

# Proceedings of the British Thoracic Society

The 1986 winter meeting of the British Thoracic Society was held on 11 and 12 December at Kensington Town Hall, London.

## Relationship of lung function to radiograph reading (ILO) in patients with asbestos-related lung disease

JE COTES, HS FULTON, B KING, JEM HUTCHINSON, V WOOLLEY *University Department of Occupational Health and Pneumoconiosis Medical Panel, Newcastle upon Tyne* The ILO classification of chest radiographs (ILO, Geneva, 1980) has been useful in surveys of workers exposed to asbestos. In this study it is used to assess the contributions to lung function of pleural and parenchymal abnormalities. One hundred and seven-two former asbestos workers were assessed following the detection of radiographic abnormalities ranging from minimal to severe. Ventilatory capacity, lung volumes, transfer factor (Tl) and the physiological response to submaximal exercise were obtained by standard methods (Cotes JE, *Lung Function*, 4th ed., Blackwells, Oxford, 1979). P-A chest radiographs were read independently and a majority reading extracted. The profusion of small opacities (PSO), obliteration of one or both costo-phrenic angles (OCPA), and composite indices of (i) chest wall diffuse pleural thickening and extent of pleural thickening (CWT) and (ii) diaphragmatic thickening and calcification (DTC) were included in multiple regression analyses together with age, stature etc. Lung function indices were the dependent variables. Chest wall thickening was related inversely to total lung capacity (TLC) and to vital capacity (FVC) independent of the other variables; OCPA and PSO also reduced the TLC. Small opacities affected particularly Tl, Kco and exercise ventilation. Unexpectedly DTC increased FVC. Abnormalities had more effect when in the right than the left hemithorax. Thus the effects of PSO, CWT, DTC and OCPA are to a large extent independent.

## Comparison of narrow section computed tomography and chest X-ray in allergic bronchopulmonary aspergillosis

DC CURRIE, JM GOLDMAN, PJ COLE AND \*B STRICKLAND *Host Defence Unit, Cardiothoracic Institute and \*Radiology Department, Brompton Hospital, London* Plain chest radiographs (CXR) are the standard radiological method for assessing lung damage in patients with allergic bronchopulmonary aspergillosis (ABPA). Bronchography is often contraindicated because of asthma. Narrow section computed tomography (CT) scans (3 mm width slices every 10 mm in full inspiration on Elscint 2002 scanner) and postero-anterior and lateral CXRs performed in 10 patients with ABPA were reported separately. The patients all had positive skin prick tests to *Aspergillus fumigatus* and a history of flitting shadows on CXR. Eight had asthma. CT showed bronchiectasis in seven patients, highlighted its

proximal and predominantly upper lobe distribution, and clearly demonstrated the extent and severity of lung damage. CXRs in these patients were characteristic of ABPA in five and showed non-diagnostic bronchiectasis in two. Mycetomas unsuspected on CXR were seen on CT scans in two patients. CT and CXR abnormalities were minimal in three of the 10 patients. Moderate or severe bronchiectasis was demonstrated on CT in 23 of 60 lobes studied but only in 15 on CXR. Serial CT may provide a more sensitive method than CXR for monitoring the extent of lung damage in ABPA.

## The role of computed tomography (CT) in staging bronchogenic cancer

SR LARGE, N PERRY, R REZNEK, C YOUNG, A MCLEAN, R HURT, GM REES, AND SJ EDMONDSON *St. Bartholomew's Hospital, London* A prospective trial to compare CT staging of bronchogenic cancer with pathological findings in 50 consecutive patients (mean age 62 years) was undertaken between April 1985 and July 1986. It followed a recent review of the large literature of this subject describing the confusing results (Zerhouni *et al*, *Radiological Clinics N. America*, 1985;3:23). All 50 patients were thought resectable on conventional grounds and underwent CT scanning of chest and upper abdomen. These scans were examined for evidence of lymph node, chest wall, great vessel and pericardial involvement by two radiologists independently. Twenty-two patients had peripheral tumours. Thirty-five had squamous cell and only two small cell carcinomas. Thoracotomy was performed on all 50 patients and 43 had lung resections. Forty-seven had regional lymph node sampling. In the past size was the only CT criterion of lymph node involvement. In this study the CT assessment of the 129 lymph nodes sampled showed four of 59 nodes  $\leq 1$  cm (7%) to have metastatic tumour and 13 of 19  $\geq 2$  cm (68%). CT assessment of lymph nodes involved was, therefore, inaccurate. CT assessment of mediastinal invasion by central tumours was poor in the presence of lung collapse. Pulmonary artery invasion was least accurately assessed. The scan of five of the seven patients with unresectable tumours at thoracotomy showed the combination of direct mediastinal invasion by the primary mass and continuity of this with both mediastinal nodal regions reviewed.

## Diagnosis of pulmonary hypertension from radiographic estimates of pulmonary arterial size

A BUSH, H GRAY, DM DENISON *The Brompton Hospital, Fulham Road, London* Measurement of right and left

descending pulmonary artery diameters (RDPa and LDPA respectively) have been reported to provide a correct diagnosis of pulmonary hypertension in 98% of patients (*Invest Radiol*, 1981;16:95-100), but these measurements may have been biased by casual increases in lung size. We studied the chest radiographs of 50 normal subjects and 27 patients undergoing right heart catheterisation for cardiac or pulmonary vascular disease, taking account of radiological magnification as described in (*Thorax* 1986;41:158-9). After such corrections an RDPa > 16.7 mm and/or an LDPA > 16.9 mm distinguished 12 of 23 pulmonary hypertensives with no false positives. We then arbitrarily squared the diameter to exaggerate differences between them and divided that product by predicted or actual lung volume to make a crude correction for stature. The new index distinguished 19 of 23 hypertensives with one false positive when the divisor was actual lung volume; and distinguished 18 of the 23 with one false positive when predicted lung volume was the divisor. Although the unadjusted figures do not support the 98% success rate reported previously, the adjusted ones suggested a success rate of 75% is achievable.

#### **The effect of terbutaline on regional mucociliary clearance in healthy never-smoking individuals**

J MORTENSEN, S GROTH, P LANGE, E MUNCK, PG SORENSEN (SPONSORED BY D PAVIA) *Department of Clinical Physiology/Nuclear Medicine, KF Finseninstitutet, DK-2100 Copenhagen O* A method for functional imaging of the large airways (bronchoscentigraphy) is presented. It is based on a predominant deposition of a radioaerosol on the airways. To make the bronchoscentigrams (BS), 10 mCi  $^{99m}\text{Tc}$ -Albumin was nebulized (35B De Vilbiss nebulizer) and inhaled by slow inspirations (600 ml) from residual volume (RV) and exhaled by forced expirations to RV until 2000 cps were obtained by a Gamma Camera. The method was evaluated as a tool for measuring regional mucociliary clearance (MC) by studying the movement of the radioactivity in the airways of 11 never-smoking individuals on two separate days with series of BS made at five minute intervals for two hours. After having made the first BS, 125 mg terbutaline or placebo was administered as five puffs from a metered dose inhaler using a randomized, double blind crossover set up. On the day of terbutaline treatment, the segmental bronchi were no longer visible after an average of 10 minutes, the lobar bronchi after 21 minutes, and the main bronchi after 33 minutes. On the day of placebo treatment, the segmental bronchi were no longer visible after 25 minutes, the lobar bronchi after 85 minutes, and the main bronchi after 114 minutes. It is concluded that series of BS can be used to examine the regional MC, since they provide analogue pictures of the transport of the radioactivity in the airways. Terbutaline significantly increases the MC ( $p < 0.01$ ).

#### **The radiological features of the pulmonary complications of AIDS**

SJ BARTER, C ROWLAND HILL, R SHAW, AJ PINCHING *Departments of Radiology and Medicine, St. Mary's*

*Hospital, London* The rapid spread of AIDS in the UK has presented a great challenge. Pulmonary complications are frequent and were the first to be stressed in the literature, but a large British series has not been previously reported. We reviewed "blind" the radiology of 118 patients with AIDS. Pulmonary complications were common (68%), 23 patients (19%) had more than one episode of pulmonary illness. Fifty-six patients had documented *Pneumocystis carinii* pneumonia (PCP), nine with two episodes. Seven of these had normal or near normal chest radiography at presentation, and all recovered. Commonly seen were perihilar infiltrates extending from the hila which coalesced over several days to give alveolar shadowing. If this progressed to severe bilateral consolidation, the outlook was grave. Several radiological abnormalities emerged as important pointers to pathology other than PCP. Pleural effusions and lymphadenopathy were not features of PCP, implying either tuberculosis, or fungal infection. Segmental consolidation was seen most commonly with pyogenic infection (19 patients). Fourteen patients had pulmonary tuberculosis, six with atypical organisms, and six patients had changes on the chest radiograph due to metastatic Kaposi sarcoma. Early recognition of the typical features of PCP, and those abnormalities suggestive of other disease is important in order that appropriate clinical measures may be taken.

#### **Respiratory symptoms in wool textile workers**

RG LOVE, T SMITH, CO JONES, D GURR, CA SOUTAR, SEATON *Institute of Occupational Medicine, Edinburgh* Relationships between respiratory symptoms and exposure to inspirable dust, measured by personal sampling, have been investigated in 2153 workers at 15 mills manufacturing woollen cloth and carpet yarns. We designed a detailed questionnaire to establish a broad range of symptoms and their possible relationship to occupation, current and cumulative dust exposure. The questionnaire was translated into Urdu for use on employees of Asian origin. Symptom prevalences in the population were: chronic bronchitis, 9%; wheeze, 31%; grade three breathlessness, 10%; persistent rhinitis, 18%; persistent conjunctivitis, 10%; persistent chills, 2%; 10 or more nosebleeds in past year, 2%. Many of these symptoms were related to current dust exposure once age, sex, smoking habit and ethnic group had been allowed for. Nine per cent of the workforce were exposed on average to inspirable dust levels greater than 10 mg/m<sup>3</sup> the nuisance dust standard, the relative risk of symptoms at this concentration ranging from 1.3 to 1.6 times that of unexposed workers. The predicted prevalence of chronic bronchitis, for example, rose from 4% for a 40 year old European, non-smoking, male, non-process worker to 8% for the equivalent worker exposed to 25 mg/m<sup>3</sup>, the 95th percentile dust concentration. Dust control strategies can be based on these results.

#### **Unemployment and airflow limitation**

AG DAVISON, PM FAYERS, JH DARBYSHIRE, AJ NEWMAN, TAYLOR *The Brompton Hospital, London* Lung function in workers who have become unemployed

compared to those who remain in employment has not been studied. In a recent occupational lung disease study two groups of age matched non-exposed referents were randomly selected from the workforce of the same factory. The first group of 30 referents (employed workers) were employed (n = 19) or had retired at 65 years of age (n = 11). The second group of 26 referents (unemployed workers) were unemployed (n = 16) or had become unemployed and remained unemployed until 65 years of age (n = 10); the majority had been made redundant. Lung function has been compared in these two groups. The mean age ( $\pm$ SD) of the employed ( $61.9 \pm 8$  years) was not significantly different from the unemployed workers ( $63 \pm 8.4$  years)  $p > 0.5$ . The mean number of pack years ( $\pm$ SD) smoked by the employed ( $22.5 \pm 20.2$ ) was not significantly different from the unemployed ( $27.1 \pm 22$ )  $p > 0.1$ . Cotes's reference equations, with corrections for age and height, were used to calculate expected values. Means of observed minus expected ( $\pm$ SE) for FEV<sub>1</sub>, were  $-386 \pm 132$  ml in unemployed and  $23 \pm 104$  ml in employed workers ( $p < 0.05$ ), and for FEV<sub>1</sub>/FVC%  $-13.5 \pm 2.7\%$  and  $-6.4\%$   $1.6\%$  respectively ( $p < 0.02$ ). Workers who had become unemployed had evidence of airflow limitation, with significantly reduced FEV<sub>1</sub> and FEV<sub>1</sub>/FVC%, when compared with a group of employed workers.

#### The economic consequences of developing occupational asthma

DC WEIR, AS ROBERTSON, S JONES, PS BURGE *Department of Occupational Lung Disease, East Birmingham Hospital, Birmingham* Using a questionnaire, partly self administered and checked, and partly doctor administered, we have investigated the effects on income of developing occupational asthma in 34 patients (25 male, nine female). All were followed up one year or more after presentation. Diagnosis was based on positive bronchial challenge testing or work related deterioration in peak flow records. Twenty patients had lost or changed their job because of asthma. Of these five had taken early retirement, five were unemployed and 10 had changed their jobs, seven within the same company. Ten had not changed employment. Twenty-five patients claimed they had lost money because of asthma, estimates in 20 varying from £20 to £7 050 (mean £2 053) per annum, and £100 to £8 000 (mean £3 250) in total. Eight of these 20 patients had asthma due to a prescribed cause, seven had applied for DHSS compensation, six successfully. The amount awarded varied from a £300 lump sum to £900 per annum. Six patients had claimed under the Industrial Accident Scheme, and 9 begun common law claims. All but two were awaiting a decision or court hearing. Occupational asthma has significant financial effects on patients. Current compensation does not offset this.

#### A randomised trial of verapamil in addition to chemotherapy for small cell lung cancer

R MILROY, L CONNERY, S BANHAM, A HUTCHEON, D MACINTYRE, B STACK ON BEHALF OF THE WEST OF SCOTLAND LUNG CANCER GROUP *Respiratory Medicine, Royal Infirmary, Glasgow* The emergence of drug resistance is the major

cause for treatment failure in small cell lung cancer (SCLC). Both *in vitro* and *in vivo*, verapamil circumvents tumour resistance to several anti-cancer drugs used in SCLC (S Kaye, S Merry, *Cancer Chemotherapy Pharmacol.* 1985;14:96-103). A randomised multicentre trial of verapamil in addition to combination chemotherapy in limited stage SCLC is therefore being undertaken. Fifty-three patients have been entered. All receive four cycles of chemotherapy with cyclophosphamide (750 mg/m<sup>2</sup>), adriamycin (40 mg/m<sup>2</sup>) and vincristine (1.4 mg/m<sup>2</sup>) on day 1, and VP-16 (100 mg/m<sup>2</sup>) on days 1-3, repeating every 22 days. Twenty-eight patients received verapamil (480 mg/day) for a total of five days beginning two days before each treatment cycle. Verapamil treatment was generally well tolerated. Mean verapamil level attained was 617 ng/ml. Myelosuppression was similar in both arms. To date 32 patients have been re-staged. There were 5/13 (38%) complete responses in the control (chemotherapy alone) arm and 12/19 (63%) complete responses in the verapamil plus chemotherapy arm. There have been six early deaths equally distributed in both arms. Overall 14/17 patients remain in sustained remission (mean follow-up six months, maximum follow up 12 months). Preliminary results suggest verapamil may enhance the effectiveness of cytotoxic chemotherapy.

#### Lung cancer in south east Scotland: histology, stage and performance status at presentation

S CAPEWELL ON BEHALF OF THE EDINBURGH LUNG CANCER GROUP *Department of Medicine, Royal Infirmary, Edinburgh* The Edinburgh Lung Cancer Group has recorded information on 2586 lung cancer patients presenting during the four years 1981-1984; this represents the largest prospective series of unselected lung cancer patients in the UK. The cell type was known in 2117 cases. The 579 women, when compared with men, had significantly more small cell carcinoma (29% v 21%) and adenocarcinoma (18% v 11%) but less squamous carcinoma (38% v 52%). Women were also significantly younger with 79% v 61% aged under 70. Small cell carcinoma was more frequent in both women and men aged under 60 (28% v 21% aged over 60). This was not due to differences in smoking habit, only 3% were lifelong non-smokers. Six hundred and fifty-one new patients were seen in 1981, 35% were stage I, 7% stage II and 58% stage III (American Joint Committee, *Am Rev Respir Dis*, 1977;127:659). Metastases were detectable at presentation in 210/651 (32%). Staging was based on clinical examination, chest radiograph, barium swallow and biochemistry. Performance status using the Karnofsky index was strongly correlated with age ( $p < 0.001$ ) and with stage (45% of stage I  $\geq 90$  Karnofsky versus 26% of stage III,  $p < 0.001$ ). Performance status was not associated with cell type.

#### Improved prognosis for oat cell carcinoma 1976-1983: a report of the thoracic group of the Yorkshire Regional Cancer Organisation

\*CK CONNOLLY, \*\*WG JONES, \*\*\*J THOROGOOD, \*\*\*C HEAD *\*Friarage Hospital, Northallerton, North Yorkshire,*

**\*\*University Department of Radiotherapy and \*\*\*YRCO, Cookridge Hospital, Leeds** The impact of chemotherapy on survival, between the years 1976 and 1983, in all patients with histologically confirmed oat cell bronchial cancer, was assessed from Regional Cancer Registry data. Histologically confirmed cases increased from 209 (8.9%) to 308 (12.3%) and the mean ages from 60.2 to 64.1 years. Nine month survival improved from 17.7% (37 cases) to 25.0% (77 cases) ( $p=0.0024$ ), despite an unchanged median survival (89 v 88 days). Patients treated with chemotherapy showed an improved prognosis at nine months whereas untreated patients did worse. At two years this difference was diminished. Patients under the age of 60 and treated after 1979 showed the most improvement. In the years 1980 to 1983 there was no difference in survival by age group in the untreated patients but survival for patients treated with chemotherapy ( $\pm$  radiotherapy) was better than for radiotherapy alone in those aged  $< 60$ . In this period 6.5% of oat cell cancers underwent radical surgery. The two year survival was 23%. The survival after chemotherapy or no treatment was  $< 5\%$ . Chemotherapy improves prognosis in the first year, especially in the under 60's as has been shown in clinical trials. There were a few long term surgical survivors.

#### **The effect of topical corticosteroids on mast cell numbers in the nasal mucous membrane**

M VIEGAS, E GOMEZ, D GATLAND, RJ DAVIES *Academic Department of Respiratory Medicine, St. Bartholomew's Hospital, London* We have recently shown, using nasal biopsies from subjects with allergic rhinitis, that there is an increase in mast cell numbers in the nasal mucous membrane as well as a redistribution of mast cells to the epithelial layer at the height of the grass pollen season compared to mid winter. Nasal biopsies were obtained from 18 subjects with seasonal allergic rhinitis during the first week of April before the grass pollen season. In a randomized double blind manner nine subjects were allocated beclomethasone dipropionate (two puffs to each nostril twice a day) and nine subjects received placebo nasal spray starting on the 1st May for 10 weeks. Nasal biopsies were repeated in the second week of July at the height of the grass pollen season. All nasal biopsies were fixed in Carnoy's solution stained with the chloracetate esterase stain and the total mast cells counted per  $\text{mm}^3$ . The mean of the total number of mast cells in the placebo group before the onset of the season was 5237 cells per  $\text{mm}^3$  which increased to 9951 cells per  $\text{mm}^3$  at the height of the season ( $p<0.05$ ). The mean of the total number of mast cells in the group receiving beclomethasone dipropionate was 5350 cells per  $\text{mm}^3$  before the onset of the pollen season and 4253 cells per  $\text{mm}^3$  at the height of the season. The results suggest that part of the beneficial effect of topical corticosteroids in allergic rhinitis may be related to their ability to prevent the increase in mast cells induced by exposure to natural allergen.

#### **Morphometric factors associated with airflow limitation in early COAD**

\*A MCLEAN, \*D LAMB, \*\*G GOULD, \*\*P WARREN, \*\*DC FLENLEY *\*Departments of Pathology and \*\*Respiratory*

*Medicine, University of Edinburgh* In 30 patients (23M, 51-71 years; 28 smokers) we measured FEV<sub>1</sub> (3.8-1.4 l), single breath N<sub>2</sub> washout, and lung volume before lung/lobe resection. Resected lobes were inflation fixed and cut sagittally at 1 cm. Six random 2 cm blocks from each lateral two slices were embedded in glycol methacrylate, cut at 3 $\mu$ , and stained with H and E. Airway circumference, lumen area, minimal and maximal diameters were measured for all bronchioles in the 12 sections and on 2-3 proximal bronchi. We excluded the 30% most elliptical bronchioli as tangential or longitudinal cuts. Peribronchiolar/alveolar attachments were measured as mean interalveolar wall length in 10 random bronchioles in each case. Emphysema was measured microscopically as alveolar wall surface area/unit volume of lung (AWUV) (*Thorax*, 1986;41:716) and macroscopically as percentage area of the slice occupied by airspaces  $> 1$  mm. Both FEV<sub>1</sub> (% predicted;  $r = -0.06$ ,  $p=0.002$ ) and slope of phase III ( $r = +0.58$ ,  $p=0.005$ ) correlated with mean intra-alveolar attachment distance, but neither correlated with macroscopic or microscopic (AWUV) emphysema, or any measure of bronchiolar or bronchial calibre. We suggest that loss of those alveolar walls supporting bronchioles is important in causing airflow limitation.

#### **Bronchial carcinoids express epithelial and neural antigens**

\*F MOSS, \*\*LG BOBROW, \*\*\*PCL BEVERLEY, \*\*\*\*RL SOUHAMI *\*Central Middlesex Hospital, London; \*\*Department of Histopathology; \*\*\*Imperial Cancer Research Fund; \*\*\*\*Department of Oncology Faculty of Clinical Studies, University College Hospital, London* Bronchial carcinoids, relatively benign bronchial tumours, possess neuroendocrine characteristics and have been shown to express a variety of neural markers. A case report describes the co-expression of cytokeratins and neuroendocrine markers by one of these tumours (Lee *et al*, *Ultrastructural Pathology*, 9:331-336). Using an indirect immunoperoxidase method a series of eight bronchial carcinoids was studied with three monoclonal antibodies which recognise cytokeratins; three which react with three other epithelial antigens; a neural marker UJI3A, and HNKI which recognises an antigen present on natural killer cells which also has been demonstrated on a variety of epithelial and neuroendocrine neoplasms. All but one of these tumours reacted with all of the anticytokeratin monoclonal antibodies and four reacted with all six of the antiepithelial reagents. Consistent staining was seen with the neural marker on all the tumours, and most stained well with HNKI. The cell of origin of these tumours has been considered to be derived from neural crest. The staining pattern seen with these monoclonal antibodies suggests that these tumours are true epithelial neoplasms.

#### **The prognostic significance of DNA ploidy in bronchopulmonary carcinoid tumours**

\*DJ JONES, \*\*PS HASLETON, \*M MOORE *\*Department of Immunology, Paterson Institute for Cancer Research, Christie Hospital, Manchester and \*\*Department of Pathology, Wythenshawe Hospital, Manchester* DNA



aneuploidy is a recognised feature of human cancers and may be of prognostic significance. Carcinoid tumours account for 1-2% of bronchopulmonary neoplasms; they vary from histologically typical endobronchial tumours to metastasizing neuroendocrine carcinomas. In this study DNA ploidy status was determined by flow cytometry, using paraffin-embedded material obtained from 33 patients presenting from 1961-83. 15/33 were DNA diploid and 18/33 DNA aneuploid. At the time of analysis seven patients had died; six were DNA aneuploid and one DNA diploid. Survival curves were calculated by the life table method, for conventional pathological features and DNA ploidy status, and compared using the log rank test and Cox regression analysis. Variables were ranked in decreasing order of prognostic significance; 1) lymph node involvement  $p < 0.0001$ , 2) undifferentiated growth pattern ( $p = 0.002$ ), 3) necrosis ( $p = 0.006$ ), 4) nuclear pleomorphism ( $p = 0.009$ ), 5) lymphatic invasion ( $p = 0.014$ ), 6) vascular invasion ( $p = 0.019$ ), 7) DNA ploidy ( $p = 0.055$ ). These results suggest that DNA aneuploidy is associated with an aggressive clinical course, but that conventional pathological assessment is a superior predictor of prognosis.

**Histochemistry in the diagnosis of pleural biopsies**

KM KERR, D COSSAR, AS KRAJEWSKI, D LAMB *Department of Pathology, University of Edinburgh* Pleural biopsies present three common problems; differentiating (a) mesothelioma and metastatic carcinoma, (b) reactive from malignant mesothelioma, (c) fibroblasts and "spindle" mesotheliomas. Using immunoperoxidase techniques with a panel of antibodies against cytokeratins (CK and CAM 5.2), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA) and pregnancy specific B1 glycoprotein (SP1), plus alcian blue/PAS staining for epithelial mucins, 49 pleural biopsies (10 reactive, 22 mesotheliomas, 17 metastatic carcinomas), 18 resected lung adenocarcinomas and 14 peritoneal mesothelial lesions were studied. All adenocarcinomas were positive for either mucin, CEA or SP1 (more than 90% were positive for any one) Mucin and CEA were absent in benign and malignant mesothelium. Anti-SP1 gave a weak staining in only two of 22 mesotheliomas. Spindle cell mesotheliomas, but not fibroblasts, stain well with CK and better with CAM 5.2, but less well with EMA. Reports suggest that EMA stains malignant mesotheliomas but not reactive mesothelial cells. Only one of our reactive cases stained, 20% of our mesotheliomas failed to stain. We believe that using a panel of techniques it is possible to differentiate adenocarcinoma and fibroblastic proliferation from mesotheliomas but there still remains difficulty in separating mesothelioma from reactive mesothelial cell proliferation.

