressor should be used for carbenicillin aerosol therapy?

SP NEWMAN, PGD PELLOW, SW CLARKE *Department of Thoracic Medicine, Royal Free Hospital, London* Aerosol antibiotics (carbenicillin and gentamicin) have been used successfully to treat respiratory tract infection in cystic fibrosis (Hodson *et al*, Lancet 1981;2:1137-9), but little information exists concerning the choice of nebuliser and compressor for use with such viscous antibiotic solutions. Aerosol output, droplet size (by Malvern Instruments 2600 HSD laser analyser) and nebulisation time have been measured *in vitro* for 1 g carbenicillin (Pyopen, Beechams) diluted with three and four ml water for injection and atomised by six brands of jet nebuliser (Cirrus, DeVilbiss, Inspiron, Turret, Unicorn and Upmist;  $n = 8$ ). Medic-Aid PortaNeb 50 and Medix Maxi compressors, producing flows through nebulisers of 6-8 and 10-12 l/min respectively, were used. The release of

"respirable" ( $< 5\mu m$  diameter) carbenicillin aerosol was greatest for Turret nebuliser ( $p < 0.01$ ). Using Turret, equal amounts of respirable aerosol were released with the three and four ml fills, but nebulisation times were reduced with the former ( $p < 0.01$ ). Significantly more respirable aerosol was released ( $p < 0.02$ ) and nebulisation times were shorter ( $p < 0.05$ ) with the Maxi compressor. For efficient nebulisation of 1 g carbenicillin in an acceptably short treatment period we recommend (a) Turret nebuliser, (b) 3 ml diluent, (c) a powerful compressor.

### Health care of adult patients with cystic fibrosis in Wessex — the patient's view

SE PARKER, CJ ROLLES, ST HOLGATE *Medicine I and Paediatrics, Southampton General Hospital, Southampton* We have assessed the clinical status and social functioning of adult cystic fibrosis (CF) patients resident in the Wessex Region. Fifty-eight patients were identified (M:F 5:3, mean age 21.6 y). Their health care was supervised by local chest physicians (30%), general physicians (7%), paediatricians (14%), specialist centre (Brompton CF Clinic) or joint care (38%). Thirty-three out of 45 (75%) patients received and returned a questionnaire. One third of patients had a family history of the disease. The majority (79%) were  $< 50$  centile for height and 61% underweight for their height, those who were underweight for height having an increased incidence of hospital admissions. At the time of survey all patients had respiratory symptoms and 42% current pseudomonas infection. Forty-two per cent had  $> one$  hospital admission in the preceding year (mean stay 18 days), of which the majority were for chest problems. Only 39% attempted regular chest physiotherapy and 15% no physiotherapy at all. Fifty-seven per cent received regular antibiotics orally and 27% by inhalation. More general problems included recurrent abdominal pain (33%), diabetes (24%) and symptoms of allergies (27%). Most of the patients (82%) were in employment or educational centres, of whom 40% were absent for  $> two$  weeks/year on account of illness. All patients wished to be spoken to directly about their disease and many expressed an interest in regional or central centres for specialist care.

### Health care for adult patients with cystic fibrosis in Wessex — the consultant's view

SE PARKER, CJ ROLLES, ST HOLGATE *Medicine I and Paediatrics, Southampton General Hospital, Southampton* Concern has been expressed over the responsibility for the continued health care of cystic fibrosis (CF) in adults. To gain current practice and opinion a postal questionnaire was sent to 18 consultants who manage 57 patients resident in the Wessex area. The response was 72% — four paediatricians and 12 general physicians (eight with an interest in chest disease). Only three consultants had more than four CF patients and the consultant with the most CF adults under his care was a paediatrician. Paediatricians passed on their CF patients to the general

physicians any time between 16 and 20 years. All consultants saw their CF patients at least twice a year. The chest physicians requested chest radiographs and pulmonary function "routinely", the others utilising these only "when clinically indicated". All consultants recommended regular physiotherapy and 70% pursuance of a physical sport. Half of the physicians advocated regular nebulised and/or intravenous antimicrobials for pseudomonas and acute infections, and all consultants recommended bronchodilators if reversibility of airflow obstruction could be demonstrated. The majority (75%) gave their patients regular pancreatic supplements but only 17% of the general physicians, in contrast to all the paediatricians, recommended dietary supplements. All consultants had a physiotherapist, nurse, social worker or dietitian who expressed an interest in CF, though 60% felt that care could be improved with the help of specialist clinics or advisory centres that could provide a wider range of skills.

#### **Respiratory patients with mobility allowances: what criteria for eligibility?**

V POSNER, JE COTES *Respiration and Exercise Laboratory, University Department of Occupational Health, Medical School, Newcastle upon Tyne* Mobility allowances are awarded by DHSS to patients who are unable or virtually unable to walk. However, in the case of chest patients there is no information on their respiratory impairment. Accordingly 150 patients who were awarded mobility allowances during 1983 on account of respiratory diseases were approached; 39 (26%) declined to be interviewed, 17 were too ill to take part, 15 had died, six had moved without trace and 73 were seen (47 men and 26 women). The mean age and FEV<sub>1</sub> were respectively 59 years and 0.82 l (32% predicted in each sex separately). Eight patients had normal or nearly normal spirometry (FEV<sub>1</sub> > 59% predicted) though two had seen a chest physician. For the group as a whole the grade of breathlessness was unrelated to the FEV<sub>1</sub> but both were weakly correlated with age and smoking history. All but one patient appeared to meet the DHSS criterion for an allowance but in 14 the disablement was not primarily respiratory; in two patients with asthma the consultants considered the awards inappropriate. Few GPs and no consultants had been associated with the applications. From 62 replies 42% of GPs considered the present arrangements satisfactory but in four of nine instances where they thought the award unnecessary the FEV<sub>1</sub> was less than 0.7 l. Spirometry would contribute to assessment of respiratory patients for mobility allowances but there remains a need for objective information on this difficult subject.

#### **Finger clubbing — a survey of patient awareness**

SE CHURCH, AJ WILLIAMS *Royal Liverpool Hospital, Liverpool* Finger clubbing (FC) has been recognised by clinicians since Hippocrates as a sign which may indicate serious underlying pathology. However, there has been no previous study which has documented patient awareness of

the deformity. We have undertaken such a study since clinicians frequently enquire whether the patient has noted any change when the diagnosis is not apparent. We have studied by questionnaire 51 consecutive patients (39 male) with gross FC ('drumstick appearance'). The majority of patients (42%) had carcinoma of the bronchus (Ca B), but the remaining diseases covered the full spectrum of known associations. 36 (70%) patients were not aware of their FC. The results have been analysed by comparing features between the two groups of patients: those aware (A) and those not aware (NA). There was no significant difference between the groups (A vs NA) for age (56 vs 60 years), smoking (40% vs 42%), social class, personal hygiene (handwashing/scrubbing), habits such as nail biting or occupations/hobbies involving concentrated 'eye-hand' contact. Likewise, the type of underlying illness and its duration was no different in the two groups. However, females were more aware of FC: 9/12 (75%) of cases compared with only 6/39 (15%) of males ( $p < 0.001$ ). One female patient with Ca B even presented because of the change in her fingers. The awareness in females was not related to manicuring, but probably due to greater consciousness of body image.

#### **Lung cavities: a complication of coeliac disease**

FM STEVENS, CE CONNOLLY, CF MCCARTHY, H HITCHCOCK *Regional and Merlin Park Hospitals, Galway, Ireland* Pulmonary complications in coeliac disease are well recognised and include fibrosing alveolitis, hypersensitivity pneumonia, sarcoid, pulmonary haemosiderosis and broncho-alveolitis (Edwards *et al*, J Clin Path 1985;38:361). Amongst the 300 patients attending an adult coeliac clinic, five subjects developed pulmonary cavities. No unifying cause could be identified for this complication. All patients died and had autopsies. Evidence of hyposplenism, raised platelet count and/or elevated 'pitted' erythrocyte numbers were found in all patients during life and three patients had small spleens at post-mortem. The thrombocythaemia may have contributed to deep venous thrombosis in two subjects and to pulmonary emboli in two patients. Fatal pneumococcal pneumonia is a well recognised sequel of splenectomy (Robinette and Fraumeni, Lancet 1977;2:127), but this particular infection was not found in any of these patients. Four patients had a history of severe Raynaud's disease, but there was no evidence at autopsy of pulmonary vasculitis, a condition associated with lung cavities (Castaneda-Zuniga and Hogan, Radiology 1976;118:45). Pulmonary cavities in coeliac disease have not previously been described and may be related to functional hyposplenism.

#### **Histocompatibility antigens in adult obliterative bronchiolitis**

MC SWEATMAN, JR MARKWICK, PJ CHARLES, SE JONES, J PRIOR, RN MAINI, M TURNER-WARWICK *Brompton and Charing Cross Hospitals, London* HLA antigen DRW4 is strongly associated with rheumatoid arthritis (RA) in Caucasians; DRW4 negative individuals may have DR1 (the prevalent

DR antigen in negroes with RA). D-penicillamine has been implicated in the pathogenesis of obliterative bronchiolitis (OB) in RA. Caucasians with RA and HLA-DR3 (especially the A1, B8, DR3 haplotype) have increased susceptibility to nephrotoxicity (and possibly mucocutaneous toxicity) with gold and/or penicillamine therapy. We compared HLA antigens in 27 patients with OB (15 with RA) with 100 normal controls to determine their relationship to drug toxicity and the pathogenesis of OB. The antigen frequencies (%) were:

	A2	A28	B40	DR1	DR4
Normal controls	46	8	11	15	21
OB	74	22	37	25	54

The significantly increased prevalence of HLA-A2 ( $p < 0.02$ ) and B40, DR4 ( $p < 0.001$ ) may be associated with an increased incidence of OB either alone or with RA. The greater frequency of A28 was not significant ( $p < 0.1$ ). HLA DR1 was increased only in OB + RA ( $p < 0.05$ ), but DR4 was more prevalent in both OB alone and OB + RA. Our patients did not have antigens associated with other gold/penicillamine toxicity (ie DRW2/3), suggesting that they might represent a distinct group. Increased prevalence of DR4 may indicate an association between the pathogenesis of both OB and RA and the HLA-DR locus.

#### Detection of small cell lung carcinoma (SCLC) in pleural effusions using monoclonal antibodies

FM MOSS, LG BOBROW, PCL BEVERLEY, RL SOUHAMI *Imperial Cancer Research Fund and Departments of Pathology and Oncology, University College London* Pleural effusions from eight patients with SCLC and ascitic fluid from one patient were stained with a panel of monoclonal antibodies which had previously been used to stain solid tumours of SCLC. Six recognise epithelially associated antigens and one (UJ13A) a neuroectodermal antigen. Immunoalkaline phosphatase was used as a detection system. UJ13A, which had been the most consistent in staining solid tumours (17/20 with  $> 75\%$  of cells staining), stained effusions poorly (1/8  $> 75\%$  of cells staining and 4/8  $< 50\%$ ). The expression of the epithelial antigens in pleural effusions was similar to that in solid tumours. Cocktails of combinations of monoclonal antibodies were also used. Although they did not improve the level beyond that seen with the best single reagent, with the cocktails a uniformly high proportion of cells stained (all  $> 60\%$ ). Variation of expression of antigens within and between tumours and possibly within the same tumour at different sites, limits the usefulness of monoclonal antibodies in detection of small numbers of malignant cells. If monoclonal antibodies are to be used, the best results are likely to be obtained with cocktails of antibodies.

#### Monoclonal antibodies against the epidermal growth factor receptor

T CERNY, D BARNES, P HASLETON, PV BARBER, K HEALY, N

THATCHER *CRC Department of Medical Oncology, Christie Hospital, and Department of Pathology, Wythenshawe Hospital, Manchester* Indirect immunoperoxidase staining of frozen sections was performed with a monoclonal antibody (mAb EGF-R1, M Waterfield 1982) on 60 biopsy specimens from 60 patients with lung tumours. Ten cases were disregarded because there were no or too few tumour cells present. Of the remaining 50 tumour samples, 25 were obtained at thoracotomy and 25 at fiberoptic bronchoscopy: 30 of 36 squamous cell carcinomas showed clearly positive staining. However, non-homogeneous staining was common with strongly positive cells adjacent to unstained cell groups. This finding suggests the possibility of either different cell clones or differing functional status. None of 10 small cell lung cancer biopsy samples was positive but often foci or faintly positive staining cells were observed, and these cells generally contained more cytoplasm. Two of three primary adenocarcinomas stained strongly, as did one pleomorphic adenoma. Two new mAbs against the cytoplasmic part of the EGF-R (EGF-RF4 and EGF-RD10, W Gullick, 1985) showed in general the same results over 21 of the 50 samples so far examined. No additional or enhanced staining compared with that with EGF-R1 was observed, a finding suggesting a lack of enhanced expression of the truncated EGF-R, which is a homologue to the v-erb B oncogene product.

#### Absence of refractory period or cumulative effect of cold air hyperventilation

B ASSOUIFI, M DALLY, S LOZEWICZ, A NEWMAN-TAYLOR, D DENISON *Brompton Hospital, London* Two features of bronchial responsiveness to cold air isocapnic hyperventilation (CAIH) were studied in asthmatics. These were the refractory period, which is characteristic of exercise induced asthma, and the cumulative effect, which is a feature of asthma provoked by drugs such as methacholine and carbachol. The possibility of a refractory period was investigated by administering paired challenge using intervals of 15, 30, and 60 minutes. Each interval was used on a separate day. The maximum bronchoconstriction following the second challenge was not reduced using these intervals. The cumulative effect was studied by comparing the bronchial response to a stepwise test performed using the method of Assoufi *et al* (Thorax 1985;40:216) with that of a single exposure given at the maximum ventilation rate using the stepwise test. There was no significant difference between the results on each occasion. Furthermore there was a good relationship between the maximum fall in FEV<sub>1</sub> following stepwise challenge and that occurring after a single exposure ( $r = 0.83$ ,  $p < 0.001$ ). The possibility of an additive effect was also investigated by administering three equal cold air challenges over a short period of time; the intervals used between exposures were five and 10 minutes. Each interval was tested on a separate day. The lowest post-challenge FEV<sub>1</sub> remained constant following each of the challenges and was unaffected by the time interval used. These results suggest that cold air does not produce a refractory period or have a cumulative effect.

**Hypertonicity as an initiating stimulus for exercise induced asthma**

NG BELCHER, PJ REES, TJH CLARK, TH LEE *Department of Respiratory Medicine, Guy's Hospital, London* We subjected six patients with exercise induced asthma (EIA) to a pair of exercise tasks separated by one hour. Three patients demonstrated a refractory period after exercise. On a subsequent day the dose of nebulised hypertonic saline (3.6%) which produced a fall in FEV<sub>1</sub> similar to that after exercise was determined. Patients were then subjected randomly to pairs of challenges: exercise/hypertonic, hypertonic/exercise and hypertonic/hypertonic. Following the initial exercise task the three patients who were refractory to further exercise were also refractory to hypertonic challenge. In these individuals initial challenge with hypertonic saline rendered the subject refractory to both hypertonic and exercise challenges. In contrast, those who were not refractory after an exercise challenge were not refractory to exercise or hypertonicity after an initial hypertonic challenge. The three refractory subjects were given inhalations of isotonic saline and histamine prior to exercise. Isotonic saline produced no decrement in pulmonary function whereas the histamine challenge was given to produce a fall in FEV<sub>1</sub> comparable to that following exercise. Neither challenge rendered the subjects refractory to EIA. These findings indicate that refractory period is not related to bronchoconstriction per se and suggest that the mechanisms of asthma elicited by exercise and hyperosmolar challenge may be similar.

