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Bronchoscopy in the elderly: helpful or hazardous?

AJ KNOX, BH MASCIE-TAYLOR, RL PAGE *Respiratory Medicine Unit, St. James's Hospital, Leeds* Recently, doubt has been cast on the safety and desirability of fibreoptic bronchoscopy in the elderly (Grant IBW, *Br Med J* 1986;**293**:286-7). To answer this question, we looked at the safety and acceptability of the procedure in 60 patients, aged 80-92 over the four year period May 1982-May 1986. Thirty-four patients were male. Sedation was with atropine, fentanyl, and diazepam, 2% lignocaine being instilled locally over the cords. There was no serious morbidity and no mortality. The diagnostic yield was similar to younger age groups. Twenty-one patients had histologically proved carcinoma of the bronchus, one a benign polyp, one tuberculosis diagnosed from washings, two collapsed lobes with re-expansion following removal of secretions. The remainder either showed infective changes or were normal. Where no tumour was seen active treatment resulted in improvement in all but four. Of those with tumour, four were treated with radiotherapy with symptomatic relief, the remainder being treated conservatively. A positive diagnosis of malignancy greatly helped the planning of future care. We conclude that fibreoptic bronchoscopy is a safe, useful procedure in this group of patients.

A randomised, double blind comparison of midazolam and diazepam (Diazemuls) as sedation for fibreoptic bronchoscopy

RG TAYLOR, F JOHNSON, JCG COX, PJH POI, AG ARNOLD *Medical Chest Unit, Castle Hill Hospital, Cottingham* Having shown that bronchoscopy patients dislike instrumentation of the nose and appreciate amnesia (Morrison *et al, Thorax* 1987;**42**:223), we compared intravenous diazepam (as Diazemuls) with midazolam, which gives more amnesia at similiar sedation. One hundred consecutive patients (median age 66.5 years) from routine bronchoscopy lists were given atropine 0.6 mg beforehand, oxygen 2 l/min throughout and lignocaine by nasal spray and endobronchially (up to seven 2 ml 2% aliquots allowed). The initial dose of midazolam 3.5 mg given over 30 s or diazepam 7.5 mg (1.5 min) was reduced by one third if the patient was small, frail or over 65 years. Increments of midazolam 0.5 mg or diazepam 1.25 mg were repeated after 2 minutes as required until the patient was drowsy with slurred speech; only then was the nose sprayed. The median (range) doses (and average ampoules/patient) were: midazolam 4 (2.5-10) mg (one), diazepam 10 (5-30) mg (two). Bronchoscopists completed questionnaires immediately afterwards, and patients the next day, returning them promptly by stamped addressed envelope. After midazolam, fewer patients remembered the nasal spray (15% vs 36%, $p<0.05$) or bronchoscope insertion (9% vs 38%, $p<0.01$); complaints fell from 48% previously to 7%. Fewer patients were difficult to bronchoscope or found it unpleasant after midazolam, though more needed extra lignocaine; these differences were not significant. Overall, the commonest complaint (32%) was of apprehension about the procedure or results but 97% would have another bronchoscopy, and 74% found it better than expected, though 93% appreciated being sedated.

Visual distraction of biofeedback? A study of patients' tolerance of fibreoptic bronchoscopy

PJV HANSON, MJ PLANT, J GOLDMAN, JV COLLINS *St. Stephen's Hospital, London* Anecdotal evidence suggests that fibreoptic bronchoscopy is better tolerated by subjects allowed to observe their bronchoscopy through a side viewing attachment. We conducted a controlled clinical trial on 73 patients undergoing bronchoscopy to assess the value of visual stimulation during the procedure. Standard premedication was given and patients randomised to three groups: 23(S) looked at slides projected onto a screen; 25(V) looked through the side viewing attachment and 25 controls (C) had no visual stimulation. The procedure was conducted by an experienced bronchoscopist who delivered a standard commentary on the basic anatomy seen during the procedure. The side piece was attached for all groups and used by the patient (Gp.V) or by an attendant (Gps. C and S). Patients in group C used a hand control to project slides onto a screen in front of them. Patient tolerance was assessed by recorded cough counts and operator and patient questionnaires. Groups (S) and (V) coughed less than controls ($p<0.02$; $p<0.05$ resp.). Group (V) found the procedure more tolerable than (S) or (C) ($p<0.05$; < 0.001 resp.). Operator's assessment of patient tolerance related inversely to degree of coughing in all groups. There was generally no correlation between operator's and patient's assessment of the procedure. Patients benefit subjectively, and cough less when using the sidepiece, perhaps due to biofeedback. Patients also cough less but do not benefit subjectively from simple visual distraction as provided by slides. The operator considered both measures beneficial, perhaps because of reduced coughing.

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An assessment of fluid flux across the alveolar membrane during bronchoalveolar lavage (BAL)

CA KELLY, J FENWICK, PA CORRIS, A FLEETWOOD, C WARD, DJ HENDRICK, EH WALTERS *Departments of Medicine, Physics and Biochemistry, Newcastle General Hospital, University of Newcastle on Tyne* Two related studies were performed to investigate and quantify the degree of fluid exchange that might occur between the pulmonary circulation and the lung segment during BAL. Using 0.005% methylene blue as a marker, we calculated the median degree of dilution of the aspirate in five subjects with normal pulmonary function undergoing 180 (3×60) ml BAL to be 24% (range 15-35%). Using ^{99m}technetium colloid it was 25% (range 16-35%), i.e. a net fluid gain of about 45 ml within the lung segment. In the same experiment, four MBq of tritiated water were also added to the introduced fluid and the degree of dilution of tritium in the aspirate was found to be greater than that of the other two markers. This suggested that a median of 57 ml (range 36-130 ml) of water had effluxed from the lung during BAL. The total fluid gain by the lung was thus about 100 ml. We performed 3×60 ml BAL in a further five subjects 12 hours after an oral dose of four MBq of tritiated water. A median of 39% (range 32-52%) of the 85 ml (range 63-124 ml) aspirated was calculated to have come from the circulation by simultaneously measuring the concentrations of tritium in plasma and aspirate. The concentration of urea, an 'endogenous marker', was also assayed simultaneously in plasma and aspirate, and fluid normally resident within the lung segment was calculated to contribute only 2% of the total aspirate. These studies offer a quantitative analysis of the complex fluid dynamics of a standard BAL.

The early diagnosis of aspergilloma using computed tomography

B STRICKLAND, KM CITRON, CM ROBERTS *Departments of Diagnostic Radiology and Thoracic Medicine, Brompton Hospital, London* The diagnosis of aspergilloma is made from the chest radiograph and tomograph, which are imperfect methods for imaging damaged and distorted lung parenchyma in which aspergillomas usually lie. The diagnosis may thus be missed. We examined the CT appearances in 26 patients referred with the diagnosis of aspergilloma made or suggested by serum precipitins and a chest radiograph. Three millimetre narrow sections and a bone algorithm (Strickland *et al, Clin Radiol* 1986;37:335-338) were used to improve definition. In nine patients histological specimens became available for comparison with the scans. There was absolute correlation in diagnosis and number of aspergillomas when CT was compared with histology. Forty-six per cent of patients had multiple lesions, far more than reported in previous radiological series, reflecting the increased resolution of CT. The appearances of both the mature fungus ball and the forming aspergilloma are described in detail. Lesions not seen on chest radiograph are identified on CT and the reason for this are elucidated. CT is an accurate method of identifying both mature and forming aspergillomas and is useful in cases where the diagnosis is suggested immunologically or clinically but not confirmed using conventional radiology. CT should also be performed before surgical resection to localise all aspergillomas.