**Antineutrophil antibodies and renal biopsy in the diagnosis and evaluation of Wegener's granulomatosis (WG)**

\*DJ HARRISON, \*C NEARY, \*\*CG WATHEN *\*Department of Pathology, University of Edinburgh and \*\*Department of Medicine, Royal Infirmary of Edinburgh* WG is a systemic disease which usually presents to ENT or chest

specialists. In a series of 17 patients (12M:5F) we performed percutaneous renal biopsies at presentation, and in nine cases we have looked for antineutrophil antibodies, a marker of WG (van der Woude *et al, Lancet*, 1985;425). Initial chest radiographs were reported as normal in 44%, but 87% had an abnormal urinary sediment. Nasal biopsies enabled a definitive diagnosis of WG in only 50% of cases, whereas 70% of renal biopsies had a focal and segmental glomerular lesion or a crescentic glomerulonephritis. In every case but one, the combination of nasal and renal biopsies would give rise to strong suspicion of WG even though definitive features were not present. Eight of nine sera tested had IgG antineutrophil antibodies detected by immunofluorescence; the ninth case had already commenced therapy. Five out of 15 patients followed for longer than one year have died; one with normal urea at outset (1/7), and four with raised urea (4/8). We conclude that the detection of antineutrophil antibodies is an aid to the diagnosis of WG, and that renal biopsy is useful in both diagnosis and assessment of WG when performed as an elective investigation at the time of presentation.

**Macrophage and neutrophil function in asthma and their relationship to bronchial hyperresponsiveness**

C KELLY, C WARD, G BIRD, C STENTON, D HENDRICK, EH WALTERS *Newcastle General Hospital, University of Newcastle on Tyne* Bronchoalveolar lavage (BAL) of a segment of middle lobe was performed in 27 patients undergoing diagnostic bronchoscopy (16 asthmatics; 11 controls). One week earlier all patients had undergone methacholine challenge to measure PD<sub>20</sub>-FEV<sub>1</sub>. 3 x 60 ml aliquots of saline were introduced and promptly aspirated into siliconised glass at 4°C. Cells were counted and resuspended in medium 199 following centrifugation at 5 x 10<sup>5</sup> cells/ml 500 µl aliquots of cell suspension were incubated with 900 µl of 10<sup>-4</sup> M luminol or lucigenin and chemiluminescence (CL) was recorded following stimulation with 100 µl 5% latex using an LKB 1250 luminometer. Luminol-enhanced CL was used to assess neutrophil (N) activity, and lucigenin-enhanced CL to measure macrophage (M) activity. Results are expressed as CL/10<sup>3</sup> N or M.

	Luminol CL/10 <sup>3</sup> N (SEM)mV	Lucigenin CL/10 <sup>3</sup> M (SEM)mV
CONTROLS (n = 11)	0.29 (0.06)	0.025 (0.007)
ASTHMA (n = 16)	0.63 (0.08)*	0.099 (0.016)**

\*p < 0.01, \*\*p < 0.001. Unpaired t-test.

Luminol CL/10<sup>3</sup> neutrophils did not correlate with PD<sub>20</sub> (r = 0.34, p = 0.22), but there was a correlation between lucigenin CL/10<sup>3</sup> macrophages and PD<sub>20</sub> (r = 0.50, p = 0.05). This study demonstrates increased activity of both neutrophils and alveolar macrophages in asthma, and suggests that macrophage activity is particularly related to bronchial hyperresponsiveness.

**Neutrophil chemotaxis in bronchiectasis**

RA STOCKLEY, J SHAW, SL HILL, D BURNETT *Lung Immunobiochemical Research Laboratory, General*

**Hospital, Birmingham** Chronic purulent bronchiectasis is associated with the persistence of microbes and recruitment of neutrophils which fail to clear the organism and release proteolytic enzymes capable of damaging lung tissues. We have investigated several aspects of neutrophil chemotaxis in bronchiectasis using a multiple blind well microassay technique. Patient or control neutrophils were assessed for their ability to move through a two micron polycarbonate membrane on a 0.45 micron cellulose acetate membrane barrier. The number of neutrophils was obtained (five power fields  $\times$  40 magnification). There was no difference in the response of isolated neutrophils from 10 bronchiectatic patients to *N*-formyl-L-methionyl-L-phenylalanine ( $10^{-3}$  moles/litre) compared to 16 healthy subjects ( $\bar{x}$  = 76 SD  $\pm$  51.5 vs  $\bar{x}$  = 129;  $\pm$  70.9). Purulent sputum obtained from patients was markedly chemotactic for control neutrophils ( $\bar{x}$  = 140.5  $\pm$  53.2) exceeding that for mucoid sputum (53.7  $\pm$  33.2; *n* = 9). Six patients responded to a two week course of antibiotic therapy and the sputum became mucoid. This was associated with a fall in chemotactic response from 121.6;  $\pm$  75.6 to 79.3;  $\pm$  57.8 by the end of treatment (*p* < 0.05). Two weeks later the activity was even lower — 33.5  $\pm$  27.3. In contrast, response to sputum obtained from seven patients who failed to clear their secretions with treatment, remained unaltered: - 135.7  $\pm$  47.0; 147.2  $\pm$  42.5; 138.5  $\pm$  67.3. The results show that bronchiectatic patients are responding appropriately to a chemoattractant in the lung secretions though its nature remains to be clarified.

#### Protein accumulation in the lungs during ARDS: assessment of the routine use of a double isotope method

GM ROCKER, D PEARSON, DJ SHALE *Respiratory Medicine Unit, University of Nottingham; Department of Medical Physics, City Hospital, Nottingham* The adult respiratory distress syndrome (ARDS) is an increasingly recognised complication of many disorders but diagnostic criteria ignore its hallmark: - protein rich pulmonary oedema. We studied 41 patients with alveolar infiltrates of acute onset using a double isotope method to label transferrin and red blood cells *in vivo*. A protein accumulation index (PAI) was calculated for each lung. Results are based on the higher value. When 20 patients first satisfied the criteria for ARDS their mean PAI was 1.67 (1.40 SD) /1000 /min, significantly different to 21 non ARDS patients (0.67, 0.76 SD, *p* < 0.01). PAI in five of 20 ARDS criteria patients with contradictory histological evidence was 0.3 (0.37 SD) with only one patient showing significant protein accumulation. Mean PAI for the remaining 15 was 2.13 (1.32 SD) of whom 14 (93.3%) showed significant protein accumulation on first and 15 (100%) at second study. Nine of 21 (43%) non ARDS patients showed significant accumulation. On all occasions when ARDS criteria held, studies of both lungs showed significant accumulation in 53/65 (81.5%) rising to 31/34 (91.2%) if higher PAI were used. This easily performed non invasive double isotope method provides an indication of protein leak in human ARDS when both lungs are studied.

#### Reimplantation injury following lung transplantation in a rat model

PA CORRIS, \*NJ ODOM, P MCARDLE, \*CGA MCGREGOR *Department of Respiratory Medicine and \*University Department of Surgery, Cardiothoracic Centre, Freeman Hospital, Newcastle Upon Tyne* Distant procurement of organs for transplantation requires satisfactory preservation to reduce injury during ischaemia and the initial phase of reperfusion. We have studied reimplantation injury following unilateral lung transplantation in isogenic rats. The heart and lungs were removed en bloc from donor rats and preserved at 4°C. After five hours the left lung was transplanted into a recipient. Radiographic and histological evidence of pulmonary oedema in the transplanted lung at 24 hours confirmed the presence of pulmonary vascular injury and this was supported by comparison of wet/dry lung weights between non transplanted and transplanted lungs in 11 rats sacrificed at 24 hours (mean (SD) 4.5 (0.4) versus 5.0 (0.7) *p* < 0.001). In five further rats we performed bronchoalveolar lavage of both non transplanted and transplanted lungs at 24 hour post transplant. Results (mean (SD) were compared with five normal controls.

	Cells $\times 10^9/l$	Neut %	Lymph %	Macro %
CONTROL	0.06 (0.03)	0.8 (0.8)	8.6 (4.8)	90.6 (5.0)
NON TRANSPLANT	0.11 (0.06)	2.8 (3.1)	9.2 (8.5)	86.0 (13)
TRANSPLANT	0.28 (0.1)	76.8 (13)	1.4 (1.1)	22.2 (14)

We conclude that reimplantation injury of the lung is characterised by pulmonary sequestration of neutrophils and these cells may play a primary role in mediating vascular damage.

#### Acute systemic and local inflammatory responses to chrysotile asbestos

MD ROBERTSON, K DONALDSON, D BROWN, A SEATON *Institute of Occupational Medicine, Edinburgh* The inhalation of asbestos is associated with alveolar inflammation and interstitial fibrosis. As acute inflammatory responses result in elevated levels of acute phase plasma proteins we have measured serum amyloid-P-component (SAP) in the serum of C57B1/6 mice, for up to four days, following intraperitoneal injection of UICC chrysotile asbestos (500  $\mu$ g). For comparison the relatively inactive dust, titanium dioxide, and a saline control were used. In addition, the influx of inflammatory leucocytes into the peritoneal cavity was monitored. Exposure to chrysotile asbestos resulted in a rapid increase in serum levels of SAP to 373 mg/l by 12 hours rising to 434 mg/l at 24 hours and falling to 159 mg/l by 96 hours (saline control 25-100 mg/l). These results correlate with the local cellular response to chrysotile asbestos where a vast increase in cell numbers of 41(4)(number of cells  $\times 10^6$ , mean (SD)) comprising 52% polymorphonuclear leucocytes (PMN) was found by 48 hours falling to 19.8 (4), 20% PMN, by 96 hours (saline control 4(1), 0% PMN). By contrast exposure to titanium dioxide caused no significant changes even although the phagocytic cells were dust laden. These results suggested that chrysotile asbestos provokes a rapid systemic as well as

local inflammatory response which may be an important contributory factor towards its pathogenicity.

#### The effect of complement on the killing of *Aspergillus fumigatus* by lung macrophages

MD ROBERTSON, \*KM KERR, A SEATON *Institute of Occupational Medicine, Edinburgh; \*Department of Pathology University of Edinburgh* The potential of the fungus *Aspergillus fumigatus* to act as an opportunistic pathogen may be related to its ability to resist the host defence network. We have assessed the capacity of lung macrophages, from humans and PVG rats, to kill spores of *A. fumigatus* and those of the non-pathogenic fungus *Penicillium ochrochloron*. The spores were opsonised with either serum or serum heat inactivated to remove heat labile complement components. Spores of *A. fumigatus* opsonised in serum were significantly more resistant to killing by human lung macrophages than similarly opsonised spores of *P. ochrochloron*: results expressed as mean % killed (SEM), *A. fumigatus* 25.8 (3.28), *P. ochrochloron* 38.1 (3.67), ( $p < 0.025$ ); a similar difference was found using rat lung macrophages, *A. fumigatus* 17.5 (2.5), *P. ochrochloron* 28.1 (4.26). Opsonisation in complement-depleted serum significantly increased the ability of human lung macrophages to kill spores of *A. fumigatus* by 87% to 48.3 (3.85), ( $p < 0.0001$ ) and by 40% with *P. ochrochloron* 53.5 (4.96), ( $p < 0.005$ ). These studies confirm that *A. fumigatus* spores are more resistant to host defences when compared with a non-pathogenic fungus. However, in the absence of complement, macrophages can kill spores of *A. fumigatus* and *P. ochrochloron* to a similar extent. Further research into the effects of complement on the interaction of *A. fumigatus* and phagocytic cells is warranted.

#### The degradation of lung basement membrane and extracellular matrix components by bronchoalveolar cells *in vitro*

GM BROWN, K DONALDSON, A SEATON *Institute of Occupational Medicine, Edinburgh* We have investigated the ability of lung-derived inflammatory cells to damage individual components of the extracellular matrix *in vitro*. Cells were obtained by bronchoalveolar lavage from control rat lung (>95% macrophages) and following intratracheal instillation of *C. parvum* (~90% polymorphonuclear cells). Three purified matrix components, collagen, laminin and fibronectin were labelled with iodine-125 and adhered to the bottom of micro-titre wells. Bronchoalveolar leucocytes were cultured on these matrices and degradation assessed by measuring counts of radio-labelled protein released into the medium; this activity was similar with each matrix. In three experiments using the collagen matrix, *C. parvum*-elicited inflammatory cells released significantly more counts 2319 (303) (mean (SEM)) than control macrophages 999 (119) ( $p < 0.005$ ). In one further experiment the counts released by inflammatory cells 1142 (51) were significantly reduced ( $p < 0.005$ ) by the specific protease inhibitors, soybean trypsin inhibitor 659 (57) and  $\alpha_1$  protease inhibitor 593

(39). These results indicate that the release of proteolytic enzymes from inflammatory cells in the alveoli can damage basement membrane and other extracellular matrix components. Such proteolytic damage may occur in any of the diseases where persistent inflammation results in permanent impairment of the alveolar structure.

#### Respiratory syncytial virus (RSV) specific helper T-cell function in mice primed with recombinant vaccinia viruses expressing single RSV proteins

PJM OPENSHAW, BA ASKONAS *National Institute for Medical Research, Mill Hill, London* Respiratory syncytial virus (RSV) is a common respiratory pathogen of veterinary and medical importance. In human infants lymphocytic bronchiolitis resulting from RSV has significant mortality, and is associated with wheezing in later life. There is no effective vaccine for human use. Trials of formalin inactivated RSV in children lead to more severe bronchiolitis during subsequent natural infection, with an 80% hospitalisation rate. Little is known about the protein specificities of the cellular immune responses to RSV. Balb/c mice were primed with RSV intranasally, or with viruses expressing the major surface glycoprotein (G vac), fusion protein (F vac) or nucleoprotein (N vac) by intraperitoneal injection. After six weeks splenocytes were co-cultured *in vitro* with normal splenocytes irradiated and infected with RSV, or similar uninfected cells. After 72 hours, supernatants were tested for IL-2 by CTLL cell thymidine uptake. RSV-specific IL-2 release was present from splenocytes from mice primed with RSV, N vac or F vac but not G vac or unprimed mice. Since G vac induces RSV-specific serum antibody, G protein appears to function as a T-independent antigen. This may contribute to the poor protection from reinfection which is a feature of RSV disease.

#### Lavage immunocytology in immunosuppressed patients with pneumonitis

H MILBURN, RM DU BOIS, LW POULTER *Royal Free Hospital School of Medicine and Departments of Thoracic Medicine and Immunology* Many immunosuppressed patients develop pneumonitis. Studies of the cell populations in bronchoalveolar lavage from such patients have been undertaken to determine whether the pneumonitis is associated with local immune reactivity. Immunocytology using monoclonal antibodies directed at subsets of lymphocytes and macrophages has been performed on cytospin preparations of lavage from bone marrow transplant patients presenting with pneumonitis. Further studies investigated the expression of activation markers on the T lymphocytes. The results reveal that no consistent differences in numbers of T4+ lymphocytes or B cells occur in the BAL of immunosuppressed patients; however high proportions of T8+ lymphocytes are present many of which express activation markers. This phenomenon is reflected in the T4:T8 ratio, which is consistently 1:1 or lower. As regards the macrophage populations, cells with the phenotype of mature macrophages are present but a significant population of the lavage express the phenotype

of immature cells. No consistent variation in the proportions of dendritic cells was noted as compared to levels in normal lavage. These observations are in sharp contrast to those obtained from pneumonitis patients not immunosuppressed and may reflect local immune dysfunction.

#### **Autologous serum impairs extracellular release of H<sub>2</sub>O<sub>2</sub> from alveolar macrophages of patients with bronchial carcinoma**

NE WOOD, JF SMYTH, GK CROMPTON, AP GREENING *Respiratory Unit, Northern General Hospital, Edinburgh and Department of Clinical Oncology, University of Edinburgh* Macrophages can exert tumouricidal effects via extracellular release of reactive oxygen species. We have examined the release of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) from alveolar macrophages (AM) from patients with bronchial carcinoma (Br.Ca.). AM were obtained by bronchoalveolar lavage from 17 untreated bronchial carcinoma, and 19 control, patients. The cells were purified by adherence and cultured overnight in medium 199 supplemented by 5% foetal calf serum (FCS) or 5% autologous serum (AS). H<sub>2</sub>O<sub>2</sub> release was measured fluorimetrically following stimulation by phorbol ester. There were no differences in the release of H<sub>2</sub>O<sub>2</sub> from AM of patients or controls when the cells were cultured in FCS (mean (SEM) nmol H<sub>2</sub>O<sub>2</sub>/10<sup>6</sup> cells/h: Br.Ca. 12.1 (1.4), controls 10.5 (1.8),  $p=0.47$ ). Autologous serum had no influence on H<sub>2</sub>O<sub>2</sub> release from control AM (FCS 10.5 (1.8); AS 9.2 (1.8)) but for AM from bronchial carcinoma patients caused substantial impairment (FCS 12.1 (1.4); AS 7.6 (1.1);  $p<0.01$ ). Preliminary data comparing the effects of different concentrations of FCS and AS suggest that the inhibitory effect of AS on AM H<sub>2</sub>O<sub>2</sub> release is "dose-dependent". We conclude that serum factor(s) can impair AM oxidative functions in patients with bronchial carcinoma.

#### **Pulmonary endothelial cell dysfunction and bleomycin lung injury in rabbits**

RR JEFFREY, MR JOHNSTON, HS STANBROOK (SPONSORED BY EWJ CAMERON) *Department of Cardiothoracic Surgery, Royal Infirmary, Edinburgh and University of Colorado Health Sciences Centre, Denver, USA* We have previously shown that in rabbits following four weeks of Bleomycin (BLM) administration, pulmonary endothelial cell function (ECF) as determined by uptake of 5-hydroxytryptamine (5HT) is reduced and total pulmonary resistance (TPR) is increased. We questioned whether ECF becomes disturbed before other indicators of lung injury are altered and studied two groups of rabbits; one group received BLM (5 mg/kg three times weekly), the other (control) received saline. ECF was measured using a multiple indicator dilution technique in which uptake of 5HT in a single passage through the lung was determined. TPR, extra-vascular lung water and wet to dry weight ratios were also determined. After two weeks there was no difference between groups in any measured index. By three weeks BLM-treated animals showed a reduction in the uptake of 5HT;  $35.0 \pm 4.8\%$  (SEM)

compared to  $49.4 \pm 6.0\%$  in control animals ( $p<0.05$ ) but no difference in other indices. After four weeks TPR was elevated from  $18.6 \pm 4.1$  to  $35.1 \pm 4.7$  mm Hg/l/min ( $p<0.02$ ); there were histological changes and uptake of 5HT was reduced from  $57.7 \pm 8.2\%$  to  $25.4 \pm 5.5\%$  ( $p<0.01$ ). We conclude that in BLM-induced injury, ECF is disturbed before other indices of lung injury are altered.

#### **Clearance of instilled surfactant lipid from the lungs of unanaesthetised sheep: lipids are differentially transported by non-lymphatic pathways**

PA DAVIS, RA GUNTHER, CE CROSS *The Departments of Internal Medicine, Surgery and Physiology, University of California, Davis, USA* The routes employed by the lung to dispose of instilled exogenous surfactant lipid components were examined using the sheep chronic lung lymph fistula preparation. Small vesicles of radiolabelled dipalmitoyl phosphatidyl choline (DPPC) either alone or with radiolabelled cholesterol (CHOL), were instilled intratracheally and samples of lung lymph and plasma were collected at 60 minute intervals for 12 hours. At any time point, the total amounts of either labelled DPPC or CHOL that appeared in lung lymph were a small fraction ( $<0.5\%$ ) of their respective amounts in plasma. Labelled DPPC, as DPPC alone or as DPPC/CHOL (2-1 molar ratio), appeared simultaneously in plasma and lymph and displayed the same time course of appearance irrespective of vesicle composition. CHOL appearance was also simultaneous in both plasma and lymph but was distinctly slower than that of DPPC. The time difference noted between the appearance of labelled DPPC and CHOL in lymph and plasma indicate that the lipid components of the instilled surfactant lipid component vesicles appear to be handled differentially during their transport from the lung. Further, the data obtained demonstrate that the lung interstitial space, as reflected by sampling the lung lymph, does not appear to be involved in the transport of exogenously administered lipid from the lung.

#### **Surfactant from rabbit, pig and human lungs suppresses proliferation of peripheral blood lymphocytes**

ML WILSHER, DA HUGHES, PL HASLAM *Cell Biology Unit, Cardiothoracic Institute, London* Although the normal lung inhales a multitude of potential allergens with each breath, the cells in the fluid lining the alveolus do not mount an immune reaction. Canine surface active material is immunosuppressive (*J Immunol* 1980;122:1063), and we have shown similar immunosuppressive properties with surfactant from rabbit, pig and normal human lungs. Bronchoalveolar lavage (BAL) was performed and the supernatant lyophilised and reconstituted. This was added to human peripheral blood lymphocytes in the presence of suboptimal, optimal and supraoptimal concentrations of phytohaemagglutinin (PHA). Surfactant, (0.25 mg/ml w/v) from pigs was highly suppressive at optimal ( $p<0.02$ ) and supraoptimal ( $p<0.02$ ) concentrations, and the rabbit at the supraoptimal concentration ( $p<0.002$ ). The human lyophilised preparation was not suppressive at this dose. These effects were not due to cell toxicity as checked by



trypan blue exclusion. Dose response studies using pig and rabbit preparations confirmed dose dependent suppression. Human and pig BAL were further purified using methanol/chloroform extraction. The protein free lipids from both proved highly immunosuppressive ( $p < 0.002$ ,  $p < 0.002$ ) at optimal concentrations of PHA; once again the pig lipids showed a greater degree of suppression. We conclude that surfactant from rabbit, pig and human lungs is immunosuppressive and that this property is due to the lipid component.

#### Markers of collagen metabolism in BAL fluid from patients with sarcoidosis

CM O'CONNOR, C POWER, K WARD, MX FITZGERALD *Department of Medicine, University College, Dublin and St. Vincent's Hospital, Dublin* Collagenase and procollagen-III-peptide (PCP) have been shown to be elevated in bronchoalveolar (BAL) fluids in fibrosing lung diseases (JE Gadek *et al*, *N Engl J Med*, 1979;301:737 and RE Low *et al*, *Lab Invest* 1983;48:755). To determine whether these markers reflect disease progression in sarcoidosis, we analysed BAL fluids from 25 sarcoid patients for both collagenase and PCP. Elevated levels of PCP were found in 14 of the 25 patients and elevated collagenase in 10. There was no correlation between BAL levels of the two markers. Only three patients displayed elevated PCP and collagenase levels. Patients with elevated lavage PCP also displayed higher levels of BAL fibronectin (Fbn) and ACE ( $p < 0.01$ ) compared to those with normal PCP levels. By contrast, patients with BAL collagenase displayed lower levels of lavage Fbn and lower T-cell Helper/Suppressor Ratios ( $p < 0.05$ ) compared to those without collagenase. Using pulmonary function tests to assess functional deterioration, eight of the 10 patients (80%) with BAL collagenase deteriorated over the period studied compared to only six (40%) of those without BAL collagenase. By contrast, 57% of patients with high BAL PCP levels and 55% of patients with normal BAL PCP deteriorated. These results suggests that BAL collagenase may be more useful than PCP in reflecting disease progression.

#### Peripheral neuropathy in chronic obstructive pulmonary disease (COPD)

G LEREBOURS, J SENANT, N MOORE, G OZENNE, PH DAVID, G NOUVET (SPONSORED BY P HOWARD) *C.H.R.U. de Rouen, 76031 Rouen Cedex, France* Eighty-nine patients with COPD (15 women, 74 men, mean (SD) age 62.5 (11.7) years, duration of COPD 16.8 (10.2) years, duration of documented hypoxia 6.7 (3.8) years (from 30 cases),  $P_{aO_2}$  8.2 (1.2) kPa  $P_{aCO_2}$  6.1 (0.9) kPa, FEV<sub>1</sub> 1003 (303) mL, VC 2396 (624) mL) having no other known cause of peripheral nerve disease were examined for peripheral neuropathy. Peroneal nerve motor conduction velocity (MCV), median nerve sensory conduction velocity (SCV), and median nerve sensory potential amplitude (SPA) were measured. None of the patients spontaneously complained of symptoms suggestive of peripheral neuropathy, though 7 (7.8%) had overt clinical signs of peripheral neuropathy. Mean MCV

was 43.6 (5.6) m/sec, mean SCV 39.2 (4.6) m/sec, mean SPA 13.4 (7.4)  $\mu$ V. Thirty-one patients had one abnormal measure (17 MCV, 11 SCV and three SPA), 21 had two abnormal measures, and in four patients all three measures were abnormal. Overall, 63% of the patients had at least one abnormal measure, and 28% had two or three abnormal measures. There was no significant correlation between tobacco or alcohol intake, age, blood gases or lung function tests, and the electrophysiological measures in our patients. Our results set the frequency of subclinical peripheral neuropathy in patients with COPD at 63%. This estimate could be on the low side, since only two nerves were explored, and alterations limited to nerves other than those explored could have escaped detection.