**Influenza vaccination in asthmatic subjects**

MK ALBAZZAZ, JE HARVEY *Bristol Chest Clinic and Ham Green Hospital, Bristol* Previous studies in asthmatic subjects given inactivated whole influenza virus vaccine have demonstrated a transient exacerbation of asthma and increased airway reactivity. In a double blind placebo controlled trial, we have studied the effect of a subcutaneous injection of a vaccine, containing inactivated viral surface antigen only, on both airway reactivity and symptoms in 23 patients with stable chronic asthma. Fourteen patients with mean age 44 (range 24-65), mean (SD) FEV<sub>1</sub> 74% (27.2) predicted, were given influenza vaccine. Nine patients, mean age 41 (range 23-64), predicted FEV<sub>1</sub> 66% (20.8), were given placebo vaccinations. Subjects recorded peak flow rates, symptoms and bronchodilator requirements daily for one week before and two weeks after vaccination. Bronchial reactivity to inhaled histamine was measured twice before and two days and two weeks after vaccination. There was no significant increase in airway reactivity following histamine inhalation, asthma symptoms, bronchodilator requirement or peak flow rates in either group. There were significant rises in antibody levels against influenza A - H3N2 (86%), influenza A - H1N1 (79%) and influenza B (79%) confined to the vaccinated group. Influenza vaccine containing viral surface antigen only is well tolerated by asthmatic subjects.

**The role of respiratory tract infection and atopy in autumnal exacerbation of bronchial reactivity in a rural population**

JR BRITTON, PGJ BURNEY, S CHINN, AO PAPACOSTA, F ANDERSON, AE TATTERSFIELD *City Hospital, Nottingham; St Thomas' Hospital, London; and Southampton General Hospital* There is in the UK an autumnal increase in asthma morbidity (Ayers, Thorax 1984;39:687) and mortality (Khot, BMJ 1984;289:23-4), the cause of which is unknown. We report the change in bronchial reactivity measured in September 1984 in a sample from a community population previously surveyed for asthma prevalence. One hundred and five subjects whose histamine reactivity and skin sensitivity to common allergens were measured in March 1984 were rechallenged with histamine in September, up to 4 µmol histamine being given (Yan, Thorax 1983;38:760-5) with extrapolation of PD<sub>20</sub> to 8 µmol. A PD<sub>20</sub> FEV<sub>1</sub> of 0.03-8 µmol was measurable on at least one occasion in 66 subjects. Mean PD<sub>20</sub> decreased in September by 0.67 (± 0.23, SE) doubling doses. Multiple regression analysis demonstrated increased reactivity was independently related to respiratory tract infection (RTI) (p<0.01), and to grass pollen skin sensitivity (p<0.05). Mean increase in reactivity was greater in subjects with RTI symptoms in either September or March, and greatest in those reporting symptoms on both occasions. After these variables had been allowed for there was no relationship between change in reactivity and other skin sensitivities or baseline airway calibre. Thus respiratory infection may be a major cause of autumnal exacerbation of asthma. Protracted effects from grass pollen sensitivity may also be important.

**Are drug induced changes in bronchial reactivity and airway calibre interdependent?**

H GARRETT, JB BRITTON, SP HANLEY, J HADFIELD, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Most drugs which are clinically effective in asthma cause changes in both airway calibre and bronchial reactivity in the short or long term. The relationship between the changes in reactivity and airway calibre is not known but it has been suggested that they may be interdependent. We have investigated this relationship by studying the effects of increasing doses of drugs with different actions, salbutamol and ipratropium. Six subjects with mild asthma were studied on 10 occasions. Baseline FEV<sub>1</sub> and histamine PD<sub>20</sub> FEV<sub>1</sub> (Yan *et al*, Thorax 1983;38:760-765) were measured. One hour later, when the FEV<sub>1</sub> had returned to within 10% of baseline, a single dose of placebo × 2, salbutamol (5, 30, 200 or 1000 µg) or ipratropium (5, 30, 200 or 1000 µg) was given double blind in random order by nebuliser over eight min FEV<sub>1</sub> was measured at intervals over the subsequent 15 min for salbutamol and 40 min for ipratropium. The histamine challenge test was then repeated. There was a dose related increase in FEV<sub>1</sub> after both salbutamol and ipratropium, with a maximum increase after the highest doses of 0.66 l and 0.68 l respectively. With salbutamol the dose related



increase in FEV<sub>1</sub> was associated with a progressive increase in PD<sub>20</sub> histamine (maximum  $\Delta$ PD<sub>20</sub>=2.86 doubling doses). With ipratropium there was no change in PD<sub>20</sub> histamine despite bronchodilatation. Thus bronchodilatation per se does not account for drug induced changes in histamine reactivity.

#### Airway response to salbutamol in wheezy infants: evidence for beta-adrenergic responsiveness

A PRENDIVILLE, S GREEN, M SILVERMAN *Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* It has been generally accepted that wheezy infants are unresponsive to inhaled beta-adrenergic agents. We have assessed the effect of nebulised salbutamol 2.5 mg on the bronchial response to histamine in eight infants with recurrent or persistent wheeze. The index of airway function, taken from partial expiratory flow-volume curves, was the maximum flow at FRC ( $\dot{V}_{max}$  FRC). Histamine responsiveness was measured by the tidal breathing method after the administration of doubling concentrations of nebulised histamine phosphate solution, as the concentration of histamine causing a 25% fall in  $\dot{V}_{max}$  FRC (PC<sub>25</sub>).

	PC <sub>20</sub> g/l (median value)	
	Before	After
Saline	1.0	2.0
Salbutamol	1.0	>8.0

The histamine PC<sub>25</sub> was measured before and after saline or salbutamol on two study days. The PC<sub>25</sub> was reproducible after nebulised saline in the five subjects who responded to histamine (Table). Nebulised salbutamol effectively abolished the histamine response (Table). We conclude that the airways of infants do possess functional beta-2-adrenergic receptors.

#### Bronchial reactivity following prednisolone in chronic obstructive airways disease

JH WINTER, R CARTER, F MORAN *Department of Respiratory Medicine, Royal Infirmary, Glasgow* A proportion of patients with chronic obstructive airways disease (COAD) will respond to corticosteroids by reducing their obstruction but no factor will clearly differentiate responders from non-responders. In COAD non-specific bronchial reactivity correlates with the degree of obstruction present; if an excessive degree of bronchial reactivity for the level of obstruction indicated steroid responsiveness then bronchial reactivity would be a useful means to determine responsiveness. Nineteen subjects (10 female, mean age 57) with COAD received two week courses of prednisolone 25 mg daily and matching placebo in a random order double blind fashion. Before therapy and after each course lung volumes, sGaw, twelve minute walking distance and histamine PC<sub>20</sub> were estimated. Compared with values obtained at baseline and following placebo, mean FEV<sub>1</sub>, sGaw and geometric mean histamine PC<sub>20</sub> were

significantly increased (all  $p < 0.01$ ). Significant correlations between log PC<sub>20</sub> and FEV<sub>1</sub> ( $r = .74$ ) and sGaw ( $r = .52$ ) were seen. No relationship between baseline reactivity and response to prednisolone was seen. Our results confirm that in COAD non-specific bronchial reactivity is related to airways obstruction, that prednisolone causes small increases in histamine PC<sub>20</sub>, FEV<sub>1</sub> and sGaw, but that histamine reactivity is not of value in predicting response to prednisolone in this population.

#### Assessment of symptoms, airway calibre and histamine reactivity in asthmatics following blind food challenge

SJ CONNELLAN, K ROCCHICCIOLI, CAC PICKERING *Chest Clinic, Wythenshawe Hospital, Manchester* Nine asthmatics were selected for a single blind study of symptoms, peak expiratory flow rate (PEFR) and histamine reactivity (HR), following challenge with suspected food allergen, identified by previous elimination diets. All were female with well established asthma, age of onset ranging from 5 to 78 years. Five were atopic and four non-atopic on skin prick testing with common allergens. All were admitted to hospital with stable symptoms, PEFR and therapy. Baseline PEFR and HR were measured on the first day. On the second and third days placebo and active challenges respectively were given at the same time of day. PEFR was measured before and quarter hourly after challenge and HR before and 24 hours after with an additional measurement four hours after if there had been no significant drop in PEFR. One patient had non-specific symptoms after placebo and active challenge but none of the others reacted to placebo. Positive reactions consisted of cough, wheeze and a fall in PEFR > 25% in four; paroxysms of coughing with chest tightness but no change in PEFR in two; abdominal discomfort and vomiting in one; non-specific malaise, chest tightness and headache in one. All symptoms came on within half an hour of active challenge. There were no significant changes in HR, either on the same day or the day following active challenge. In conclusion six out of nine asthmatics had acute airway responses to food challenge, four had acute drops in PEFR, but two had coughing and chest tightness without PEFR change.

#### The relationship between the bronchial response to inhaled histamine and 24 hour sodium excretion

P BURNEY, J BRITTON, S CHINN, A TATTERSFIELD, H PLATT, AO PAPACOSTA, M KELSON *Department Community Medicine, United Medical and Dental Schools (St Thomas's), London, Department of Respiratory Medicine, Nottingham, and Department of Chemical Pathology, Basingstoke* Migrant studies and other studies in developing countries have shown a strong relationship between asthma prevalence and economic development. The possibility that part of this relationship might be explained by differences in salt intake is supported by the observation that table salt purchases in the regions of England and Wales are correlated with asthma mortality

among adult males aged 15-64 and children of both sexes aged 5-14 years. Although this relationship is strong and specific to asthma mortality, correlations between groups of subjects may be spuriously high. A survey of bronchial reactivity in two Hampshire villages was therefore extended to assess the relationship between reactivity and 24 hour sodium excretion. One hundred and thirty-eight men had their response to histamine measured and produced a satisfactory 24 hour collection of urine. After allowing for the effects of smoking, atopy, age, and the 24 hour excretion of potassium and creatinine, there was a significant ( $p < 0.05$ ) relationship between 24 hour sodium excretion and bronchial response to histamine. This supports the relationship noted earlier between mortality and table salt consumption.

#### Assessing the relevance of skin prick tests

J OSMAN, RJ DAVIES *Academic Department of Respiratory Medicine, St. Bartholomew's Hospital, London* Skin prick tests (SPT) with allergens are widely used in the assessment of patients with respiratory disease, yet there are no standardised criteria for a positive result and their significance remains uncertain. We describe a method for the assessment of the clinical relevance of the size of positive SPT. Freeze dried, lyophilised extracts of house dust mite (HDM) and mixed grass pollens (GP) (Bencard, Brentford) were studied in patients with asthma or rhinitis. SPT were performed with serial dilutions of the allergen extracts and the weals produced by each recorded. Bronchial (HDM 28 patients, GP 22) or nasal (HDM 16, GP 15) provocation tests were performed, positive challenges being considered clinically relevant for each dilution of extract. For each dilution of extract graphs were constructed of the true positive rates (TP = positive SPT with positive provocation test) against the false positive rate (FP = positive SPT with negative provocation test) for increasing weal areas. From these graphs the optimal weal area for a positive test can be chosen and the clinician apprised of its significance, for example a 6 mm weal area on SPT with the HDM extract gave a TP of 90% and FP of 13%.

#### Peripheral blood eosinophil counts and bronchial reactivity

KJ TAYLOR, AR LUKSZA *Department of Thoracic Medicine, Fazakerley Hospital, Liverpool* We have studied the relationship between peripheral blood eosinophil count and bronchial reactivity in 23 asthmatic subjects (14 atopic and nine intrinsic). Patients taking oral steroids were excluded. Oral theophyllines were discontinued for 48 hours and inhaled bronchodilators for 12 hours before testing. Baseline eosinophil counts were determined using a modified Fuchs-Rosenthal counting chamber (Rud, Acta Psychiatrica et Neurologica 1947, Suppl. 40) while bronchial reactivity was assessed by histamine challenge testing (Cockcroft *et al*, Clin Allergy 1977;7:235-243). In the atopic subjects there was a strong inverse correlation between baseline eosinophil count and histamine PC<sub>20</sub> ( $r_s$

$-0.84$ ,  $p < 0.01$ ). There was no correlation between baseline FEV<sub>1</sub> and baseline eosinophil count or histamine PC<sub>20</sub>. But in the intrinsic subjects there was an inverse correlation between baseline eosinophil count and both histamine PC<sub>20</sub> ( $r_s -0.68$ ,  $p < 0.05$ ) and baseline FEV<sub>1</sub> ( $r_s -0.68$ ,  $p < 0.05$ ). The results demonstrate a relationship between blood eosinophil count and bronchial reactivity in both atopic and intrinsic asthma. In assessing atopic asthma measurement of the blood eosinophil count may distinguish those with increased reactivity, which is independent of baseline FEV<sub>1</sub>.

#### Plasma histamine concentration in acute asthma

PW IND, PJ BARNES, CT DOLLERY *Departments of Medicine and Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London* Elevated plasma histamine concentrations, thought to reflect increased pulmonary mast cell degranulation, have previously been reported in acute asthma (Charles *et al*, Clin Sci 1979;57:39). However, serial measurements of airflow obstruction were not made and baseline histamine values, by single isotope assay, were high. Twelve patients, with acute asthma, nine male, were studied on presentation to casualty. Mean age was  $30 \pm 4$  (SEM) years and peak expiratory flow (PEF)  $134 \pm 14$  l/min ( $25 \pm 3\%$  predicted). Initial plasma histamine concentration (by double isotope method) was  $5.0 \pm 0.6$  nmol/l, which is significantly elevated compared with normal or mild asthmatic subjects in remission ( $p < 0.001$ ). Serial measurements of PEF and plasma histamine were obtained in seven patients. PEF increased to  $349 \pm 23$  and  $391 \pm 36$  l/min at 24 and 48 hours with standard treatment. Plasma histamine was significantly reduced at 48 hours ( $p < 0.05$ ) but remained elevated compared with remission values ( $p < 0.05$ ). Assuming values of clearance calculated for infused histamine in asthmatic subjects the persisting elevation of plasma histamine over 48 hours would require release of approximately 20% of total lung histamine, which appears unlikely. This suggests that circulating basophils contribute to the plasma histamine concentration and indicates that increased basophil degranulation may occur during an acute asthma attack.