Correlation of lung CT density with respiratory function in smokers and patients with bullous emphysema

GA GOULD, W MACNEE, AT REDPATH, MF SUDLOW, JJK BEST, D FLENLEY *Rayne Laboratory, Departments of Respiratory Medicine, Medical Physics, and Medical Radiology, Edinburgh* We have previously shown a strong correlation between lung CT density and the severity of microscopic emphysema, using precise morphometric measurements of distal air space size to define emphysema (Gould *et al, Thorax* 1986;41:717). Using the same method of CT analysis we have recorded the EMI number of the lowest 5th percentile of the CT density histograms (as a measure of peripheral lung density) in 77 smokers (60M, 17F; 23-82 years; FEV_1 15-125% predicted; Kco 15-139% predicted) and 27 patients with bullous disease (25M, 2F; 31-69 years; FEV_1 15-84% predicted; Kco 20-114% predicted) correlating respiratory function with lung CT density, excluding any bullous areas of the lung from analysis. In both groups lung CT density correlated with functional measurements thought to reflect the severity of emphysema, such as air flow limitation (FEV/FVC% predicted, $r = -0.73$) and impairment of gas transfer (CT density vs Kco $r = -0.76$). The extent of bullous disease was not a major determinant of respiratory function. We conclude that 1) lung CT density correlates with functional impairment and thus quantifies the severity of emphysema, 2) impairment of respiratory function in patients with bullous disease relates mainly to the degree of emphysema in the non-bullous area of lung, 3) the combination of lung CT density and gas transfer (Kco) measurements is a sensitive and specific method for non-invasively quantifying the severity of pulmonary emphysema.

Analysis of QCT lumbar spine densitometry values in patients with obstructive lung disease

WJH LECKIE, M ALCOCK, P BALDOCK, A MCALINDON, S BURDON JONES, JM ROWLANDS, SDR HOMAN *Thoracic Medicine Unit, The Queen Elizabeth Hospital, Woodville, South Australia* Vertebral fractures are common among older patients with chronic obstructive lung disease with (COLD) especially in thin smokers with exogenous hypercorticism. Whether there is a threshold corticosteroid dose related either to daily intake or to duration of treatment below which it is no longer a significant risk factor in osteoporosis remains in doubt. A survey of vertebral fractures and single energy QCT spinal densitometry (*Computed tomography of the Body, ch 23; Saunders, 1984*) of 153 patients suffering from COLD has been undertaken and the relationship of CT and fractures to some known risk factors determined. Patients with other conditions causing osteoporosis were excluded. There was a positive correlation (see table) between number of patients with fractures and QCT, and between number of fractures and QCT. Only in postmenopausal women was there a significant relationship between QCT and the annual

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(though not the total) prednisolone dose. Even in this subgroup corticosteroids accounted for no more than 20% of the osteoporosis found (men 63% and women 79% of normal values of a North American series: C Cann 1985, personal communication). Current activity was the only other factor which independently correlated (positively) with QCT, particularly in men. It seem likely that oral corticosteroids have only a minor role in the osteopenia found in COLD, particularly when a daily dose of >10 mg is used, and then only in postmenopausal women.

	QCT ≤ 60	CT ≥ 100	
Total patients	42	38	
No with fractures	25	6	$p < 0.0005$
No of fractures	58	10	$p < 0.005$

Factors influencing survival in lung cancer

S CAPEWELL ON BEHALF OF THE EDINBURGH LUNG CANCER GROUP *Department of Respiratory Medicine, City Hospital, Edinburgh* The Edinburgh Lung Cancer Group has registered over 3,000 new patients presenting with lung cancer since 1981. Only 57 of 651 patients registered in 1981 survived four years (9%). Survival was highest in 41 of the 116 (35%) selected for surgery and in this group was related to cell type ($p<0.01$), to stage of disease ($p<0.02$) and possibly to Karnofsky performance status ($p=0.08$). The 116 surgical patients differed from the "non-surgical" patients in terms of age (34% vs 22% under 60), histology (6% vs 25% small cell), stage of disease (86% vs 32% stage I or II) and performance status (75% vs 26% Karnofsky $\geq$ 90%) (all $p<0.01$). Forty-two of the 535 "non-surgical" patients were given radical radiotherapy alone and eight (19%) survived four years, whereas only eight of the remaining 493 (2%) survived four years following radiotherapy, chemotherapy (alone or in combination), or symptomatic treatment only. Median survival (MS) varied markedly with cell type (adenocarcinoma MS 2.6 months vs squamous carcinoma MS 6.2 months), stage (stage I MS 8.5 months vs stage III MS 4.0 months) and performance status (Karnofsky $\geq$ 90 MS 9.3 months vs Karnofsky $\leq$ 50 MS 1.2 months) (all $p<0.001$). Age had no independent prognostic value in any group. Performance status was highly correlated with stage (and age) and represents the "best single prognostic factor" in clinical practice.

Smoking pattern, occupational risk, family history, and dietary and alcohol intake in lung cancer: results of a case-control study in males

RJ PIERCE, LF WATSON, GA KUNE, S KUNE, L VITTETTA, B FIELD, D MERENSTEIN, A HEY, LB IRVING *Department of Thoracic Medicine and Melbourne University Department of Surgery, Heidelberg Repatriation Hospital, Victoria, Australia* In a case-control study of 72 consecutive new male cases of lung cancer and 73 male hospital control patients, smoking pattern, occupational history, family history of lung and other cancer, previous diet and alcohol intake were investigated by univariate and multiple logistic regression analyses using GLIM. The cases and controls were similar in age, country of origin, area of residency and marital status. Smoking duration was longer for cases (44.3 (SEM 1.2) years) than for controls (34 (1.8) years) with a relative risk (RR) of 1.06/years ($\chi^2=19.0$, $p<0.0001$). For ex-smokers time since cessation of smoking was shorter for cases (4.5 (0.9) years) than for controls (13.4 (1.9) years), giving RR = 0.92/year ($\chi^2=21$, $p<0.0001$). These two factors showed a stronger association than pack years (cases 50.8 (4.1), controls 33.6 (3.3), RR = 1.02/pack year, $\chi^2=10.4$, $p<0.001$). The average number of cigarettes per day (cases 23.3 (1.9), controls 19.2 (1.7), (RR = 1.03/cig, $\chi^2=3.6$, $p=0.06$) and the prevalance of smoking (66 cases, 62 controls, RR = 3.4, $\chi^2=4.3$, $p=0.04$) were weaker associations. Individual occupations, as assessed in this study, were not associated with the risk. A priori nominated at-risk occupations, were seen in 20 cases and 14 controls — RR smoking adjusted (RRs) = 1.67 ($p=0.27$). Self-reported dust exposure was noted in 23 cases and 17 controls RRs = 1.72, $p=0.24$). Of 28 cases and 22 controls who reported a cancer in a first degree relative (RRs = 1.77, $p=0.22$), this was a lung cancer in four cases and in three controls. Using a frequency assessment of previous dietary intake, broad food groups were similar for cases and controls. Examining individual food items showed that cases had a higher intake of cream and lower intake of fruit and fish than controls but only the association with fish remained significant after smoking adjustment (RRs = 0.90, $\chi^2=4.2$, $p=0.04$). Although serum levels of retinol and β carotene were significantly lower in cases than controls, a dietary difference for these was not detected by the frequency method. Alcohol intake was similar in cases and controls.