#### Increased incidence of peripheral neuropathies in patients with hypoxic and chronic obstructive lung diseases

\*D NOWAK, \*\*W EICKHOFF, \*\*G PFEIFFER, \*\*K KUNZE, \*H MAGNUSSEN SPONSORED BY TJH CLARK *\*Krankenhaus Großhansdorf, Zentrum für Pneumologie und Thoraxchirurgie, 2070 Großhansdorf, FRG; \*\*Neurologische Universitätsklinik 2000 Hamburg 20, FRG* In patients with severe chronic obstructive lung disease (COLD), peripheral neuropathies (PN) can be observed which are not attributable to known risk factors (e.g. diabetes, heavy alcohol intake, use of neurotoxic drugs etc.). To better establish chronic hypoxemia as a risk factor for the development of PN, we studied lung function, blood gases, clinical signs of PN and neurophysiological function in 30 patients with COLD without known risk factors for PN. Mean (SD) age was 62 (13) years, with an average duration of the disease of 12 (8) years. Mean FEV<sub>1</sub>/VC was 41 (14) %, mean arterial  $P_{O_2}$  was 59 (9) torr. At least two clinical PN symptoms were found in half of the patients, and two thirds of the patients showed EMG alterations in at least two muscles studied. Conduction velocities of sensory nerves were lowered in one quarter of the patients, whereas motored conduction velocity was impaired in two patients only. These data show that in our patients PN occurred more often than expected from reference values. Chronic hypoxemia with impaired oxygen delivery to peripheral nerves or effects of long term treatment may be factors responsible for these findings.

#### Blood gas changes following fiberoptic bronchoscopy in intensive care

AG DAVISON, RM DU BOIS, SW CLARKE *Royal Free Hospital, London* Blood gas changes following bronchoscopy have usually been studied in patients having routine bronchoscopy. We have studied these changes in 23 severely ill patients being ventilated using IPPV. The indications for bronchoscopy were undiagnosed pneumonia in 14, lobar collapse in eight, aspiration of foreign body in one. Ventilation settings remained constant for 30 minutes before and during bronchoscopy. Fiberoptic bronchoscopes with an external diameter of 4.9 mm to 5.9 mm were used. A Portex fiberoptic bronchoscope swivel connector was used attached to a cuffed Portex, endo or nasal tracheal or tracheostomy tube. The internal diameter

(ID) of these were 9 mm in eight cases, 8 mm in 10 cases 7.5 mm in two cases and 7 mm in three cases. Blood gases were measured immediately before and after bronchoscopy. The mean  $F_{iO_2}$  was  $0.52 \pm 0.2$ . The mean  $P_{aO_2}$  before bronchoscopy was  $13.4 \pm 7$  kPa, with a mean fall of  $-0.9 \pm 2.25$  following bronchoscopy (NS). The change in  $P_{aO_2}$  after bronchoscopy ranged from  $+5.3$  kPa, where collapse was reversed, to  $-5.1$  kPa. The mean  $P_{aO_2}$  fell by 3.4 kPa in the five patients who had tracheal tubes with internal diameters of 7.5 mm or less; three had substantial falls of 5.1, 5.1 and 3.4 kPa. Bronchoalveolar lavage was performed in eight, and the mean fall in  $P_{aO_2}$  was  $1.4 \pm 2$  kPa (NS). There was a significant rise in the mean  $P_{aCO_2}$  in the 23 patients of  $0.57 \pm 1.12$  kPa. Variable changes in blood gases occur following bronchoscopy through tracheal tubes in patients ventilated using IPPV; substantial falls in  $P_{aO_2}$  may occur using small tracheal tubes (ID < 7.5 mm).

#### **Ambulatory monitoring in COPD patients using portable oxymeters**

C BRAMBILLA, P LEVY, B LEPAULLE, M COLONNA, F BLANC-JOUVAN, C BERARD, JP HERAIL, B PARAMELLE (SPONSORED BY P HOWARD) *Department of Lung Disease, Pavillon D, C.H.R.G., B.P. 217X, 38043 Grenoble Cedex, France* Transcutaneous oxygen saturation ( $StcO_2$ ) measurement is a reliable method to monitor arterial oxygenation level. New technology for the transducer and the digital output process make this technique easier to apply. We performed  $StcO_2$  continuous recordings using portable ear or finger oxymeters. COPD patients with slight, moderate or severe hypoxemia were studied in conditions similar to their daily routine activities. We confirmed the validity of  $StcO_2$  measurements compared with blood gases (Biox 3700  $n=100$ ,  $r=0.88$ ; Biox IV A  $n=100$ ,  $r=0.80$ ). The Biox 3700 4.2 kg, eight hours internal memory) was used for sleep studies in the hospital and at the patients home:  $n=33$ , mean saturation breathing room air was:  $StcO_2$   $88 \pm 3.69\%$  and breathing low flow oxygen:  $StcO_2$   $93 \pm 2.55\%$  ( $p<0.001$ ). Using this apparatus, eight hours daytime studies were performed during patient activities (walking, sitting, eating). Using Biox IV A (3.8 kg), effort studies adapted to these patient's conditions were realised: 12 minutes walking test and four minutes stair climbing test, with or without oxygen. We found significant desaturations during exercise and the results for the mean saturation exhibited the correction with low flow oxygen ( $n=20$  walking test:  $StcO_2$  was when breathing air 88%, vs 93% when breathing oxygen,  $p<0.001$ , climbing stairs:  $StcO_2=87\%$  vs 92%,  $p<0.001$ ). These monitoring techniques appeared useful in adapting an oxygen therapy program to a patient, not only at rest but also in daily life activity.

#### **The Ohmeda 3700 pulse oximeter: evaluation and use as a screening device for sleep hypoxaemia**

ARH WARLEY, JR STRADLING, J MITCHELL *The Osler Chest Unit, Churchill Hospital, Oxford* The Ohmeda 3700 is a new portable pulse oximeter. It stores the lowest  $SaO_2$  seen in each 12 seconds to memory for eight hours. It should

therefore be particularly suitable as a screening device for breathing disorders during sleep. Sixty-five comparisons with arterial samples using the three different probes showed good correlation ( $r=0.98$ , 0.96 and 0.94 for flex, finger and ear probes respectively). The response times of the 3700 were similar to the HP-47201A and Biox 2A oximeters. A pulsatile signal that is inadequate for accurate estimation of  $SaO_2$  (reduced arterial supply) activates an alarm and no data are stored. We have found that nearly all inaccurate readings are thus rejected but movements of the probe, simulating a pulse, can cancel this alarm. This rarely happens and simultaneous recordings overnight from opposite hands are always comparable. Computer simulation showed that the 12 second sampling algorithm was capable of reproducing the original signal as long as the cycle length of  $SaO_2$  oscillations was greater than 35 seconds, which would be sufficient for all cases of sleep apnoea seen in this department to date. In conclusion, the Ohmeda 3700 measures  $SaO_2$  accurately, it is unlikely to record artefacts and saves an adequate version of overnight  $SaO_2$  values for later inspection and analysis.

#### **An oxygen conservation device in patients with cor pulmonale: an unsustained effect?**

TW EVANS, JC WATERHOUSE, AJ SUGGET, P HOWARD *Academic Division of Medicine, University of Sheffield* Patients with hypoxaemia secondary to chronic obstructive pulmonary disease (COPD) are frequently prescribed oxygen therapy for short and long term domiciliary use. Oxygen administered via nasal cannulae incorporating a small collapsible reservoir (Oxymizer, Chad Therapeutics Inc. Ca. USA) improves transcutaneous oxygen tensions over a six minute study when compared to standard nasal cannulae, (*Thorax* 1985;40:817). We assessed the effects of this device on arterial oxygen ( $PaO_2$ ) tensions over 60 minutes in 12 patients with severe hypoxaemia ( $6.29 \pm 1.0$  kPa, mean  $\pm$  SD) and hypercapnia ( $7.46 \pm 1.24$  kPa) already taking domiciliary oxygen for at least 15 hours per day. A radial artery cannula was inserted and baseline gas tensions measured. Oxygen was then administered using standard nasal cannulae and further gas tension measured at 15 minute intervals for one hour. Patients were then changed to the "Oxymizer" and after 30 minutes equilibration arterial gas analysis performed every 15 minutes for a further 60 minutes. Mean  $PaO_2$  for the group as a whole increased on the Oxymizer by  $1.09 \pm 0.7$  kPa ( $p<0.001$ ), but  $PaO_2$  measured after 45 minutes on the Oxymizer was significantly greater than that measured after 90 minutes. Two patients showed a significant rise in  $PaO_2$  using the Oxymizer, although there was no change for the group as a whole. The Oxymizer device increases  $PaO_2$  in patients with severe hypoxaemia but can increase  $P_{aCO_2}$ . The effect may be unsustained.

#### **The effect of nocturnal hypoxaemia on survival of patients with chronic airways obstruction**

JR STRADLING, WOCM COOKSON, ARH WARLEY, DJ LANE *The Osler Chest Unit, Churchill Hospital, Oxford* Forty-two

men with chronic airway obstruction (CAWO) were assessed between 1979-80 with full lung function tests, estimation of red cell mass (RCM), blood gas estimations and overnight oximetry. Overnight  $\text{Sao}_2$ , both mean falls and biggest falls, correlated with daytime  $\text{Sao}_2$  ( $r=0.87$  and  $0.67$  respectively, *Clin Sci* 1983;64:213). We have now asked 'did the variability in nocturnal hypoxaemia from patient to patient affect their subsequent survival?'. Forty-one have been followed since then, and 27 (66%) have died. The median survival was 38 months. Survival was not significantly related to age, obesity index, A-a oxygen gradient, FEV<sub>1</sub>, RCM or transfer factor. There was however a strong relationship between daytime  $\text{PaO}_2$  (or  $\text{Sao}_2$ ) and survival ( $\text{PaO}_2 > 7.3$  kPa median survival = 65 mths,  $< 7.35$  kPa = 23 mths,  $p=0.005$ ), and between daytime  $\text{Paco}_2$  and survival ( $\text{Paco}_2 < 6.2$  kPa median survival  $> 75$  mths,  $\text{Paco}_2 > 6.2$  kPa = 24 mths,  $P=0.005$ ). There was no relationship between the variability in either the mean or maximal drop in nocturnal oxygen saturation and survival. This study indicates that nocturnal hypoxaemia in patients with CAWO predicts survival no better than daytime hypoxaemia and hypercapnia alone, which do relate strongly to survival.

#### Do sleep studies contribute to the clinical management of chronic bronchitics?

JJ CONNAUGHTON, JR CATTERALL, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* Many physicians in Europe and North America advocate studies of breathing and oxygenation during sleep in patients with chronic bronchitis and emphysema (CB and E), particularly to diagnose "excess nocturnal hypoxaemia" and to identify unsuspected cases of the sleep apnoea syndrome. We have therefore studied the breathing and oxygenation traces obtained in 56 patients with severe CB and E (34M, 22F, FEV<sub>1</sub> 0.4-1.2 l, age 38-73) to determine: 1) The frequency of co-existing unsuspected sleep apnoea syndrome. 2) Whether excess nocturnal hypoxaemia affected survival over 3-8 years follow-up. We defined excess nocturnal hypoxaemia as occurring in patients who were more hypoxic at night than predicted from the linear relationship found for these patients between oxygen saturation when awake and the lowest oxygen saturation recorded during sleep ( $r=0.73$ ,  $p<0.001$ ). 1) Only one patient had more than 15 apnoeas/hour of sleep. He was an obese somnolent snorer in whom the diagnosis was strongly suspected on history. 2) There was no correlation between survival and excess nocturnal hypoxaemia, actuarial survival curves showing no effect of excess hypoxia at any stage. Survival was significantly correlated with sex (women dying significantly more rapidly than men) and negatively with VC% predicted and expiratory reserve volume. We conclude that clinical sleep studies in CB and E detect neither unsuspected sleep apnoea nor clinically important "excess hypoxaemia" and are thus not indicated in routine management.

#### Efficacy of drug treatment in sleep hypopnoea syndrome

KF WHYTE, GA GOULD, GB RHIND, H JAPPY, NJ DOUGLAS *Department of Respiratory Medicine and Rayne Laboratory, City Hospital, Edinburgh* Most studies of drugs in treating sleep apnoea have centered on their effects on apnoea/hypopnoeas rather than symptoms. As the primary aim is to reduce symptoms the balance between symptomatic relief and side effects is important. Thus, in a double blind randomised crossover study we have examined the effects of two weeks therapy with protriptyline (P) (20 mg nocte), acetazolamide (A) (250 mgs Q.D.S.) and placebo on not only breathing and oxygenation but also symptoms. We studied seven patients (6M, 34-64y, 124-209% ideal wt) with the sleep hypopnoea syndrome. Patients were restudied after two weeks therapy. Symptoms and side effects were assessed by a detailed questionnaire using visual analogue scales. Two patients had minor side effects on placebo. (A) caused barely tolerable paraesthesia in six of seven patients, and only one patient's symptoms improved, although there was a trend to fewer hypopnoeas (placebo  $39 \pm 31$  (SD); A  $15 \pm 19$ /hour). All seven patients had major anti-cholinergic side effects with P but two out of seven reported improved symptoms with marked improvement in sleep quality and somnolence but only slight falls in hypopnoea indices ( $90 \rightarrow 64$ ;  $39 \rightarrow 20$ /hour). Overall P only reduced hypopnoeas from  $39 \pm 31$  to  $31 \pm 24$ /hour.

#### The effect of protriptyline on asphyxial and hypercapnic ventilatory response in normal subjects

AK SIMONDS, N CARROLL, NA SAUNDERS, MA BRANTHWAITE *Brompton Hospital, London* The stimulant tricyclic agent protriptyline diminishes nocturnal desaturation in patients with obstructive sleep apnoea and nocturnal hypoventilation secondary to neuromuscular and restrictive chest wall disorders. The improvement in nocturnal oxygenation is correlated with a reduction in REM sleep-associated apnoeic and hypopnoeic episodes but an independent action on asphyxial and hypercapnic ventilatory response has not been excluded. This was investigated by double blind crossover trial in seven normal subjects (3M, 4F; mean age 36.1 years). Each subject received in random order placebo, 10 mg and 20 mg protriptyline daily for two weeks. Measurements of asphyxial hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) were made before treatment, six-eight hours after the first dose of each phase and after two weeks treatment. The position of the HVR and HCVR slopes was established by calculating minute ventilation at  $\text{Sao}_2$  95% (V95) and  $\text{Pco}_2$  55 mm Hg (V55), respectively. Mean HVR and HCVR following 10 and 20 mg protriptyline did not differ significantly from measurements on placebo for the single dose study or after two weeks. V95 and V55 were unaltered. We conclude that the beneficial effect of protriptyline in sleep disordered breathing is unlikely to be mediated by augmentation of ventilatory drive.

### Obstructive sleep apnoea following topical oropharyngeal anaesthesia in heavy snorers

GA CHADWICK, P CROWLEY, R O'REGAN, MX FITZGERALD, WT MCNICHOLAS *Departments of Respiratory Medicine and Physiology, University College and St. Vincent's Hospital, Dublin, Ireland* We have previously shown in normal subjects that oropharyngeal anaesthesia (OPA) promotes obstructive apnoeas and hypopnoeas (OAH) during sleep (*Am Rev Resp Dis* 1985;131:A302), implying a role for upper airway reflexes in maintaining oropharyngeal patency during sleep. We sought a similar phenomenon in heavy snorers. After an acclimatisation night each of seven otherwise asymptomatic heavy snorers (age 37(4.3) years (mean(SEM))) underwent two overnight sleep studies in random order: a control study (C) and an anaesthesia study (A) in which topical OPA was induced using 10% lignocaine and 0.25% bupivacaine. Respiratory movements were measured using inductance plethysmography. OAHs rose from 116(43) during C to 178(56) during A ( $p < 0.01$ ). Central apnoeas and hypopnoeas were unchanged (3.8(2) vs 5.1(2.1)). Two subjects who had few OAHs during C (1 and 13) developed frank obstructive sleep apnoea (OSA) during A (43 and 82 OAHs). Sleep stage distribution, the duration of OAHs and the degree of oxyhaemoglobin desaturation measured by ear oximetry were unchanged between the two studies. These data indicate that defective upper airway reflexes may be important in the pathophysiology of OSA, particularly in the initiation of obstructive apnoea.

### Synchronised video polysomnography

CJ GRIFFITHS, BG COOPER, GJ GIBSON *Departments of Medical Physics and Respiratory Medicine, Freeman Hospital, Newcastle Upon Tyne* Nocturnal supervision of patients with suspected sleep apnoea is labour intensive and inconvenient. Simpler screening methods may not allow confident interpretation of events. We have therefore developed a system for display of analogue signals (flow, chest wall motion, oxygen saturation, EEG, EOG) synchronised with a video recording. A low light camera views the patient together with a clock and the warning lights of an ear oximeter. The simultaneously recorded analogue signals are added to the black and white video image as coloured traces scrolling across the screen. Long time constant AC coupling (22s) is used to avoid offset problems. Synchronization and display are achieved with an "analogue to video" convertor and mixer originally designed to display urodynamic electrical and radiographic signals (CJ Griffiths, PD Ramsden, *Proc International Continence Soc* 1985;p375). The combined signal is recorded on a VHS cassette and a microphone records snoring and other sounds. Oxygen saturation and flow are also sampled by a microprocessor-controlled datalogger (1 Hz) for subsequent plotting against time. The video recording is examined by replaying the tape in fast search mode ( $\times 10$ ) or by using the record of  $SaO_2$  to identify periods of interest. Using this system correct positioning of probes and electrodes can be confirmed, the patient's sleeping position can be viewed and sound aids recognition of events. A video monitor at the nurses' station allows

occasional observation and repositioning of displaced sensors.

### Carotid body enlargement in response to intermittent hypoxia in the rat

\*†J MOORE-GILLON, \*\*E SHEFFIELD, \*\*B CORRIN, \*IR CAMERON *\*Department of Medicine, UMDS (St. Thomas' Hospital); \*\*the Cardiothoracic Institute, Brompton and †London Chest Hospitals* Carotid body enlargement occurs in chronic hypoxia, but the effect of intermittent hypoxia on the carotid body is unknown. We have investigated this in the rat. Young adult rats, in groups of 10, were successively maintained in an environmental chamber for 28 days. Group A remained normoxic throughout, and Groups B, C and D breathed a hypoxic atmosphere of 12%  $O_2$  for two, four and 24 hours each day, respectively. On day 28, rats were killed and their carotid bifurcations dissected out, fixed in 4% formalin and paraffin embedded. Four  $\mu m$  thick sections were taken at 20  $\mu m$  intervals and stained with haematoxylin and eosin. In each section, cross-sectional area of the carotid body was measured by tracing its outline on an image digitising tablet linked to a microcomputer. Carotid body volume was calculated using Simpson's rule for estimation of organ volume from serial cross sectional area. Carotid body volume in the normoxic Group A was  $9.07 \pm 0.48 \mu m^3 \times 10^6$  (Mean  $\pm$  SEM), less than half that of the continuously hypoxic Group D:  $18.69 \pm 0.68 \mu m^3 \times 10^6$  ( $p < 0.001$ ). Groups B and C had mean carotid body volumes 6% and 25% greater than controls at  $9.36 \pm 0.39$  and  $11.33 \pm 0.43 \mu m^3 \times 10^6$  respectively, the latter being statistically significant ( $p < 0.05$ ). Intermittent hypoxia will stimulate carotid body enlargement, suggesting such changes might be found in patients with sleep-disordered breathing and consequent nocturnal desaturation.

### The contribution of mast cell mediators to AMP-induced bronchoconstriction in intrinsic asthma

GD PHILLIPS, P RAFFERTY, CRW BEASLEY, ST HOLGATE *Medicine I, Southampton General Hospital, Southampton* Inhaled adenosine 5'-monophosphate (AMP) causes bronchoconstriction in allergic asthma, probably after conversion to adenosine. It has been suggested that adenosine potentiates preformed mediator release from mast cells on the mucosal surface of the airways by interacting with specific purinoceptors, without affecting the release of newly generated mediators. In this study we have investigated the airways response of nine non-allergic asthmatics to inhaled AMP and the influence on this response of the oral, selective  $H_1$ -histamine receptor antagonist, terfenadine. Geometric mean provocation concentrations of histamine and AMP required to produce a 20% fall in  $FEV_1$  ( $PC_{20}$ ) were 1.82 and 13 mM/L respectively. In subsequent time-course studies the  $FEV_1$  response to a single inhalation of the  $PC_{20}$  histamine was ablated after pretreatment with oral terfenadine 180 mg. On a second study day this dose of terfenadine inhibited bronchoconstriction caused by the  $PC_{20}$  AMP by 72.6% when areas under the time course response curves were



compared. Terfenadine 600 mg failed to increase protection against AMP, but both doses of terfenadine delayed the time at which the mean maximum fall in FEV<sub>1</sub> was achieved after AMP. These data may be interpreted as AMP potentiating mediator release, including histamine, from already activated mast cells in the bronchial mucosa in intrinsic asthma, thereby incriminating this cell in pathogenesis.

#### Enhanced leukotriene B<sub>4</sub> (LTB<sub>4</sub>) generation by circulating neutrophils (PMN) following exercise-induced asthma (EIA)

JP ARM, CE HORTON, TH LEE *Guy's Hospital, London* EIA is associated with leukocyte activation. Since LTB<sub>4</sub> is the major leukotriene produced by activated PMN, we have compared the levels of LTB<sub>4</sub> generated by PMN isolated pre- and post-challenge in 10 subjects with EIA. The LTB<sub>4</sub> generated by PMN both spontaneously and in response to 2 and 4 × 10<sup>8</sup> unopsonised zymosan particles and 10 μm A23187 were measured by radioimmunoassay and by integrated UV absorbance after RP-HPLC. There was a 2-80 fold (mean 22) enhancement in LTB<sub>4</sub> generation in response to zymosan and A23187 at three and six hours after exercise as compared to PMN obtained pre-challenge. These changes were not observed in six subjects who did not develop EIA after a similar exercise task and were also not observed after methacholine challenge. Maximal LTB<sub>4</sub> generation correlated with the severity of the early bronchoconstriction (r = 0.65), but there was no correlation with the development of a late response. The finding that there was also enhancement in the generation of 5-HETE and 6-trans LTB<sub>4</sub> by PMN at three and six hours suggested that there was up-regulation of the whole 5-lipoxygenase pathway. Thus EIA is followed by the development of increased 5-lipoxygenase pathway activity in PMN but this activation is dissociated from the induction of a late reaction.

#### Leukotrienes (LT) B<sub>4</sub> and C<sub>4</sub> in bronchoalveolar lavage fluid in bronchial asthma and other respiratory diseases

AJ WARDLAW, H HAY, O CROMWELL, P HASLAM, \*JV COLLINS, AB KAY *Cardiothoracic Institute and \*Brompton Hospital, London* LTC<sub>4</sub> and LTB<sub>4</sub> are potent pro-inflammatory mediators with a wide range of biological activities including bronchoconstriction and leucocyte activation; properties which may be of importance in the pathology of asthma and other respiratory diseases. We have investigated the concentrations of LTC<sub>4</sub> and LTB<sub>4</sub> in bronchoalveolar lavage (BAL) fluid from 16 atopic asthmatic (eight symptomatic, eight asymptomatic) and compared them with 14 non-asthmatics (six hayfever, eight non-atopic) as part of a study of "day-to-day" asthma. LTs were extracted in methanol from 10 ml of BAL and measured by radioimmunoassay. The concentration of LTC<sub>4</sub> and LTB<sub>4</sub> in BAL of the symptomatic asthmatics was significantly higher than controls (LTB<sub>4</sub>: 0.58 ± 0.06 vs 0.36 ± 0.05 pmoles/ml, p < 0.05; LTC<sub>4</sub>: 0.36 ± 0.1 vs 0.12 ± 0.02 pmoles/ml, p < 0.01). However when results were expressed as amount of LTs recovered, no significant

differences were observed due to the reduced recovery of BAL in the asthmatic subjects. Amounts of LTC<sub>4</sub> and LTB<sub>4</sub> were also measured in 17 patients with interstitial lung diseases (nine CFA, three sarcoidosis, four miscellaneous). Concentrations and amounts of LTB<sub>4</sub> recovered were significantly greater in the CFA group when compared with normals (0.69 ± 0.3 vs 0.36 ± 0.05 pmoles/ml, p < 0.01). No differences in amounts of LTC<sub>4</sub> were observed. This study does not provide any convincing evidence for increased amounts of LTs in the airways of mild asthmatics, but suggests that LTB<sub>4</sub> may be playing a part in the recruitment of granulocytes into the lung in CFA.

#### Immune complexes prepared from allergic bronchopulmonary aspergillosis sera generate leukotriene C<sub>4</sub> from human eosinophils

O CROMWELL, P FITZHARRIS, C HARVEY, R MOQBEL, RJ SHAW, AB KAY *Department of Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* IgG covalently coupled to agarose beads, elicited leukotriene C<sub>4</sub> (LTC<sub>4</sub>) generation by human eosinophils (RJ Shaw *et al*, *Nature*, 1985;316:150). We have extended this observation using an immobilised IgG/antigen complex as a stimulus for mediator production. An extract of *Aspergillus fumigatus* was covalently coupled to agarose beads and incubated with the IgG fraction of immune serum from patients with allergic bronchopulmonary aspergillosis (ABPA). This resulted in the generation of 11.6 ± 1.4 pmoles of LTC<sub>4</sub> per 10<sup>6</sup> normal eosinophils (> 86% purity) (n = 5). Significantly less LTC<sub>4</sub> (0.73 ± 0.19 pmoles per 10<sup>6</sup> cells, n = 3) was produced by eosinophils after incubation with beads treated with IgG from normal, non-immune serum. LTC<sub>4</sub> was measured by radioimmunoassay and validated by RP-HPLC. The amount of LTC<sub>4</sub> generated was dependent upon the concentration of *A. fumigatus* specific IgG, and release of the mediator was completely abolished by prior absorption of the IgG fraction with Protein A (*Staphylococcus aureus*). These results suggest that IgG antibody/antigen dependent stimulation of eosinophils might provide a mechanism whereby these cells contribute to the inflammatory changes associated with ABPA.