#### Histamine in the sputum in infective lung disease: the potential role of *Haemophilus influenzae*

BD SHEINMAN, JL DEVALIA, SJ CROOK, RJ DAVIES *Academic Department of Respiratory Medicine, St Bartholomew's Hospital, London* Using a new high performance liquid chromatography method for histamine analysis developed in our laboratory we have shown large increases in the histamine levels in sputum from patients with chronic bronchitis (mean  $\pm$  SE =  $2123 \pm 448$  ng ml<sup>-1</sup>) and cystic fibrosis (mean  $\pm$  SE =  $2066 \pm 1135$  ng ml<sup>-1</sup>) when incubated at 37°C for 72 hours. Both heating at 100°C and the addition of antibiotics such as flucloxacillin, amoxycillin, gentamicin and latamoxef sodium completely abolished these rises, strongly suggesting that bacteria were responsible for this phenomenon. Following preliminary

experiments, we examined the histamine forming potential of *H influenzae*, a bacterial species commonly isolated in both conditions. Using a histidine enriched liquid culture medium we found histamine production by 7/12 isolates. Histamine increases ranged from 130 to 3360% and were accompanied by increases in counts of *H influenzae*. The identity of histamine was independently confirmed by diamine oxidase treatment, thin layer chromatography and the effect of purified extracts of the culture medium on the isolated guinea-pig ileum preparation. Although *H influenzae* has been isolated frequently from the sputum of patients during exacerbations of chronic bronchitis, its role in the pathogenesis of airflow limitation has been questioned. Our results raise the possibility that *H influenzae* may contribute to airflow obstruction and pulmonary inflammation by the production of histamine.

#### Authoradiographic visualisation of VIP receptors in human lung

K LEYS, A MORICE, A HUGHES, M SCHACHTER, P SEVER *Clinical Pharmacology, St Mary's Hospital Medical School, London* Vasoactive intestinal peptide (VIP) is a neuropeptide causing relaxation of bronchial and pulmonary artery smooth muscle *in vitro* and *in vivo*. We have recently characterised specific VIP receptors in human lung membranes (Morice *et al*, BJ Pharmacol, in press) and have now localised these receptors by light microscope autoradiography using  $^{125}\text{I}$  labelled VIP. Resection and post-mortem specimens of human lung were used. Sections ( $10\mu\text{m}$ ) were incubated with  $^{125}\text{I}$ -VIP (0.25 nM) for 2 hours at room temperature. Non-specific binding was defined by the addition of  $1\mu\text{M}$  VIP. After washing, sections were opposed to emulsion coated cover slips and developed after three days. Highest grain density was found to be in association with smooth muscle and over the alveolar walls. The inhibition of specific  $^{125}\text{I}$ -VIP binding was determined by incubating similar lung sections with VIP, peptide histidine and secretin.  $K_i$  values (VIP: 1.6 nM, PHM: 47 nM, secretin 0.9  $\mu\text{M}$ ) agree with those previously obtained in human lung membrane preparations. The localisation of VIP receptors to smooth muscle is further evidence that relaxation mediated by VIP in the bronchus and pulmonary artery is a direct action on these tissues. The role of the alveolar VIP receptor is unknown.

#### Potentiating effect of forskolin on isoprenaline in isolated trachea

G MARTIN, A HUGHES, AH MORICE, M SCHACHTER, PS SEVER *Clinical Pharmacology, St Mary's Hospital Medical School, London* Forskolin is a diterpine which has been shown to be a bronchodilator *in vitro* and *in vivo* (J Chang *et al*, Eur J Pharm 1984;101:271-274). It activates adenylate cyclase by an unknown mechanism and may therefore potentiate the effect of other agents whose action is mediated by cyclic AMP. We have investigated the relaxant effect of forskolin alone and in combination with isoprenaline in an isolated rabbit tracheal preparation. Two adjacent segments of trachea (3-4 mm length) from six

male New Zealand White rabbits were suspended in a tissue bath containing aerated Krebs buffer and constricted using carbachol ( $1\mu\text{M}$ ). In one of each pair of tracheal rings a concentration-response curve for forskolin was determined. After washout a subthreshold dose of forskolin was then added to one of the pairs of rings and isoprenaline concentration-response curves constructed for both rings. Both forskolin and isoprenaline relaxed isolated tracheal rings in a concentration dependent manner ( $\text{IC}_{50}$  4.2 and 0.6  $\mu\text{M}$  respectively). The addition of a subthreshold concentration of forskolin significantly reduced the  $\text{EC}_{50}$  for isoprenaline by 45% ( $p < 0.02$ ) by paired *t* test). The potentiation of  $\beta$ -agonist induced relaxation by forskolin may have therapeutic implications in asthma.

#### The effect of airflow limitation on gas diffusion in the lungs

MR MILLER, D SHAW, T HIGENBOTTAM *Department of Respiratory Physiology, Papworth Hospital, Cambridge* After a wash-in period breathing a mixture of 2% helium and 2%  $\text{SF}_6$  in air, the washout of these gases was recorded using a mass spectrometer and a pneumotachograph linked to a computer. This was done to determine if they washed out according to their molecular weights (He 4,  $\text{SF}_6$  146). Log relative gas concentration was plotted against cumulative ventilation. The volume intercept for zero gas concentration (Vo) was determined by regression. In six normal subjects Vo $\text{SF}_6$  was on average 7.6% (SEM=1.3) larger than VoHe, indicating a gas diffusion effect. Histamine challenge in three subjects (20% reduction in  $\text{FEV}_1$ ) prolonged both Vo $\text{SF}_6$  and VoHe, Vo $\text{SF}_6$  being on average 0.4% (SEM=0.9) smaller than VoHe. In two subjects with severe chronic obstructive lung disease, one, whose conventional tests suggested dominant emphysema, showed wider separation of the gases with Vo $\text{SF}_6$  16.4% greater than VoHe, whereas for the other subject, who had dominant airflow limitation, Vo $\text{SF}_6$  and VoHe were identical. These findings suggest a gas diffusion effect in normal lungs and show that this effect is overwhelmed by the presence of airflow limitation.

#### Frequency dependence of respiratory resistance in smokers

CI COE, H JOYCE, A WATSON, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, London* An early manifestation of smoking induced lung damage is inhomogeneity of mechanical properties leading to uneven ventilation, particularly at higher breathing frequencies. We have measured the difference in respiratory resistance (Rrs) between six and 26 Hz in 35 male cigarette smokers aged 34-64 years using the pseudo random noise method of Lansder *et al* (J Appl Physiol 1976;41:101-106). Mean Rrs at 6Hz rose from  $2.37 \pm 0.29$  SEM  $\text{cmH}_2\text{O.l}^{-1}.\text{s}$  at mean age 36.9 y to  $3.24 \pm 0.25$  at mean age 56.5 y. Frequency dependence of Rrs ( $\geq 15\%$  fall between six and 26 Hz) was present in 14 of 27 smokers aged 50-64 y but in only one of eight smokers less than 40 y. All 10 smokers with Rrs at 6Hz  $\geq 3.75$  showed abnormal frequency dependence. Increases in Rrs at 6Hz and abnormal frequency dependence of Rrs were related to

FEV<sub>1</sub> %pred. ( $r = -0.65$ ) and to FEV<sub>1</sub>/VC% ( $r = -0.54$ ) but Rrs was frequently abnormal when spirometry was in the low normal range. Rrs was also related to an abnormal single breath N<sub>2</sub> test ( $r = 0.40$ ). We conclude that abnormalities of Rrs are common after 30 or more years of smoking but probably develop at a later stage of smoking induced lung damage than frequency dependence of compliance, suggesting that Rrs is less sensitive to disease in the lung periphery.

#### The Respiradyne: a pocket size pulmonary function monitor

SC JENKINS, NC BARNES, J MOXHAM *Department of Thoracic Medicine, King's College School of Medicine and Dentistry, London* Home monitoring of PEFR is extensively utilised in the diagnosis and management of patients with airways obstruction. PEFR may be inadequate to detect change in some patients with chronic bronchitis and emphysema and is unhelpful in monitoring restrictive defects. The Respiradyne ((R) Chesebrough-Pond's Inc.) is a self-calibrating, simple to use, pocket sized, battery operated pulmonary function monitor weighing 370 g. Following a maximal expiratory manoeuvre a solid state pressure transducer measures flow rate, which is analysed by a micro-computer to give a digital display of FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC%, PEFR and MEF<sub>25-75%</sub>. We compared (R) with a spirometer ((S) Vitalograph Ltd) and a Wright's PEF meter (W) in 70 subjects (normals and patients) with a range of FEV<sub>1</sub> 0.5-5.7 l by comparing the mean of three blows (R) with the mean of three blows (S) at BTPS and three blows (W). The Respiradyne was in close agreement with the spirometer (regression equations: FVC 0.98S + 0.1; FEV<sub>1</sub> 0.95S + 0.13). Agreement of (R) and (W) for PEFR was less good ( $R = 1.13W - 20$ ). Repeated calibration of (R) with a 1 and 3 l syringe gave a maximum error of 3%. The Respiradyne is an accurate monitor of pulmonary function which may allow patients to make detailed measurements within their homes.

#### Stimulant effect of nasal airflow on ventilation during sleep

WT McNICHOLAS, M COFFEY, T BOYLE, MX FITZGERALD *Department of Respiratory Medicine, St Vincent's Hospital, Dublin* Oxygen therapy by nasal prongs is widely used in hypoxaemic patients, yet there is disagreement on the effect of nasal airflow on ventilatory drive. We studied the effects on ventilation of increasing and decreasing nasal airflow during sleep, thereby avoiding the voluntary and behavioural influences on breathing seen during wakefulness. After an acclimatisation night, each of eight normal volunteers (ages 20-28) underwent overnight sleep study using standard techniques. Ventilation was measured by inductance plethysmography. Each sleep study had three phases of 90-180 minutes each, namely (1) control, (2) added nasal flow of four litres air by nasal prongs (ANF), and (3) mouthbreathing (MB). During non rapid-eye-movement (nonREM) sleep, minute ventilation rose to 5.45 (0.25) l/min with ANF, compared with 4.91 (0.025) l/min during MB ( $p < 0.02$ ). Tidal volume rose to 389

(17) ml with ANF compared with 369 (15) ml during control, and 372 (11) ml during MB ( $p < 0.05$ ). Respiratory frequency was lowest during MB. Mean inspiratory flow rate (Vt/Ti), which is an index of respiratory drive, rose to 266 (8) ml sec<sup>-1</sup> with ANF compared with 238 (11) ml sec<sup>-1</sup> during MB ( $p < 0.05$ ). These indices were variable during REM sleep, and no significant changes were seen. We conclude that added nasal airflow stimulates ventilation during sleep.

#### Lung function in hyperthyroidism before and after treatment

AH KENDRICK, JF O'REILLY, G LASZLO *Respiratory Department, Bristol Royal Infirmary, Bristol* Hyperthyroidism has been found to cause abnormalities of vital capacity and exercise ventilation. An association with bronchial asthma has been postulated. We determined spirometric values, lung volumes, transfer factor and its subdivisions, maximal respiratory pressures, effects of methacholine challenge, arterial blood gases and exercise capacity in 16 patients before treatment for hyperthyroidism (mean T4 = 203 nmol/l, range 105-287; mean T3 = 6.15 nmol/l, range 4.4-7.8). Methacholine challenge showed three patients with increased airway reactivity. Maximal pressures varied widely, FRC was reduced. Exercise ventilation, breathing frequency, cardiac frequency and respiratory exchange ratio were increased in many patients at their maximum oxygen uptake. Nine patients were studied 3-6 months after treatment. Respiratory pressures increased significantly. Maximal exercise work load increased in all subjects, but maximal oxygen uptake and ventilation did not increase significantly. We conclude that (1) improved exercise tolerance after treatment of hyperthyroidism is not caused by an increase of ventilatory capacity, but may be associated with a reduced requirement for oxygen during exercise; (2) patients with hyperthyroidism do not generally have increased airway reactivity.

#### Phrenic nerve stimulation

A MIER, C BROPHY, J MOXHAM, M GREEN *Brompton Hospital, London* When investigating patients with diaphragm weakness it is important to determine the integrity of the phrenic nerves, but phrenic nerve stimulation is often considered to be difficult and unreliable. We recorded the time in which the right and left phrenic nerves could be located and adequately stimulated in 75 subjects, aged 12-73 years, 24 of whom had diaphragm weakness. Each phrenic nerve was stimulated transcutaneously in the neck with square wave impulses 0.1 msec in duration at 1 Hz and 80-100 volts, using bipolar electrodes. Phrenic nerve stimulation was confirmed by the production of diaphragm muscle action potentials recorded with surface electrodes in the 7th and 8th intercostal spaces and simultaneous inward motion of the rib cage and outward motion of the abdomen (monitored with magnetometers). The time to locate both phrenic nerves was between six seconds and 22 minutes (mean two min 50



sec) in 72 subjects. In one subject with severe diaphragm weakness due to muscular dystrophy, neither nerve could be located even after 60 minutes. In two further subjects, one with previous poliomyelitis and one with polymyositis, only one nerve could be located. Transcutaneous stimulation of the phrenic nerves is not a time consuming procedure, is well tolerated and was successful in 96% of subjects.

#### A new symptom of diaphragm weakness

A MIER, C BROPHY, J MOXHAM, M GREEN *Brompton Hospital, London* Diaphragm weakness can be difficult to diagnose clinically. Whilst patients may complain of orthopnoea and disturbed sleep, their symptoms are often non-specific. We have noted a new symptom that was a presenting complaint in three patients with gross diaphragm weakness. Two males and one female, aged 26, 46 and 54 years, reported difficulty in swimming for several months. They could paddle comfortably in shallow water but when they waded in and the water level rose progressively above their abdomen, they became increasingly dyspnoeic. Measurement of transdiaphragmatic pressure (Pdi) with balloon catheters revealed severe diaphragm weakness in all three patients; Pdi at total lung capacity was 2.5, 10 and 17.5 cm H<sub>2</sub>O (normal >25 cm H<sub>2</sub>O); Pdi during a maximal sniff was 7, 20 and 23 cm H<sub>2</sub>O (normal >80cm H<sub>2</sub>O) (Miller *et al*, Clin Sci 1985;69:91-96). In the presence of severe diaphragm weakness the additional weight of water compressing the anterior abdominal wall can be sufficient to prevent adequate diaphragm descent on inspiration. Inability to stand comfortably in deep water should be considered a relevant symptom suggestive of diaphragm weakness.

#### Inspiratory muscle function after thoracoplasty

WJM KINNEAR, MS PHILLIPS, JM SHNEERSON *The Assisted Ventilation Unit, Newmarket General Hospital, Suffolk* Inspiratory muscle strength was assessed in nine females and 13 male patients of mean (SD) age 62.2 (4.3) years. Twenty patients had unilateral and two patients had bilateral thoracoplasties. Seven also had unilateral phrenic nerve crushes. The mean (SD) vital capacity was 49.9 (18.6)% of predicted. Maximum inspiratory pressure at the mouth (Pi max) was measured at residual volume with an occluded mouthpiece and standard leak. The mean (SD) Pi max was 56.0 (24.5)% of predicted values. There was no correlation between Pi max and vital capacity or Paco<sub>2</sub> but an inverse correlation between Pi max and residual volume ( $p < 0.05$ ). Transdiaphragmatic pressure (Pdi) was measured during sniffs at residual capacity in 16 subjects. The mean (SD) Pdi was 54.3 (24.2)% of predicted and there was an inverse correlation between Pdi and Paco<sub>2</sub> ( $p < 0.05$ ). The mean relaxation rate of Pdi was reduced at 6.04/second. There was no significant difference in Pdi between those patients who had previously had a phrenic nerve crush and those who had not. Diaphragmatic strength is reduced after thoracoplasty and is an important factor in determining the Paco<sub>2</sub>. Global inspiratory muscle strength

is also reduced, but is less important in determining Paco<sub>2</sub>.