Lung cancer: survival, tumour size and kinetic data at presentation

KM KERR, D LAMB *Department of Pathology, University of Edinburgh, Edinburgh* In a series of 46 classical primary bronchogenic carcinomas we have measured the thymidine labelling index (TLI: a measure of cell proliferation) in all cases and tumour volume doubling time (DTact) in 13 cases. These patients were followed up for five years and these data compared with postoperative survival, tumour volume at operation and pathological staging. Unlike breast, lymphoid and brain malignancies we find a higher TLI does not correlate with a more aggressive clinical course for the tumour. Five year survivors had smaller tumours than non-survivors ($p=0.015$) but no correlation was found, in those dying of malignancy, between size of tumour and length of postoperative survival. Larger tumours have higher TLIs than smaller lesions ($0.01 > p > 0.001$). If this implies tumour progression with time then cell loss would also have to increase in parallel with cell production rate since tumour growth rate is relatively constant. Tumour size at operation may predict likelihood of cure but not postoperative survival. Tumour cell proliferation, taken alone, is not useful in either context.

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Treatment duration in small cell lung cancer (SCLC): a randomised comparison of four versus eight courses of initial chemotherapy

SG SPIRO, HM EARL, RL SOUHAMI, CM ASH, DM GEDDES, PG HARPER, JS TOBIAS, H QUINN *Department of Respiratory Medicine, University College Hospital, London* Six hundred and sixteen patients with SCLC were entered into a randomised trial comparing different treatment durations and the value of chemotherapy on relapse. Patients were staged by isotope bone scan and liver ultrasound, and stratified according to stage (limited or extensive). Patients were then randomised to receive either four or eight courses of chemotherapy (cyclophosphamide 1g/m^2 day 1, vincristine 2 mg day 1, etoposide 100 mg t.d.s. days 1-3) three weekly. At presentation patients were also randomised for treatment at relapse, to receive either further chemotherapy (adriamycin 50 mg/m^2 and methotrexate 50 mg/m^2, every three weeks) or symptomatic treatment alone. Response rates to short (S) and long (L) initial chemotherapy were similar (S = 61%, L = 63%), as were response rates to relapse chemotherapy (S = 25%, L = 18%). Overall median survival (MS) from course one was analysed by intention to treat, and patients randomised to eight courses of initial chemotherapy had a slightly longer MS than those randomised to four courses (MS, 39 vs 32 weeks, $p = 0.085$). Progression free interval (PFI) after initial chemotherapy was longer in patients receiving eight rather than four courses (median, 31 vs 23 weeks, $p = 0.0002$). Survival from relapse was longer for patients receiving relapse chemotherapy than those receiving symptomatic treatment alone (MS, 17 vs 12 weeks, $p = 0.0004$). The only treatment strategy associated with a significantly worse survival was short initial chemotherapy, followed by symptomatic treatment on relapse.

A randomised trial of short course intravenous versus oral chemotherapy for small cell lung cancer (SCLC)

PA CORRIS, B CANTWELL, J BOZZINO, D VEALE, AL HARRIS *North East Lung Cancer Group, Department of Respiratory Medicine, Freeman Hospital, and University Department of Clinical Oncology, Newcastle General Hospital, Newcastle upon Tyne* Conventional therapy for small cell lung cancer (SCLC) includes hospital based intravenous chemotherapy. Oral chemotherapy has been shown to be effective treatment in other chemosensitive malignancies such as Hodgkin's disease, and has advantages in terms of expense and ease of administration. We have carried out a randomised trial of hospital based short course intravenous (IV) chemotherapy versus outpatient based oral chemotherapy in two hundred patients with small cell lung cancer. Randomisation was stratified for extent of disease and all patients gave informed consent. The initial course of IV chemotherapy comprised adriamycin 40 mg/m^2 vincristine 2 mg, etoposide 100 mg/m^2 on day one and etoposide 300 mg orally on days two and three. Subsequent courses of IV chemotherapy comprised adriamycin 30 mg/m^2, vincristine 2 mg, etoposide 200 mg/m^2 and 24 hour infusion of ifosfamide 5 g/m^2 plus MESNA. All courses of oral chemotherapy comprised chlorambucil 6 mg/m^2, procarbazine 150 mg, prednisolone 20 mg each day for 10 days and etoposide 300 mg daily for the first three days. Each treatment was given every three weeks to a total of four courses and good responders received prophylactic cranial and consolidation mediastinal radiotherapy. The results of survival up to a maximum of 32 months have been compared in the first 150 patients, of whom 76 received IV and 74 oral chemotherapy. There were no significant differences in survival between IV and orally treated patients either when compared overall or when subdivided by stage at presentation (log rank test). Overall median survival for all patients from the first course of therapy was eight months and nine months after oral and IV drugs respectively. Oral chemotherapy was not only easier to administer but also significantly cheaper than the intravenous drugs. We conclude that oral outpatient chemotherapy confers the same early survival benefit as more expensive hospital based IV chemotherapy in patients with small cell lung cancer.

Survival after radiotherapy for lung cancer

LM MATHESON, S CAPEWELL, MF SUDLOW, GA NEWAISHY ON BEHALF OF THE EDINBURGH LUNG CANCER GROUP *Department of Clinical Oncology, Western General Hospital, Edinburgh* The Edinburgh Lung Cancer Group (ELCG) registered 2586 new cases of lung cancer prospectively during 1981-84. Thirty-one per cent of patients were treated initially with radiotherapy compared with 19% undergoing surgery, 12% chemotherapy and 38% considered suitable for symptomatic therapy only. During 1981, 233 patients with non-small cell cancer received radiotherapy as primary treatment; 41 (17%) received radical radiotherapy (radical RT: 42-57 Gy) and 192 palliative radiotherapy (palliative RT: 18-30 Gy). Positive histology was available in 32/41 radical RT (78%) and 156/192 (81%) palliative RT patients. The radical RT patients were more selected in terms of stage (61% vs 28% stage I; $p<0.001$), age (76% vs 57% < 70 years; $p<0.02$) and performance status (Karnofsky index > 80 in 79% vs 49%; $p<0.001$). Four years survival after radical RT was 12.5% (4/20) for patients with positive histology; 7/192 (3.7%) palliatively treated patients survived four years.