#### The effect of an orally active leukotriene D<sub>4</sub> (LTD<sub>4</sub>) antagonist L-649,923 on the airway response to inhaled antigen in asthma

J BRITTON, SP HANLEY, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* LTD<sub>4</sub> is a potent bronchoconstrictor which may be an important mediator in the pathogenesis of asthma. We have assessed the effect of a new LTD<sub>4</sub> antagonist L-649,923 on the airway response to inhaled antigen in eight male subjects with asthma known to show both early and late responses to antigen challenge. After measurement of lung function (sGaw, Vmax<sub>25</sub>, FEV<sub>1</sub> and PEF<sub>R</sub>) on two days not less than 14 days apart, subjects ingested either L-649,923 1000 mg or placebo in a randomised double blind design. At two hours, lung function was measured immediately before subjects inhaled the dose of antigen known to induce a 20%

fall in FEV<sub>1</sub>. Lung function was then measured at ten minute intervals for the first hour, and at hourly intervals for eight hours. One subject was excluded from analysis because FEV<sub>1</sub> fell after L-649,923 and was much lower before antigen than after placebo. In the remaining seven subjects L-649,923 caused no change in baseline pulmonary function. Following antigen, there was a significant but small reduction in the early response after L-649,923 for FEV<sub>1</sub>, PEFR and Vmax<sub>25</sub> (analysis of variance p<0.05), but not for sGaw (six subjects only). The maximum fall in FEV<sub>1</sub> after L-649,923 was 1.35 l and after placebo was 1.78 l (p<0.05). L-649,923 did not affect the late response. Seven subjects experienced abdominal discomfort or diarrhoea after L-649,923. This study shows that an orally active leukotriene D<sub>4</sub> antagonist causes a small reduction in the early response to inhaled antigen and has no effect on the late response.

**The effect of an oral leukotriene antagonist L-649,923 on histamine and leukotriene D<sub>4</sub> induced bronchoconstriction in normal man**

N BARNES, PJ PIPER, JF COSTELLO *Department of Thoracic Medicine, King's College School of Medicine and Dentistry, London and Department of Pharmacology, Royal College of Surgeons, London* We have investigated the ability of an oral leukotriene antagonist L649,923 ((±) - 4((3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl)thio)-α-hydroxy-β-methylbenzenebutanoic acid) to antagonise bronchoconstriction induced by histamine and leukotriene D<sub>4</sub> (LTD<sub>4</sub>) in a double blind, placebo controlled, randomised cross-over trial. Twelve normal, males, mean age 30.4 years were studied. There were four study days. On each day baseline measurements of FEV<sub>1</sub>, specific airways conductance, (sGaw) and flow at 30% of vital capacity above residual volume (V̇max<sub>30</sub>) were made. Subjects then ingested 1g of L649,923 or placebo; 1 hour later FEV<sub>1</sub>, sGaw and V̇max<sub>30</sub> measurements were repeated. Subjects then underwent an inhalation challenge test with either histamine or LTD<sub>4</sub> and sGaw and V̇max<sub>30</sub> were measured frequently after each concentration. Dose response curves for histamine and LTD<sub>4</sub> were constructed and the concentration of the agonist necessary to cause a 35% fall in sGaw (PC<sub>35</sub> sGaw) and a 30% fall in V̇max<sub>30</sub> (PC<sub>30</sub> V̇max<sub>30</sub>) were calculated. Eleven subjects completed the trial. Neither L649,923 or placebo had any effect on baseline lung function. There was no significant difference in the histamine response between L649,923 and placebo. L649,923 caused a shift to the right of the LTD<sub>4</sub> dose response curve in all 11 subjects. The geometric mean shift for the group being 3.8 fold (p<0.001) students t test) for both PC<sub>35</sub> sGaw and PC<sub>30</sub> V̇max<sub>30</sub>. The only side effects were crampy abdominal pains and/or diarrhoea. We conclude that LTD<sub>4</sub> inhalation challenge testing can be used to test the potency of LT antagonists in man. We have shown that L649,923 is an LTD<sub>4</sub> antagonist.

**Leukotriene E<sub>4</sub> (LTE<sub>4</sub>) enhances airway histamine responsiveness in asthmatic subjects**

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asthmatic patients have been subjected to four histamine inhalation challenges which were each separated by approximately one week. Each histamine challenge was preceded by either saline (S), methacholine (M), a low dose of LTE<sub>4</sub> (0.026-0.26 nmol; LTE<sub>4</sub><sup>S</sup>) or a bronchoconstricting dose of LTE<sub>4</sub> (2.6-26 nmol; LTE<sub>4</sub><sup>H</sup>). Inhalation of S, M, LTE<sub>4</sub><sup>S</sup> and LTE<sub>4</sub><sup>H</sup> elicited 3 ± 0.6, 37 ± 2.3, 10 ± 1.1 and 36 ± 3.2 decreases (mean ± SEM) in specific conductance (sGaw) respectively. The decreases in sGaw recovered spontaneously to baseline values over 60-90 min prior to the construction of a histamine cumulative dose response curve. The dose of histamine which caused a 35% fall in sGaw (PD<sub>35</sub>) after inhalation of S, M, LTE<sub>4</sub><sup>S</sup> and LTE<sub>4</sub><sup>H</sup> was 2.5 ± 1.5 μmol, 1.5 ± 0.6 μmol, 1.4 ± 0.6 μmol and 0.7 ± 0.3 μmol (mean ± SEM), respectively. In each subject the change in histamine PD<sub>35</sub> sGaw following LTE<sub>4</sub><sup>H</sup> exceeded that following M (p<0.05). These changes in histamine responsiveness following a bronchoconstricting dose of LTE<sub>4</sub><sup>H</sup> were not observed in three normal subjects. These findings indicate that the prior inhalation of LTE<sub>4</sub> increases airway histamine responsiveness by an average 3.5 fold in asthmatic, but not normal, subjects and that this is not simply related to the development of bronchoconstriction alone.

**Bronchial hyperreactivity induced by platelet-activating factor (PAF): modification by a beta-agonist**

KF CHUNG, PJ BARNES *Department of Clinical Pharmacology, Cardiothoracic Institute and Brompton Hospital, London* PAF, a potent mediator of inflammation, causes a sustained increase in bronchial reactivity in man (Cuss *et al*, *Lancet*, 1986;ii:189-192). We examined the effects of salbutamol (S, 200 μg) and of placebo (P) aerosols on the airway effects of PAF in six normal subjects in a double blind crossover study. PAF (2 μg/ml) was inhaled in six equal doses every 15 min, 20 min after S or P. Airway calibre was assessed as the partial expiratory flow rate at 30% vital capacity (Vp<sub>30</sub>) and airway reactivity was measured as the methacholine concentration needed to cause a 40% fall in Vp<sub>30</sub> (PC<sub>40</sub>) before and at 1, 3 and seven days after PAF. The first inhalation caused a 56% ± 3.5% (SEM) fall in Vp<sub>30</sub>, facial flushing and coughing. There was rapid tachyphylaxis to subsequent doses. S only partially blocked the bronchoconstrictor effect of PAF with a 22% ± 12% fall in Vp<sub>30</sub> after the first dose and did not prevent the facial flushing and coughing. After P, mean PC<sub>40</sub> fell from 19.7 mg/ml (GSEM 1.35) to a minimum of 6.4 mg/ml (1.24) at day 3; after S, from 19.1 μg/ml (1.42) to 9.5 mg/ml (1.34). PC<sub>40</sub> on day three was higher after S than after P (p<0.05). Bronchial reactivity remained significantly enhanced on day seven after S and after P. Baseline Vp<sub>30</sub>'s were not significantly different for each study day. We conclude that a therapeutic dose of S only partly inhibits the acute bronchoconstriction and has a minor effect on bronchial hyperreactivity induced by PAF in man.

### Mediators of increased vascular permeability during anaphylaxis in sensitised guinea-pigs

TW EVANS, DF ROGERS, NM ROBERTS, KF CHUNG, PJ BARNES *Department of Clinical Pharmacology, Cardiothoracic Institute, Brompton Hospital, London* We examined the pharmacological mechanisms underlying the microvascular leakage induced by iv injection of ovalbumin (OA) in OA sensitised guinea-pigs. Prior to challenge, animals were treated with BN 52063, a platelet activating factor (PAF) receptor antagonist, or the H1, H2 receptor blockers chlorpheniramine and cimetidine, or nedocromil sodium, a chromoglycate-like compound. Microvascular leakage was measured by extravasation of Evans blue dye, which binds to albumin. After anaesthesia, Evans blue dye was given iv followed by OA one minute later. After five minutes, animals were perfused with paraformaldehyde and the trachea, main bronchi and intrapulmonary airways removed. Evans blue was extracted in formamide and quantified by spectrophotometry. Sensitised animals showed an increase in vascular permeability in all tissues compared to controls ( $p < 0.05$ ). BN 52063 did not significantly reduce the effect. H1, H2 receptor blockade reduced the effect in main bronchi only, but nedocromil sodium caused a significant reduction in extravasation in all tissues ( $p < 0.05$ ). Increased microvascular leakage during anaphylaxis may be partially mediated through histamine receptors, particularly in the central airways. Nedocromil sodium inhibits this effect, suggesting that other mast cell derived mediators may be involved.

### Activation of human eosinophils by PAF-acether and other inflammatory mediators

R MOQBEL, GM WALSH, AJ MACDONALD, AJ WARDLAW, AB KAY *Cardiothoracic Institute, Brompton Hospital, London* Activation of eosinophils is associated with increased expression of complement and Fc (Ig) receptors and increased effector function. PAF-acether substantially enhanced complement and antibody-dependent eosinophil cytotoxicity. Maximum enhancement was obtained at  $10^{-8}$  M ( $p < 0.01$ ). Histamine was effective only at  $10^{-5}$  M while lyso-PAF had no significant influence on eosinophil cytotoxicity. We have also examined the effect of PAF-acether on eosinophil Fc (IgG and IgE) receptor expression and compared it with lyso-PAF,  $LTB_4$  and histamine. Receptor expression was measured by a rosette technique employing monoclonal antibodies covalently linked to sheep erythrocytes. PAF-acether caused a dose-dependent increase in Fc (IgE) and Fc (IgG) receptor expression on normal eosinophils which was optimal at  $10^{-7}$  M ( $p < 0.05$ ) and  $10^{-6}$  M ( $p < 0.01$ ) respectively. No significant increases were observed with lyso-PAF.  $LTB_4$  also caused enhancement of eosinophil IgE and IgG (Fc) receptors (optimum  $10^{-7}$  M,  $p < 0.05$ ), which was similar in magnitude to PAF-acether. Histamine gave a lesser but significant enhancement of eosinophil Fc (IgE and IgG) receptors at high concentrations ( $10^{-5}$  M,  $p < 0.05$ ). Enhancement of receptor expression was maximal after 30 min incubation with each of the mediators. These results suggest that PAF-acether may amplify inflammatory

responses involved in asthma and other eosinophil-associated diseases.

### PAF-acether is a highly effective chemotactic agent for human eosinophils

AJ WARDLAW, R MOQBEL, AB KAY *Cardiothoracic Institute, Brompton Hospital, London* Platelet activating factor (PAF-acether), an inflammatory mediator with a wide range of biological activities including neutrophil aggregation and chemotaxis, was studied for its effect on human eosinophil locomotion. Chemotaxis and chemokinesis were studied using a Boyden chamber technique. Human eosinophils were obtained from donors with a variety of diseases associated with hypereosinophilia (8-95%). PAF-acether elicited directional locomotion of eosinophils, in a time- and dose-dependent fashion, at concentrations from  $10^{-5}$  to  $10^{-8}$  M (optimum  $10^{-6}$  M); lyso-PAF had minimal activity over the same dose range. Compared to PAF-acether, the eosinophil locomotory responsiveness of  $LTB_4$ , histamine, the valyl- and alanyl-ECF-A tetrapeptides and  $PGD_2$  was negligible. Conversely, neutrophil responsiveness to PAF-acether (optimum  $10^{-6}$  M) was comparable in effect to  $LTB_4$  (optimum dose  $10^{-8}$  M). PAF-acether elicited both chemotaxis and chemokinesis of eosinophils. Contaminating neutrophils had no apparent influence on the response of eosinophils to PAF-acether. Comparison of normal density and light density eosinophils revealed no qualitative difference in the response to PAF-acether and the other chemoattractants, although the light density cells seemed to demonstrate a greater degree of locomotion to PAF-acether and  $LTB_4$ . Thus, PAF-acether appears to be a highly effective eosinophilotactic agent which may play a rôle in inflammatory reactions characterized by eosinophil infiltration.

### Ascaris allergic dogs: a model of human asthma?

NC TURNER, RW FULLER, \*DM JACKSON, CT DOLLERY *Department of Clinical Pharmacology, Royal Postgraduate Medical School, London and \*Fisons PLC, Loughborough* We have investigated the mediators released into the airways and the accompanying cell influx in *Ascaris* sensitive Beagle dogs. Four Beagle dogs (10.5-15 kg) were studied. Five ml of antigen ( $10-50 \mu\text{g}/\text{kg}$ ) or saline was instilled through a bronchoscope wedged in a fourth generation bronchus and lavaged 90 s later with 50 ml of warm saline. The lavage was repeated two and 24 hours after challenge. Total lung resistance, compliance and responses to intravenous histamine were determined. The recovered lavage fluid was examined for major cell types and analysed for mediators. Antigen challenge caused an acute increase in lung resistance and fall in compliance. There was an increase in response to intravenous histamine at 2 hours (RL  $4.38 \pm 1.2$  compared to  $1.5 \pm 0.37$  cm  $\text{H}_2\text{O}/\text{l}/\text{s}$ ). Histamine ( $106 \pm 25.3$  ng/ml) and  $PGD_2$  ( $1.4 \pm 0.56$  ng/ml) concentrations were greater from the challenge lobe. Histamine concentrations were still elevated at 2 hours in the challenged lobe whereas  $PGD_2$  and 6-oxo- $PGF_1$  were elevated in both. Lung function, histamine

and prostanoid concentrations returned to control levels by 24 hours. Lysosomal enzyme activity, protein content and eosinophil number ( $3.9 \pm 1.3$  compared with  $0.27 \pm 0.3 \times 10^4$  cells per ml) were elevated in the challenge lobe at 24 hours. We conclude that acute bronchospasm, bronchial hyperreactivity and eosinophil influx following antigen challenge may be a consequence of mast cell activation.

### Rapid decline of airway function leads to death on long term oxygen therapy

CB COOPER, JC TWEENEY, P HOWARD *University Department of Medicine, Royal Hallamshire Hospital, Sheffield* We have reported an analysis of survival on long term oxygen therapy (LTOT) in a 12 year study involving 72 patients with hypoxic cor pulmonale (Cooper *et al*, *Thorax*, 1986;41:235). Five year survival was 62%; however 10 year survival was only 26% due to an observed acceleration of death rate about this time. In order to examine the pathophysiological process leading to death we studied serial measurements of respiratory function and blood gas tensions in 37 patients who died during LTOT using the moment of death as a fixed point in the analysis. All assessments were made during periods of clinical stability and blood gas tensions were measured whilst breathing air. At commencement of LTOT this sub-group was aged 60.1 (8.0) years. mean (SD). FEV<sub>1</sub> was 0.78 (0.33) L, Pao<sub>2</sub> was 6.6 (1.0) kPa and Paco<sub>2</sub> was 6.7 (0.9) kPa. At death their age was 65.0 (7.9) years. During the year before death FEV<sub>1</sub> was 0.57 (0.20) L, Pao<sub>2</sub> was 5.1 (1.1) kPa and Paco<sub>2</sub> was 7.2 (1.3) kPa. Mean values were obtained for each year leading up to death. A rapid decline of FEV<sub>1</sub> was observed (75 ml year<sup>-1</sup>) accompanied by a progressive fall in Pao<sub>2</sub>. Paco<sub>2</sub> did not change. Survival was related to initial FEV<sub>1</sub> ( $p < 0.02$ ) and death appears to be associated with a rapid decline in airway function.

### Results of treatment of adults with pulmonary tuberculosis in England and Wales notified in 1983

JH DARBYSHIRE, SP BYFIELD, AJ NUNN, KM CITRON, W FOX *MRC TB and Chest Diseases Unit, Brompton Hospital* All adult patients with pulmonary tuberculosis of White or Indian subcontinent (Indian, Pakistani and Bangladeshi) ethnic origin who had not been treated previously and who were notified in the first six months of 1983 have been followed up two years later. Information on 1063 patients (98% of those eligible) has already been obtained. Chemotherapy was completed in 85% of the 1063 patients; 3% had defaulted, 10% had died and 1% had left the UK. Of the 911 patients who completed chemotherapy, 891 (97.8%) were reported to be cured when last seen, and 10 (1.1%) were not yet cured. A further seven (0.8%) had died and three (0.3%) were lost from follow-up. Cure had been achieved on the primary course of chemotherapy in 872 (95.7%) and a second course in 18 (2.0%) including seven because of failure or relapse. Treatment was completed as planned by the clinician in charge in 683 (75%) of the 911 patients who completed chemotherapy. The problems occurring in the remainder included toxicity (10%), poor compliance (6%), and slow response or

deterioration (2%). In the 683 patients who completed chemotherapy as planned, 85% were treated with isoniazid plus rifampicin with either ethambutol initially (66%), pyrazinamide initially (7%), or both drugs (12%). The median duration for the patients treated with ethambutol initially was 9.0 months and for those having both ethambutol and pyrazinamide 8.5 months.

### Long term trial of almitrine bismesylate in chronic obstructive airways disease: Vectarian multicentre study group

P HOWARD, C VOISIN, JC ANSQUER *University Department of Medicine, Royal Hallamshire Hospital, Sheffield and Servier International Research, Neuilly, University Department of Medicine, University of Lille, France* Almitrine bismesylate, a chemoreceptor agonist, has been shown in short term studies to improve arterial oxygen tension and reduce arterial carbon dioxide tension in patients with chronic respiratory failure associated with chronic obstructive airways disease. A one year, placebo controlled double blind trial was set up in many centres throughout Europe to determine whether the effect persisted for at least a year and whether the improvement of respiratory failure was associated with clinical and physiological benefit. Seven hundred and one patients entered the study. They were predominantly male of mean age  $61.9 \pm 8.3$  years and moderately severely disabled on a six minute walking test achieving  $334.7 \pm 113$  metres. Mean Pao<sub>2</sub> was  $7.6 \pm 0.9$  kPa, mean Paco<sub>2</sub>  $6.0 \pm 0.9$  kPa, mean FEV<sub>1</sub>  $0.87 \pm 0.36$  L mean FVC  $2.32 \pm 0.71$  L on entry. 50 mg b.d. of Almitrine bismesylate or identical placebo tablets were administered in addition to conventional therapy. Patients already receiving oxygen were randomised separately. Three hundred and forty-four patients received the active compound and 357 patients, placebo. Pao<sub>2</sub> significantly improved only in the active group from  $7.7 \pm 0.8$  kPa to  $8.5 \pm 1.3$  kPa after one year of treatment ( $p < 0.001$ ). Arterial carbon dioxide tension was unchanged but there was a slight improvement of FEV<sub>1</sub> from 0.93 to 0.96 L in the active group. Patients in the active group were hospitalised less during the period of study. A number of patients accumulated high blood levels. The drug has a useful and sustained effect but revised dosage schedules are required.

### Recognition of upper airway obstruction (UAO) in patients with chronic obstructive airways disease (COAD)

DA ROBERTSON, CR SWINBURN, TN STONE, GJ GIBSON *Department of Respiratory Medicine, Freeman Hospital, Newcastle Upon Tyne* We have investigated how the presence of COAD affects recognition of additional narrowing of the upper airway. UAO was simulated by introducing orifices at the mouth with diameters 4-12 mm. Maximum flow volume curves were obtained from twelve patients with COAD of varying severity and twelve healthy control subjects. The effect of each orifice was quantified as the reduction in maximum flow with the orifice in position compared to the unobstructed flow. In the patients the reductions in  $\dot{V}_{E,max}$



at high lung volumes were less than in normal subjects, both in absolute terms and as a proportion of unobstructed flow. There was no significant difference between the groups in the effect of UAO on  $\dot{V}_{I\max_{50}}$ . Consequently the commonly used ratios of  $\dot{V}_{E\max_{50}}/\dot{V}_{I\max_{50}}$  and of FEV<sub>1</sub>/PEF were less sensitive to the presence of UAO in patients than in normal subjects ( $p < 0.001$ ,  $p < 0.05$  respectively). Linear regression analysis within the patient group showed that the more severe the COAD the smaller the reduction in PEF (both in absolute and proportional terms) resulting from simulated UAO. When the patients breathed a helium/oxygen mixture the proportional increases in PEF and  $\dot{V}_{I\max_{50}}$  were larger with a 6 mm orifice than unobstructed ( $\Delta$  PEF 37.4 vs 20.2%,  $p < 0.05$ ;  $\Delta \dot{V}_{I\max_{50}}$  44.3 vs 12.6%,  $p < 0.001$ ). Narrowing of the upper airway is difficult to detect in patients with COAD but is suggested by an unusually large increase in effort-dependent flow when breathing a helium/oxygen mixture.

#### The role of pulmonary function measurements in the diagnosis of the pulmonary complications of AIDS

RJ SHAW, C ROUSSAK, SM FORSTER, JRW HARRIS, AJ PINCHING, EE KEAL *St. Mary's Hospital, London* Pulmonary function was measured in 61 male patients (pts) with Human Immunodeficiency Virus (HIV) infection, comprising nine asymptomatic seropositive individuals (HIV + ve), 11 with persistent generalised lymphadenopathy (PGL), 10 with AIDS related complex (ARC), seven AIDS pts with no respiratory symptoms (AIDS alone), 18 AIDS pts with respiratory complications (AIDS + SOB), and six pts at least one month following pneumocystis pneumonia (post PCP). Thirty-nine pts were smokers. There was no significant difference in the FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, PEFR, or MEF<sub>50</sub> between the groups. The TLCO (per cent predicted  $\pm$  SEM) was reduced in those with AIDS + SOB ( $59 \pm 4$ ) and those post PCP ( $66 \pm 3$ ), compared with HIV + ve ( $87 \pm 7$ ) ( $p < 0.002$ ,  $p < 0.05$ ) and PGL ( $89 \pm 5$ ) ( $p < 0.002$ ,  $p < 0.02$ ). ARC ( $76 \pm 5$ ), and AIDS alone pts ( $82 \pm 5$ ), had intermediate values. Similarly the KCO was reduced in the AIDS + SOB ( $72 \pm 4$ ), compared to HIV + ve ( $90 \pm 5$ ) ( $p < 0.02$ ), and PGL ( $87 \pm 5$ ) ( $p < 0.05$ ). All pts with a TLCO of  $< 60\%$ , respiratory symptoms or abnormal CXR, were examined by fibre-optic bronchoscopy (FOB), bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB). Seven of the AIDS + SOB had PCP, but eight of the 13 pts with TLCO  $< 60\%$  predicted did not have PCP, and PCP was identified in one pt with a TLCO 97% predicted. These results suggest that isolated pulmonary function measurements, in particular TLCO, may provide a useful guide to the presence of the respiratory complications of HIV infection, but they cannot predict the results of FOB, BAL and TBB examination of the lung.

#### Traditional Chinese acupuncture for chronic disabling breathlessness

KA JOBST, JH CHEN, DJ LANE *Osler Chest Unit, Churchill Hospital, Oxford* The efficacy of available symptomatic

treatment for chronic disabling breathlessness is limited. Disability is related to the perception of severity of breathlessness, itself governed by a complex interaction of subjective and objective variables. Recent work has shown that opiates and benzodiazepines reduce distressing dyspnoea and that both classes of drug have endogenous analogues within the central nervous system (CNS). Traditional Chinese Acupuncture (TCA) has been shown to mediate the release of endogenous opiates (enkephalins and endorphins) in the CNS of both animals and human subjects. We therefore set out to investigate whether TCA could reduce the perception of, and disability due to, chronic obstructive pulmonary disease (COPD). Patients with COPD were selected from outpatients, randomly allocated into genuine treatment or placebo groups and matched for age, sex, severity of dyspnoea and FEV<sub>1</sub>. Results were assessed single blind. All patients thought they were receiving genuine TCA. All treatments were given by the same individual. Each pair had identical attention, number of needles and duration of treatment. Results from 12 pairs were analysed by the Wilcoxon signed rank test and after three weeks showed a highly significant improvement in general well being, shortness of breath, oxygen cost, modified Borg and six minute walk scores for those in the genuine treatment group.