#### The effect of abdominal binders on breathing in tetraplegic patients

JM GOLDMAN, SJ WILLIAMS, D DENISON, JR SILVER *Lung Function Unit, Brompton Hospital, London and National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, Bucks* Abdominal binders are commonly used in the treatment of tetraplegic patients with postural hypotension and respiratory difficulties. There are few data on their effect on breathing. Danon *et al* (Am Rev Resp Dis 1979;119:909-919) showed in two C1 tetraplegic patients undergoing phrenic pacing that compression of the abdomen with a sphygmomanometer cuff increased tidal volume and AP and lateral rib cage expansion. Conventional binders bind the lower rib cage as well as the abdomen. We designed one that did not inhibit the lower rib cage and compared its effect with the conventional type. We studied seven patients with complete tetraplegia seated, supine and at 70° on a tilt table and measured transdiaphragmatic pressure during maximal sniff (sniff Pdi), maximum inspiratory mouth pressure (PI max) and vital capacity (VC) in each posture with and without each binder. The binders had no effect on supine patients. When they were seated both binders improved VC ( $p < 0.01$ ), the conventional binder by 11.5% (260 ml SED = 50 ml) and the new binder by 8% (180 ml SED = 40 ml). At 70° tilt both binders improved VC, the conventional binder ( $p < 0.01$ ) by 15% (290 ml SED = 70 ml) and the new binder ( $p < 0.001$ ) by 24% (470 ml SED = 70 ml). Both binders also improved sniff Pdi, the conventional binder ( $p < 0.05$ ) by 19.5% (10 cm H<sub>2</sub>O SED = 3.0 cm H<sub>2</sub>O) and the new binder ( $p < 0.02$ ) by 26% (13.5 cm H<sub>2</sub>O SED = 3.5 cm H<sub>2</sub>O); there was no difference between the effect of the two binders. These results suggest that patients with tetraplegia will benefit their breathing by wearing an abdominal binder when they are seated or semi-recumbent, but not when they are supine.

#### Intermittent positive pressure hyperinflation (IPPH) in restrictive chest wall disease

AK SIMONDS, RA PARKER, MA BRANTHWAITE *Brompton Hospital, London* The immediate and long term effects of IPPH were investigated in ten patients with severe scoliosis (vital capacity 22-43% predicted). Six had coincident respiratory muscle weakness and all suffered exertional dyspnoea, with falling lung volumes demonstrated over 2-3 years in six. A volume preset, time cycled device was used in six patients and a pressure cycled, patient triggered machine in four matched cases. Hyperinflation was performed three times a day for five minutes with the aim of doubling spontaneous tidal volume with each delivered breath. Progressive reduction in lung volume was reversed by the volume preset device, which increased mean vital capacity from 29% to 33% predicted after three months ( $p < 0.05$ ), with improvement maintained after nine months. This machine offered a significant advantage over the pressure cycled device, which at maximum or near maximum

inflation pressures produced less hyperinflation and had no beneficial effect on lung volumes. Improvement in vital capacity was correlated with the degree of hyperinflation ( $r=0.65$   $p<0.05$ ). The effect of hyperinflation on arterial blood gas tensions lasted less than an hour and was not accompanied by an increase in accessible alveolar volume.

#### Symptomatic oxygen therapy in hypoxic chronic bronchitis

CB RHIND, KL PRINCE, W SCOTT, DC FLENLEY *Rayne Laboratory, City Hospital, Edinburgh* Breathing oxygen during exercise improves exercise tolerance in chronic bronchitis as shown by increased 12 minute walking distance (Legget RJE, Flenley DC, BMJ 1977;iii: XXX), but this liquid system is available to few. Many patients with cylinders take oxygen "as required", often before or after exercise (Jones MM *et al*, BMJ 1978;iii: XXX), but we do not know if this is helpful. We determined the effect of 30 min O<sub>2</sub> therapy pre-exercise, and the effect of post-exercise O<sub>2</sub> therapy on recovery time. We studied 12 chronic bronchitis (FEV<sub>1</sub> 0.56, PaO<sub>2</sub> 7.3 kPa, 6MD 306 m) in a double blind cross over study of O<sub>2</sub> and air given by nasal prongs from cylinders. O<sub>2</sub> given for 30 min before exercise yields no change in six minute walking distance (O<sub>2</sub>,  $13 \pm 1/20$ ; air,  $14 \pm 1/20$ ) or pulse rate increase (O<sub>2</sub>,  $27 \pm 4$  beats/min; air,  $30 \pm 5$  beats/min). O<sub>2</sub> saturation (SaO<sub>2</sub>), although starting higher (O<sub>2</sub>,  $95 \pm 1\%$ ; air,  $88 \pm 5\%$ ), fell to the same level after exercise (O<sub>2</sub>,  $79 \pm 9\%$ ; air,  $80 \pm 9\%$ ). When O<sub>2</sub> is given after a six minute walk, patients do not recover more quickly (O<sub>2</sub>,  $5.6 \pm 0.7$  min air,  $5.5 \pm 1.1$  min) despite SaO<sub>2</sub> rising to pre-exercise levels more rapidly (O<sub>2</sub>,  $5.8 \pm 1$  min; air  $7.2 \pm 1.2$  min;  $0.1 > p > 0.05$ ). We conclude that O<sub>2</sub> given before exercise does not improve performance, and after exercise does not aid subjective recovery. There is no evidence that O<sub>2</sub> therapy given in this way is useful in chronic bronchitis.

#### A comparison of six and twelve minute walk distance with 100 metre walk times in subjects with chronic bronchitis

H GARRETT, S VATHENEN, RA HILL, P EBDEN, JR BRITTON, AE TATTERSFIELD *City Hospital, Nottingham and Glenfield General Hospital, Leicester* The twelve minute walk test is a simple method of exercise tolerance testing for subjects with respiratory disease. Recently it has been suggested that measurement of the six minute walk distance or the time taken to complete the third 100 m walk (100 m time) are more convenient alternatives, but the repeatability of the three procedures has not been compared. We measured 100 m times and six and twelve minute distances in 15 subjects with chronic bronchitis and airflow obstruction (FEV<sub>1</sub>  $<60\%$  predicted), who performed twelve minute walk tests on five occasions. Tests were performed in a flat 33m corridor at 9 a.m., at least 6 hours after inhaled and 24 hours after oral bronchodilators. One practice was performed prior to entry into the protocol. Twelve minute distance ranged from 500 to 1185 metres. There was no order effect for any of the tests. Twelve and six minute distances were correlated with each other ( $r=0.957$ ) and with 100 m times ( $r=-0.905$  and  $-0.923$  respectively), all

$p<0.001$ . Repeatability was highest for twelve minute distances, the ratio of within to between subject variance being 0.92, compared with 1.18 and 2.06 for six minute distance and 100 m time respectively. The twelve minute distance is the most reliable of these three measurements of exercise tolerance, but both twelve and six minute distances are substantially more reliable than 100m walk time.

#### Portable oxygen therapy via a transtracheal catheter during exercise

NR BANNER, MH LLOYD, P LOCKWOOD, JR GOVAN *Harefield Hospital, Harefield, Middlesex* Transtracheal oxygen (TTO) has recently been introduced for treatment of chronic lung disease (Heimlich, Ann Otol Rhinol Laryngol 1982;91:643). We studied portable TTO therapy in five patients with severe irreversible chronic obstructive airways disease (mean FEV<sub>1</sub> 0.72 litres) and hypoxaemia (mean arterial oxygen tension 6.8 kPa). Each patient performed two six minute walks breathing air and 1½ litres per minute (LPM) TTO. The mean distance walked increased from 248 yards (SE 58 yards) to 291 yards (SE 61 yards) with oxygen ( $p<0.05$ ). Each patient underwent three graded exercise tests on the bicycle ergometer (in random order), for "Test A" receiving 3 LPM air via nasal cannulae, "Test B" receiving 3 LPM oxygen via nasal cannulae and "Test C" 1½ LPM TTO. The maximum work rate achieved was not increased by oxygen; however, at 50% of the maximum work rate achieved in "Test A" breathlessness (as measured by 10 cm visual analogue scales) was reduced from 4.7 (SE 1.24) to 4.3 (SE 1.48) in "Test B" (not significant) and to 3.2 (SE 0.72) in "Test C" ( $p<0.01$ ). TTO increases walking distances and reduces breathlessness at low oxygen flow rates facilitating portable therapy.

#### Distribution of bronchial blood flow during histamine infusion in unanaesthetised sheep

DC LINDSEY, W CHIH-HSIUNG, CE CROSS, GC KRAMER *Departments of Internal Medicine and Human Physiology, School of Medicine, University of California, Davis, CA 95616, USA.* Histamine increases microvascular permeability in bronchial venules while having little effect on the pulmonary microcirculation (Circ Res 1971;29:323). The present study examines the distribution of bronchial blood flow (BBF) in airways and lung parenchyma of unanaesthetised sheep during two hours of iv histamine infusion (2 µg/min/kg). BBF was measured with 15 µ radionuclide labelled microspheres. Transient occlusion of the left pulmonary artery was used to prevent left lung pulmonary trapping of peripherally shunted microspheres. Mean results are shown for cardiac output (CO), mean arterial pressure (MAP), tracheal mucosa, tracheal muscularis, lobar bronchi, and left lung.

	CO (l/min)	MAP (mmHg)	Mucosa	Muscularis	Bronchi	L Lung
	(ml/min per 100 g)					
Baseline	4.7	98	137.1	11.6	26.5	17.7
15 min	4.0	86	499.0	42.2	141.4	26.7
120 min	4.6	88	728.8	31.5	165.9	31.3

Blood flows in skin, skeletal muscle, liver and kidney decreased or were unchanged. Despite a significant fall in MAP and CO, systemic blood flow to tracheal mucosa and lobar bronchi was elevated five to seven fold. Total BBF to lung parenchyma, estimated at left lung perfusion times total lung weight, increased from 1.7% of CO to 3.1% during histamine infusion. BBF was unchanged in control sheep given a saline infusion. We conclude that histamine is a potent and selective vasodilator of the bronchial circulation.

#### Changes in transcutaneous oxygen and carbon dioxide in response to histamine bronchial challenge

B GRAY, N BARNES, C NYEKO, A MARQUIS *Department of Thoracic Medicine, King's College School of Medicine and Dentistry, London* Gas exchange is the prime function of the lung, but bronchial challenge tests have focused on changes in airway calibre and less on changes in blood gases (ABGs). Transcutaneous  $\text{PO}_2$  ( $\text{tcPO}_2$ ) and transcutaneous  $\text{PCO}_2$  ( $\text{tcPCO}_2$ ) are accurate indicators of ABG when calibrated *in vivo* (Gray *et al*, Thorax 1983;38:712). We have used  $\text{tcPO}_2$  and  $\text{tcPCO}_2$  measurements to assess changes in ABGs during histamine challenge in five normal subjects. Each subject inhaled a saline aerosol, generated by a Wright nebuliser, for two min.  $\text{tcPO}_2$  and  $\text{tcPCO}_2$  were continuously monitored, and the flow rate at 30% of vital capacity above the residual volume ( $\dot{V}_{\text{max}30}$ ) was measured at 2.5 min intervals for 10 min. The procedure was repeated with histamine ranging from  $10^{-3}$  mol/l to  $10^{-1}$  mol/l in 3.2 fold increments. The mean baseline values ( $\pm$  SEM) were  $\text{tcPO}_2$   $97 \pm 2.5$  and  $\text{tcPCO}_2$   $38 \pm 1$  mm Hg. Mean  $\dot{V}_{\text{max}30}$  fell progressively at each histamine concentration. Mean  $\text{tcPO}_2$  showed small increases at the lower histamine concentrations and a large fall at  $3.2 \times 10^{-2}$  mol/l, the highest concentration which all subjects inhaled. At this concentration mean  $\text{tcPO}_2$  was  $77 \pm 7.2$  mm Hg and mean  $\dot{V}_{\text{max}30}$   $75.1 \pm 7.4$  of baseline. Mean  $\text{tcPCO}_2$  did not vary significantly from baseline values. We conclude that histamine induced bronchoconstriction causes significant hypoxaemia in normal subjects.  $\text{tcPO}_2$  and  $\text{tcPCO}_2$  monitored during bronchial challenge is a simple, non-invasive technique which may provide further information on the mechanism of action of bronchoconstrictor substances.

#### Effect of sodium cromoglycate on leukotriene $\text{D}_4$ induced bronchoconstriction in asthmatic patients

JA ROBERTS, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow* The mechanism of action of sodium cromoglycate (SCG) is unclear. In anaesthetised guinea pigs SCG has been shown to inhibit the bronchoconstriction produced by inhaled leukotriene  $\text{D}_4$  (LTD $_4$ ) (Advenier *et al*, Brit J Pharm 1983;78:301-306). To determine whether a similar mode of action of SCG occurs in man we have examined the effect of SCG on the bronchoconstriction produced by LTD $_4$  in six atopic asthmatic patients (age 22-49, FEV $_1$  83-139% predicted). On separate days after pretreatment with placebo or SCG

(20 mg/ml) administered on a double blind basis, LTD $_4$  was inhaled to a maximum of  $10 \mu\text{g/ml}$ . Aerosols of the drug were generated by a Wright's nebuliser (50 lb/in $^2$ , 8 l/min) over five minutes. Results were expressed as the provocation concentration (PC) producing a 35% fall in specific airways conductance ( $\text{PC}_{35\text{sGaw}}$ ) and a 30% fall in flow rate at 30% of vital capacity, determined from partial expiratory flow-volume curves ( $\text{PC}_{30\dot{V}_{30(\text{p})}}$ ). SCG did not alter baseline sGaw or  $\dot{V}_{30(\text{p})}$ . Geometric mean (SEM)  $\text{PC}_{35\text{sGaw}}$  was 0.33 (0.15) after saline and 0.40 (0.16) after SCG (NS). The  $\text{PC}_{30\dot{V}_{30(\text{p})}}$  was 0.21 (0.17) after saline and 0.19 (0.17) after SCG (NS). These results suggest that, in man, SCG does not act as an LTD $_4$  antagonist.