Pulmonary manifestations of prostatic adenocarcinoma

H MESTITZ, RJ PIERCE, PW HOLMES *Department of Thoracic Medicine, Repatriation General Hospital, Victoria, Australia* Of four patients with intrathoracic metastases from primary prostatic adenocarcinoma, two presented initially with pulmonary involvement, whereas the other two patients had previously treated prostatic cancer. One represented with haemoptysis due to multiple pulmonary nodules which resolved after orchidectomy, and the other developed asymptomatic hilar and mediastinal lymphadenopathy which partially responded to orchidectomy. These cases demonstrate: 1) Pulmonary, pleural and mediastinal metastases occur in advanced stages of this disease. 2) Intra-

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	CASE 1: Lymphangitis carcinomatosa	CASE 2: Isolated pleural effusion
Respiratory symptoms	Dyspnoea. Cough	None
Urinary symptoms	None	Frequency. Nocturia.
Prostate examination	Hard. Fixed.	Enlarged. "Benign"
Serum prostatic acid phosphatase (S.P.A.P.)	Markedly elevated	Normal
Bone scan	Positive	Normal
Diagnosis	Transbronch. biopsy	Prostatic aspiration
Specific tissue stain	Pleural aspirate	Pleural aspirate
Orchidectomy response	Rapid improvement	Unchanged

thoracic metastases may be the presenting feature of otherwise inapparent prostatic cancer. 3) Rectal examination and a normal S.P.A.P. do not exclude the prostate as the primary site. 4) Other causes of intrathoracic disseminated adenocarcinoma respond poorly to any treatment whilst secondary prostatic cancer responds radiologically and symptomatically to orchidectomy. We recommend that males with intrathoracic adenocarcinoma have prostatic aspiration cytology and immunocytochemical stains for prostatic specific antigen and prostatic acid phosphatase performed on lung, pleural or mediastinal biopsy specimens.

Immunohistological investigation of bronchiectasis

J SILVA, P COLE, A JONES, LW POULTER *Host Defence Unit, Cardiothoracic Institute, Brompton Hospital, and the Department of Immunology, Royal Free Hospital and School of Medicine, London* Mononuclear cells are prominent in the histology of bronchiectasis (Whitwell, *Thorax* 1952;7:213-39). This study was designed to determine the contribution of acquired immunological mechanisms to the inflammatory damage occurring in this disease. Cryostat sections were prepared from microscopically involved but non-ulcerated areas of the resected bronchial tree (n = 7) or from endoscopic biopsy specimens obtained from segmental bronchi of affected lobes (n = 2) in nine patients with proved bronchiectasis without pan-hypoglobulinaemia. A panel of monoclonal antibodies was used to identify the presence and distribution of lymphocyte and macrophage subsets. Of the lymphocytes present, 90% were T cells with the exception that in 1/9 cases follicles of B cells were seen. The T cells were predominantly found infiltrating the surface epithelium and in some cases (6/9) the glandular epithelium within the lamina propria. These T cells were mostly CD8 + ve cells, although some CD4 + ve cells were found (mostly in the lamina propria). Very few cells were seen to express IL2 receptors (Tac + ve), but significant numbers had high concentrations of CD7 antigen on their surface. Macrophage-like cells were of two types: RFD1 + ve dendritic cells predominantly found within T cell infiltrates — including those adjacent to or in the epithelium; RFD7 + ve macrophages were diffusely distributed throughout the lamina propria. We conclude that the inflammatory reaction in bronchiectasis is associated with a T cell mediated immune response. This response appears in, or associated with, the epithelial surface as well as the lamina propria.

Characterisation of the local immune response causing pneumonitis in bone marrow transplant patients

HJ MILBURN, RM DU BOIS, LW POULTER *Departments of Immunology and Thoracic Medicine, Royal Free Hospital and School of Medicine, London* A previous report to this society described an association between pneumonitis in bone marrow transplant (BMTX) and a lymphocytosis in bronchoalveolar (BAL) fluid resulting from increased numbers of CD8 + (suppressor/cytotoxic) T cells. Subsequent immunocytochemical studies (reported here) characterise the full membrane antigen phenotype of these BAL cells. The majority of CD8 + cells (60-80%) express high concentrations of CD7 antigen and CD25 (IL2 receptors). 25% express HLA-DR molecules. Using McAbs RFT10 (CD38), RFT1 (CD5) and Leu7, two major populations of CD8 + cells, were found in lavage. One was CD8 + CD5 − Leu7 − CD38 + while the other was CD8 + CD5 + Leu7 + CD38 −. The latter cell phenotype reflects that of the predominant circulating CD8 + population in BMTX patients who develop graft versus host disease (GVHD) and/or overwhelming viral infections. It differs, however, from the CD8 + cells found in the infiltrates of GVHD skin. These findings suggest that the pneumonitis in these patients results from a local T cell mediated immune response against viral infection which possibly becomes uncontrolled, leading to a local GVHD reaction in the lung.

Lymphocyte-macrophage interactions: peripolesis in human lung cells

DJ LYONS, A GAUTAM, J CLARKE, JS MILLEDGE, MG HARRIES, BM BALFOUR *Departments of Immunological Medicine and Anaesthesia, Clinical Research Centre, Harrow* Lymphocyte-macrophage interactions occur in a variety of cell mediated immune responses. One such interaction is peripolesis, in which one or more lymphocytes bind to a target cell and move rapidly over its surface in a purposeful manner. This phenomenon has been associated with cell mediated cytotoxicity. We report for the first time that peripolesis occurs in cells recovered from the human lung. Cells obtained by bronchoalveolar lavage were centrifuged, washed twice and resuspended at a concentration of 5×10^5/ml in RPMI culture medium with penicillin, streptomycin and 10% fetal calf serum. Cells were cultured for 24 hours at 37°C in 5% CO_2 and observed by inverted phase-contrast microscopy. Cellular movements were recorded by time-lapse cinemicrography. A technique for fixing individual cells for electron microscopy was developed. Cells from nineteen patients were studied; in 6/19, mobile lymphocytes attached to adherent macrophages and peripolesis occurred, beginning between four and eighteen hours from the start of culture. Patients with inflammatory conditions such as sarcoidosis and tuberculosis, with a high lymphocyte count in BAL fluid, were most likely to show peripolesis. In no case was there evidence of a cytotoxic effect mediated by peripolesing cells. Transmission electron microscopy showed that peripolesing cells were lymphocytes but not the large granular type associated with cytotoxicity. Scanning

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electron microscopy confirmed that the non-motile cells were alveolar macrophages.

Antitumour activity of pulmonary alveolar macrophages (PAM) in patients with lung cancer

CF McDONALD, RC ATKINS *Department of Nephrology, Prince Henry's Hospital, and Department of Thoracic Medicine, Repatriation General Hospital, Melbourne, Victoria, Australia* Macrophages are thought to play an important immune effector cell role in antitumour host defence. Despite several previous studies it is still not clear whether PAM antitumour activity in lung cancer patients is abnormal. Therefore this study examined PAM cytostasis in a group of lung cancer patients and controls, and determined whether the *in vitro* PAM response could be enhanced by gamma interferon. Seven untreated lung cancer patients and 15 control patients with non-malignant respiratory disease underwent bronchoalveolar lavage (BAL). Antitumour activity of PAMs was assessed by tumour growth inhibition (cytostasis). Cytostatic activity was estimated by inhibition of incorporation of tritiated thymidine into the tumour target cell U937, as previously described. (Andreesen *et al, Cancer Res* 1983;43:5931-5936). There was a significant difference in baseline cytostatic activity between cancer (57.6 (SD 5.08%)) and control patients (86.3 (4.6%))($p<0.05$). The increase in cytostatic function obtained after stimulation with 1250μg/ml gamma interferon was higher in the cancer group (33.46 (12.8%) increase from baseline) than in controls (7.68 (2.96%)) ($p<0.01$). Post-stimulation cytostasis was not significantly different between the two groups. These results indicate (a) that PAM baseline cytostatic activity in cancer patients is lower than in controls and (b) that gamma interferon can significantly augment cytostatic function in cancer patients, to levels comparable with those achievable in non-cancer patients. It may be inferred from these results that PAMs from lung cancer patients are not fully stimulated *in vivo*, and this may provide an avenue for future therapeutic endeavours.