#### Premedication for fibreoptic bronchoscopy: a comparison of neuroleptanalgesia, diazepam and papaveretum

JFJ MORRISON, RG TAYLOR, FG SIMPSON, AG ARNOLD *Pulmonary Function Laboratory, Killingbeck Hospital, Leeds and Medical Chest Unit, Castle Hill Hospital, Hull* In a double blind prospective trial of premedication for fibreoptic bronchoscopy (FOB) a comparison was made of intravenous (iv) neuroleptanalgesia as phenoperidine 2 mg and droperidol 10 mg, iv diazepam as diazemuls 10 mg and intramuscular (im) papaveretum 20 mg given 30-60 minutes prior to FOB. All drugs were given in addition to im atropine 0.6 mg. One hundred and four consecutive patients (67 male; mean age 67) from routine FOB lists were studied and both patients and operators filled out questionnaires after the procedure. Neuroleptanalgesia suppressed cough significantly more than diazepam ( $p < 0.01$ ) and papaveretum ( $p < 0.05$ ), (diazepam vs papaveretum NS). Supplemental lignocaine or diazepam was required less with neuroleptanalgesia than papaveretum ( $p < 0.01$ ) or diazepam ( $p < 0.01$ ). There was no significant difference between diazepam and papaveretum. No regimen caused serious side effects or a reduction in arterial oxygen saturation (ear oximetry) when oxygen was given by nasal cannula at 2 L per minute. Neuroleptanalgesia and diazepam gave significantly better amnesia than papaveretum ( $p < 0.01$ ). No differences were found in scores of pain, preference for general anaesthesia, sore throat, expectations or unpleasantness of the procedure between the three regimens. Patients found topical nasal anaesthesia and FOB instrumentation of the nose were the most unpleasant parts of the procedure (48%). Overall neuroleptanalgesia appears to be a better premedication for FOB than diazepam or papaveretum.

### Anatomical distribution and movement of fluid introduced at bronchoalveolar lavage (BAL)

KELLY CA, KOTRE CJ, WARD C, HENDRICK DJ, EH WALTERS *Newcastle General Hospital, University of Newcastle on Tyne* In order to directly visualise the anatomical distribution of lavage fluid, we performed BAL of a middle lobe segment in two young male volunteers, introducing 3 × 60 ml aliquots (A1, A2 and A3) of sterile buffered saline, containing a 5% solution of radio-opaque dye (Niopam) of similar osmolality and viscosity to 0.9% saline. Each aliquot was separately introduced and promptly aspirated. Digital imaging radiography was used to record AP images prior to and after the introduction of predetermined volumes, and images were also taken after the aspiration of each aliquot. Computer subtraction of the mask image from each subsequent picture provided good low-contrast sensitivity. The amount of dye in six equally proportioned areas of interest along the line of the segmental bronchus was recorded for each image. In order to correct for the variable AP diameter of the middle lobe, the AP thickness of each middle lobe segment was measured along the segmental bronchus in three males at post mortem. The amount of dye per unit lung volume was related to distance from the bronchoscope for each aliquot. At introduction, most of A1 stayed close to the tip of the bronchoscope, while A2 and A3 were more evenly distributed throughout the whole of the segment. Subtraction of pre- from post-aspiration images showed that fluid was aspirated from close to the bronchoscope after introduction of A1, but moved back more evenly through the whole segment for A2 and A3. Although this study could not take account of possible fluid mixing or flux, it supports the contention that increasing volumes of introduced fluid reach more peripheral sites and that aspiration does move fluid back from these areas.

### Differential cell counts in asthma and their relationships to bronchial hyper-responsiveness

C KELLY, C WARD, G BIRD, C STENTON, D HENDRICK, EH WALTERS *Newcastle General Hospital, University of Newcastle on Tyne* Methacholine challenge was performed one week prior to diagnostic bronchoscopy in 27 patients. Sixteen had a history and physiological evidence of asthma, with a measurable PD<sub>20</sub>-FEV<sub>1</sub>. In the remaining 11 (controls) with normal pulmonary function, a PD<sub>20</sub> could not be obtained. Bronchoalveolar lavage (BAL) of a middle lobe segment was performed using 3 × 60 ml aliquots of sterile buffered saline which were promptly aspirated into siliconised glass at 4°C. Absolute cell count was performed using a Neubauer chamber, and differential cell counts were performed on Giemsa-stained cytospin preparations. Mean (SEM) results are expressed × 10<sup>8</sup>/L and as a per cent of total cell count.

	TOTAL	Macro.	Lymph.	Neut.	Eosin.
CONTROLS (11)	1.51(0.2)	1.29(0.2)	0.16(0.02)	0.05(0.01)	0.01
ASTHMATICS (16)	2.02(0.3)	1.57(0.3)	0.33(0.12)	0.09(0.03)	0.03
CONTROLS % count		83.3(2.5)	13.7(2.3)	2.7(0.9)	0.3
ASTHMATICS % count		77.0(4.1)	16.8(3.7)	4.9(1.7)	1.3*

\*p < 0.05 Unpaired t-test

Smokers had significantly higher total cell counts than non-smokers, both among controls (n=5, p<0.05) and asthmatics (n=7, p<0.01). There was no correlation between PD<sub>20</sub> and the total cell count or absolute numbers of neutrophils, macrophages lymphocytes or eosinophils. However PD<sub>20</sub> is inversely correlated with percentage neutrophil count (n=16, r=0.76, p<0.001). From this morphological analysis, the only firm indication that inflammation may be involved in the aetiology of airway hyperresponsiveness is the relationship between percentage neutrophil count in BAL and PD<sub>20</sub>.

### Leucocytes and mediators in bronchial mucus and bronchoalveolar lavage (BAL) during allergen-induced late-phase asthmatic reactions

\*P DIAZ, \*C GONZALEZ, \*F GALLEGUILLOS, \*P ANCI, O CROMWELL, AB KAY *\*Clinica de Enfermedades Respiratorias, Santiago, Chile, and Cardiothoracic Institute, Brompton Hospital, London* We have measured the total and differential cell count, the percentage of monocyte complement rosettes (MCR), IgG, IgA, IgM, C3, albumin, histamine, leukotrienes C<sub>4</sub> and B<sub>4</sub> in both BAL and bronchial mucus, six hours after challenge with either antigen (Ag) or diluent (D) control in seven patients with antigen-induced single early reactions (SER), and six subjects with dual (early- and late-phase) (LPR) responses. The total cell counts in BAL remained virtually unchanged in both groups challenged with either Ag or D, whereas there were significant increases in lymphocytes, neutrophils and eosinophils (p<0.05), and significant decreases in the percentage of lung mast cells in LPR (p<0.05). Furthermore, the percentage of MCR increased significantly (p<0.05) in LPR, but not SER. There were significant (p<0.05) increases in the percentage of mucus neutrophils in SER, and of eosinophils in LPR, with significant decreases in mucus macrophages in both groups. The only significant changes observed with Ig's, LT's and histamine was an increase in mucus LTB<sub>4</sub> in SER (p<0.05) and of elevated baseline LTC<sub>4</sub> in SER compared with LPR (p<0.005). These findings support the hypothesis that eosinophils (and to a lesser extent neutrophils) play a major role in tissue injury in LPR and that eosinophil infiltration may be associated with macrophage activation.

### Changes in phospholipid profiles in bronchoalveolar lavage in sarcoidosis and extrinsic allergic alveolitis

DA HUGHES, PL HASLAM *Cell Biology Unit, Cardiothoracic Institute, London* Phospholipids (PL) are essential materials for the tensio-active properties of pulmonary surfactant, but there have been very few studies in patients with interstitial lung diseases. A striking deficiency of the major component phosphatidylcholine (PC) (% total PL) has been reported in extrinsic allergic alveolitis (EAA) (Jouanel *et al*, *Clinica Chimica Acta* 1981;115:211) contrasting with normal proportions in sarcoidosis (Higenbottam *et al*, *Am Rev Respir Dis* 1986;133(s):A321). These reports need confirmation. We have analysed PL profiles in bronchoalveolar lavage (BAL) samples from untreated patients with sarcoidosis (12) and EAA (12)

compared with controls (12). Lipids were isolated by chloroform methanol extraction, individual PL components were identified by thin layer chromatography and quantified by reflectance densitometry. The mean total PL level ( $\mu\text{g/ml}$  BAL) was significantly higher in the sarcoidosis group compared with controls (mean (SD); 21.0 (5.6); 15.9 (8.2) respectively,  $p < 0.05$ ). PL profile analysis showed no significant differences in %PC, but compared with controls both disease groups had decreased proportions of phosphatidylethanolamine (sarcoidosis;  $p < 0.02$ ; EAA,  $p < 0.002$ ). The sarcoidosis group had a raised proportion of phosphatidylglycerol ( $p < 0.05$ ). In conclusion, changes in PL profiles have been observed in granulomatous lung diseases, but we have been unable to confirm that the estimation of %PC levels is of diagnostic value.

#### **Abnormal macrophage-like cells in sarcoid lavage and their correlation with disease activity**

GM AINSLIE, LW POULTER, RM DU BOIS *Royal Free Hospital School of Medicine, Departments of Thoracic Medicine and Immunology* The phenotypes of macrophage-like cells in bronchoalveolar lavage from 18 patients with sarcoidosis and seven normal volunteers were investigated. Immunocytological investigations on cytopins of lavage were performed using a panel of monoclonal antibodies that phenotypically discriminated subsets of macrophages. The numbers of dendritic antigen presenting cells (APCs) (RFDI+) and mature macrophages (RFD7+) as well as cells expressing both of these markers (RFDI+/RFD7+) were significantly raised in sarcoid patients when compared to the control subjects. Results on individual patients were plotted against serum angiotensin converting enzyme levels (SACE), lung function tests and chest radiographic stage. No correlation was found between SACE or results of lung function tests. A direct relationship was established however between the proportions of dendritic cells RFDI+, the abnormal DI+/D7+ cells and the chest radiographic stage. Subsequent investigation of lymphocyte markers also revealed a correlation between proportions of T blasts expressing high concentrations of RFT2 antigen (CD7) and chest radiographic stage. Given that high numbers of DI+ dendritic cells and activated T cells in lavage reflect interstitial inflammation it is concluded that chest radiographic represents the most meaningful clinical indicator of local disease activity.

#### **BAL T lymphocyte helper: suppressor cell ratio does not predict subsequent change in pulmonary function in sarcoidosis**

K WARD, C ODLUM, C O'CONNOR, A VAN BRED, MX FITZGERALD *Department of Medicine, University College and St. Vincent's Hospital, Dublin, Ireland* Forty-five patients with biopsy proven sarcoid (newly diagnosed or no treatment for > six months) had bronchoalveolar lavage (BAL) and the T lymphocyte helper : suppressor ratio (TH:TS) calculated. Fourteen patients had a high TH:TS (>4) (Group A) and 31 a low TH:TS ratio < 4 (Group B). The TH:TS ratio was not used in patient decisions. Patients

were followed up for a median period of two years (range 1-3.1 years) with serial pulmonary function tests (PFTs) (median eight sets of PFTs/patient). There was no difference between the groups in the initial PFTs or serum angiotensin converting enzyme (sACE). Initial gallium scan lung/thigh ratio (normal < 4.0) was higher in Group A (mean 4.6, SD 1.6) than Group B (mean 3.7, SD 1.6) ( $p = .017$ ). Linear regression analysis of each PFT vs time revealed no differences in the rate of change of any PFT between the groups. There was no difference between the groups at the end of the follow-up period in PFTs or sACE or requirement for steroid therapy. These results were not affected by excluding patients with active erythema nodosum nor by using a lower TH:TS cut off ratio (2.0). In this cohort of patients a high BAL TH:TS ratio did not identify patients whose pulmonary function was more impaired than others either at diagnosis, or during or after follow-up.

#### **Preoperative pulmonary function (PF) as predictors of morbidity in thoracic operations**

RD MILLER, T TINSTMAN, K OFFORD *Mayo Clinic, Rochester, USA* To assess which PF values are most sensitive predictors, we followed the postoperative course of 199 consecutive patients who had thoracic operations during one year. Excluding those under 20, the age range was 20-85. Most significant predictor of a respiratory complication was the MVV ( $p < 0.001$ ). Other predictors in order of significance included: VC ( $p = .002$ ), PV ( $p = .014$ ), FEV<sub>1</sub> ( $p = .034$ ). The FEF<sub>25-75</sub>% was not significant ( $p < .10$ ). Pao<sub>2</sub> was done only in those with more severe flow impairment and did not serve as an additional predictor ( $p = .075$ ) among the more severely flow-impaired group. Those few patients (10) receiving steroids had a high complication rate suggesting that hyperactive airways is a risk factor for morbidity. The high significance of the MVV for avoiding respiratory complications may be explained by the close association between that manoeuvre and the more rigorous, time-consuming maximum sustained ventilation. These manoeuvres may relate to the ability for postoperative cough and deep ventilation. Although the MVV has been proposed for deletion from routine PF testing by some, its retention for preoperative evaluation seems essential.

#### **Longterm use of silicone rubber endotracheal prostheses for injury or inoperable major airways obstruction**

S WESTABY (INTRODUCED BY ER TOWNSEND) *The John Radcliffe Hospital, Headington, Oxford* The Westaby (T) tube, or tracheobronchial (T-Y) stent, has been used in 20 patients (pts) with complex injury or inoperable major airways obstruction. Three pts with severe blunt laryngeal trauma, two with inoperable tracheal tumours, two with neuromuscular disorders requiring tracheal suction and two with a failed tracheal anastomosis were managed with the T tube. The T-Y stent was used for palliation in eight pts with extrinsic intrathoracic compression by mediastinal tumour and for seven pts with unresectable tracheal or carinal tumours. Two of these patients had previously undergone



laser therapy. Two pts with extensive endotracheal burns, one with stab wounds and tracheo-oesophageal fistula, and one with a ruptured right main bronchus were also managed with the T-Y stent. The methods of insertion are simple, non-invasive and once in place both tubes can be left in situ for many months. Asphyxia due to trauma, tumour or secretions was relieved effectively in all pts for periods up to seven years (T-Y stent). Both are comfortable and well tolerated with disappearance of the cough impulse after 48 hours and excess secretions within a week. Both provide respiration through the nasopharynx so that humidification and phonation are maintained. Those patients with acute respiratory failure due to tracheal obstruction were able to undergo radiotherapy without fear of asphyxia.

#### **Cervical thymectomy for non-thymomatous myasthenia gravis**

RI WHYTE, RJ DONNELLY *Adult Regional Cardiothoracic Unit, Broadgreen Hospital, Liverpool* A relationship between the thymus gland and myasthenia gravis was first suggested by Weigert in 1901, but it was not until 1939 that Blalock demonstrated a therapeutic role for thymectomy. This role has been confirmed by many authors, but the timing of thymectomy and the choice of the transsternal or transcervical route has not been definitively decided. We have reviewed 40 patients who underwent cervical thymectomy between 1976 and 1986. There were 10 males and 30 females. Using the Osserman clinical classification, there was a statistically significant symptomatic improvement in 26 patients after thymectomy. There was also a reduction in average medication requirements. An analysis was made of age, sex, duration of symptoms, thymic weight and histological appearances. None of these factors was significant in predicting response to thymectomy. Mortality was zero and morbidity low. Only two patients have been admitted to intensive care in the last six years. Mean postoperative hospital stay was 6.7 days. The majority of patients are female and the cervical approach has important cosmetic advantages. Sternotomy is not excluded at a later date if thought necessary and we would recommend cervical thymectomy as the initial surgical approach in patients with non thymomatous myasthenia gravis.

#### **Thoracoscopy — a technique for physicians?**

AC DAVIDSON, RJD GEORGE, CD SHELDON, G SINHA, DM GEDDES *London Chest Hospital, London* Thoracoscopy is of proven diagnostic value in cases of pleural effusion of unknown aetiology. Although general anaesthesia is conventionally employed, physicians in Europe commonly perform thoracoscopy using local anaesthesia ("medical thoracoscopy"). We have performed "medical thoracoscopy" in 30 patients in whom pleural aspiration and pleural biopsy had been unhelpful. Papaveretum (IM) supplemented by IV diazepam was used for sedation. A rigid thoracoscope (Storz) was used in the initial 10 patients. Subsequently the pleural cavity was examined with both the Storz thoracoscope and with a fibreoptic

bronchoscope (FOB), the biopsy specimens taken with the two instruments being processed separately and reported blind. The procedure was well tolerated and was without significant complication. Diagnostic tissue was obtained in 24 cases (malignancy 18) and was suggestive but not diagnostic of mesothelioma in three patients. Two false negatives occurred (adenocarcinoma at PM and at open thoracotomy). In one case inadequate tissue was obtained (normal lung). Complete concordance was seen between the FOB and thoracoscopic specimens. The procedure was supplemented by successful tetracycline pleurodesis in 14 out of 17 cases. "Medical thoracoscopy" proved safe and acceptable to patients, is easily learnt, has a high diagnostic yield and can be performed by physicians since the FOB proved satisfactory when used as a thoracoscope.

#### **Mediastinoscopy as the primary investigation of mediastinal lymphadenopathy**

CW PATTISON, A WETTER, S WESTABY, ER TOWNSEND *Harefield Hospital, Uxbridge, Middlesex* Mediastinoscopy was introduced by Carlens in 1959 and is widely accepted for staging bronchogenic carcinoma. Its role in investigating primary mediastinal lymphadenopathy is less well defined, except in suspected sarcoidosis. A retrospective review of 110 consecutive patients undergoing mediastinoscopy for primary mediastinal lymphadenopathy was made (Harefield Hospital 1982-1986). Mediastinoscopy gave a positive histological diagnosis in 74.5% (82) of cases; 27 patients with sarcoidosis, 25 with metastatic carcinoma, 19 tuberculosis, seven lymphoma and four with mediastinal fibrosis. Of the remaining 25.5% (28 patients) with normal histology, 23 were followed up by the referring hospital and subsequently discharged. Five patients with normal mediastinoscopy, cytology and bronchoscopy were subsequently shown to have bronchogenic carcinoma. The average hospital stay was three days. A pneumothorax occurred due to pleural damage and was treated by intercostal drainage. There was no mortality or other complications. Six patients with superior vena caval obstruction underwent mediastinoscopy without complication. Although conventional and computerized tomography had been performed in 33 patients prior to referral and confirmed mediastinal lymphadenopathy, they did not contribute to the diagnosis. We consider them unnecessary and advocate mediastinoscopy as the investigation of choice to gain a histological diagnosis upon which treatment, if required, may be immediately based.

#### **A survey of the management of primary spontaneous pneumothorax in the UK**

RJA BUTLAND, GP SPICKETT, D SEATON *Heath Road Wing, Ipswich Hospital, Ipswich, Suffolk* One hundred and sixty-one physicians and 57 thoracic surgeons replied to a pneumothorax questionnaire (74% response). Surgeons adopted invasive procedures at a smaller median size of pneumothorax than physicians (20% vs 30%). Twenty-one per cent of surgeons and 51% of physicians sometimes used syringe aspiration. There was no consensus on what volume.



of air may be aspirated before abandoning this procedure. Thirty-nine per cent aspirate once, 53% twice and 8% three or more times, before resorting to intercostal tube drainage. Thirty-six per cent of doctors sometimes employed a flutter valve. In siting an intercostal drain, there was a marked preference (5:2) for the axilla over the anterior chest wall, especially in females. Seventy-seven per cent of physicians clamp an intercostal tube after full expansion, removing it the next day. Thirty-seven per cent of surgeons concur but the majority do not clamp the tube, but remove it the same day (12%) or the next day (44%). Fifty-one per cent of surgeons employed suction routinely, compared with only 2% of physicians. Fifteen per cent of physicians never use suction. Definitive surgical procedures were advised after the second ipsilateral pneumothorax by 51% and after the third by 49%. Yet only 43% recommend surgery if the second pneumothorax is contralateral. There is considerable variation in the management of primary spontaneous pneumothorax, with surgeons adopting more active treatment than physicians.

#### Does laser treatment improve lung perfusion?

PJM GEORGE, \*G CLARKE, \*S TOLFREE, MR HETZEL *Departments of Chest Medicine and \*Radioisotope Scanning, University College Hospital, London* It is well known that perfusion to a lung affected by bronchogenic carcinoma may be markedly impaired. Although spirometry has shown that endoscopic laser resection of bronchial tumours improves ventilation, it is possible that this treatment does not help perfusion. We have investigated this possibility by performing  $^{81m}\text{Kr}$   $^{99m}\text{Tc}$  perfusion scans immediately before and four days after laser treatment in 14 patients with histologically proven bronchial carcinoma. All patients were treated with a neodymium YAG laser under general anaesthesia. Ventilation and perfusion in the affected lung was expressed as a ratio of that in the unaffected lung and the pre- and post-treatment scans were compared by computer subtraction. Ventilation improved in 13 patients (93%), the mean ratio for all patients rising from 0.42 to 0.64 ( $p < 0.001$ ). Perfusion improved in 11 patients (79%); the mean perfusion ratio for all patients rose from 0.39 to 0.50 ( $p < 0.02$ ). Incremental changes in ventilation and perfusion ratios were positively correlated ( $p = 0.01$ ). Mean values for spirometry, six minute walking distance, Karnofsky performance index and breathlessness scores were also significantly improved ( $p < 0.05$ ). We conclude that endoscopic laser treatment leads to a matched improvement in ventilation and perfusion in most patients, together with improved symptom scores and spirometry.

#### Effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease (COPD)

J EFTHIMIOU, J FLEMING, C GOMES, SG SPIRO *Department of Medicine, University College Hospital, London* Two groups, each of seven poorly nourished patients with COPD, matched for lung function (FEV<sub>1</sub> 30.4% predicted, Group 1; 32.4% Group 2) and body weight % ideal (79.5%

Group 1 and 81.5% Group 2) were studied for nine months. Daily dietary intake, respiratory muscle strength (inspiratory and expiratory maximal mouth pressures (PI and PE max), sternomastoid maximum voluntary contraction (MVC) and fatiguability), and hand grip strength were recorded at monthly visits. After three months Group 1 received supplementary Build-Up (320 kCal, 18 g protein/sachet) to increase their mean daily calorie intake from 1429 to 2118 kCal, (that is, during months 4-6), reverting to normal diet for the remaining three months. Group 2 remained on their normal diet (mean 1410 kCal/day). All measurements remained unchanged in the control Group 2 during the nine months. In Group 1 taking Build-Up for three months caused a mean weight gain of 4.2 kg ( $p < 0.05$ ). P<sub>I</sub>max increased from  $45.7 \pm 9.8$  to  $55.0 \pm 13.3$  cmH<sub>2</sub>O ( $p < 0.05$ ). Both sternomastoid MVC and handgrip strength increased with Build-Up ( $p < 0.05$ ) and sternomastoid fatiguability (ie. fall in 20:50 ratio 10 and 60 min after the performance of 50 fatiguing head lifts) decreased significantly ( $p < 0.05$ ). Subjective assessments including a 10 cm general well being score line, breathlessness score, and six minute walking distance all improved significantly during the Build-Up period. Simple oral supplementation can significantly improve respiratory muscle strength in poorly nourished patients with COPD.

#### The rib cage and abdominal components of respiratory system compliance in tetraplegic patients

JM GOLDMAN, SJ WILLIAMS, DM DENISON *Lung Function Unit, Brompton Hospital, London* The respiratory system (chest wall and lungs) compliance of patients with complete tetraplegia is less than that of normal subjects (Estenne *et al*, *Am Rev Respir Dis* 1983;120:1002-1010), whilst abdominal wall compliance is twice normal (Goldman *et al*, *Thorax* 1986;41:513-518). This suggests that the system as a whole is less compliant because the rib cage is stiff. To test this hypothesis we measured respiratory system (RS) compliance and partitioned it into rib cage (RC) and abdominal (ABD) components in eight supine patients with stable complete tetraplegia. Expiration was impeded with a series of spring loaded resistances and end expiratory pressure plotted against change in chest wall volume, which was measured by an optical contour mapping system and divided into RC and ABD displacements. The compliance of each compartment was normalised to predicted TLC to give its specific compliance (SC<sub>RS</sub>, SC<sub>RC</sub>, SC<sub>ABD</sub>). Mean SC<sub>RS</sub> was 8.1 ml/cm H<sub>2</sub>O/L TLC (SD=4.1 ml/cm H<sub>2</sub>O/L TLC), 64.7% of the predicted value for supine paralysed normal subjects derived from the data of (Vellody *et al*, *Am Rev Respir Dis* 1978;118:479-491). SC<sub>RS</sub> for tetraplegic patients was composed of a mean of 75.5% SC<sub>ABD</sub> and 24.5% SC<sub>RC</sub>, whilst in normal subjects 50% of SC<sub>RS</sub> is partitioned to each compartment. The rib cage is thus significantly stiffer in tetraplegic patients. This should limit paradoxical rib cage motion on inspiration and may be an advantage.

#### Rib cage expansion after median sternotomy

TJ LOCKE, TL GRIFFITHS, A SUTTON, GJ GIBSON *Departments*

*of Respiratory Medicine and Cardiothoracic Surgery, Freeman Hospital, Newcastle Upon Tyne* A restrictive ventilatory defect occurs after median sternotomy, but the mechanism is unclear. Measurements were made of lung volumes and of chest wall motion using four pairs of magnetometers (lateral rib cage, anteroposterior (AP) abdomen and two AP rib cage dimensions) in ten men undergoing coronary artery grafting, preoperatively, and one week and three months after surgery. Reductions in lung volumes one week after surgery were similar to those reported previously and were more marked in the supine posture (mean VC sitting and supine 67%, 56% respectively of preoperative values). At three months lung volumes were not significantly different from preoperative values. Magnetometry at one week showed reductions in the amplitude of rib cage displacement but only the reduction in rib cage motion in the supine posture was statistically significant. Recovery was complete at three months. Coordination of rib cage motion was assessed by measuring the phase angle between each linear displacement and airflow. At one week this was outside the preoperative range for one or more rib cage dimensions in three of eight sitting patients and in seven patients when supine. Phase abnormalities persisted in three patients at three months. No abnormalities of abdominal motion were detected. The results suggest that discoordinate rib cage expansion contributes to the restrictive ventilatory defect that follows median sternotomy.