#### The action of nedocromil sodium on sulphur dioxide induced bronchoconstriction

CMS DIXON, RW FULLER, PJ BARNES *Departments of Medicine and Clinical Pharmacology, Royal Postgraduate Medical School, London* Nedocromil is a pyranquinoline acid which inhibits mast cell degranulation. The effect of inhaled nedocromil sodium (N) (2 and 4 mg) and matched placebo (P) on sulphur dioxide ( $\text{SO}_2$ ) induced bronchoconstriction was investigated in a double blind study on six mild asthmatics, three female (mean age 39). On the first occasion a dose response to  $\text{SO}_2$  was obtained to find the concentration of  $\text{SO}_2$  to be inhaled on the subsequent visits. On the next three visits baseline flow at 30% of total lung capacity during a partial expiratory flow-volume manoeuvre was measured ( $\dot{V}_{\text{p}30}$ ). Then either 2, 4 mg N or P were administered and  $\dot{V}_{\text{p}30}$  was monitored for 30 min. At 30 min a dyspnoea score was recorded on a visual analogue scale (VAS).  $\dot{V}_{\text{p}30}$  and VAS were then monitored for 30 min following inhalation of  $\text{SO}_2$ . The fifth visit repeated the dose-response to  $\text{SO}_2$  with no pre-treatment to ensure that the subjects' sensitivity to  $\text{SO}_2$  had not altered. No significant difference was found between the baseline  $\dot{V}_{\text{p}30}$  on each of the five days. N (4 mg) significantly reduced the maximum change after  $\text{SO}_2$  by 77% ( $p < 0.05$ ). Both doses of N also significantly reduced the duration of bronchoconstriction and dyspnoea score. N therefore inhibits  $\text{SO}_2$  induced bronchoconstriction, which may involve neural mechanisms.

#### The effect of nedocromil sodium on nasal allergen

OJ CORRADO, E GOMEZ, DL BALDWIN, RJ DAVIES *Department of Respiratory Medicine, St Bartholomew's Hospital, London* Early studies have suggested that nedocromil sodium may be a useful agent for the treatment of bronchial asthma. We report for the first time the effect of this compound on nasal provocation with allergen. Ten patients (six male and four female, mean age 23 years) with extrinsic allergic rhinitis were investigated in a random order, double blind, placebo controlled crossover study. Each patient underwent allergen provocation to establish the dose required to produce a positive response defined as at least two of the following: 1.  $> 300\%$  increase in nasal airways resistance (NAR); 2.  $> 5$  sneezes; 3.  $> 0.5$  ml of

secretion. This allergen dose was readministered on two subsequent weekly occasions 20 minutes after intranasal treatment with either nedocromil sodium (1% w/v) or placebo. Three variables were recorded after allergen provocation: number of sneezes, volume of rhinorrhoea and change in NAR measured by anterior rhinometry. Nedocromil sodium was significantly more effective than placebo in preventing allergen induced nasal obstruction ( $p<0.01$ ), rhinorrhoea ( $p<0.01$ ) and sneezing ( $p<0.05$ ). Side effects were mild (bitter taste and nasal irritation) but reported by six patients after taking nedocromil sodium, and one after placebo. Our findings suggest that nedocromil sodium is a potentially useful agent for the treatment of allergic rhinitis.

#### Intranasal salbutamol in perennial rhinitis

A MORICE, C SNAPE, PW EWAN *Allergy Department, St Mary's Hospital, London* Degranulation of the nasal mast cell is thought to be important in the genesis of allergic rhinitis. Salbutamol has been shown to inhibit lung mast cell degranulation both *in vitro* and *in vivo*, but its effect in nasal allergy has not been investigated. We have studied the effect of topical intranasal salbutamol in nine subjects with rhinitis due to allergy to house dust mite (HDM). All subjects had positive skin prick test responses to HDM. Symptoms were recorded on diary cards and after an initial run-in period of one week subjects received in a double blind cross over fashion, either intranasal salbutamol 200  $\mu$ g qds or placebo (propellant) from a meter dose inhaler each for one week. At the end of each treatment period, nasal challenge with purified HDM extract was performed. Salbutamol caused protection against nasal challenge, mean protection being one log dose of HDM extract. Increased sensitivity on nasal challenge occurred in one subject only. Salbutamol improved the mean symptom score, but this effect did not reach statistical significance. These preliminary observations suggest that salbutamol reduces allergen induced mediator release in the nose, and may have a place in the treatment of allergic rhinitis.

#### Should nebulised salbutamol and ipratropium bromide be administered sequentially or as a mixture?

BRC O'DRISCOLL, M KING, GM COCHRANE *Department of Thoracic Medicine, New Cross Hospital, London* Many patients are treated with salbutamol (S) and isotonic ipratropium bromide (IB) administered by nebuliser. There is considerable controversy concerning possible synergistic effects of these drugs when used sequentially or as a mixture. Four non-smoking asthmatic patients and four smokers with chronic bronchitis and reversible airways obstruction took part in a double blind study to compare the changes in FEV<sub>1</sub>, FVC and peak flow over a period of 90 minutes following the inhalation of the following nebulised solutions: (i) placebo (saline); (ii) 10 mg S; (iii) 0.5 mg IB; (iv) S and IB given sequentially; (v) S and IB mixed. All solutions were made up to 4 ml in saline. The response to a mixture of S and IB was identical to the response to sequential therapy with these medications and no adverse

reactions occurred. Combined treatment with S and IB produced greater increases in FEV<sub>1</sub>, FVC and peak flow rate than IB alone, but the response to S alone was identical to the response to combined therapy. We conclude that mixing nebuliser solutions of salbutamol and ipratropium bromide is safe and effective; however the response to combined therapy was no greater than the response to a supramaximal dose of salbutamol alone.

#### Domiciliary nebuliser therapy: a double blind dose-response assessment

JW HADFIELD, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* This study was designed to assess the effect of dose of  $\beta_2$  agonist given by nebuliser in severe airways obstruction and whether patients needing higher doses could be identified in the laboratory. Eighteen patients with asthma or bronchitis, using nebulised bronchodilators regularly at home, entered a randomised crossover study of nebulised salbutamol 200  $\mu$ g, 1 mg and 5 mg qid for two weeks at each dose. A five minute unpaced step test and 24 hour Holter monitoring were performed once during each treatment period. One patient withdrew with headache (5 mg dose), one with breathlessness (200  $\mu$ g) and three for reasons apparently unrelated to dose. Symptom scores, twice daily PEF and exercise tolerance in the remaining 13 patients (mean FEV<sub>1</sub> = 0.78 l) tended towards improvement with increasing dose, but differences were small and not significant. Four patients preferred the 5 mg dose, one the 1 mg, four the 200  $\mu$ g and four had no preference. Six patients showed no benefit from increasing salbutamol dose whilst eight showed some benefit in one or other measure of response. The two groups could not be identified from the laboratory dose-response assessment. No dose related heart rate changes or dysrhythmias were identified. The results suggest that large differences in dose cause small differences in response overall, and that many patients receiving nebulised beta agonists could be equally well controlled with lower dose inhaler devices.

#### Terfenadine as a potent and specific H<sub>1</sub> histamine receptor antagonist for human airways in asthma

P RAFFERTY, ST HOLGATE, P LEWIS, MSTG WHEELLEY *Medicine 1, Southampton General Hospital, Southampton, and Merrell Dow Pharmaceuticals Ltd, Staines, Middlesex* Terfenadine is a potent H<sub>1</sub> receptor antagonist that appears to be free from side effects. We have carried out a double blind, placebo controlled study to assess the protective effects of terfenadine on bronchoconstriction induced by inhalation of histamine and methacholine. Nine patients were studied. Each underwent separate inhalation challenge tests involving doubling concentrations of histamine and methacholine three hours after placebo or terfenadine 60, 120, 180 mg. Baseline FEV<sub>1</sub> values were not significantly different on any of the study days. There was significant bronchodilation three hours after terfenadine 120 and 180 mg when compared with placebo and with all three doses of terfenadine the PC<sub>20</sub> FEV<sub>1</sub> for histamine was significantly greater (3.8, 8.13 and 8.7 mg/ml) than that



following placebo (0.59 mg/ml,  $p < 0.01$ ). Calculated concentration ratios for the three doses of terfenadine 60, 120 and 180 mg were 14.8, 22.9 and 34.3 respectively. Terfenadine, at any of the doses used, had no significant effect on methacholine responsiveness. No side effects were noted at any dose of terfenadine. These results suggest that oral terfenadine is a highly effective  $H_1$  receptor antagonist for asthmatic airways with no detectable anticholinergic activity.

#### Measurement of serum theophylline concentration on admission to hospital before administration of intravenous aminophylline: is it essential?

J WIGGINS, OA ARBAB, DE STABLEFORTH, JG AYRES *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham*, Measurement of serum theophylline concentration (T) may prevent intravenous aminophylline being used hazardously in patients taking oral theophyllines. Fifty patients (23 females) (mean (SD) age 59.3 (4.2) years) with worsening airflow obstruction, taking oral theophyllines and needing i.v. aminophylline, were randomised into two groups. Aminophylline doses were calculated using formulae with (group A) or without (group B) knowledge of admission T. Four patients were subsequently excluded. PEFR, T and visual analogue toxicity scores were measured on admission and during i.v. aminophylline at ½, 1, 3, 5, 7, 12 and 24 hours. Mean (SD) admission T were similar (group A 8.4 (6.0) mg/l; group B 7.2 (5.7) mg/l), as were aminophylline doses used. There were no overall significant differences either in T during i.v. aminophylline (mean (SD) T): 1 hour; group A 14.0 (6.9) mg/ml, group B 13.4 (4.1) mg/l; 24 hours; group A 11.3 (5.7) mg/l, group B 11.3 (4.6) mg/l or in numbers of patients with T > 20 mg/l (group A 5/24; group B 4/22) although subsequent T in group A patients with admission T < 2.5 mg/l were suboptimal. Therapeutic outcome was similar with little toxicity (1 patient in each group vomited). Knowledge of admission T was valuable in identifying those patients with very low (< 2.5 mg/l: 10/46) or high levels (> 20 mg/l: 1/46), but in the remainder this information did not effect subsequent T or clinical outcome.

#### Effect of intravenous hydrocortisone in addition to oral prednisolone in the treatment of patients admitted to hospital with severe asthma but not in ventilatory failure

BDW HARRISON, TC STOKES, GJ HART, DA VAUGHAN, NJ ALI, AA ROBINSON *Department of Respiratory Medicine, West Norwich Hospital, Norwich, Norfolk* Fifty-two severely ill asthmatic patients requiring acute admission to hospital entered a double blind placebo controlled trial to determine whether or not intravenous hydrocortisone in addition to oral prednisolone plus standard bronchodilator therapy produced a more rapid recovery. Patients were stratified according to whether or not they had received injected steroid before their arrival in the ward. Patients given pre-admission injected steroid treatment had been deteriorating for a significantly shorter period before admission, had

received significantly more injected or nebulised bronchodilator therapy and had significantly higher admission peak flows than those who had not received injected steroids before admission. Twenty-four hours after admission there were no significant differences in peak flows when the following were compared: those given injected steroids before admission and those not so treated; those given intravenous hydrocortisone following admission and those given placebo; and those given pre-admission injected steroid plus intravenous hydrocortisone and those not given injected steroids either before or during admission. This study provides no evidence to support the continued use of intravenous hydrocortisone in addition to 45 mg oral prednisolone and standard bronchodilator therapy daily in the treatment of patients admitted to hospital with severe asthma but not in ventilatory failure.

#### Nebulised aerosols

M CLAY, D PAVIA, S CLARKE *Department of Thoracic Medicine, Royal Free Hospital, London* The fate of nebulised aerosols of three different sizes (MMAD: 1.8  $\mu$ m; 4.6  $\mu$ m and 10.3  $\mu$ m) has been investigated using a radiotracer technique. Six mild asthmatics (FEV<sub>1</sub> 81% predicted) inhaled on three separate occasions  $^{99m}\text{TcO}_4^-$  in physiological saline delivered as nebulised aerosols of the required size distributions. The aerosols were given in a randomised single blind manner. The subjects were seated with their backs against a large field gamma camera and the aerosols inhaled over two minutes with a respiration rate of 14 breaths a minute with inspiration lasting one third of the cycle and a tidal volume of 700 ml. Immediately after inhalation an image of the distribution of aerosol within the lungs, stomach, oesophagus and oropharynx was collected and the amount of exhaled radioaerosol measured from a filter in the expiratory line. Of the aerosol released during inhalation  $23 \pm 6\%$ ,  $25 \pm 4\%$  and  $24 \pm 4\%$  (mean (SEM)) was trapped in the expiratory filter for the 1.8, 4.6 and 10.3  $\mu$ m aerosols respectively. The distributions of the three aerosols within the body showed that the smallest aerosol deposited significantly more ( $p < 0.05$ ) in the lungs than the other aerosols and the 4.6  $\mu$ m aerosol was also significantly better than the 10.3  $\mu$ m aerosol ( $p < 0.05$ ): 1.8  $\mu$ m,  $79 \pm 3\%$ ; 4.6  $\mu$ m,  $59 \pm 4\%$ ; and 10.3  $\mu$ m,  $44 \pm 5\%$ . The remaining aerosol was to be found within the oropharynx and stomach. We conclude that small aerosols deliver a larger dose to the lungs.

#### Analysis of the power of asthma trials

MJ WARD *Department of Tuberculosis and Chest Diseases, University of Wales College of Medicine, Llandough Hospital, Penarth, S Glamorgan* Many studies of therapy in severe asthma have compared two treatments and on finding 'no significant' difference have concluded that the treatments produce equal effects. ( $p = 0.05$ ) means that the observed difference between treatments could arise by chance once in 20 trials (Type I error), and a non-significant difference does not mean that the treatments produce the same result. Because of their low power many trials

reporting no difference between treatments are never likely to demonstrate a significant difference (Type II error). All 15 randomised double blind studies investigating the treatment of severe acute asthma published between 1974 and 1984 were analysed in terms of their power and 95% confidence limits. Only three reported clearly significant differences between treatments. The remaining 12, which failed to detect significant differences in treatment, reported the treatments to produce equal effect. Because of low power, however, each of these 12 studies had greater than 40% probability of missing a true 25% difference in treatment (Type II error). The trials involved comparisons between corticosteroid and placebo; aminophylline and sympathomimetic; and sympathomimetic with or without aminophylline.

Annual asthma treatment outside hospital in the UK 1975-1983

T HIGENBOTTAM, J FULLER *Papworth Hospital, Cambridge and Middlesex Hospital, London* There have been major changes in the treatment of asthma over the last 15 years. It is therefore of value to review the relative usage of the newer therapies as a first step of auditing our practice. We have used the estimated prescriptions of asthma treatments in the UK, from 1975 to 1983 obtained from samples of chemist prescriptions nationwide. This excludes hospital and private practice. Prescriptions of inhaled bronchodilators including vagal antagonists have increased from 2.3 (1975) to 7.7 (1983) million. Oral beta agonists enjoyed an increased usage in 1978, 4.8 million, but have fallen to 3.8 million (1983) whilst oral theophyllines have increased from 2.0 (1980) to 3.7 (1983) million. Nebulized bronchodilator prescriptions including vagal antagonists have increased from 1.6 (1975) to 135 (1983) thousand. Prophylactic therapy such as topical inhaled steroids have increased from 0.6 (1975) to 2.2 (1983) million whilst non-steroid inhaled prophylaxis has only slightly increased (1.3 (1975) to 1.6 (1983) million prescriptions). These data, whilst not including hospital or private prescriptions, still demonstrate a marked degree of under prescribing for asthma given its estimated prevalence and the fact that many patients with chronic obstructive lung disease also receive these drugs.