Do macrophage subsets determine the pathogenesis of cryptogenic fibrosing alveolitis (CFA)?

BK NOBLE, RM DU BOIS, LW POULTER *Departments of Immunology and Thoracic Medicine, Royal Free Hospital and School of Medicine, London* Using a comprehensive panel of monoclonal antibodies (McAbs) immunohistological techniques have been employed to investigate the distribution and phenotype of non-lymphoid mononuclear cells in sections of lung tissue from 10 patients with CFA. McAbs that in normal tissues identify antigens on monocytes (UCHM1), macrophages (RFD7), dendritic cells (RFD1) and epithelioid cells (RFD9) were used. It was found that the macrophages packed into the air spaces were all D9+,D1+ and 50% were D7+. The cells of the interstitium were D9−,D1+ and 30% of these were D7+. Within follicular clusters of lymphocytes macrophage-like cells were either D1+ or D7+. Very few ($\leq$5%) of non-lymphoid cells were UCHM1+. These results suggest: 1) few monocytes are attracted into the inflammatory reaction; 2) the macrophage-like cells in the air spaces express a highly abnormal phenotype and 3) cells with the phenotype of antigen-presenting cells are present within lymphoid follicles. Subsequent double immunofluorescence studies indicated that the D7+ but not the D1+ cells in the interstitium contained fibronectin while the D9+D1+ cells in the air spaces both contained and appeared to be "secreting" fibronectin. These results raise the possibility that macrophages may induce local T cell responses in CFA as well as subsequent fibrosis.

Human T cell lines and clones specific for the house dust mite *Dermatophagoides farinae* — a tool for research in asthma and rhinitis

RE O'HEHIR, JR LAMB, AB KAY *Cardiothoracic Institute, Brompton Hospital, and MRC Tuberculosis Unit, Hammersmith Hospital, London* The precise role of cell-mediated immunity in atopic allergy and extrinsic asthma remains unclear. Since there are usually very small numbers of circulating allergen-specific T cells, cloning techniques have to be employed in order to obtain sufficient numbers of homogeneous cells for detailed study. We have raised human T cell lines from peripheral blood lymphocytes of atopic individuals with perennial rhinitis or asthma using a modification of a previously described method (Lanzavecchia *et al, Clin Exp Immunol* 1983;52:21-28). From these lines a panel of T cell clones (n=40) has been derived which are responsive to the house dust mite *D farinae*, one of the commonest clinically relevant aeroallargens in asthma. One such clone, DD11, has been characterized in detail and found to be highly antigen-specific. It is unreactive to *D pteronyssinus* and a panel of other common aeroallergens. The response is MHC class II restricted at the DR level and dependent on the presence of antigen-presenting cells. Phenotypic analysis showed the lines and clone DD11 to be of T helper type. Such clones might provide an *in vitro* system for further evaluation of the role of the T lymphocyte in the pathogenesis of allergic disease.

Injection of virus-specific cytotoxic T cells can enhance disease in mice infected with respiratory syncytial virus

PJM OPENSHAW, MJ CANNON, BA ASKONAS *Immunology Division, National Institute for Medical Research, London* The pathogenesis of bronchiolitis induced by respiratory syncytial virus (RSV) is poorly understood. Clincal studies have shown an association with strong cell-mediated immunity to RSV, but it has been shown that passive transfer of RSV-specific cytotoxic T (T_C) memory cells can clear virus from the lungs of persistently infected immunodeficient mice. Similarly, mice given a lethal dose of influenza A virus can recover if injected with cloned influenza-specific T_C cells. Lines and clones of RSV-specific T_C cells were derived from mice primed with RSV. After intranasal challenge with live human RSV, normal mice given these T_C cells intravenously became ill, and some given more than 10^6 cells died. Neither virus nor cells

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alone caused appreciable illness. At day five cells were recovered by bronchoalveolar lavage as previously described (Openshaw *et al, Clinical Science* 1987;**72 (suppl 16)**:35). Mice infected with RSV showed increased proportions of lymphocytes, whilst mice also given T_C cells had increases in neutrophils and red cells in addition. Mice given cells alone showed none of these effects. We conclude that cloned T_C cells may cause haemorrhagic neutrophilic pneumonitis in RSV infected mice.

A longitudinal study of non-specific bronchial responsiveness in asthma

LK JOSEPHS, I GREGG, DJG BAIN, ST HOLGATE *Medicine I and Aldermoor Health Centre, University of Southampton, Southampton* While increased non-specific bronchial responsiveness is of significance in the pathogenesis and diagnosis of asthma, the contribution of this abnormality in day-to-day asthma is not known. In this study we have investigated the longitudinal relationship between bronchial reactivity to methacholine (Yan *et al, Thorax* 1983;**38**:760-765), measured as that dose producing a 20% fall in FEV_1 (PD_{20}), and respiratory symptoms, changes in PEFR, and treatment requirements in a group of 19 patients in whom the clinical diagnosis of asthma had been established. Over a period of 12-18 months these patients underwent 15-33 (mean 25) provocation tests at 2-3 week intervals. No constant relationship could be discerned in the group as a whole between PD_{20} and baseline airway calibre, diurnal variation in PEFR or symptom score, over three days surrounding each challenge test. However, in individual subjects three patterns of response emerged: 1) reactivity varying during the study period in parallel with symptoms and changes in PEFR, 2) reactivity that varied little despite obvious symptoms and falls in PEFR, 3) changes in reactivity that were not necessarily accompanied by parallel changes in symptoms and/or PEFR. In three subjects the fall in FEV_1 was frequently insufficient to derive a PD_{20}. We conclude that the relationship between bronchial hyperresponsiveness and clinical episodes of asthma is complex and that this functional airway abnormality is only one component contributing to symptomatic bronchoconstriction.