#### Respiratory and limb muscle strength in myasthenia gravis

A MIER, C BROPHY, J MOXHAM, M GREEN *Brompton Hospital, Fulham Road, London* In myasthenia gravis (MG), a condition characterised by fatiguable muscle weakness, respiratory muscle involvement may be difficult to detect clinically. We therefore wondered whether respiratory muscle weakness in MG could be predicted from limb muscle involvement. Studies were performed on 17 patients aged 20-63 years with a history of MG ranging from six months to 45 years (mean 12 years). All patients complained of dyspnoea on exertion (SOB) which was graded 1-5 on the MCR scale. Maximal voluntary contractions (MVC) of the quadriceps femoris muscles were measured in a specially adapted chair. An index of respiratory muscle strength (RMS) was calculated from the sum of maximal static expiratory and inspiratory mouth pressures. Transdiaphragmatic pressures (Pdi) were measured using balloon catheters during maximal sniffs (sniff Pdi). MVC's were abnormal in all 17 patients (range 20-74% pred; mean 45%). RMS was reduced in 15 patients (range 29-106% pred; mean 53%). Sniff Pdi was reduced in eight patients (range 15-132 cm H<sub>2</sub>O; mean 78 cm H<sub>2</sub>O : NR > 80). There was no correlation between SOB and either RMS ( $r=0.0$ ) or sniff Pdi ( $r=0.20$ ). Similarly there was little correlation between MVC and either RMS ( $r=0.57$ ) or sniff Pdi ( $r=-0.36$ ). However RMS and sniff Pdi were correlated ( $r=0.77$ ). These results indicate that neither the grade of dyspnoea nor the degree of quadriceps muscle weakness provide an adequate indication of respiratory muscle involvement in patients with MG. Thus

direct measurement of Pdi must be made in order to detect weakness of the diaphragm.

#### Diaphragm strength in patients with a raised hemidiaphragm

CM LAROCHE, AK MIER, M GREEN *Brompton Hospital, London* We studied respiratory muscle function in 11 patients with a raised hemidiaphragm on chest X-ray, temporally related to aortic valve replacement (three cases), cervical spine injury (1), chest infection (4), motor neurone disease (1), and to no obvious related cause (2). Three patients complained of severe breathlessness, five mild to moderate, and one only on singing. Seven patients had a maximum inspiratory mouth pressure below 70% predicted (17-70 cm H<sub>2</sub>O, mean 48 cm H<sub>2</sub>O), while only two patients had a reduced maximum expiratory mouth pressure. Transdiaphragmatic pressure (Pdi), measured using oesophageal and gastric balloons during a maximal sniff, was reduced in 10 patients (range 20-87 cm H<sub>2</sub>O, mean 53 cm H<sub>2</sub>O, NR > 98cm H<sub>2</sub>O). These patients had a reduced or absent twitch Pdi on stimulation of the phrenic nerve on the affected side. In five patients the phrenic nerve conduction time was also prolonged indicating that the abnormality was related to a defect of the phrenic nerve rather than primarily of the muscle. We conclude that an isolated raised hemidiaphragm may be associated with significant inspiratory muscle weakness and even breathlessness. The functional significance of this is likely to be compounded by the presence of other lung pathology.

#### Airway response to deep inspiration in diabetic patients with autonomic neuropathy

AJ DORWARD, BM FISHER, BM FRIER, NC THOMSON *Departments of Respiratory Medicine and Diabetic Medicine, Western Infirmary and Gartnavel General Hospital, Glasgow* Bronchodilatation follows deep inspiration in normal subjects with pharmacologically induced bronchospasm, but this is reduced or absent in some asthmatics. To investigate the role of vagal pathways in this reflex, we compared six diabetics with autonomic neuropathy and cardiovascular evidence of vagal damage, with a control group of five diabetics without neuropathy. After bronchial provocation with methacholine, maximal expiratory flow rates at 30% of forced vital capacity from partial (V<sub>30(p)</sub>) and complete (V<sub>30(c)</sub>) flow volume curves were measured. The provocation concentration (PC) of methacholine producing a 30% fall in V<sub>30(p)</sub> and V<sub>30(c)</sub> were obtained and the effect of lung inflation expressed by the ratio PC<sub>30 V<sub>30(p)</sub>/PC<sub>30 V<sub>30(c)</sub></sub>. All patients had a ratio of less than one, i.e. they showed bronchodilation to deep inspiration. The mean ratio (range) was 0.20 (0.07:0.35) in the neuropathy group and 0.19 (0.08:0.81) in the control. Two patients had an increased bronchial reactivity as measured by PC<sub>20</sub> FEV<sub>1</sub>. One in the neuropathy group had symptoms of asthma and one in the control group had hay fever. Both patients bronchodilated normally to full inspiration. We conclude that the bronchodilator response to deep inspiration is not mediated through vagal pathways.</sub>

**Electrophrenic respiration (diaphragm pacing) using quadripolar electrodes**

WJM KINNEAR, P TALONEN, JM SHNEERSON *Assisted Ventilation Unit, Newmarket General Hospital, Newmarket* Bilateral quadripolar phrenic nerve stimulators have been implanted in a 68 year old male with central hypoventilation. On each phrenic nerve the four electrodes were positioned to stimulate one quadrant of the nerve. The ventilation produced by stimulation of these quadrants was produced by using a supramaximal stimulus amplitude with a stimulus pulse interval of 15 milliseconds. The tidal volume (Vt) produced was different for stimulation of each phrenic nerve quadrant, the largest Vt obtained being 1.57 l on the right and 0.99 l on the left. The minimum Vt obtained with stimulation of a single quadrant was 0.78 l. The Vt produced when stimulating two or three quadrants simultaneously, was related to the sum of the Vt's obtained with the same quadrants stimulated alone. Stimulation of the quadrant producing the largest Vt also produced the largest electromyographical signal recorded with surface electrodes either anteriorly, laterally or posteriorly in the seventh ICS. On either side, stimulation of quadrants other than that producing the largest Vt induced shoulder pain. Stimulation of different phrenic nerve quadrants is possible using quadripolar electrodes and may be of value in long term diaphragm pacing.

**Presenting features of patients with pulmonary emboli**

A FENNERTY, H SHETTY, D PAYTON, P ROUTLEDGE, IA CAMPBELL *Llandough Hospital, Penarth, South Glamorgan* The presenting features of 100 patients with pulmonary emboli (PE) diagnosed by ventilation perfusion scanning were reviewed. The most frequent symptoms were pleuritic chest pain, 62%, and dyspnoea, 59%, cough and haemoptysis occurring in 30% and 26%. Chest pains were the only symptom in 19% and dyspnoea in 9%. Ten per cent presented with features of a chest infection and only one subject was clinically shocked. Physical signs were generally unhelpful in making the diagnosis. Examination was normal in 27%, 29% had a tachycardia, 26% crackles and only 10% had a pleural rub. Localised tenderness was present in 6%. The chest radiograph was normal in 38%, the commonest abnormalities being consolidation, 27%, and effusion, 26%. The ECG was abnormal in 60%, the commonest abnormality being T wave changes, 20%; the S<sub>1</sub>Q<sub>3</sub>T<sub>3</sub> pattern occurring in only 3%. When blood gases were measured the PaO<sub>2</sub> was less than 80 mm Hg in 70%. Only 15% of patients were free from any associated disease or risk factors for PE. Chronic obstructive lung disease was the commonest associated disease, 21%, and 19% were post-operative. Forty-two per cent were current smokers and 27% ex-smokers of at least two years' duration. The drugs most frequently used prior to the PE were diuretics 18% and corticosteroids 12%.

**Regional ventilation-perfusion mismatch in lung fibrosis: a false positive pulmonary embolism scan**

JMB HUGHES, D HART, D CARR, JP LAVENDER, NB PRIDE *Departments of Medicine and Radiology, Royal*

*Postgraduate Medical School, Hammersmith Hospital, London* In 1972 thick lung sections from one of our cases of fibrosing alveolitis showed lower zone fibrotic changes with replacement of the upper zones apparently by "emphysematous bullae". Physiologically, the vital capacity was normal but transfer factor grossly reduced (7% predicted). Regional perfusion (<sup>133</sup>Xe) to the upper zones was absent but regional ventilation was normal. In 1985, we saw two cases of typical cryptogenic fibrosing alveolitis whose radioisotope V/Q scans strongly suggested pulmonary embolism. They were anticoagulated without benefit. Subsequently, CT scans showed that the ventilated but unperfused regions (mostly in upper zones) consisted of thick walled cysts, more akin to honeycomb lung (with unusually large air spaces) than to emphysematous bullae. Regional V/Q mismatch has since been found in a further six (out of seven) cases of interstitial fibrosis, associated with cystic spaces on the CT scan. Ventilation of these spaces suggests that they are very compliant and are supplied by patent airways in contrast to classical bullae. The practical message is that physiologically they mimic the vascular obstruction of pulmonary embolism.

**The effect of airway lability on tracheobronchial clearance and viscoelastic properties of bronchial secretion in patients with chronic bronchitis**

M MORETTI, MT LOPEZ-VIDRIERO, D PAVIA, SW CLARKE *Department of Thoracic Medicine, Royal Free Hospital and School of Medicine, London* A wide variation in the rheological properties of sputum and tracheobronchial clearance (TBC) has been reported in chronic bronchitic (CB) patients (Lopez-Vidriero, Reid, *Am Rev Respir Dis* 1978;117:465; Pavia *et al*, *Eur J Respir Dis* 1983;64 suppl 127:41). The aim of this study was to ascertain if interpatient variation could be due in part to differences in bronchial lability assessed as bronchodilator response to an inhaled beta-2 agonist (fenoterol 400 µg). Bronchial lability (% change in FEV<sub>1</sub>) was treated in 24 CB patients at the same time of the day on three separate occasions, at least one week apart. Tracheobronchial clearance was measured by a radioaerosol technique; an oscillatory viscometer was used for measuring viscosity and elasticity (G'), at 0.352 Hz. The number of coughs, wet weight of sputum and its radioactive content were recorded during the six hour TBC period as well as 24 hour sputum production. Ten patients had a change in FEV<sub>1</sub> between 5-15% (Group 1) and in 14 patients < 15% (Group 2). Patients in group 2 had a faster TBC which was significant between three-six hours, (p<0.05). Sputum viscosity and G' were significantly lower in group 2 (mean ± SD 339 ± 341 mPa s; 1701 ± 1141 mPa) than in group 1 (752 ± 271; 4383 ± 2151). The daily sputum production in group 2 was significantly higher than in group 1 (p<0.05). These findings indicate that CB patients with labile airways have a faster mucociliary transport in the peripheral airways and their secretion seems to be more suitable for mucociliary transport.

### Variability and reproducibility in the measurement of tracheobronchial clearance in healthy subjects and patients with different obstructive lung diseases

M DEL DONNO, D PAVIA, \*JE AGNEW, MT LOPEZ VIDRIERO, SW CLARKE *Department of Thoracic Medicine and Medical Physics\*, Royal Free Hospital and School of Medicine, London* The purpose of this study was to evaluate the inter and intra-subject/patient variability of tracheobronchial clearance (TBC), measured for six hours, using a radioaerosol technique (5  $\mu\text{m}$  diameter  $^{99\text{m}}\text{Tc}$  labelled polystyrene particles). The inter-subject variability was evaluated in five groups: 33 non-smokers (NS); 19 asymptomatic smokers (S); 40 asthmatics (A); 27 chronic bronchitics (CB) and 12 bronchiectatics (B). The intra-subject variability was evaluated in 16 A and 27 CB studied twice. Furthermore, we were able to estimate the number of patients required to be entered into a study when investigating the effect of a drug or of a therapeutic intervention on TBC. The inter-subject/patient coefficient of variation (COV) was 13% for NS and for the remaining four groups it ranged from 28-39%. The intra-patient COV was about half of the intersubject/patient COV. Inter-subject COV (for A and CB) appeared to be independent of initial deposition of radioaerosol and cough. In order to estimate in CB and A patients, a difference of 15% in TBC attributable to therapeutic intervention, at a statistical significance level of 5% and with a power probability of success of 80%, it is necessary to study at least 14 and 10 patients respectively, in a cross-over design study.

### High dose salbutamol in COAD

AS VATHENEN, J BRITTON, P EBDEN, R HILL, JB COOKSON, AE TATTERSFIELD *Department of Medicine, Glenfield General Hospital, Leicester Respiratory Medicine Unit, City Hospital, Nottingham* Patients with chronic bronchitis often receive beta agonists though the benefits are relatively small, the ratio of benefits to side effects was difficult to assess and the optimum dosage is still unclear. Thirty patients with chronic bronchitis (mean age 63 years, mean  $\text{FEV}_1$  0.9. and <15% response to 200  $\mu\text{g}$  salbutamol) were given placebo, 400  $\mu\text{g}$ , 1 mg, 2 mg and 4 mg salbutamol by rotacaps in random order on separate days. Response was measured over six hours as change in airway calibre ( $\text{FEV}_1$ , VC and PEFR), 12 minute walk test, tremor, oxygen saturation and heart rate. Symptoms of tremor, headache, and palpitation were assessed by visual analogue scores (VAS).  $\text{FEV}_1$ , VC and PEFR all showed dose related increases with mean maximum response ranging from 88-196 ml for  $\text{FEV}_1$ , 265-427 ml for VC and 16-50 l/min for PEFR. The duration of effect was also dose related as was heart rate and finger tremor. There was no significant dose related difference in walk distances, VAS or  $\text{O}_2$  saturation. Thus the higher doses of salbutamol were well tolerated and produced slightly more bronchodilatation than the low doses but this was not reflected by increase exercise tolerance.

### A study of the time course of response to corticosteroids in chronic airflow obstruction

DC WEIR, AS ROBERTSON, RI GOVE, PS BURGE *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* One hundred and twenty patients with adult onset chronic airflow obstruction, without clinical asthma, underwent a double blind, randomised, crossover trial of oral prednisolone 40 mg daily, inhaled beclomethasone dipropionate (BDP) 500  $\mu\text{g}$  t.d.s., or placebo. Each treatment was given for two weeks, with a two week washout between phases. Twenty-five patients showed a response ( $\geq 20\%$  increase) in mean PEFR during the second week of treatment, 15 patients completed readings for at least 14 days following the treatment phase. Five responders to prednisolone, and three to BDP did not reach maximum mean daily PEFR until the final day of the treatment phase. For the others the mean was 11 (range 6-13) days for prednisolone and 9.2 (range 7-12) days for BDP. Pre treatment values were reached within 14 days in only eight patients with post treatment readings, and after 28, 29, 41 and 42 days in four patients. Trial of corticosteroids in chronic airflow obstruction should include more than 14 days treatment to produce maximum benefit in all patients, and should have at least six weeks between treatment phases or have the placebo period first.

### Why bother with acute reversibility tests for asthma?

CR HORN, GM COCHRANE *Chest Clinic, New Cross Hospital, London* There is much debate on the criteria necessary to make a diagnosis of "asthma". Many authorities consider the demonstration of acute reversibility to an inhaled bronchodilator to be mandatory. We have examined the value of acute reversibility testing in the prediction of long term response to treatment of airflow obstruction. One hundred and forty-one adults performed spirometry and the improvement in  $\text{FEV}_1$  20 minutes after 800 mcg isoprenaline recorded. The patients were then treated with increasing doses of inhaled salbutamol and beclomethasone dipropionate for nine months. The maximal improvement in  $\text{FEV}_1$  was determined. The mean baseline  $\text{FEV}_1$  was 73.5 ( $\pm 26.9\%$ ) predicted. On average there was a 17.5 ( $\pm 19.2\%$ ) improvement acutely to isoprenaline and a 18.9 ( $\pm 20.7\%$ ) increase over the ensuing months. Although there was a reasonable correlation between these variates ( $r = 0.42$ ) there was wide individual variation. Fifty-two per cent of those with definite acute reversibility ( $>15\%$ ) had no material improvement in the longer term whilst 24% of those with less than 15% acute reversibility were responsive to longer term treatment ( $\text{FEV}_1$  rising by more than 20%). These results confirm the short comings of an acute reversibility test to diagnose asthma.

### The role of preservatives in atrovent-induced bronchoconstriction

CRW BEASLEY, P RAFFERTY, ST HOLGATE *Medicine I, Southampton General Hospital, Southampton* Atrovent, the marketed isotonic ipratropium bromide (IB) nebuliser



solution, has been reported to cause bronchoconstriction when inhaled by asthmatic subjects. In addition to IB Atrovent contains two preservatives, benzalkonium chloride (0.25g/l) and EDTA (0.5g/l). We investigated the role of these preservatives in the development of this bronchoconstriction. Twenty-two asthmatic patients were challenged with 4 ml nebulised Atrovent solution (1 mg IB), and six (27%) developed bronchoconstriction with a fall in  $FEV_1 > 20\%$ . On three separate days these six patients were challenged with 4 ml solutions of preservative-free IB and increasing concentrations of benzalkonium chloride (0.125-5.0g/l) and EDTA (0.25-10.0g/l). In these six patients Atrovent produced rapid bronchoconstriction with a mean  $\pm$  SEM fall in  $FEV_1$  of  $32.0 \pm 6.1\%$  at five minutes, whereas preservative-free IB caused bronchodilation with a mean increase in  $FEV_1$  of  $16.0 \pm 4.5\%$  at five minutes. The preservatives inhaled separately caused dose-related bronchoconstriction. The cumulative geometric mean concentration producing a 20% fall in  $FEV_1$  was 0.30 (0.13-2.0) g/l with benzalkonium chloride and 2.5 (1.2-12.8) g/l with EDTA. We conclude that the bronchoconstriction observed with nebulised Atrovent is due to the presence of benzalkonium and EDTA and not the IB in the solution.

#### Dose response to three concentrations of ipratropium bromide: a double blind placebo controlled study

AB MILLAR, A BUSH, H AL-HILLAWI, JM GOLDMAN, DM DENISON *The Brompton Hospital, Fulham Road, London* Ipratropium bromide administered by metered dose inhaler is effective in asthma and bronchitis at the standard dose of 20  $\mu$ g/puff (*Br Med J* 1975;1:430-432). Recent work suggests that a greater and more prolonged response may be produced with higher doses (*Br J Dis Chest* 1985;79:379-384). We report a randomised, placebo-controlled, double blind trial of its effect at 20, 40 and 100  $\mu$ g/puff in twenty patients (age  $51 \pm 17$  years) with chronic stable asthma (mean, SD  $FEV_1$  47, 16% predicted, reversibility of  $FEV_1$  27, 14). One patient withdrew from the study following use of the highest dose inhaler. The effects of drug or placebo were assessed by measuring  $FEV_1$  and FVC at -5, 0, 5, 30, 45, 60, 90, 120 minutes and hourly thereafter to eight hours after inhalation of two puffs. Data were analysed by a three-way, mixed model analysis of variance.  $FEV_1$  and FVC were significantly higher at all times on all three doses than on placebo. There was no difference between the 20 and 40  $\mu$ g inhalers, but the 100 mcg caused a significantly higher peak  $FEV_1$  and FVC (25% greater rise on 100 mcg compared with 20 and 40  $\mu$ g  $p < 0.01$ ) and a more prolonged duration of action. We conclude that the use of 100  $\mu$ g/puff ipratropium bromide may be more effective than the doses commonly used.

#### Subcutaneous adrenaline versus terbutaline in the treatment of acute severe asthma

MA SPITERI, AB MILLAR, D PAVIA, SW CLARKE *Department of Thoracic Medicine, The Royal Free Hospital, London* About 2000 patients continue to die annually in England and Wales despite increasing self-referral to

hospital and more intensive conventional therapy. Inhalers and tablets may not work and self-administered adrenaline or selective  $\beta_2$ -adrenergic drugs may be vital in those patients with "abrupt attacks". As adrenaline has gone out of favour, and other adrenergic drugs are not widely used for self-medication, our double blind study assessed 20 patients with acute severe asthma, receiving either 0.5 mg (0.5 ml) adrenaline or 0.5 mg (0.5 ml) terbutaline subcutaneously on presentation. Peak expiratory flow rate (PEFR), heart rate (HR), blood pressure (BP) and pulsus paradoxus (PP) were recorded prior to and at 5, 15, 30 and 45 minutes after injection. All patients reported a reduction in chest tightness within three minutes without any adverse effects. The mean  $\pm$  SEM baseline PEFR in the adrenaline group was  $130 \pm 21$ l/min, increasing to  $157 \pm 25$ l/min ( $\approx 21\%$  rise) and  $174 \pm 34$ l/min ( $\approx 35\%$ ) at five and 15 minutes after injection respectively; with terbutaline, the baseline PEFR was  $111 \pm 13$ l/min rising to  $134 \pm 11$ l/min ( $\approx 23\%$ ) and  $154 \pm 20$ l/min ( $\approx 40\%$ ) at five and 15 minutes respectively. There was no significant difference in HR (117 beats/min), BP (124/80 mm Hg) or PP (15 mm Hg) between the two groups at any time. Continuous ECG showed no abnormalities in either group. We conclude that subcutaneous adrenaline or terbutaline provides effective and safe initial therapy for self medication in acute severe asthma attacks.

#### Subcutaneous terbutaline is effective in the treatment of brittle asthma by achieving high serum terbutaline levels

\*AP SYKES, \*\*AJ HIGGINS, \*JG AYRES *\*Department of Respiratory Medicine, East Birmingham Hospital, Birmingham and \*Astra Pharmaceuticals, Edinburgh* We have previously reported that subcutaneous terbutaline by continuous infusion (CSIT) or by six hourly divided doses (QDST) effectively treat brittle asthma/severe morning dipping where other treatment failed (Ayres *et al*, *BMJ* 1984;288:1715). In Birmingham we have now successfully treated 13 patients. This effect could be due to higher blood terbutaline levels (implying down regulation of  $\beta$  receptors), increased drug metabolism and/or the existence of a specific group of  $\beta$  receptors more accessible to circulating rather than inhaled drug. We measured serum terbutaline levels by mass spectrometry (AB Draco) in four patients using QDST (mean daily dose 10 mg) (trough and 30 min post injection) and in one patient using CSIT (12 mg/day). The mean (SD) terbutaline level in the QDST patients was: trough, 42.5 (38.1) nmol/l; peak 194.8 (126.0) nmol/l; CSIT patient, 155 nmol/l. This compares to the range of 10-20 nmol/l in patients taking 7.5 mg po bd of terbutaline. These findings suggest that  $\beta$  receptors may be down regulated in these patients and that enhanced drug metabolism is not implicated in the difficulty in treating these patients.

#### Can ambulance men give nebulised salbutamol?

CWG TURTON, DA CHAMBERLAIN, G MILLER, R GRAINGER *Chest Unit and Cardiac Department, Brighton Hospitals and The East Sussex Ambulance Service* So that severely ill asthmatics could be treated as early as possible,

22 ambulancemen already trained in advanced cardio-pulmonary resuscitation were taught to administer salbutamol 2.5 mgs nebulised by oxygen at six L/min according to simple guidelines. One hundred and eighty "Ventolin" nebulisers were distributed and after six months 61 ambulance case sheets returned for analysis. There were 34 males and 27 females aged between three and 92 years (median 58). Diagnoses were asthma (47), chronic airflow obstruction (6), chest infection (3), lung cancer (1) and unrecorded (4). Ambulancemen considered 47 patients to show good or fair response and nine slight or no response (one patient refused the nebuliser and no data was available for three). All patients were taken to the emergency department where 16 were discharged back to the care of their general practitioner and 45 admitted to hospital. One patient needed intermittent positive pressure ventilation, but all survived except for the patient with lung cancer who died 30 days after admission. Ambulancemen can give nebulised salbutamol with benefit and without risk. We would encourage this extension of the role of the ambulance service.

#### Changes in airway beta-adrenergic responses during the menstrual cycle in women with premenstrual asthma

PN BLACK (INTRODUCED BY RW FULLER) *Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand* One third of women with asthma report a worsening of their symptoms premenstrually. Airway reactivity has been examined in asthmatic women without premenstrual asthma and has not been found to change during the cycle. In this study airway reactivity was measured in six women with a history of premenstrual asthma. One woman was taking an oral contraceptive. Histamine challenges were performed at midcycle (12th to 14th days of the cycle) and premenstrually (nought to seven days period). A histamine aerosol generated from a Mini-Hudson nebuliser was inhaled for one minute and FEV<sub>1</sub> measured one minute later. Histamine was administered at five minutes intervals until a concentration was reached causing a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>). Immediately following this 100 µg of salbutamol was inhaled from a metered dose aerosol. The histamine challenge was then repeated 90 minutes later. The mean PC<sub>20</sub> before inhalation of salbutamol did not change during the cycle being 0.08 mg/ml at midcycle and 0.09 mg/ml premenstrually. However, the mean PC<sub>20</sub> after salbutamol decreased premenstrually being 0.14 mg/ml compared with 0.38 mg/ml at midcycle ( $p < 0.025$ ). This indicates that in women with premenstrual asthma the airway reactivity to inhaled histamine does not change premenstrually but the beta adrenergic responsiveness decreases.