Lymphocyte adrenoceptors and their modulation by theophylline

SJ TITINCHI, B CLARK, KR PATEL *Departments of Biochemistry and Respiratory Medicine, Western Infirmary, Glasgow*  $\alpha_2$ - and  $\beta_2$ -adrenoceptor numbers and affinity on peripheral lymphocytes in four normal subjects and four asthmatic patients were measured at 0800 and 1800 hours on and off oral theophylline. FEV<sub>1</sub> and FVC were also recorded at these times. The asthmatic patients were in remission and were taken off all sympathomimetic drugs for one week and none was on corticosteroid therapy. By means of radioligand binding technique, <sup>125</sup>I-HYP (for  $\beta_2$ -adrenoceptors) and <sup>3</sup>H-yohimbine (for  $\alpha_2$ -adrenoceptors), receptor number

(Bmax) and affinity (Kd) were determined for each type from Scatchard analysis. A significant circadian variation in Bmax of  $\beta_2$ -adrenoceptors was observed in both normals and asthmatic patients, which was abolished on giving theophylline therapy, while Kds were not significantly affected by the administration of theophylline. On theophylline, "up-regulation" of  $\alpha_2$ -adrenoceptor Bmax occurred in both normals and asthmatic patients only in the 0800 hour samples (p<0.05). The results contain no evidence that either  $\alpha_2$ - or  $\beta_2$ -adrenoceptors of asthmatic patients are functionally different from those of normal subjects.

The effect of isoprenaline on  $\beta$ -adrenoceptor number in peripheral tissue following chronic hypoxia in rats

RJD WINTER, RM RUDD, PS SEVER, KEJ DICKINSON *London Chest Hospital and St Mary's Hospital, London* Pharmacological manipulation of the  $\beta$ -adrenoceptor ( $\beta$ AR) can alter the response to chronic hypoxia (CH) and susceptibility of the  $\beta$ AR to downregulation by prolonged treatment by agonist is reduced during CH (Dickinson *et al*, Br J Pharmacol 1985;78:220P). This study was designed to investigate the effect of a single dose of isoprenaline (Iso) on  $\beta$ AR density on peripheral tissue during exposure to CH (FiO<sub>2</sub>=10%). Littermate Wistar rats were maintained in either CH or normoxia for 28 days. Animals were treated with Iso (5mg/kg i.p.) or saline and after 30 min membranes of spleen and lung were prepared in the conventional manner.  $\beta$ AR number (binding site maxima; Bmax, fmol/mg protein) and affinity (dissociation constant; Kd, pM) for the radioligand <sup>125</sup>I-iodocyanopindolol (<sup>125</sup>I-CYP) was measured by saturation curve analysis (n=8 for both lung and spleen).

		Control		Iso Treated	
		Normox	Hypox	Normox	Hypox
SPLEEN	Bmax	67.8 ± 8.1	62.6 ± 8.2	**27.5 ± 9.5	56.1 ± 9.7
	Kd	14.5 ± 3.6	8.0 ± 2.7	10.9 ± 2.4	16.9 ± 2.9
LUNG	Bmax	530 ± 45	586 ± 46	*354 ± 50	412 ± 71
	Kd	42.3 ± 9.6	37.4 ± 9.7	26.7 ± 5.2	34.2 ± 7.7

\*\*p=0.006, \*p=0.02 compared with normoxic controls.

These data suggest that CH confers protection against downregulation of  $\beta$ ARs. The mechanism may be a direct action on membrane phospholipids or an indirect effect possibly through increased endogenous glucocorticoid production.

Respiratory health following acute chlorine exposure

H WEILL, RN JONES, J HUGHES, HW GLINDMEYER *Tulane University School of Medicine, 1700 Perdido Street, New Orleans, Louisiana, 70112* One hundred and fifty-three persons were exposed when a railway accident spilled 50 tons of chlorine with a resultant large, slowly dispersing gas cloud. Eight persons died, 23 required hospital admission, 25 others had signs of respiratory abnormality, and 97

lacked such signs. One hundred and thirteen, including 20 of 23 admitted and 21 of 25 others with respiratory abnormality, were tested, 102 on multiple occasions. All subjects were examined in area hospitals for respiratory effects within 48 hours of exposure, and their "triage status" was used to categorize for degree of acute chlorine injury. Sixty-four adults tested three weeks after exposure had normal mean lung function ( $FVC=108$ ,  $FEV_1=100$ ,  $FEF_{25-75}=85$ , (% predicted)), with expected smoking differences, but no difference according to distance from spill or triage status. Testing was repeated annually, and 60 adults had a suitable number and separation of data points to examine the course of longitudinal change. Linear declines in lung function over six years were:  $FVC=27$  (SD  $\pm 39$ ) and  $FEV_1=25$  (SD  $\pm 33$ ) ml/y, and  $FEF_{25-75}=30$  (SD  $\pm 56$ ) ml/sec/y. These also showed expected differences for smoking, but none for distance from spill or triage category. We conclude that chlorine injury had no discernible effect on early postexposure lung function, or on annual change over the subsequent six years.

### Mesothelioma in Cyprus — the role of tremolite

K McCONNOCHIE, L SIMONATO, JC WAGNER *University of Wales College of Medicine, Department of Tuberculosis and Chest Diseases, Llandough Hospital, Penarth; IARC 150 Curs Albert Thomas, Lyon, France; MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, S Glamorgan* There is little doubt that the amphibole asbestos mineral crocidolite can induce mesothelioma, but evidence that chrysotile, the only serpentine asbestos, acts similarly is non-conclusive. Mineralogical analyses of lung tissue from cases of mesothelioma thought only to have had chrysotile exposure, from a variety of industrial sources, have shown the presence of amphiboles including crocidolite, tremolite and amosite. Cyprus has a chrysotile mine in the central mountains and no other appreciable industrial source of asbestos; hence it has been regarded as a useful area to seek pure chrysotile induced mesothelioma. Twelve cases have now been reported from the island. Lung analysis of the first case, a housewife, revealed both tremolite and chrysotile fibres. The remaining cases comprised five asbestos miners, three miners' wives and three other residents with only environmental exposure. Mineralogical evaluation of dust samples from domestic and natural environments surrounding the mine with analysis of lung tissue from sheep lungs gave further evidence that tremolite is widely distributed. Levels suggest that the amphibole burden is relatively high. Tremolite fibres found have a similar morphological form to crocidolite. Our studies suggest that mesotheliomas in Cyprus may be due to either chrysotile or tremolite with the present evidence favouring tremolite.

### Potentially tissue damaging enzymes in organic dust

JH EDWARDS, DM TROTMAN *MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, South Glamorgan* The introduction of certain enzymes — for example, papain — into the lung can result in emphysema owing largely to the

effect of the elastase activity on the pulmonary architecture. Other enzymes (for example, trypsin) also a role in the inflammatory response. Source of enzymes may be exogenous (for example, bacterial) or endogenous (for example, polymorphs). Other sources may be residual enzymes in inhaled organic dust, as in pigeon droppings (Berrens L, Guikers CLH, *Int Arch Allergy* 1972;43:337) or mouldy hay dust (Edwards JH, *Immunology* 1979;37:91). Respirable fractions of pigeon droppings, mouldy hay and 11 other organic dusts associated with immediate or late allergy or non-allergic lung disease were assessed for the four enzyme groups serine, cysteine, aspartic and metallo proteases. Trypsin, chymotrypsin and elastase were identified by specific substrates. Only those dusts associated with late allergy — budgerigar and pigeon droppings and mouldy hay dust — had significant protease activity. All enzymes were in the serine group and had trypsin function. Only mouldy hay dust had additional chymotrypsin activity and only pigeon droppings had additional elastase activity. It is possible, therefore, that the hypersensitivity reaction to these dusts is exacerbated by the presence of these enzymes.

### Occupational asthma caused by salbutamol

RM AGIUS, AG DAVISON, AJ NEWMAN TAYLOR *Department of Occupational Medicine, Cardiothoracic Institute, Brompton Hospital, London* In salbutamol manufacture, asthma caused by an intermediate compound, but not salbutamol itself, has been described (*Clinical Allergy* 1976;6:405). We report occupational asthma caused by inhaled salbutamol base (used in metered dose aerosols). Two men (41 and 49 years) had worked for a pharmaceutical firm for six years having previously been free of any history of asthma. They worked occasionally in the sulphation of batches of salbutamol base and in salbutamol packaging respectively. One had an 18 month history of asthmatic symptoms in the evenings following work on the salbutamol process while the second developed asthma after scooping salbutamol base. Self measured peak flow records in both showed a fall in mean and minimum daily readings when working with salbutamol base, but not when working with other substances or off work. Only one worker agreed to bronchial inhalation testing. This showed a 22% fall in  $FEV_1$  three hours after inhaling salbutamol base. There was no reaction to lactose control or salbutamol sulphate. Following relocation they have remained asymptomatic (five and two years respectively). Salbutamol base may cause occupational asthma.

### Occupational asthma due to oil mists

AS ROBERTSON, GA WIELAND, PS BURGE *Department of Thoracic Medicine, East Birmingham Hospital, Birmingham* Nineteen workers exposed to oil mists reported symptoms suggestive of asthma related to work. These workers kept two hourly peak expiratory flow recordings both at home and at work. Analysis of these records showed nine workers with definite work related asthma. Seven workers had patterns that were equivocally

work related, two had normal records and one had asthma that was not work related. Patterns of peak flow response were heterogenous, even in the same worker. The most common pattern was of progressive work day deterioration. Some had deterioration maximal on the first work day; deterioration equivalent on each work day was the least common pattern seen. Bronchial provocation testing was performed on three workers. Two of these workers showed significant reactions to the clean oil, reproduced by exposure to the reoderant alone. The third worker reacted only to the used oil. We have shown exposure to oil mists at work to be a significant cause of occupational asthma. Patterns of peak flow response and provocation testing show that there is more than one type of response. Deterioration, progressive throughout the work week, was associated with specific reactions to clean oils, whereas deterioration on the first work day was associated with reaction only to used oil. This may be due to bacterial contamination of the oil.

# **Occupational asthma in a bathtub resurfacers due to pentamethylene diethylene triamine**

SR DURHAM, S DAVIES, K VENABLES, B GRANEK, AJ NEWMAN-TAYLOR *Department of Occupational Medicine, Brompton Hospital, London* Pentamethylene diethylene triamine (PDT) is used as a hardener in epoxy resin paint systems. We have identified PDT as a cause of occupational asthma in a 46 year old man who had worked as a bathtub resurfacers for three years. The subject was a non-atopic, non-smoker who gave a nine month history of work related respiratory symptoms. Peak expiratory flow recordings confirmed asthma and suggested an occupational cause. Bronchial provocation by spraying paint, solvent and PDT for 1-5 minutes resulted in a dose dependent late asthmatic reaction at 2-8 hours (maximal FEV<sub>1</sub> decrease 33-35% at 3-4 hour). There was an associated increase in histamine responsiveness (histamine PC<sub>20</sub> 1.8 mg/ml pre-challenge, 0.35 mg/ml (lowest value) at 24 hours when FEV<sub>1</sub> 90% pre-challenge, 2.0 mg/ml at 48). These changes were not observed after a control challenge, nor when PDT was brush painted (as opposed to sprayed) for up to 30 min. These findings prompted an on-site review of the subject's four work associates, in whom no evidence of asthma was identified. These results suggest PDT to be the cause of this patient's asthma and emphasise the importance of reproducing as closely as possible the subject's work exposure in provocation testing.

# **Allergy to locusts *S gregaria* and *L migratoria***

RD TEE, DJ GORDON, ER HAWKINS, J LACEY, AJ NUNN, KM VENABLES, AJ NEWMAN-TAYLOR *Department of Occupational Medicine, Brompton Hospital, London* Allergic disease (asthma, rhinitis and urticaria) occurs in those occupationally exposed to locusts. We have developed a reliable radioallergen sorbent test (RAST) to measure specific IgE antibodies to locust extracts. Thirty-five research centre workers were studied by questionnaire, skin prick tests and specific IgE antibody measurements.

Specific skin prick test reactions were found in all the nine locust exposed workers with allergic symptoms, but in only three of the 26 without symptoms. Positive RAST results correlated significantly with exposure, symptoms, skin prick test results but not atopy. RAST inhibition assays and specific skin prick tests enabled us to identify the allergen source as peritrophic membrane, which is present in the gut and surrounds faeces. The allergens have been partially characterised by gel filtration, RAST inhibition and immunoelectrophoretic techniques, and were found to have approximate molecular weights of 66K, 54K, 43K, 25K and 14K daltons and pI<sup>s</sup> between 3.7 and 6.1. By use of an immunochemical method involving high volume air sampling in the locust rearing room and logit transformation of RAST inhibition lines allergen was identified in the atmosphere and found to have immunological identity with intact locust and gut extracts.

# **Occupational asthma caused by maleic anhydride: bronchial provocation testing and immunological data**

BJ GRANEK, SR DURHAM, M TOPPING, RD TEE, R HAWKINS, AJ NEWMAN-TAYLOR *Department of Occupational Medicine, Cardiothoracic Institute, Brompton Hospital, London* The acid anhydrides phthalic (PA), trimellitic (TMA), and tetrachlorophthalic (TCPA) cause asthma, and specific IgE antibodies to conjugates of the causative anhydride and human serum albumin (HSA) may be identified in their sera. Only one case of asthma caused by maleic anhydride (MA) has previously been described (Geurin JC *et al*, Poumon-coeur 1980;36:393-395). We report four cases of asthma in patients working with MA. In three, inhalation tests with MA provoked a late asthmatic reaction and an increase in airway responsiveness to inhaled histamine. Only one of these three had specific IgE antibodies in serum, in low titre (RAST score 2.5), which may be cross reacting with IgE to TMA, to which he was also occupationally exposed (RAST score 24.5) and which provoked a lone immediate reaction without increasing airway reactivity. The fourth patient had a RAST score of 8.3 without significant scores for the other anhydrides. However, inhalation testing with MA was negative, and peak flow records demonstrated asthma only without work relationship. The discordance between immunological and airway responsiveness in these patients contrasts with observations in those with asthma caused by other anhydrides. Electrophoresis of HSA ± MA suggests conjugation, and the conjugate identified specific IgE in patient four. It is possible that other mechanisms may be involved. This seems surprising when compared with other acid anhydrides. In considering MA as a possible cause of asthma, evidence of specific IgE should not be considered an essential diagnostic requirement.