Volume history effects on bronchial hyper-responsiveness in smokers

J PERTUZÉ, A WATSON, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Smokers with mild airflow obstruction but without asthmatic features show bronchial hyperresponsiveness (BHR), but some aspects of their BHR differ from asthma. Thus, we studied volume history effects and whether a plateau of partial bronchoconstriction (bc) occurs, in 10 male smokers (age 60.8 (SD 5.2) years) with baseline FEV_1 85.3 (17%) predicted. During histamine-induced bc we measured FEV_1 and flow at 40% initial vital capacity (VC) during maximum ($\dot{V}m_{40}$) and partial ($\dot{V}p_{40}$) flow volume manoeuvres. Baseline $\dot{V}m_{40}/\dot{V}p_{40}$ ratios averaged 0.77 (0.19); with bc, $\dot{V}p_{40}$ fell more than $\dot{V}m_{40}$ and the $\dot{V}m_{40}/\dot{V}p_{40}$ ratio rose to 2.08 (1.25) during max. bc. BHR assessed by $\Delta\dot{V}p_{40}$ ($PC_{40}\dot{V}p$) was 3.02 mg/ml, while $PC_{40}\dot{V}m$ was 3.7 mg/ml significantly different from PC_{20} FEV_1, which was 5.22 mg/ml. VC assessed from max. flow-volume curves (VCm) during baseline conditions was 3.47 (0.76) l and VCp was 3.51 (0.67) l. With max. bc VCm decreased to 2.48 (0.64) l whereas VCp decreased to 2.19 (0.45) l. Seven of the men inhaled further concentrations of histamine after reaching a $>20\%$ fall in FEV_1; average max. falls from baseline were 44% (10%) for FEV_1, 74% (12%) for $\dot{V}m_{40}$ and 87% (12%) for $\dot{V}p_{40}$. Only one man showed a plateau of FEV_1 and $\dot{V}m_{40}$ dose-response curves and none on the $\dot{V}p_{40}$ response. In summary three features characteristic of asthma — 1) low baseline $\dot{V}m_{40}/\dot{V}p_{40}$ ratio in "spontaneous" airway narrowing, 2) increase in $\dot{V}m_{40}/\dot{V}p_{40}$ ratio with induced airway narrowing and consequent greater sensitivity of $PC_{40}\dot{V}p > PC_{20}FEV_1$, 3) absence of limited bc as found in normal subjects — were also found in smokers with BHR.

Correlation between the airway reactivity to ultrasonically nebulised hypertonic saline, exercise and histamine in asthmatic subjects

N BELCHER, TH LEE, TJH CLARK, PJ REES *Department of Respiratory Medicine, Guy's Hospital, London* Ten asthmatic subjects 6M, 4F mean age 21 years (range 16-25 years) undertook three different bronchial challenges. No therapy was taken for 12 hours before studies. Challenges were performed each day at the same time of day in random order. Challenges were spaced over 2-4 weeks. Baseline FEV_1s differed by less than 10% in the study. FEV_1 was taken as the best of two readings. On one day ultrasonically nebulised hypertonic saline (3.6%) was inhaled in 10-15 litre aliquots with FEV_1 recorded 30 seconds later. The dose required to produce a 20% fall in FEV_1 (PD_{20}HS) varied between nine and 75 litres (mean 31.6 l). Exercise challenges consisted of eight minutes of exercise on a fixed cycle ergometer at 60% of maximal predicted oxygen uptake. FEV_1 was recorded at the end of exercise and 60 minutes thereafter. The mean maximum post exertional fall in FEV_1 was 23.6% (range 6-54%). On a third day bronchial reactivity to histamine was measured and expressed as the PC_{20} FEV_1 (PC_{20}Hist) mean 1.89mg/ml (range 0.03-3.6 mg/ml). Correlations between pairs of challenges in individuals were calculated using Spearman's rank correlation test. Bronchial reactivity to HS correlated with EX ($r=0.659$, $p<0.02$), and also PC_{20}Hist ($r=.74$, $p<0.02$) but there was no correlation between PC_{20}Hist and EX ($r=0.311$, $p<0.1$).

Increases in airway histamine responsiveness precede allergen-induced late asthmatic responses

CF CRADDOCK, SR DURHAM, WOCM COOKSON, MK BENSON *Osler Chest Unit, Churchill Hospital, Oxford* Seven atopic asthmatic subjects underwent inhalation challenge with allergen (*D pteronyssinus* five subjects, Timothy grass two subjects) and a separate

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control challenge with allergen diluent. The challenges were given in random order with an interval of 14 days. Airway histamine responsiveness (Cockcroft, *Clin Allergy* 1977;7:235-243) was measured pre-challenge and at 3 hours, 24 hours and 48 hours post-challenge. The mean (SEM) maximal early (0-60 minute) and late (4-12 hour) % falls in FEV_1 after allergen were 32.9 (3.0) and 24.9 (7.0) respectively. The geometric mean changes in histamine PC_{20} (expressed as the ratio pre-challenge: post-challenge PC_{20}) after allergen were: 3 hours, 3.66 (when mean FEV_1 was 98% the pre-challenge value); 24 hours, 3.66 (FEV_1, 97%); 48 hours 2.33 (FEV_1, 98%). These changes in histamine PC_{20} were significant at all three time points when compared with the corresponding values after diluent ($p<0.05$), Wilcoxon paired test). When these changes in histamine PC_{20} were compared with the maximal late % falls in FEV_1, the correlation coefficients (Spearman's method) were: 3 hours, $r=0.86$ ($p<0.05$); 24 hours $r=0.75$ ($p<0.1$); 48 hours $r=-0.07$ ($p<0.1$). We conclude that increases in airway histamine responsiveness precede the late asthmatic response, occur independently of changes in airway calibre and correlate with the magnitude of the late response.

Histamine stimulation causes tachyphylaxis to both inhaled histamine and acetylcholine in asthmatic subjects

PJ MANNING, PM O'BYRNE *Department of Medicine, McMaster University, Hamilton, Ontario, Canada* Tachyphylaxis occurs to inhaled histamine but not acetylcholine in mild asthmatic subjects. Histamine tachyphylaxis is therefore not a consequence of bronchoconstriction alone. The purpose of this study was to determine whether histamine causes tachyphylaxis to subsequent acetylcholine inhalation. Eight mild asthmatic subjects with previously demonstrated histamine tachyphylaxis were studied on four separate days. On each day two inhalation tests were done one hour apart as described by Cockcroft *et al (Clin Allergy* 1977;7:235-43). The response was expressed as the provocative concentration of histamine causing a 20% fall in FEV_1 (histamine PC_{20}). The tests were as follows: Histamine and histamine; histamine and acetylcholine; acetylcholine and acetylcholine; acetylcholine and histamine. The mean baseline FEV_1 values were similar before each inhalation test on each study day ($p>0.25$). Acetylcholine did not cause tachyphylaxis to either acetylcholine or histamine. However, tachyphylaxis occurred following histamine inhalation tests to both histamine and acetylcholine in all subjects. Thus, the mean PC_{20} histamine increased from 3.74 mg/ml (%SD 1.65) to 5.92 mg/ml (%SD 2.02) ($p<0.005$) and the mean PC_{20} acetylcholine increased from 3.59 mg/ml (%SD 2.00) to 7.76 mg/ml (%SD 1.80) ($p<0.0005$). This study confirms that tachyphylaxis occurs following histamine but not acetylcholine inhalation and that prior histamine inhalation reduces airway responsiveness to acetylcholine.

Effect of inhaled terbutaline on nocturnal change in bronchial reactivity in asthma

AS VATHENEN, A KNOX, B HIGGINS, J BRITTON, TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* To determine whether a rebound increase in reactivity occurs overnight in asthmatic patients using inhaled beta agonist therapy we have investigated the effect of regular doses of inhaled terbutaline on bronchial reactivity measured at intervals over 24 hours. Eight subjects aged 18 to 45 with mild asthma were given placebo, 50 μg or 2000 μg terbutaline via a Nebuhaler at 10, 16 and 22 hours on separate non-consecutivie days in a randomised, double blind design. Histamine PD_{20} FEV_1 was measured at 09, 11, 15, 21 and 23 hours and overnight at 03, 06 and 09 hours with additional FEV_1 measurements at 07 and 08 hours. Following placebo there was a circadian change in mean FEV_1 and in geometric mean histamine PD_{20} FEV_1 with peak trough differences of 0.29 l and 1.3 doubling doses (DD) of histamine respectively. The lowest values of both measurements occurred at 23.00 hours. Both doses of terbutaline increased mean FEV_1 (0.45 and 0.4 l after the first dose of 500 μg and 2000 μg respectively, $p<0.001$) which remained elevated relative to placebo except at 0700 hours after the 500 μg doses when the FEV_1 fell to the value seen after placebo. Histamine PD_{20} FEV_1 was also increased after terbutaline (2.2 DD and 3.4 DD one hour after the first 500 μg and 2000 μg dose, $p<0.001$) and remained elevated relative to placebo throughout the 24 hours. Thus terbutaline caused no rebound increase in reactivity at any time in these subjects with mild asthma.