#### Inhibition of exercise induced asthma by nifedipine

P PAFFERTY, J VARLEY, \*J EDWARDS, ST HOLGATE *Southampton General Hospital, Southampton and \*Bayer U.K.* Nifedipine is a derivative of 1,4 dihydropyridine which blocks the voltage dependent calcium channel and, *in vitro*, has been shown to inhibit contraction of airway smooth muscle. In single dose studies

nifedipine and other calcium antagonists have been shown to inhibit bronchoconstriction induced by histamine, methacholine, allergen and exercise but the protective effect has often been small. We have now investigated the dose response relationship of nifedipine against exercise induced asthma (EIA). Eleven mild asthmatics with a history of EIA were studied. On four separate days patients undertook matched six minute exercise tests on a treadmill thirty minutes after oral placebo or nifedipine 10, 20 or 30 mg. Airway calibre was assessed by measurement of FEV<sub>1</sub> before and for 30 minutes following exercise. Nifedipine had no significant effect on baseline airway calibre. The three increasing doses of nifedipine 10, 20 and 30 mg protected the airways against EIA in a dose related manner inhibiting the overall bronchoconstrictor response to exercise by  $23 \pm 15\%$  (NS),  $73 \pm 15\%$  ( $p < 0.05$ ) and  $59 \pm 16\%$  ( $p < 0.05$ ). The effects of the 20 and 30 mg doses were not significantly different from each other. This study has confirmed the efficacy of nifedipine in inhibiting EIA.

#### Bacterial respiratory tract infection and asthma

CRW BEASLEY, ED COLEMAN, PE HOLST, TV O'DONNELL *Department of Medicine, Wellington Clinical School of Medicine, Wellington Hospital, Wellington, New Zealand* We investigated the role of bacterial respiratory tract infections in precipitating acute exacerbations of asthma. Thirty-one atopic asthmatic patients (15-56 years) recorded symptoms of asthma and peak expiratory flow rate daily for a year. They reported for detailed investigation every four weeks or as soon as possible after the onset of symptoms of respiratory tract infection or increased asthma. On all occasions a throat swab was taken if pharyngitis was present, sputum cultured for bacteria, and spirometry performed. Pharyngitis was recorded on 72 occasions but the only micro-organisms recovered from throat swabs were candida species (12 occasions). Bacterial pathogens were found in 17 of 41 sputum samples. Sixteen of these infections occurred in two men (41 and 56 years) who had chronic bronchitis in addition to asthma. *Branhamella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* were the most prevalent organisms and were found alone and in various combinations. Bacterial infection was demonstrated in eight of 178 exacerbations of asthma and on 14 of the 182 occasions when symptoms of respiratory tract infection were present. We conclude that in adult asthmatic patients bacterial respiratory tract infections are uncommon and rarely precipitate asthma. They are unlikely to account for symptoms suggestive of respiratory infection unless chronic bronchitis is also present. Antibiotics should not be the basis of treatment for adults with exacerbations of asthma.

#### Viral respiratory tract infection and asthma

CRW BEASLEY, ED COLEMAN, \*Y HERMON, PE HOLST, TV O'DONNELL, \*M TOBIAS *Department of Medicine, Wellington Hospital, Wellington and \*National Health Institute, Porirua, New Zealand* We investigated the role of viral respiratory tract infections in precipitating acute asthma. Thirty-one atopic asthmatic patients, (15-56 years

kept a diary of symptoms of respiratory disease and peak expiratory flow rate daily for one year. They were seen for detailed investigation every four weeks and additionally as soon as possible after the onset of either symptoms of respiratory tract infection or of an exacerbation of asthma. At these visits we performed: spirometry, nasopharyngeal aspiration for viral identification, and serological testing for viral antibodies. Viruses were identified on 30 occasions: 12 by immunofluorescence, 12 by serology, eight by cell culture and one by direct electron microscopy. Viral respiratory tract infection was demonstrated in 18 of 178 exacerbations of asthma. The viruses associated with asthma were respiratory syncytial virus, rhinovirus and parainfluenza virus, adenovirus was not associated with asthma. There were 182 episodes suggestive of respiratory tract infection and viruses were demonstrated in 23 of these illnesses. The majority (109) of asthma exacerbations were accompanied by symptoms suggestive of respiratory tract infection. We conclude that a minority of asthma attacks in adults are related to viral infection of the respiratory tract. The symptoms which are commonly regarded as those of respiratory tract infection are not usually due to viral infection, but are so frequently associated with deterioration of asthma that they should be regarded as a warning of this possibility.

#### **The outcome of severe community acquired pneumonia treated in the intensive care unit**

M ALKHAYER, PF JENKINS, BDW HARRISON *Department of Respiratory Medicine, West Norwich Hospital, Norwich* Before 1980 no patients with community acquired pneumonia (CAP) were admitted to our ITU. Since then 16 patients (nine men) age 28-66 with CAP have received intensive care. Fifteen had severe pneumonia using BTS criteria:- confusion on admission in 11; admission respiratory rate  $\geq 30$ /minute in 14; admission diastolic pressure  $\leq 60$  mm Hg in four; blood urea  $> 7$  mmol/l during admission in 12. Eleven had bilateral radiographic consolidation; five had unilateral multilobar changes. Nine patients were previously fit. A casual pathogen was identified in nine. Thirteen were ventilated (IPPV) for progressive hypoxia ( $P_{aO_2}$  3.6-7.2 kPa despite 60%  $F_{iO_2}$ ), and two following respiratory arrest, all within four days of admission. One man "sat" by the ventilator. Duration of IPPV ranged from 1-35 days; six were ventilated for over three weeks. Sixteen CVP and/or Swan Ganz (10) lines were inserted. Three patients developed a pneumothorax (bilateral in one), three developed renal failure requiring treatment and three had myocarditis. One patient became jaundiced and one developed pulmonary emboli. Five patients (31%) died (disseminated candidiasis (1), multi-organ failure (1), inability to wean from ventilator (1), brain death (2)). Intensive care and IPPV play a vital role in the treatment of progressive, sustained and dangerous hypoxia in severe CAP. Our study suggests that three-four of the 50-60 patients admitted to our unit annually with CAP require intensive care.

#### **Is nosocomial pneumonia (NP) a problem in Britain?**

MA WOODHEAD, JT MACFARLANE *Department of Thoracic Medicine, City Hospital, Nottingham* Studies from the U.S.A. suggest that NP is a common and important problem with a high mortality and morbidity, but no comparable studies have been performed in Britain. We analysed HAA statistics for the Trent region. There were about 500 recorded cases of NP annually between 1982 and 1984 of which about 40% were related to 13 common operations, particularly cholecystectomy, inguinal hernia repair and laparotomy. A six week prospective study of NP on 16 adult medical and surgical wards in the City Hospital, Nottingham identified 16 such cases (11 male) of whom seven (44%) died. Ten occurred post operatively, following thoracic operations in seven and abdominal in three, and six occurred as complications of the following medical conditions: cardiac failure, chronic obstructive airways disease, lung cancer (2), chronic liver disease and pneumococcal pneumonia. Despite antibiotics having been given to 11 patients (69%) prior to being studied, pathogens were detected in seven cases (44%) including *Streptococcus pneumoniae* (3), *Klebsiella pneumoniae* (2), *Escherichia coli* (1) and *Haemophilus influenzae* (1). NP is an underrated cause of morbidity in British hospitals, has a high mortality, is caused by a different spectrum of pathogens from community-acquired pneumonia and, although difficult to define and investigate, merits further study.

#### **The production of virus specific IgG antibodies in the lung in bone marrow transplant (BMT) recipients with CMV pneumonitis**

HJ MILBURN, JE GRUNDY, PD GRIFFITHS, RM DU BOIS *Departments of Thoracic Medicine and Virology, Royal Free Hospital, London* Cytomegalovirus (CMV) pneumonitis is a common and often fatal complication in BMT recipients. However, treatment with CMV hyperimmune globulin has had some success suggesting that the inability to mount a humoral immune response in the lung may have contributed to the high mortality. We have therefore studied the local production of IgG antibodies to CMV in these patients. Antibody levels were measured by radioimmunoassay in bronchoalveolar lavage (BAL) fluid and serum in 24 BMT recipients, 12 of whom had CMV pneumonitis and 12 with pneumonitis due to other causes. Albumin measurements were used to correct for serum leakage. CMV-specific IgG antibodies were demonstrated in BAL in 8/12 patients with CMV pneumonitis but also in 6/12 patients with pneumonitis due to other causes. These results suggest that BMT recipients are capable of local production of IgG in the lung; however the antibodies produced were not always specific to the infecting agent and may thus represent local polyclonal B cell activation.

### Pharmacokinetic study of the interaction between rifampicin and ketoconazole

N DOBLE, C ROWLAND-HILL, RJ SHAW, \*DW WARNOCK, \*\*M LUSH, EE KEAL *St. Mary's Hospital, London, \*Department of Mycology, Bristol Royal Infirmary, \*\*Merrel Dow Research Institute, Egham* Interactions have been reported between rifampicin and ketoconazole used in AIDS patients (*N Engl J Med* 1984;311:1681-83, *Br Med J* 1985;291:849-50). Despite the limited availability of the drug assays in AIDS patients, a reduction was observed in the circulating concentrations of both drugs when used in combination. In this pharmacokinetic study, the interaction was studied in six healthy volunteers. Venous samples were collected over 24 hours, with measurement of the plasma concentration of the drugs by HPLC. After a three day "run in" period of oral rifampicin (600 mg), peak plasma concentrations (mean  $\pm$  SEM) on day four and five occurred within four hours of the drug, and were 12.8 ( $\pm$  3.4) and 12.0 ( $\pm$  2.6) mcg/ml. Following concurrent administration with oral ketoconazole (200 mg), in single or repeated doses, maximal rifampicin concentrations of 12.8 ( $\pm$  4.7) and 9.8 ( $\pm$  2.6)  $\mu$ g/ml, occurred within four hours. Oral ketoconazole and intravenous rifampicin together, resulted in peak plasma concentrations of rifampicin (16.6  $\pm$  3.6  $\mu$ g/ml) within two hours. Whether given orally or intravenously, rifampicin inhibited the rise of plasma ketoconazole with subtherapeutic peak concentrations up to 2.0  $\mu$ g/ml. This study confirms the interaction between ketoconazole and rifampicin, with marked diminution of plasma ketoconazole concentrations. No inhibition of the increase in circulating rifampicin was observed when these drugs were used in conjunction.

### Lung $^{99m}\text{Tc}$ DTPA transfer in HIV antibody positive patients with *Pneumocystis carinii* pneumonia

MJ O'DOHERTY, CJ PAGE, D BARLOW, DN CROFT, NT BATEMAN *St. Thomas' Hospital, London* *Pneumocystis carinii* is a serious opportunistic pathogen in patients who are immunocompromised, and the most common organism in AIDS related pneumonia. We have assessed the transfer of  $^{99m}\text{Tc}$  DTPA in ten patients who were human immunodeficiency virus (HIV) antibody positive non-smokers and twenty HIV antibody positive smokers. Four patients had *Pneumocystis carinii* pneumonia (PCP) proved by transbronchial biopsy, three were non-smokers and one a smoker.

Two findings emerged:-

- 1) Patients with pneumocystis infection had increased lung  $^{99m}\text{Tc}$  DTPA transfer (mean T50  $\pm$  SEM = 2  $\pm$  0.2 min) compared with non-smokers (62.3  $\pm$  8.5 min) and smokers (16.3  $\pm$  1.8 min).
- 2) The lung  $^{99m}\text{Tc}$  DTPA transfer curves were monophasic in smokers and non-smokers but biphasic in patients with pneumocystis pneumonia. In two patients, with PCP, these curves became monophasic two months after therapy. The observed biphasic curve is indicative of diffuse alveolar damage and might be useful in patients with a normal chest radiograph to predict PCP, and allow early prediction of PCP even in smokers.

### Adverse effects and safety of long term high dose amoxicillin in patients with bronchiectasis

DC CURRIE, \*Y YAKUBU, \*MV CHADWICK, \*H GAYA, P COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute and \*Department of Bacteriology, Brompton Hospital, Fulham Road, London* Thirty-eight patients with bronchiectasis were randomly allocated to receive oral amoxicillin (3 g) or placebo sachets twice daily for 32 weeks in a double blind study. Of the 19 on the antibiotic (placebo numbers in brackets), 8(8) developed gastrointestinal discomfort, 7(2) diarrhoea, 7(4) new upper respiratory tract symptoms, 4(5) nausea, 3(1) arthralgia, 2(0) genital candidiasis, 2(0) reversible black discolouration of the teeth, 2(1) urinary tract infection, 2(4) exacerbations unresponsive to conventional doses of oral antibiotics and 1(0) skin rash. Therapy was stopped prematurely because of side effects in two on antibiotics (one due to diarrhoea, one skin rash) and in one on placebo due to *de novo* proctitis. Minimum inhibitory concentrations (MIC) of four different antimicrobials for *Haemophilus influenzae* and coliforms isolated from sputum were similar in both groups. One patient on antibiotic was newly colonised by *Pseudomonas aeruginosa* but the occurrence of other potential pathogens was sporadic. Stool specimens were cultured from 27 patients before, during, at the end of and after the treatment period. *Clostridium difficile* was never isolated. Many coliforms were resistant to antibiotics before treatment; MICs of four antimicrobials in the remainder were similar in both groups throughout. In conclusion, long term oral amoxicillin (3 g bd) was associated with diarrhoea but without evidence of emergence of new resistant organisms in the stool.

### Short course high dose amoxicillin in the treatment of acute exacerbations of chronic bronchitis

JB BENNETT, SJ CROOK, RJ DAVIES *Academic Department of Respiratory Medicine, St. Bartholomew's Hospital, London* Work by (Cole, *J Antimicrob Chemother* 1983;11:109-113) and Hill *et al*, *Thorax* 1986;41:559-65) has suggested that conventional doses of antibiotics are not as effective in bronchiectasis as higher doses in the clearance of infection from the bronchial tree. We have recently performed a randomised double blind, double dummy, trial of amoxicillin 3 g bd for three days versus amoxicillin 500 mg tds for seven days in the treatment of acute exacerbations of chronic bronchitis. Forty-one patients (40 males and one female) admitted to St. Bartholomew's Hospital with acute exacerbations of their chronic bronchitis were entered into the study. Their mean age was 71 years (range 40-85) and the mean FEV<sub>1</sub> was 0.7 litre (range 0.3-2 litres). Twenty patients received amoxicillin sachets 3 g bd for three days and 21 patients received amoxicillin capsules 500 mg tds for seven days. There was no significant difference between the two groups in terms of duration of hospital admission, reduction in sputum volume or clearance of pus from the sputum, and number of treatment failures. No patient developed unwanted effects from treatment with high dose amoxicillin. Twenty eight patients were followed for one year, and there was no



difference in the number of exacerbations experienced by patients treated with short course high dose therapy compared with low dose therapy. It is concluded that short course high dose amoxicillin is as effective as conventional dose amoxicillin and may be used where compliance is expected to be a problem.

### Bacteriology of daily purulent sputum

CL STEINFORT, H TODD, E HIGGS, PJ COLE *Host Defence Unit, Department of Thoracic Medicine Cardiothoracic Institute, Brompton Hospital, London* The bacteriology of sputum was compared with that of nose and throat swabs, contamination-free endobronchial brushes and bronchoscopy trap specimens in 14 patients with daily purulent sputum (DPS) with or without chronic sinusitis (10 bronchiectasis, two Young's syndrome, two DPS without bronchiectasis). No patients had suffered an acute exacerbation and 12 had not taken antibiotics during the month preceding the study. Specimens were obtained, transported and processed within two hours of sampling by the study coordinators. Sputum was diluted 1:1 with sterile PBS and homogenised using a vortex mixer. Each specimen was Gram stained, and quantitatively or semiquantitatively cultured aerobically and anaerobically on selective media. Results showed that sputum culture reliably grew the endobronchial bacteria (sensitivity 87%) but was often contaminated with nasal and oropharyngeal organisms (specificity 57%). Lower respiratory tract (LRT) bacteria were often also found in the nose and throat, particularly *Haemophilus influenzae* and *Pseudomonas aeruginosa*. Half the patients had multiple, potentially pathogenic, bacteria in their LRT (counts >10,000 CFU/ml). Anaerobic bacteria were found in the LRT of 14% of patients. Sputum Gram stain lacked sensitivity (46%) despite fair specificity (73%) in predicting LRT organisms.

### Multiresistant *Pseudomonas aeruginosa* in cystic fibrosis patients treated with ceftazidime

MJ SMITH, G FULLER, G HUTCHINSON, M CHADWICK, H GAYA, ME HODSON, JC BATTEN *Brompton Hospital, Fulham Road, London* Third generation cephalosporins have been responsible for inducing multiple antibiotic resistance in certain gram negative bacteria by stable derepression of chromosomal type 1  $\beta$ -lactamases. Between September 1984 and August 1986 strains of *Ps aeruginosa* resistant to multiple  $\beta$ -lactams were isolated from the sputum of 67 adult cystic fibrosis (CF) patients (approximately 20% of our adult CF population). The incidence of new cases rose from five, between September-December 1984, to 22 between January-April 1986. Coincident with this dramatic increase in multiresistant *Ps aeruginosa* (MRP) there was a marked increase in the use of ceftazidime. Seventy-five IV courses were given in the second half of 1985 compared with only 28 during 1983. Forty-five of the 67 patients had definitely received ceftazidime (35 IV; 10 nebulised). Six patients had never received ceftazidime. The remaining 16 patients may have received it before referral. In 14 patients there was a close temporal relationship between the

isolation of MRP and a course of ceftazidime. Results of serotyping, phage typing and pyocin typing in 36 of these strains suggest that cross-infection was not the major cause of this outbreak. Of 19 strains tested, all produced the chromosomal  $\beta$ -lactamase and in 14 of these production was partially (5) or fully de-repressed (9). Many of these strains were also resistant to aminoglycosides and quinolones. The results suggest that the dramatic increase in MRP encountered in our adult CF patients may in part be related to ceftazidime usage.

### Increased fat absorption and weight gain in cystic fibrosis using enteric-coated microspheres of pancreatin compared with a standard enteric-coated preparation

RJ STEAD, I SKYPALA, ME HODSON, JC BATTEN *Department of Cystic Fibrosis, Cardiothoracic Institute and Brompton Hospital, Fulham Road, London* Inactivation of enzyme supplements by low pH is a major cause of persistent steatorrhoea in cystic fibrosis (CF). Standard enteric-coated preparations of pancreatin (SECP), widely used in the UK, may alleviate this but data comparing them with the newer enteric-coated microspheres of pancreatin (ECMP) are lacking. In an open, randomised, cross-over study 23 adults with steatorrhea due to CF received SECP (Pancrex V Forte) and ECMP (Creon), over two consecutive 28 days treatment periods. Lipase intake was equal to the patients' previous needs and was constant throughout the study. Patients completed diary cards daily throughout and performed 72 hour faecal collections at the end of each month. Comparing the month on ECMP with that on SECP: there was a reduced frequency of bowel actions ( $p < 0.001$ ) and abdominal pain ( $p < 0.05$ ), and improvement in stool character ( $p < 0.001$ ). Faecal fat excretion was 44% less on ECMP than on SECP and similarly in 86% of patients coefficient of fat absorption was greater on ECMP than SECP (mean difference 13%, 95% confidence limits seven to 19%;  $p < 0.001$ ). Additionally, body weight increased on ECMP ( $p < 0.02$ ). Eighty-one per cent of patients preferred ECMP to SECP. ECMP are more effective than SECP in the treatment of steatorrhoea in CF.

### Ciprofloxacin compared with intravenous azlocillin and gentamicin in the treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis (CF)

ME HODSON, CM ROBERTS, RJA BUTLAND, MJ SMITH, JC BATTEN *Department of Cystic Fibrosis, Cardiothoracic Institute, Brompton Hospital, London* Acute exacerbations of infection in patients with CF who grow *Pseudomonas aeruginosa* in their sputum are routinely treated with intravenous chemotherapy using an anti-pseudomonal penicillin or cephalosporin and an aminoglycoside. An oral treatment would be a great advantage to these patients. Ciprofloxacin is a compound of the quinolone type. It has a high *in vitro* activity against *Ps aeruginosa* when given orally. Forty adult patients (22M, 18F; age range 18-35 years) with acute exacerbations of infection due to *Ps aeruginosa* were randomly allocated to receive a 10 day course of intravenous azlocillin 5 g and

gentamicin 80 mg tds (A) or oral ciprofloxacin 500 mg tds (C). They were assessed on days 1, 10 and 38. There was a statistically significant improvement in PEFr, FEV<sub>1</sub> and FVC between days one and 10 for both treatments (p<0.001). Significant improvement was maintained at six weeks after treatment C (p<0.001) but not after treatment A. Analysis of covariance found C better at day 10 for PEFr and FEV<sub>1</sub>. With both treatments there was a decrease in sputum (p<0.001), symptoms improved and there was no toxicity and no significant side effects. No more drug resistant organisms were isolated from Group C than from Group A. Seventeen of the 20 patients who received C preferred it to previous courses of intravenous antibiotics. Oral ciprofloxacin is a useful short-term treatment for these patients.

#### Defective opsonisation of *Haemophilus influenzae* by serum of elderly patients

N GARBETT, \*G MATHARU, D SYKES, \*\*B LIVESLEY, P COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London*; \**Burton District Hospital, Burton-on-Trent, Staffs* and \*\**St. Francis Hospital, London* The elderly appear to be prone to respiratory infection. Opsonisation of bacteria is an important early defence mechanism but there are conflicting reports in the literature concerning the capacity of the elderly to perform this function. One reason for this may be the use of tests in which the "target" is clinically unrealistic. We have asked whether the use of a clinically more realistic target microorganism, *Haemophilus influenzae*, in assaying the opsonising capacity of serum from elderly persons, allows detection of such abnormalities. Sera from 45 inpatients over the age of 70 years, without known immune deficiency or infection, were compared with sera from 12 healthy subjects less than 35 years of age, for their capacity to opsonise the routinely used target *Staphylococcus aureus* (Oxford strain) and a clinically isolated non-typable, unencapsulated *H influenzae*, using luminol-enhanced chemiluminescence (CL) (Williams *et al*, *Immunology* 1980;41:903). Results are expressed as % CL (mean  $\pm$  SE) of control pooled serum. There was no significant difference between the elderly (87  $\pm$  5%) and the young (100  $\pm$  10%) with regard to opsonisation of *Staph aureus*. However, the opsonisation of *H influenzae* was poor in the elderly (58  $\pm$  5%) when compared to the younger group (93  $\pm$  13%, p<0.01). We conclude that use of the more clinically relevant target organism, *H influenzae*, appears to differentiate a group of the elderly with reduced opsonic capacity and it remains to be determined prospectively whether these individuals are, in fact, more prone to infection.

#### Perception of dyspnoea in patients with transplanted heart and lungs

NP FENNER, TW HIGENBOTTAM, J WALLWORK, AL JOHNSON, M FITZPATRICK *Cambridge University School of Clinical Medicine* The role of the vagus in mediating breathlessness can be found only by studying patients who have had lung transplantation (Killian, *Chest* 1985;88:2

Aug Suppl). Five patients with transplanted heart and lung and six normal subjects were progressively exercised to maximum voluntary oxygen uptake on a treadmill recording heart rate, metabolic rate and perception of dyspnoea (using a bipolar visual analogue scale 0-36) at one minute intervals. There was no significant difference in perceived dyspnoea between the two groups over the last four minutes of exercise using a two factor (group  $\times$  time) analysis of variance (F=1.7 df=3,26 p>0.5). Perceived dyspnoea was adjusted for minute ventilation and for duration. (Guz *et al*, *Clin Sci* 1966;30:161-70) showed that visceral afferents arising within the lung and travelling via the vagus do not appear essential for load detection. We suggest that the vagus may not be essential in perceiving dyspnoea during exercise.

#### Pattern of ventilatory response to CO<sub>2</sub> after heart or heart and lung transplantation

TW HIGENBOTTAM, ME FITZPATRICK, J WALLWORK *Respiratory Physiology Department, Papworth Hospital, Cambs* There remains a belief that pulmonary stretch receptors are important in regulating the tidal volume (V<sub>T</sub>) and frequency of breathing. To answer this question we have assessed the ventilatory response to rebreathing CO<sub>2</sub> (Read's technique), with hyperoxia and progressive hypoxia (air in rebreathing bag), in patients who have undergone combined heart and lung transplantation (XHLT, n=5). Breath-by-breath analysis using a microcomputer provided inspiration time (T<sub>I</sub>), expiration time (T<sub>E</sub>), tidal volume (V<sub>T</sub>) and end-tidal CO<sub>2</sub> (PETCO<sub>2</sub>). The ranges of PETCO<sub>2</sub> were similar in all groups (mean 4.9-6.5%). The V<sub>T</sub> (%VC) and mean T<sub>I</sub> were calculated for each group. The slope of the relation between V<sub>T</sub>/T<sub>I</sub> and PETCO<sub>2</sub> and the r value of T<sub>I</sub> vs T<sub>E</sub> were also calculated. The ranges of V<sub>T</sub> (%VC) during hyperoxic hypercapnia were 23-41% XHLT; 17-36% XHT; 11-28% N. During hypoxic hypercapnia V<sub>T</sub> (%VC) ranges for each group were 23-53% XHLT; 17-44% XHT; 11-31% N.