# **Specific IgE to storage mites in Essex farmworkers**

AD BLAINEY, MD TOPPING, S OLLIER, RJ DAVIES *Department of Respiratory Medicine, St Bartholomew's Hospital, and Health and Safety Executive Occupational Medicine Laboratories, London* Studies in Scottish farmworkers



have suggested that occupational respiratory symptoms may result from exposure to storage mites in stored hay. We have surveyed farmworkers from grain producing areas in Essex to assess the relationship between respiratory symptoms and storage mites. 101 farmworkers from 24 arable farms (88% of available workforce) were studied on site with questionnaire and skin prick testing for common inhalant allergens and five storage mite (SM) extracts. Specific IgE was measured by RAST and results expressed as per cent binding. RAST was considered positive if mean % binding  $>$  mean binding to cord serum  $+ 2.5 \times \text{SD}$ . 21% of farmworkers reported work related attacks of cough, wheeze or breathlessness. Work related symptoms were significantly associated with atopy, positive skin prick responses and RAST to SM and to *Dermatophagoides pteronyssinus* (DP), but not current smoking or duration of employment. In those with positive RAST, mean RAST binding for SM but not for DP was significantly higher in subjects with work related symptoms. Weal areas from skin prick tests and RAST binding correlated significantly between SM and DP ( $r = 0.87$ ,  $p < 0.001$ ). These findings of high levels of specific IgE to SM in association with work-related symptoms suggest that storage mites may be responsible for work related symptoms in some Essex farmworkers, and that there may be some cross reactivity between SM and DP allergens.

#### Validation of smoking histories in a study of occupational lung disease

AG DAVISON, P LEWIS, AJ NEWMAN-TAYLOR *Department of Occupational Medicine, Cardiothoracic Institute, Brompton Hospital, London* Smoking histories have fallen into disrepute largely as a result of studies from smoking and cardiovascular clinics showing that up to 40% of smokers may falsely claim to have stopped smoking. Little is known about the reliability of smoking histories obtained in studies of occupational lung disease, where "compensation factors" could lead to inaccurate smoking histories. We have assessed current cigarette smoking histories, during a study of the effects of inhaling cadmium fume, by comparing plasma thiocyanate levels in workers exposed to fume and controls. The former knew that cadmium was potentially toxic and claims for compensation had been made. The thiocyanate level which best discriminated between the 42 current smokers and 54 non-smokers in the controls was  $63 \mu\text{mol/l}$ . This level produced 93% agreement between the smoking history and plasma thiocyanate level. The validity of the smoking history in the cadmium fume workers was assessed by using the same thiocyanate level of  $63 \mu\text{mol/l}$ . There were 33 current smokers and 32 non-smokers according to the history. The smoking history had a sensitivity of 96%; only one cadmium worker who stated that he was a non-smoker had a thiocyanate level above  $63 \mu\text{mol/l}$ . There was no evidence that workers inhaling potential toxic fumes lied about smoking.

#### The effect of cigarette smoking on the prevalence of extrinsic allergic alveolitis (EAA)

K ANDERSON, C MCSHARRY, G BOYD *Department of Respiratory Medicine, Royal Infirmary Glasgow* A reduced prevalence of EAA in smokers, which has been previously suggested in a small group (Warren CPW, *Thorax* 1977;32:567-569), is confirmed by analysis of 669 individuals. Three survey populations (farmers,  $n = 116$ ; pigeon breeders,  $n = 521$ ; factory workers exposed to air humidifier contaminants,  $n = 26$ ) were assessed concerning symptoms, smoking and the antibody response to the relevant antigens. EAA was diagnosed (on the basis of symptoms: breathlessness with febrile episodes after antigen exposure with or without cough, malaise or weight loss) in 19/219 smokers (8.7%) and in 75/371 non-smokers (20.2%) ( $\chi^2 = 13.2$ ,  $p = 2.86E-4$ ). This difference was neither age related nor limited to the length or intensity of antigen exposure within each group. A strong association was found between EAA and serum antibody to these antigens ( $\chi^2 = 103.9$ ,  $p = 2.15E-14$ ). The symptoms of EAA occurred in 16/79 ex-smokers (20.3%), which was similar to non-smokers. Increased antibody occurred in 29 ex-smokers (36.7%), which was intermediate between non-smokers (171/371, 46.1%) and smokers (23/219, 10.5%), suggesting that the effects of smoking are reversible.

#### Bronchial challenge tests in humidifier related lung diseases

AS ROBERTSON, GA WIELAND, P SHERWOOD BURGE *Department of Thoracic Medicine, East Birmingham Hospital, Birmingham* Six printing workers with pulmonary disease due to occupational exposure to a contaminated humidifier, and two asthmatic controls (unrelated to work), were investigated by bronchial provocation tests using antigen from the humidifier. Five of the affected workers had a repeat challenge performed on two consecutive days. Of the six workers investigated two had an extrinsic allergic alveolitis (EAA), two work related asthma and two symptoms of humidifier fever. Temperature, spirometric values, lung diffusing capacity and symptoms were monitored throughout. Those with EAA developed a delayed pyrexia, headache and generalised aches and pains associated with a fall in  $\text{FEV}_1 > 20\%$  maximal between 4 and 12 hours and fall in Kco. Second day exposure in one resulted in no change in spirometric values, symptoms improved but Kco remained depressed. Of the two workers with occupational asthma one showed no fall in spirometric values, but developed humidifier fever, which resolved despite repeat challenge. The other worker had a fall in  $\text{FEV}_1$  of 24% at 11 hours and generalised symptoms. Changes in spirometric values on repeat challenge were less marked. Neither showed a change in Kco. The two workers with humidifier fever developed marked symptoms of humidifier fever (one failed to develop a pyrexia) but Kco and spirometric values remained unchanged. Symptoms improved despite repeat challenge. There was no reaction in either control subject. These challenges in eight subjects show widely differing responses. Unlike in classical antigen mediated asthma and alveolitis repeat challenge on a second day resulted in

substantially reduced reactions in four of the five workers tested, suggesting a different mechanism for these reactions.

#### Cilioinhibitory factors in the sputum of patients with chronic bronchial sepsis

D SYKES, R WILSON, D CURRIE, C STEINFORT, P COLE *Host Defence Unit, Department of Medicine, Cardiothoracic Institute, Brompton Hospital, London* Sputum sols (SS) from patients with chronic bronchial sepsis (CBS) slow human nasal ciliary beat frequency (CBF) *in vitro* (Smallman *et al*, Thorax 1984;39:663). We measured the slowing of nasal CBF in SS from eight patients with CBS by a photometric technique. Recordings of CBF performed at hourly intervals for four hours at 37°C in SS were compared with control readings from cilia in phosphate buffered saline. SS causing ciliary slowing were retested after complete inhibition of elastolytic activity with  $\alpha_1$  anti-protease and after chloroform extraction. All sols were cultured microbiologically and their elastolytic activity assayed. Five of eight SS slowed cilia ( $n = 5$ ; mean reduction 47%;  $p < 0.001$  Student's *t* test). Elastolytic activity did not correlate with ciliary slowing. *Pseudomonas aeruginosa* was cultured from all five active SS but from only one of the inactive SS. Three of five active SS caused gradual ciliary slowing associated with epithelial disruption and was inhibited by  $\alpha_1$  anti-protease. Two of five active SS caused immediate slowing associated with ciliary dyskinesia and stasis without epithelial disruption. This immediate slowing was not inhibited by  $\alpha_1$  anti-protease but was extracted by chloroform. Sputum from patients with CBS contains at least two factors, which slow ciliary beating — only one inhibited by  $\alpha_1$  anti-protease, the other chloroform extractable.

#### Effect of *Streptococcus pneumoniae* on human ciliary function *in vitro*

C STEINFORT, R WILSON, D SYKES, P J COLE *Host Defence Unit, Department of Medicine, Cardiothoracic Institute, Brompton Hospital, London* Five strains of *Streptococcus pneumoniae* were cultured for 14 to 24 hours in broth at 37°C and then centrifuged. The supernatant fluid was filtered (0.2  $\mu$ m) and diluted 50:50 with fresh medium 199, then added to human nasal cilia in four hour controlled experiments, during which the *in vitro* ciliary beat frequency (CBF) was measured by a photometric technique (Rutland J, Cole PJ, Lancet 1980;ii:564). Three out of the five filtrates produced significant slowing of cilia (15 to 27%;  $p < 0.02$  Student's *t* test, 18 degrees of freedom). A dose-response effect was demonstrated. The capacity to slow cilia was destroyed by heating to 56°C for one hour, was stable at room temperature for 24 hours and was still present after being stored at -30°C for at least two months. The factor(s) responsible for ciliary slowing was not extracted by chloroform. The factor was released during log phase growth of the organism and had maximum potency at the peak of the growth curve. Factor(s) activity was maximal at pH 6.5. Pneumococcal lysis products failed

to enhance the ciliary slowing effect, suggesting that the factor(s) was released by the dividing organism. *Strep pneumoniae* produces a factor(s) which slows human cilia *in vitro* and may therefore facilitate colonization of the respiratory tract.

#### A heat stable factor produced by *Haemophilus influenzae* which slows and disorganises the beating of human cilia *in vitro*

R WILSON, T PITT, A RUTMAN, D ROBERTS, P COLE *Host Defence Unit, Department of Medicine, Cardiothoracic Institute, Brompton Hospital, London and Division of Hospital Infection, Central Public Health Laboratories, Colindale* Non-typable, uncapsulated *Haemophilus influenzae* is associated with, and may cause, exacerbations of chronic bronchitis and bronchiectasis. Type b strains may colonise the upper respiratory tract and cause meningitis in infants. *H influenzae* culture supernatants have been observed to cause ciliostasis in rat and chick tracheal rings, although this was only evident after 48 hours (Denny F, J Infect Dis 1974;129:93). We have studied the effect of sterile 18 hour culture filtrates (four non-typable, one type b) on normal human nasal ciliary beat frequency by a photometric technique. Each filtrate caused significant ( $p < 0.001$  Student's *t* test) ciliary slowing which was rapid in onset. The more active filtrates produced ciliary dyskinesia and stasis. The type b strain was most potent. During a 36 hour culture, filtrate ciliary slowing activity appeared during the stationary phase and became pronounced during bacterial cell death. Filtrate activity was stable to boiling, dialysable (M W 14 000), not chloroform extractable and not neutralised by trypsin digestion. The ultrastructure of cilia exposed to filtrate was normal, but extrusion of ciliated and non-ciliated cells from the epithelium was seen. Release of such factors *in vivo* may contribute to delayed mucociliary clearance, thus aiding colonisation of the respiratory tract by this organism.

#### Further studies of the pathogenic mechanisms of *Branhamella catarrhalis*: lack of IgA1 protease production

DT McLEOD, MJ CROUGHAN, F AHMAD, R BRETTE MA CALDER *The Chest Unit and Department of Bacteriology, City Hospital, Edinburgh* *Branhamella catarrhalis*, though part of the nasopharyngeal flora, is a potential pathogen and has become the third commonest cause of infective exacerbations of chronic pulmonary diseases on our chest wards (McLeod *et al*, Br Med J 1983;ii:1446-7). The reason for this increase in virulence is not known. The usual organisms, *Streptococcus pneumoniae* and *Haemophilus influenzae*, both elaborate the enzyme immunoglobulin A1 (IgA1) protease, which cleaves IgA1 to give Fc and Fab fragments (Male CJ, Infect Immun 1979;26:254-261) and may thus convey some advantage to the organism by damaging this important defensive immunoglobulin barrier which coats mucous membranes. As *Neisseria meningitidis* and *Neisseria gonorrhoeae* produce this enzyme (Plaut *et al*, Science 1975;190:1103-05) and belong to the same Neisseriaceae family as *B*

*catarrhalis*, we tested whether pathogenic strains of *B catarrhalis* also produce this enzyme. Twenty clinical isolates from patients with bronchopulmonary infection were tested using immunoelectrophoresis with human IgA1 (myeloma) as the substrate. Of these 20 strains, 10 produced  $\beta$  lactamase and 10 were  $\beta$  lactamase negative. None of the *B catarrhalis* strains demonstrated IgA1 protease activity. Three different culture media failed to promote enzyme production. With the same technique, clinical isolates of *N meningitidis*, *N gonorrhoeae* and *Strep pneumoniae* type 6 did cleave IgA1 satisfactorily. The pathogenic mechanism of *B catarrhalis* does not appear to necessitate the elaboration of IgA1 protease.

#### Anti-elastases in bronchoalveolar lavage fluid from patients with $\alpha_1$ -proteinase inhibitor deficiency or chronic obstructive bronchitis

HM MORRISON, JA KRAMPS, D BURNETT, JH DIJKMAN, RA STOCKLEY *General Hospital, Birmingham, and University Hospital, Leiden, Netherlands* Antielestases are thought to protect the lung from proteolytic enzymes. We have assessed anti-elastase function in bronchoalveolar lavage fluid (BAL) from five patients with  $\alpha_1$ -proteinase inhibitor deficiency ( $\alpha_1$  PID) and 10 with chronic obstructive bronchitis (COB), using the synthetic substrate SLAPN. Neutrophil elastase (NE) and porcine pancreatic elastase (PPE) were used to determine total elastase inhibition and  $\alpha_1$ PI function respectively. All results are given as median with range. The  $\alpha_1$ PI concentration and  $\alpha_1$ PI/albumin ratio were lower in  $\alpha_1$ PID than COB ( $p < 0.005$ ), but anti-leukoprotease (ALP) and  $\alpha_2$ -macroglobulin levels were similar between the groups. Equimolar amounts of  $\alpha_1$ PI and ALP were found in BAL from COB, but ALP was the dominant inhibitor in  $\alpha_1$ PID. Alpha<sub>1</sub>-PI was about 45% active in each group, but BAL from  $\alpha_1$ PID inhibited 0.04  $\mu$ g PPE/ml (0-0.09), whereas in COB it inhibited 0.8  $\mu$ g PPE/ml (0.34-1.75). Total elastase inhibition was similar for  $\alpha_1$ PID (4.61  $\mu$ g NE/ml; 3.22-52.30) and COB (4.06; 1.05-8.51). However, not all inhibition could be accounted for by the known inhibitors in  $\alpha_1$ PID (5.46 moles NE inhibited/mole known inhibitors) whereas it could in COB (0.98; 0.51-1.27). These results confirm that  $\alpha_1$ PI is not the only inhibitor in BAL and suggest the presence of at least one additional unknown anti-elastase in  $\alpha_1$ PID.