Gas exchange during exercise in patients recovering from acute asthma

GE PACKE, W FREEMAN, RM CAYTON *Department of Respiratory Physiology, East Birmingham Hospital, Birmingham* In patients recovering from acute severe asthma, disturbance of lung function may persist despite improvement in symptoms at rest (McFadden *et al, N Engl J Med* 1973;288:221-5). Little is known about the effects of exercise in such patients, particularly on gas exchange. We studied 17 adults (seven male, 10 female; mean age 26 (SD 8) eight years) recently treated in hospital for acute asthma. PEFR and arterial blood gas tensions (breathing air) were measured on admission. Before discharge, when asymptomatic at rest, patients performed five minutes steady-state exercise on a bicycle ergometer (100W male, 75W female). Ventilation, oxygen uptake and carbon dioxide output were measured before and during exercise. Blood gas tensions were measured on arterialised ear-lobe capillary blood taken at rest and during the last 15 seconds of exercise.

	Admission	*Rest*	*Exercise*
PEFR (% Pred.)	26.8 (5.7)	87.6 (21.0)	—
PaO_2 (kPa)	8.64 (1.26)	13.19 (1.39)	13.93 (1.34)
A-aO_2 (kPa)	5.98 (1.34)	1.71 (1.32)	1.67 (1.24)

Symptomatic improvement paralleled improvement in PEFR, arterial oxygen tension (Pa_{O_2}) and alveolar-arterial

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oxygen gradient ($A\text{-}aO_2$). There was no significant change in $A\text{-}aO_2$ during exercise. Early resumption of moderate exercise in young patients recently treated for acute asthma is unlikely to have an adverse effect on gas exchange.

Reproducibility of walking tests in chronic obstructive airways disease

AJ KNOX, JFJ MORRISON, MF MUERS *Respiratory Medicine Units, St James's and Killingbeck Hospitals, Leeds* Previous workers have suggested that the learning effect in the performance of repeated walking tests is confined to the first two walks, but none has evaluated it fully. We studied 36 patients with chronic bronchitis and airflow obstruction to examine the reproducibility of walking tests, spirometry, and subjective scores when 12 five minute walking tests were performed either over three consecutive days or four consecutive weeks. In 12 subjects we randomised walks to fixed and random starting points to assess the role played by visual clues. Distance walked increased with walk number ($p<0.001$) and with day ($p<0.001$); subjective breathlessness decreased with day ($p=0.012$). Spirometric values did not change either with day or with walk number. Randomising the starting point did not affect distance walked. Five minute distance correlated with all spirometric values but not subjective scores. Whilst walks 1-3 showed the greatest increase in walking distance, a further 12% increase occurred between walks 3 and 12, learning effects continuing throughout the first 10 walks. The corridor walking test is not as reproducible as previously thought. It should not be used as an indicator of an individual's response to therapy, e.g. during steroid trials. In clinical studies a placebo group is essential.

Upper airway obstruction due to goitre

MR MILLER, AC PINCOCK *Department of Medicine, University of Birmingham* Upper airway obstruction (UAO) due to goitre has previously been thought to be rare. We have recorded flow volume loops (FVL) on 144 subjects with goitre who complained of either breathlessness, a sense of choking or neck discomfort. Presence of UAO was determined by inspection of the FVL. UAO was diagnosed in 44 subjects (31%) and 29 of these plus 14 without evidence of UAO were retested after subtotal thyroidectomy. The 14 without UAO showed no change in FVL. Of the 29 with UAO, 23 showed improvement in FVL and symptoms, two did not improve but still had marked UAO and four were deemed false positives. This suggests that FVL shape has 100% sensitivity, 86% specificity and 91% accuracy in diagnosing UAO. Of many indices tested as predictors of UAO only Empey Index ($EI=FEV_1$ in ml divided by PEF in l/min) was helpful. An $EI>8$ had a 68% sensitivity, 94% specificity and 79% accuracy in diagnosing UAO. An $EI>10$ had only a 36% sensitivity. We conclude that UAO due to goitre is more common than previously believed and that a FVL should be recorded routinely on patients with symptomatic goitre.

The effect of low dose nebulised morphine on exertional dyspnoea in patients with chronic lung disease

IH YOUNG, E DAVISKAS *Department of Thoracic Medicine, Royal Prince Alfred Hospital, Sydney, N.S.W., Australia* We have studied the effect of low dose (approx. 0.6 mg) nebulised morphine which could have a direct action on lung afferents to relieve dyspnoea. Seventeen adult patients with advanced chronic lung disease (FEV_1 range 0.4-1.5 l) performed a one minute progressive exercise test on an electrically braked cycle ergometer to determine maximum work load (WMAX) and limiting symptom. Eleven patients (nine with COPD, two with IPF) were limited by dyspnoea and two hours later proceeded to an endurance test at 80% WMAX. One hour later, they inhaled SOL1 (5 ml of either 1 mg morphine/ml (A) or saline placebo (B)) for 12 minutes from a jet nebuliser (Hudson) driven by 6 l/minute oxygen. An endurance test was repeated 15 minutes later and the per cent change in endurance time calculated. The above was repeated on a separate day with SOL2. The allocation of A or B as SOL1 or SOL2 was double blind and in random order. All tests were performed inhaling 100% O_2 from a demand valve.

n	*80% WMAX* watts	*NEB. MORPHINE* Total mg.	*%INCR. ENDUR. TIME* Morph.	Placebo
11	40.5 (23.4)*	1.7 (0.7)*	34.9 (10.5)**	0.8 (6.7)**
	*mean (SD)		**mean (SEM)	

The paired differences between endurance time responses to morphine and placebo were all positive (34.1% (10.8%);** $t=3.15$, $p<0.02$, paired *t* test). There was no correlation between nebulised dose and endurance time response ($r=0.32$). Assuming 30% retention of the nebulised dose by each patient, approx. 0.6 mg (mean) morphine improved exercise tolerance. It is possible the small amount delivered to the lungs (approx. 0.2 mg mean) acts directly on lung afferents.