	MEAN T <sub>I</sub>		V <sub>T</sub> /T <sub>I</sub> vs PETCO <sub>2</sub> SLOPE		T <sub>I</sub> /T <sub>E</sub> r VALUE	
	H	HYPER	H	HYPER	H	HYPER
XHLT	1.49	1.60	.42	.24	.33	.32
XHT	1.68	1.81	.52	.55	.50	.20
N	2.26	1.93	.30	.25	.21	.07

Abbrev: H-Hypoxic; Hyper-Hyperoxic

The pattern of the response to the hypercapnic stimulus appears similar in all groups, suggesting that pulmonary stretch receptors are not important in determining V<sub>T</sub> or T<sub>I</sub>.

#### Opsonic activity of a new intravenous immunoglobulin pentaglobin, compared with sandoglobin

N GARBETT, P COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* Standard preparations of immunoglobulin(Ig) for intravenous(IV) use are prepared

Thorax, first published as 10.1136/thx.1987.42.3.202 on 1 March 1987. Downloaded from http://thorax.bmj.com/ on April 17, 2014 by guest. Protected by copyright.

from Cohn fraction II (CF-II) of human plasma and contain predominantly IgG. However, antibodies elicited by Gram negative pathogens are frequently of the IgM class and these precipitate predominantly in CF-III. Opsonisation is an important biological defensive function of Ig. We have used a chemiluminescence (CL) assay to assess the *in vitro* efficacy of a new CF-III derived IV-Ig preparation, pentaglobin (Biotest; containing 76% IgG, 12% IgM and 12% IgA), to restore the opsonic activity of hypogammaglobulinaemic (HG) sera, and compared the results with those obtained from a standard CF-II derived preparation, Sandoglobin (Sandoz; 96% IgG, 3.6% IgM and 0.4% IgA). Sera were obtained from five HG patients (IgG 0.7-3.7g/l) and serum was pooled from 12 normal people as control. The IV-Ig preparations were added to sera at a final concentration of 10g/l IgG and the sera tested against six different target microorganisms. Results are expressed as %CL (mean  $\pm$  SE) of the control pool. Both preparations restored opsonic activity for all organisms to control levels except for Sandoglobin against *Pseudomonas aeruginosa* (40  $\pm$  8%). However, Pentaglobin was significantly better at opsonising *E coli* (p<0.001), *Kleb pneumoniae* (p<0.001), *Ps aeruginosa* (p<0.01) and *Pneumococcus* (p<0.001), while Sandoglobin was significantly better at opsonising *H influenzae* (p<0.02). We conclude that Pentaglobin demonstrates significant *in vitro* opsonic activity, particularly for Gram-negative bacteria and especially *Pseudomonas aeruginosa*, when compared to a standard CF-II derived IV-Ig preparation.

**Modified Kirchner medium compared to Lowenstein-Jensen medium in the isolation of tubercle bacilli from specimens other than sputa**

P KELLY, P WATSON, C BYRNE, F DENHAM, T HEALY, L CLANCY *Peamount Hospital, Newcastle, Co. Dublin* In a year long prospective study 625 specimens other than sputa were cultured for tubercle bacilli using both Lowenstein-Jensen Medium (L-J) and a modified Kirchner (K) medium (Oxoid Lt. Basingstoke).

SPECIMENS	TOTAL				
	TOTAL	CULT.POS	L-J+K	L-J ONLY	K ONLY
Pleural fluid	76	22	16	3	3
Pus/Wound Swabs	47	12	5	4	3
Urine	218	15	12	1	2
BAL/Aspirate	169	8	3	2	3
C.S.F.	15	1	0	0	1
Miscellaneous	99	15	13	2	0
<b>TOTAL</b>	<b>625</b>	<b>73</b>	<b>49</b>	<b>12</b>	<b>12</b>

A total of 73 positive cultures were obtained and 12 of these (16%) were positive only on Kirchner Medium. In six patients these were the only positive cultures obtained. Twelve specimens were positive on L-J alone and in two patients these were the only positive cultures obtained. Our results are in agreement with those of (Mitchison *et al J Clin Path*, 1983;36:1357-61) who had 53 positive cultures out of 2949 using L-J, Kirchner and a selective 7H11 agar slope and underlines the need to culture non-sputum specimens on two media.

**Antibodies to *Mycobacterium tuberculosis* in health and disease**

C O'MAHONY, P KELLY, A WHELAN, L CLANCY, C FEIGHERY *St. James' Hospital, Dublin and Peamount Hospital, Newcastle, Co. Dublin* In addition to a potent cell mediated immune response infection with *Mycobacterium tuberculosis* (MTB) elicits a specific antibody response. The purpose of this study was to examine the frequency of anti-MTB antibody in patient and control groups. Using PPD as antigen in an enzyme linked immunosorbent assay (ELISA) the presence of anti-PPD antibody (G,A,M) was assessed in: patients with confirmed TB(43), patients with presumed TB(20), healthy controls (45), disease controls (30) and controls undergoing BCG vaccination (6). Elevated anti-PPD antibody was found in the control groups in one healthy control and one patient with Crohn's disease. BCG vaccination did not induce a rise in antibody level. Twenty-eight (65%) of the confirmed TB patients had elevated levels. Of the presumed TB group, assessment 2½ years later indicated that eight had unequivocal evidence of TB: six of these had elevated anti-PPD antibody. The remainder of the group had normal levels.

This study suggests:

1. BCG vaccination, despite inducing a marked cellular response does not induce a specific antibody response to PPD.
2. Measurement of specific antibody can provide useful evidence of infection; however elevation of antibody level does not occur in all patients with active infection.

**Isocapnic hyperventilation and exercise: equivalent challenges to the bronchial tree?**

IFC HAY, A WOOD, TW HIGENBOTTAM *Respiratory Physiology Department, Addenbrooke's Hospital, Cambridge* Increased respiratory heat and water loss are considered to trigger exercise induced asthma (Chandler Deal, *J Appl Physiol* 1979;46:476). Isocapnic hyperventilation (IHV) is used in the laboratory to provide an equivalent bronchial challenge. Respiratory heat loss is replenished from the pulmonary, not the bronchial circulation, the former increasing several times during exercise (EX). Thus the bronchial thermal environments during IHV and EX may differ. Six normal volunteers (1) exercised on a bicycle ergometer and (2) isocapnicly hyperventilated, with matched tidal volumes and respiratory rate for 10 minutes, breathing air at -20°C. Inspired and expired air temperatures (Ti,Te) were measured by fast response thermocouples within the insulated two channel mouthpiece. IHV and EX were performed in random order, separated by 30 minutes, in duplicate on separate days.

	Exercise Te $\pm$ SEM °C	IHV Te $\pm$ SEM °C	
0	32.5 $\pm$ 0.21	32.3 $\pm$ 0.17	p NS
5	29.1 $\pm$ 0.13	28.3 $\pm$ 0.18	p< 0.01
10	28.9 $\pm$ 0.16	28.0 $\pm$ 0.13	p< 0.01

Core body temperature monitored continuously and spirometry before and after challenges showed no

significant differences/changes. Te is lower after IHV than after Ex implying that less heat is available from the pulmonary circulation. The likeliest explanation is greater V/Q mismatch during IHV. IHV and EX do not provide equivalent airway thermal challenges.

#### Airway responsiveness and thyroid hormone

\*JA ROBERTS, \*\*AR MCLLELLAN, \*\*WD ALEXANDER, NC THOMSON *\*Department of Respiratory Medicine, Western Infirmary, Glasgow and \*\*University Department of Medicine, Glasgow University* Airway responsiveness is an important feature of asthma. Hyperthyroidism is associated with deterioration of symptoms in asthma. Asthma may develop coincident with thyrotoxicosis. Treatment of hyperthyroidism improves asthma control. These facts could be explained if thyroid hormone (T4) enhanced airway smooth muscle sensitivity. To investigate this we have measured bronchial responsiveness in 10 patients presenting with hyperthyroidism before and on treatment. Non-specific bronchial responsiveness (NSBR) was assessed by giving doubling concentrations of histamine (0.5-64 mg/ml) for two minutes through a Wrights nebuliser (50 psi, 8 l/min). Results were expressed as the provocation concentration (PC) producing a 10% fall in FEV<sub>1</sub> (PC<sub>10</sub> FEV<sub>1</sub>) and a 40% fall in the partial expiratory flow rate at 30% of TLC (PC<sub>40</sub> V<sub>30(p)</sub>). Nine of the 10 patients were female. Their ages ranged from 22 to 68. Five were current smokers and four were atopic. The two test days were separated by six to 14 months. Baseline FEV<sub>1</sub> range from 85 to 137% of predicted. Mean (SEM) T4 fell from 226.9 (18.0) nmol/l to 116.9 (12.2) nmol/l and T3 fell from (5.44 nmol/l to 1.61 (0.15) mol/l. Geometric mean (range) PC<sub>10</sub> FEV<sub>1</sub> was 10.6 mg/ml (2.9->64) before treatment and 9.1 mg/ml (1.6-54.3) after treatment. PC<sub>40</sub> V<sub>30(p)</sub> was 9.2 mg/ml (2.9->64) before treatment and 9.2 mg/ml (1.4-28.2) after treatment. These hyperthyroid patients did not exhibit increased NSBR and there was no significant change in NSBR on return to the euthyroid state. We conclude that T4 does not have a significant influence on NSBR in human airways.

#### Respiratory function after propranolol in hyperthyroidism

YT WANG, SC POH (INTRODUCED BY NB PRIDE) *Department of Medicine III, Tan Tock Seng Hospital, Singapore* We assessed 35 hyperthyroid patients before treatment, after treatment with propranolol, and after antithyroid drugs. In 17 patients, the following tests were performed at all three assessment points: forced expired volume in the first second (FEV<sub>1</sub>), vital capacity (VC), functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC), maximal mid-expiratory flow rate (MMFR), diffusing capacity for carbon monoxide (DLCO), maximum static inspiratory and expiratory mouth pressures (P<sub>1</sub>max and P<sub>Emax</sub>) and arterial blood gases. As there were no significant changes in the FRC, RV, TLC, MMFR, DLCO and blood gases either after propranolol or after antithyroid drugs, only the FEV<sub>1</sub> VC P<sub>1</sub>max and P<sub>Emax</sub> were performed in the remaining 18 patients at the three assessment points. After propranolol, only mean P<sub>1</sub>max

increased significantly (from 46.5 to 53.2 cmH<sub>2</sub>O, p<0.01). After antithyroid drugs, P<sub>1</sub>max increased further to 65.2 cmH<sub>2</sub>O (p<0.005). Mean P<sub>Emax</sub> increased slightly from 52.8 to 56.4 cmH<sub>2</sub>O with propranolol, and increased further to 63.6 cmH<sub>2</sub>O (p<0.02) after antithyroid drugs. Mean FEV<sub>1</sub> and VC did not change with propranolol but increased significantly after antithyroid drugs (FEV<sub>1</sub> from 80.4 to 87% predicted p<0.001; VC from 81.6 to 88.2% predicted p<0.001). In conclusion, we found that propranolol partly reversed thyrotoxic inspiratory muscle weakness. Antithyroid drugs restored respiratory muscle strength, FEV<sub>1</sub> and VC.

#### The effect of bronchography via the fiberoptic bronchoscope on pulmonary function

JM GOLDMAN, DC CURRIE, AD MORGAN, JV COLLINS *Brompton Hospital, London* Bronchography using a fiberoptic bronchoscope (FOB) to introduce contrast medium has advantages over the conventional method using a naso-tracheal catheter, as it allows direct inspection of the airways and collection of microbiological specimens from specific bronchi. We assessed the effect on lung function of bilateral bronchography via FOB using 10-20 ml of aqueous contrast medium, by monitoring arterial oxygen saturation (SaO<sub>2</sub>) with a Biox III ear oximeter, and performing spirometry before and one hour after the procedure. All the patients (n=8) had a normal baseline SaO<sub>2</sub>, which dropped by a mean of 5% (SD=3%) after bronchoscopy, by 12.5% (SD=8%) after unilateral contrast injection, and by 20.5% (SD=9%) after bilateral contrast injection. Four patients failed to regain baseline SaO<sub>2</sub> after three hours. Spirometric values were decreased by 50% one hour after bronchography. The introduction of aqueous contrast medium via FOB, has a greater effect on SaO<sub>2</sub> and spirometry than conventional bronchography using an oily contrast medium, during which SaO<sub>2</sub> may drop by 8% (HL Motley, JF Tomaszefski, *Amer J Physiol* 1951;167:832) and vital capacity by 33% (AJ Christiforidis *et al*, *Am Rev Respir Dis* 1962;85:127-129). This may be due to the physical presence of the FOB in the bronchi, or the different properties of the contrast media.

#### The pulmonary artery response to atrial peptides in the pig

AH MORICE, TLTA JANSEN, MJ BROWN *Clinical Pharmacology Unit, Addenbrooke's Hospital, Cambridge* Atrial Natriuretic Peptide (ANP), a 28 amino acid peptide is released in response to increasing right atrial pressure. The effect of h-ANP and the closely related peptides AP I (21 amino acids) and ANP III (24 amino acids) have been examined in precontracted pulmonary artery segments of the pig and compared to the responses of the renal artery. Arterial segments (0.2 to 1.5 cm) were obtained immediately post mortem and placed in aerated Krebs buffer under a resting tension of 1 g. Isometric changes were measured using a Grass force-displacement transducer FT03D. The preparations were submaximally constricted with noradrenaline (3 μmol) and peptides added in a cumulative fashion in the presence of indomethacin (10 μmol) and propranolol (8 μmol). ANP potently relaxed the



pulmonary artery significantly more than the renal artery, with a potency ratio of approximately 10. AP III was slightly but significantly less potent in the pulmonary artery and AP I was much less potent than ANP, potency ratios were approximately two (AP III vs ANP;  $p < 0.05$ ) and 20 (AP I vs ANP;  $p < 0.001$ ). Removal of the vascular endothelium by gentle rubbing, as shown by failure to relax to acetylcholine ( $10 \mu\text{mol}$ ), made no significant difference to the pulmonary artery responses. In man ANP has its highest circulating concentration in the pulmonary artery and the demonstration of its potent relaxant effects indicates a possible role in the modulation of the pulmonary arterial tone in response to increasing right atrial pressure.

### Survival from primary pulmonary hypertension (PPH)

TW HIGENBOTTAM, M FITZPATRICK, J WALLWORK *Papworth Hospital, Papworth Everard, Cambridge* Intravenous prostacyclin ( $\text{PGI}_2$ ) is probably the best vasodilator to test for reversible vasoconstriction in PPH (Simmonneau *et al*, *Am Rev Respir Dis* 1986;133:A222). We have used it to test whether the pressure of vasoconstriction or underlying pathology are the major determinants in survival from PPH in 19 patients, in whom histological examination of the lungs was available in 12. None of the patients had evidence of 'proximal' thromboembolism on V/Q lung scan or pulmonary angiography. Patients were classified into thromboemboli (THPH), idiopathic (IPH), venoocclusive (VOD) according to histology, and unknown PPH (UPPH) without histology.

	(TEPH)	(IPH)	(VOD)	(UPPH)
No of subjects	5	5	2	7
Survival beyond 3/12	2	4	0	7
PVR before $\text{PGI}_2$	1820	1881	1179	1828
PVR after $\text{PGI}_2$	1525	1285	740	1214
(sed)	(217)	(145)	(310)	(180)
% change	16	33	37	33

Survival cannot be related to the presence of  $\text{PGI}_2$  vasodilatation, underlying disease appears more important. This argues in favour of the view that obliteration of the peripheral pulmonary vasculature rather than vasoconstriction is the principle pathogenic mechanism. (LM Reid, *Chest* 1986;89:278-288).

### Ventilation and respiratory pattern during methacholine challenge in normal subjects

WN GARDNER, DY MAYEUX, NC BARNES, MS MEAH *Department of Thoracic Medicine, Kings College School of Medicine and Dentistry, London* Mild asthma stimulates breathing with reduction of arterial  $\text{PCO}_2$  (McFadden *et al*, *N Engl J Med* 1968;278:1027); the mechanism is uncertain. Controlled bronchoconstriction was induced in 11 normal subjects by two minute inhalation of placebo followed at 10 minute intervals by doubling doses of methacholine from 1 mg to 32 mg/ml or until  $\text{FEV}_1$  fell by more than 20%. After each inhalation, flow for 40 consecutive breaths was recorded by pneumotachograph and analysed in real time by Altos

computer to produce mean values of inspiratory and expiratory times, tidal volume, peak flows, mean inspiratory flow, minute ventilation and shape parameters for expiratory flow. Values were averaged across all subjects and mean placebo values were compared with the mean of the final values attained in each protocol. Two subjects did not bronchoconstrict. In the remaining nine there was a mean fall in  $\text{FEV}_1$  of 24.5% but no change in any aspect of the respiratory cycle including the shape of expiratory flow; ventilation changed by only  $0.33 \pm 0.63$  SE from a mean placebo value of 8.9 l/min. In conclusion, bronchoconstriction and stimulation of cholinergic pathways to this extent do not stimulate breathing; other mechanisms for the hyperpnoea in mild-moderate asthma must be sought.

### The effect of altering posture on airway response to inhaled histamine

YT WANG, CI COE, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Altered airway geometry can potentially affect airway reactivity. We studied the effect of changes in posture, and the associated passive change in mid-tidal lung volume (MTLV), on the response to inhaled histamine in eight subjects (4F, mean age  $30 \pm 5$  SD years, mean  $\text{FEV}_1$   $3.5 \pm 0.6$  l). Each subject was studied in both sitting and supine postures on two different days. Airway calibre was assessed by measuring total respiratory resistance (Rrs) with a forced oscillation technique applied over 16 s of tidal breathing; results at 6 Hz are presented. Appropriate doses of histamine were selected by preliminary experiments and were always inhaled in the supine posture. MTLV was larger in the sitting ( $2.8 \pm 0.8$  l) than in the supine posture ( $2.3 \pm 0.5$  l). Baseline Rrs was lower in the sitting than the supine posture ( $2.03 \pm 0.44$  and  $3.12 \pm 0.76$   $\text{cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$  respectively). Mean absolute  $\Delta$  Rrs after the same dose of histamine was  $1.22$   $\text{cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$  sitting (60.1% increase over baseline) and  $1.39$   $\text{cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$  supine (44.6% increase over baseline). Absolute change in specific respiratory conductance (SGrs) after histamine was  $0.071$   $\text{cm H}_2\text{O}^{-1} \cdot \text{s}^{-1}$  sitting (38% fall from baseline) and  $0.059$   $\text{cm H}_2\text{O}^{-1} \cdot \text{s}^{-1}$  supine (38.3% fall from baseline). Thus, higher baseline values of Rrs were associated with a larger absolute rise in Rrs after a standard dose of histamine, but airway responsiveness would appear similar in the two postures using the common convention of allowing for lung volume and normalizing to baseline values.

### Increased bronchial reactivity to methacholine following combined heart-lung transplantation

NR BANNER, L HOLLINGSHEAD, L DEAR, \*R HEATON, \*A GUZ, MH YACOB *Harefield Hospital, Harefield, Middlesex and \*Charing Cross Hospital, London* In an attempt to define the influence of pulmonary denervation on bronchial reactivity, we studied the response to bronchial challenge with methacholine of 12 patients following heart-lung transplantation (HLT). The results were compared to 12 orthotopic heart transplant (HT) recipients and 12 normal

controls (C). The ages (mean  $\pm$  SD) of the groups were HLT: 27.9  $\pm$  9.1, HT:29.3  $\pm$  9.6 and C:27.5  $\pm$  eight years. The FEV<sub>1</sub>s (mean  $\pm$  SD) for the groups were HLT: 3.0  $\pm$  0.6, HT: 3.2  $\pm$  0.7, C: 3.6  $\pm$  0.3 litres and FVCs (mean  $\pm$  SD) HLT: 3.2  $\pm$  0.6, HT: 3.8  $\pm$  0.9, C: 4.0  $\pm$  0.6 litres. HLT and CT patients were receiving Cyclosporine and Azathioprine immunosuppression. The dose of Methacholine that caused at least a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) was defined. One HLT, 5 HT and 6 C subjects did not react to the maximum concentration used (64 mg/ml). Median PC<sub>20</sub> for the groups were: C>64 mg/ml (range 16 to > 64), compared to HLT 8 mg/ml (range 2 to > 64), (p<0.01), and HT 64 mg/ml (range 8 to >64) (NS). It is concluded that HLT results in increased bronchial reactivity which probably represents denervation hypersensitivity of muscarinic receptors.

**Characterisation of aerosol induced cough in normal subjects**

R LOWRY, A WOOD, IFC HAY, TW HIGENBOTTAM *Respiratory Physiology Department, Addenbrooke's Hospital, Cambridge* Control of the common respiratory symptom cough is poorly understood. We have demonstrated previously that cough is induced by inhalation of ultrasonically nebulised aerosols deficient in chloride (Godden *et al*, *Clin Sci* 1986;70:301). Laryngeal rapidly adapting vagal receptors (RARs) exhibit a similar chloride-sensitive response (Boggs *et al*, *J Appl Physiol* 1982;53:455). Tonicity and pH responsiveness is defined for RARs but not yet adequately for cough. Fourteen normal volunteers were studied using our standard method (Godden *et al*). Solutions were presented blind in random order on separate days. Cough frequency was recorded over one minute. Solutions of pH 2.6-10 were obtained by buffering isotonic saline with glycine or phosphate. Seventy-seven 1232 m. osmol dextrose and saline solutions were matched for pH by adding NaOH. pH manipulation changed osmolarity insignificantly.

Experiment (i)					
pH	2.6	4.8	8.0	10.0	
Mean cough frequency (MCF)	2.1	0	0	3.6	p<0.005
Experiment (ii)					
Tonicity (m. osmols)	77	154	308	616	1232
MCF dextrose	7.6	9.6	12.0	11.5	12.1
MCF saline	8.1	2.1	0	0	1.3
					p<0.005

Extremes of pH induce cough. Tonicity has little effect but the importance of chloride is confirmed. Aerosol induced cough chemoresponsiveness appears to mirror that of laryngeal RARs.

**Evaluation of a turbine volume transducer in the measurement of ventilation**

CB COOPER, ND HARRIS, P HOWARD *University Department of Medicine, Royal Hallamshire Hospital,*

*Sheffield* Turbine transducers are widely used for the measurement of fluid flow in industry and have been successfully adapted for human spirometry (Chowienczyk and Lawson, *Br Med J* 1982;285:15-17). The new instrument is a twin emitting turbine volume transducer (PK Morgan, Kent) linked to a microprocessor which corrects for the inertia and over run characteristics of the turbine. Static flow calibration was performed using reference rotameters. The response was linear over the range 12.5 to 34.0 l min<sup>-1</sup> (r=0.99) and accurate to within 3%. Pulsatile flow was generated from a volume cycled ventilator (Cape, Warwick). The flow characteristics were modified by damping to simulate a human breathing pattern. The accuracy of the turbine was tested by connecting it in series with a water seal spirometer (Gould, Godart, Bilthoven). Comparative measurements of ventilation were made whilst varying tidal volume (V<sub>T</sub>) from 0.253 to 1.312 l and respiratory rate (fR) from 10 to 35 mm<sup>-1</sup>. At levels of ventilation from 20 to 46 l min<sup>-1</sup> the turbine was accurate to within 3% irrespective of changes in V<sub>T</sub> or fR. At lower levels of ventilation the instrument tended to under read with increasing fR. Nevertheless the error remained within 3% at a ventilation of 10 l min<sup>-1</sup> with fR < 15 min<sup>-1</sup>. The turbine transducer compares more favourably with other measuring systems throughout a working range of normal human ventilation.

**Does arterial pH determine outcome in patients with acute exacerbations of chronic bronchitis and emphysema?**

AA JEFFREY, PM WARREN, KF WHYTE, DC FLENLEY *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* One hundred and eight episodes of acute on chronic respiratory failure (PO<sub>2</sub><6.5 kPa, PCO<sub>2</sub>>6.5 kPa), studied from 1970-76 showed that age, and the lowest pH recorded were the best indicators of short term survival (Warren *et al*, *Lancet* 1980;i:467-71). We now describe a prospective study of 139 admissions in 95 similar patients to see if these guidelines for therapy (PO<sub>2</sub>> 6.5 kPa, without pH falling below 7.25), remain valid. One hundred and twenty-three patients had a PO<sub>2</sub><6.5 kPa and PCO<sub>2</sub>>6.5 kPa when breathing air and 16 had a PCO<sub>2</sub>>8.0 kPa on air or O<sub>2</sub>. When breathing air the PO<sub>2</sub> ( $\pm$ SD) was 4.95 ( $\pm$ 0.90) kPa, PCO<sub>2</sub> 8.23 ( $\pm$ 1.18) kPa and pH 7.34 ( $\pm$ 0.04), the mean age being 63.9 ( $\pm$ 7.9) years. The episode rate was 13% compared with 24% in 1970-76. There was no difference in admission PO<sub>2</sub>, PCO<sub>2</sub>, or pH nor in sex, white blood count, or body weight between those who survived and died. Arterial pH below 7.25 occurred in 50% in 1970-76, but only in 24% of the 1979-86 admissions. During admissions in 1979-86, pH fell below 7.25 in 34 episodes, nine of these (26%) being fatal whereas in 105 episodes, pH remained above this level and only eight of these died (8%; p<0.05). We thus confirm that the lowest pH during treatment is a useful guideline.

Thorax: first published as 10.1136/thx.42.3.207 on 1 March 1987. Downloaded from http://thorax.bmj.com/ by guest on 17 February 2024. Protected by copyright.