#### Serum acute phase proteins in purulent bronchiectasis

SL HILL, JC SHAW, SR SMITH, D BURNETT, RA STOCKLEY *The Lung Immunobiochemical Research Laboratory, Clinical Teaching Block, General Hospital, Birmingham* Patients with purulent bronchiectasis have a persistent inflammatory response within the lung even when "clinically well" (Stockley *et al*, Thorax 39:408-413). We have assessed the sputum response to antibiotic together with serum acute phase proteins to determine whether such patients have a systemic reaction to their lung pathology. Twenty-eight antibiotic studies were performed on patients with purulent secretions. Sputum and serum samples were collected before and during (day 14) treatment. Sputum and

serum albumin concentration ratios, sputum elastase and serum acute phase proteins alpha<sub>1</sub> antichymotrypsin and C-reactive protein (CRP) were measured. A clear change in sputum colour was used to indicate a positive response to treatment. Fifteen patients responded and this was associated with a significant reduction in: a) sputum to serum albumin ratios from  $\bar{x}$   $4.26 \times 10^{-2}$  (SEM  $\pm 0.85$ ) to  $1.55 \times 10^{-2}$  (0.36) during treatment;  $p < 0.001$ ; b) alpha antichymotrypsin from  $\bar{x}$  710.5 mg/l (52.3) to 584.9 mg/l (119.2);  $p < 0.001$ ; c) CRP from  $\bar{x}$  49.5 mg/l (27.9) to 8.4 mg/l (5.4);  $p < 0.001$ , whereas only the CRP changed in patients not showing sputum clearance, from  $\bar{x}$  64.8 mg/l (45.4) to 18.4 mg/l (6.9);  $p < 0.005$ . Of the 15 patients who responded to treatment 12 had elastase positive secretions, which disappeared in nine as sputum cleared. However elastase persisted in all but one of the 13 patients who failed to respond. These results show the presence of a systemic acute phase response in these patients who are "clinically well". It is reduced if sputum purulence is cleared with antibiotics, suggesting that more active treatment may be indicated.

#### Viscoelastic properties of sputum from patients with Young's syndrome

MT LOPEZ-VIDRIERO, D PAVIA, M GREENSTONE, WF HENDRY, SW CLARKE *Department of Thoracic Medicine, Royal Free Hospital School of Medicine; Cardiothoracic Institute; St Bartholomew's Hospital, London* Patients with primary obstructive azoospermia and chronic respiratory disease — Young's syndrome — have abnormal tracheobronchial clearance (Pavia *et al*, Chest (supp)1981;80:892-895). Since the function and ultrastructure of bronchial ciliated cells is known to be normal, it is possible that changes in the physical properties of airway mucus could be responsible for the reduction in tracheobronchial clearance. We have studied the viscoelastic properties of sputum from eight patients with Young's syndrome. Sputum samples were collected from 0900 to 1200 hours and were tested within 1 hour. An oscillatory viscometer was used for measuring viscosity and elasticity. Measurements were carried out at 37°C and at a frequency of 0.352 Hz. Six samples were infected. The mean (SEM) apparent viscosity ( $\eta$ ) ( $549 \pm 118$  Pa.s) and elasticity ( $G'$ ) ( $2841 \pm 742$  mPa) were within the levels found in non-infected sputum from chronic bronchitis ( $\eta$ :  $529 \pm 115$ ,  $G'$ :  $3012 \pm 525$ ). Although most of the samples were infected both viscosity and elasticity were found to be lower than in infected sputum from patients with bronchiectasis ( $\eta$ :  $695 \pm 145$ ,  $G'$ :  $3277 \pm 696$ ) and cystic fibrosis ( $\eta$ :  $926 \pm 109$ ,  $G'$ :  $4326 \pm 1662$ ). A significant difference emerged for  $\eta$  ( $p < 0.05$ ) only with the cystic fibrosis group. These findings suggest that the viscoelastic properties of expectorated airway mucus from patients with Young's syndrome are consistent with those found in patients with chronic mucus hypersecretion.

Reproducibility of tracheobronchial clearance measured by means of a radioaerosol technique

MV HENGSTUM, J FESTEN, W BUIJS, WVD BROEK *University Lung Centre and Department of Nuclear Medicine, St. Radboudhospital, Nijmegen, The Netherlands* To evaluate intersubject and intrasubject reproducibility of tracheobronchial clearance this was measured twice in 10 healthy non-smoking subjects, using a radioaerosol technique (5 micron <sup>99</sup>Tc labelled polystyrene particles) as described by Thomson (Br J Dis Chest 1974;68:21). The area under the clearance curve up to 6 hours after inhalation (AUC360) was calculated. This parameter has the advantage of taking all uncorrected counts during a particular period into account and is therefore less subject to accidental variations. The intersubject coefficient of variation (COV) using this parameter was 36%. The mean intrasubject COV was 8.5% (SD ± 4.5). The results with this strictly standardized method are better than those reported in other studies dealing with reproducibility of tracheobronchial clearance in healthy subjects using different techniques and parameters, for instance Puchelle reporting an intrasubject COV of 16% (Scand J Resp Dis 1979;60:307) and Yeates reporting an intrasubject COV of 20% (Ann Occup Hyg 1982;26:245-257). It is concluded that, although there exists a distinct interindividual variation in tracheobronchial clearance rate, there is a good intraindividual reproducibility, sufficient for applying this technique to cross over studies, in which preferably the AUC 360 should be used to quantitate the results.

Upper respiratory tract viral infection and mucociliary clearance

R WILSON, A RUTMAN, P HIGGINS, WA NAKIB, D TYRELL, P COLE *Host Defence Unit, Department of Medicine, Cardiothoracic Institute, Brompton Hospital, London, and MRC Common Cold Unit, Harvard Hospital, Salisbury* Twenty-six normal volunteers were exposed to rhinovirus or influenza B virus. Investigations were performed before exposure: day 0 (V1), during viral incubation period, day 2 (V2); and at the time of expected overt infection, day 4 (V3). Nasal mucociliary clearance (NMCC) was performed by the saccharin method. Cilia were obtained by a brushing technique from the inferior turbinate of the nostril. Ciliary beat frequency (CBF) was measured by a photometric technique, per cent ciliated epithelium (PCE) examined by direct light microscopy, and ciliary ultrastructure by transmission electron microscopy. Patients were grouped as having overt infection (OI), subclinical infection (SI) or no infection (NI), by viral culture from nasal washings, rise in serum antibody titres, and clinical scores. There were no significant changes in any of the measurements between V1 and V2. Results at V3 are presented in the table below. No significant abnormalities of ciliary ultrastructure were detected during infection. We conclude that overt viral upper respiratory tract infections usually prolong NMCC owing to loss of ciliated epithelium. This does not occur during the viral incubation period or during subclinical infection.

	NMCC at V3 > 30 min longer than at V1	Mean CBF at V3	<50 PCE at V3
OI	6/9*	11.4	6/7*
SI	0/6	12.4	0/5
NI	0/10	12.7	0/9

\*p<0.02 Mann-Whitney U test

How badly impaired is the pulmonary mucociliary clearance of patients with Kartagener's syndrome?

D PAVIA, JE AGNEW, PP SUTTON, MT LOPEZ-VIDRIERO, DC CURRIE, PJ COLE, SW CLARKE *Royal Free Hospital and School of Medicine and Host Defence Unit, Cardiothoracic Institute, London* Published reports (Mossberg *et al*, Scand J Resp Dis 1978;59:55; Rossman *et al*, Am Rev Respir Dis 1980;121:1011) have indicated that patients with Kartagener's syndrome (KS) have no significant pulmonary mucociliary clearance. With the radioaerosol technique we measured over a six hour observation period the tracheobronchial clearance (TBC) of nine non-smoking patients with KS (mean(SE) age: 30(4) y and % predicted FEV<sub>1</sub>: 79(5) %). TBC of the KS patients compared with that of 29 healthy subjects (mean(SE) age: 31(3) y and % predicted FEV<sub>1</sub>: 119(3) %) was significantly reduced (p<0.02). However, even when allowance was made for productive coughing during the observation period, the reduced clearance was much better than anticipated from published reports which confined their observations to a two hour period. The TBC of the KS patients, adjusted for productive coughing, was similar to that found in an older (smoking) group of patients with chronic obstructive airways disease (mean(SE): 69(3) y; % predicted FEV<sub>1</sub>: 48(7)%; and pack-years: 78(25)) who refrained from expectorating during the equivalent test period. Our study implies one or more of the following: (i) a spectrum of mucociliary impairment in KS patients, (ii) cough may be effective deeper in the lung than hitherto believed and (iii) two phase flow of mucus cephalad may be an effective mechanism in KS.

Tracheobronchial clearance in bronchiectasis

DC CURRIE, D PAVIA, JE AGNEW, MT LOPEZ-VIDRIERO, PD DIAMOND, PJ COLE, SW CLARKE *Royal Free Hospital and School of Medicine and Host Defence Unit, Cardiothoracic Institute, London* Lourenco *et al* (Am Rev Respir Dis 1972;106:857-65) demonstrated impaired lung clearance in patients with bronchiectasis and mild airways obstruction but not in similar patients with marked airways obstruction. To investigate this discrepancy we have measured tracheobronchial clearance (TBC) of inhaled radioaerosol and partitioned it from alveolar deposition (AD). Ten patients (mean age 57 years; 6M, 4F) with definite bronchiectasis (median involvement 3 lobes), daily purulent sputum production (mean 51 ml/day) for a median of 46 years and marked airways obstruction (mean (SE) FEV<sub>1</sub> % predicted, 44(4)) were studied. Five of the patients were ex-smokers. None had primary ciliary dyskinesia. Their results were compared with those of ten



healthy subjects (FEV<sub>1</sub> 113 (6)%) matched for age, sex, height and weight. Five  $\mu$ m diameter <sup>99m</sup>Tc labelled polystyrene particles were inhaled in a standard manner (Pavia *et al*, Thorax 1985;40:171-5) and total lung radioactivity measured every 30 minutes for six hours and then at 24 hours and 48 hours. TBC was impaired as judged by amount of radioaerosol still available to be cleared at six hours (patients 41(7)%; controls 11(2)%;  $p < 0.01$ ) despite coughing. The degree of impairment was similar to that observed in patients with chronic obstructive airways disease (FEV<sub>1</sub> 47(6)%). There was no correlation between individual FEV<sub>1</sub> and TBC. AD was reduced ( $p < 0.01$ ) in the bronchiectatic patients (mean 20(4)%) compared with controls (44(4)%).

### **<sup>111</sup>Indium labelled neutrophils migrate to the lungs in bronchiectasis**

DC CURRIE, S NEEDHAM, AM PETERS, PJ COLE, JP LAVENDER *Host Defence Unit, Cardiothoracic Institute, and Department of Diagnostic Radiology, Hammersmith Hospital, London* An exuberant host response to the colonising microbial load with release of inflammatory products may cause lung damage in patients with bronchiectasis. The presence of neutrophils and elastolytic activity in the sputum and raised serum immunoglobulins are only indirect evidence of local host response in the lungs. <sup>111</sup>Indium labelled leucocyte scanning (Saverymuttu SH *et al*, Scand J Haematol 1983;30:151-60) allows direct measurement of one aspect of the local host response in bronchiectasis. Imaging of <sup>111</sup>indium labelled autologous neutrophils, maintained in plasma during cell separation, in eight patients (mean age 50 years; 5F, 3M) with bronchiectasis (median four lobes) and long standing daily purulent sputum production (mean 60 ml/day) showed migration of cells to the lungs, in some patients visible at 40 minutes, in all by four hours and still present after 18-24 hours. Quantitation of cells migrating and lost from the body was by means of whole body counting at three hours and again at 5-7 days. In the eight patients retained activity after 5-7 days was (mean (SE)): 75(7)% compared with a range of 93-98% in four control subjects showing no migration of cells. (All counts were corrected for decay of radioactivity and for background radiation.) In patients with severe bronchiectasis, up to 50% of the neutrophils are migrating to the lungs and being lost, confirming that there is considerable local host activity.

### **IgA subclass bearing cells in the bronchi of subjects who have died with chronic bronchitis or bronchiectasis**

D BURNETT, J CROCKER, RA STOCKLEY *Lung Immunobiochemical Research Group, The General Hospital and East Birmingham Hospital* Although IgA is the major lung immunoglobulin, little is known about IgA plasma cells in the normal or diseased lung. We have measured the number of cells containing IgA1 or IgA2 in

the major bronchi of post mortem specimens from 10 subjects with no history of lung disease, 10 who died with chronic bronchitis and 10 with bronchiectasis. Tissue was fixed in formal-saline and wax embedded and IgA1- or IgA2-containing cells were stained using monoclonal antibodies in the indirect immuno peroxidase technique. The number of cells staining positively in 10 fields ( $\times 40$  mag) was counted. The average number of total IgA positive cells in the control group was 97 (SD 17) and these were predominantly IgA1 ( $\bar{x}$  73  $\pm$  15). Total IgA cells were increased ( $2p < 0.001$ ) in subjects with bronchitis ( $\bar{x}$  269  $\pm$  32) and those with bronchiectasis ( $\bar{x}$  230  $\pm$  39). However, the increase in IgA1 cells was greater ( $2p < 0.005$ ) in bronchitic subjects ( $\bar{x}$  218  $\pm$  32) than in bronchiectasis ( $\bar{x}$  175  $\pm$  24). The increase ( $2p < 0.001$ ) in IgA2 cells was similar in both bronchitic ( $\bar{x}$  51  $\pm$  12) and bronchiectatic subjects ( $\bar{x}$  56  $\pm$  18) compared with controls ( $\bar{x}$  24  $\pm$  49). The proportion of IgA2/total IgA cells was similar in the control ( $\bar{x}$  24.8%  $\pm$  4.8) and bronchiectatic subjects (23.7%  $\pm$  4.2) but reduced ( $2p < 0.001$ ) in bronchitis (19%  $\pm$  4.6). The results show an increase in IgA plasma cells from the lungs of patients with bronchitis and bronchiectasis but the former group show a disproportionate increase in IgA1 cells.

### **Action of *Aspergillus fumigatus* on the respiratory burst of neutrophils**

D SYKES, R WILSON, P COLE *Host Defence Unit, Cardiothoracic Institute, London* Phagocytes play a crucial role in protecting the lung from colonization by *Aspergillus fumigatus* (AF) (Schaffner, J Clin Invest 1982;69:617). We have looked for products of AF acting on the respiratory burst of neutrophils. Three day cultures of AF in medium 199 were centrifuged and the supernatant (AS) filtered (0.2  $\mu$ m) before use. In all experiments neutrophil ( $10^6$  cells/ml) function was tested in medium 199/AS (v/v 1:1) and in medium 199 alone as control. The oxidative burst was studied after stimulation with opsonized xymosan (particle:cell 100:1) using luminol enhanced chemiluminescence (CL) and standard assays for superoxide ( $-O_2$ ), hydrogen peroxide ( $H_2O_2$ ) and oxygen ( $O_2$ ) consumption. Neutrophil killing of opsonized *Pseudomonas aeruginosa* and *Staphylococcus aureus* was also assessed after incubation for 90 minutes at 37°C (bacteria: cell 10:1). AS reduced mean peak CL by 35% ( $n=15$ ) and also reduced detectable  $H_2O_2$  from 6.5 nmoles/ $10^6$  cells/15 min. to zero ( $n=6$ ). However, AS altered neither  $-O_2$  release,  $O_2$  consumption nor bacterial killing by the stimulated neutrophils. The reduction in CL and detectable  $H_2O_2$  in the stimulated cells appeared to be due to a heat stable activity released from AF, which abrogated the  $H_2O_2$  extracellularly with the production of oxygen. We suggest that AF releases a heat stable catalase which modifies the extracellular results of the respiratory burst of neutrophils but which does not affect intracellular bacterial killing *in vitro*.