The use of negative pressure ventilation (NPV) to facilitate weaning from intermittent positive pressure ventilation (IPPV)

AK SIMONDS, EH SAWICKA, N CARROLL, MA BRANTHWAITE *Brompton Hospital, London* Restoration of spontaneous ventilation following IPPV may be difficult in patients with chronic respiratory disease. We report the use of NPV to wean 10 patients (5M, 5F; age 18-61 years) with acute on chronic respiratory insufficiency in whom conventional weaning methods had failed. Six were scoliotic (mean VC 25% predicted) and four had chronic airflow limitation two with emphysema, one with cystic fibrosis, one with pulmonary sarcoid; mean FEV_1 30% predicted). In three IPPV had been required following thoracic surgery (pleurectomy, pneumonectomy and drainage of bullae) and the remainder were ventilated for acute respiratory failure, in four associated with evidence of respiratory tract infection. Mean duration of IPPV was 8.4 days. Subjects were able to breathe spontaneously for 15 minutes, had intact airway reflexes, stable cardiovascular system and functioning gastrointestinal tract before extubation in the iron lung. In seven patients NPV was then successfully

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withdrawn over one-two weeks. Two others were returned to IPPV as copious sputum production made control of ventilation impossible. One was later weaned using NPV. One patient died of postoperative complications unrelated to NPV. Using this technique, arterial blood gas tensions can be controlled and respiratory muscles rested without the disadvantages of endotracheal intubation. NPV should be considered before performing tracheostomy as this limits formation of an adequate neck seal.

Direct measurement of pressure and gas concentrations within emphysematous bullae

MDL MORGAN, J MORRIS, HR MATTHEWS *East Birmingham Hospital, Bordesley Green East, Birmingham*
Emphysematous bullae are often described as structures with poor ventilation containing gas under pressure which compresses surrounding lung. Since direct evidence is lacking, we have performed percutaneous puncture of bullae in four patients immediately before thoracotomy. Gas samples for analysis of P_{BO_2} and P_{BCO_2} were withdrawn during spontaneous ventilation and at one minute intervals during oxygen wash in. Simultaneous arterial blood gas samples were taken. In three patients the intrabulla pressure (Pbul) was recorded, combined in two cases with oesophageal pressure (Poes) and later with airway pressure (Paw) during IPPV. P_{BO_2} (12.9 (SD 0.7) kPa) was greater than Pa_{O_2} (8.4 (1.3) kPa). After four minutes of oxygen wash in there was an increase in P_{BO_2} (26.7 (11.5) kPa) but it was always overtaken by the rise in Pa_{O_2} (39.2 (16.6) kPa). The inspiratory excursion in Pbul was always negative (range -7 to -12 cm H_2O) and was similar in degree and phase to Poes. During IPPV, Paw was poorly transmitted to the bulla but did produce PEEP within it. We conclude that during tidal breathing bullae have patent airway communications but ventilate slowly. The relationship between Pbul and Poes suggests that compression is unlikely to be the cause of collapse of peribullous lung and PEEP rather than peak Paw is the major hazard during IPPV.

Carcinoma of the bronchus with microscopic resection line involvement

DK KAPLAN, RI WHYTE, DAC SHARPE, RJ DONNELLY *Broadgreen Hospital, Regional Adult Cardiothoracic Unit, Thomas Drive, Liverpool* In a series of 560 consecutive pulmonary resections for bronchial carcinoma, unsuspected microscopic tumour was present at the bronchial resection margin in 26 cases (4.5%). Adjuvant chemotherapy or radiotherapy was given in two cases. In follow-up ranging from one to 60 months (mean 16 months), 62% of patients were alive and free of recurrent disease. Twelve patients underwent periodic surveillance bronchoscopy in an attempt to identify early local recurrence. Ninety-two per cent of these patients were alive and disease-free in follow-up from four to 49 months (mean 18 months). No cases of local recurrence were identified. It was concluded that microscopic residual resection-line tumour does not preclude prolonged survival and that no benefit from surveillance bronchoscopy could be demonstrated in this small patient sample.

Management of tracheal lesions

K MOGHISSI *Humberside Cardiothoracic Surgical Centre, Castle Hill Hospital, Cottingham, N. Humberside*
Eighty-seven patients with tracheal lesions are reviewed. These are divided into Group one (n = 32) non-neoplastic and Group 2 (n = 55) neoplastic lesions. Twenty-six of Group one patients had post-intubation tracheal stenosis, of whom 23 had resection and reconstruction with one hospital death (4.3%) and one late recurrence; 21 patients are well after 5-16 years: three other patients with stenosis were treated by endoscopic Nd YAG laser with complete success. One patient with amyloid tumour was treated successfully by endoscopic laser, two with tracheomalacia were treated conservatively and two remaining patients with traumatic rupture underwent operation; all are alive and well. Group two patients are subdivided into 2a (n = 18) primary tumours, 2b (n = 5) bifurcation lesions and 2c (n = 32) with secondary tracheal tumours: 47 of Group 2 patients had resection and reconstruction (21 with patch graft of Marlex mesh + pericardium); five died (10.6%) and 10 (21%) survived more than five years. Six remaining patients had laser therapy with or without radiotherapy. We conclude: 1) The majority of tracheal lesions require excision and reconstruction, some with a patch graft. 2) Some lesions can be treated by laser and achieve a cure (when benign) or a good palliation (when malignant).

Postpneumonectomy achalasia of the cardia — a new entity?

K MOGHISSI, PB RAJESH *Humberside Cardiothoracic Surgical Centre, Castle Hill Hospital, Cottingham, N. Humberside* Primary idiopathic achalasia of the cardia and its variants is well documented in the literature. Secondary achalasia is, however, rare. Achalasia occurring after major pulmonary surgery has not been reported. In this paper we present four patients with achalasia of the cardia after pneumonectomy. There were three male and one female, age range 52-63 (mean 57.5) at the time of operation. There were three right and one left pneumonectomies and at the time of operation no complaints or abnormalities referrable to the alimentary tract were recorded. The time lapse between pneumonectomy and the presenting symptoms were from 4 to 18 years (mean 14.25 years). In three patients the diagnosis was made endoscopically and radiologically; in one (living) patient the diagnosis was further confirmed by manometric and isotope scan. We believe that interference with the vagus nerves is the basis of the secondary achalasia, after pneumonectomy. All patients in this series were treated by repeated oesophagoscopy and dilatation.

Open lung biopsy in patients with Hodgkin's disease and pulmonary infiltrates

JR CATTERALL, RE MCCABE, JS REMINGTON *Division of Infectious Diseases, Stanford University Medical Center, California; Department of Respiratory Medicine, Edinburgh* We have reviewed the results of open lung biopsy (OLB) in 41 patients with previously diagnosed

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Hodgkins's disease (HD: 17 with stage II; 10, stage III; and 14, stage IV) who were found to have pulmonary opacification on chest radiography. Nineteen (46%) of the diagnoses from OLB were specific and 22 non-specific. The most common specific diagnosis was Hodgkin's disease (12 patients), the others being *P carinii* pneumonia (3), solitary fungal granulomas (2), cytomegalovirus pneumonia (1) and adenocarcinoma (1). Specific diagnosis were made in 11 (69%) of the 16 patients with nodules or masses on chest radiography but in only eight (32%) of the 25 patients with non-nodular radiographic opacification. Eleven (58%) of 19 patients who were asymptomatic or had had symptoms for > four weeks had specific diagnoses, compared to one of six patients (17%) symptomatic for < one week. Survival of hospitalisation correlated more with stage of HD than with specific diagnosis. However, treatment was changed on the basis of the OLB result in 18 (44%) of the patients biopsied. Three of the patients with a non-diagnostic OLB had progressive infiltrates which were diagnosed as HD, either by necropsy or sputum cytology, 3-16 months later. Three patients had increased respiratory failure after OLB but no complication could be attributed unequivocally to the procedure. These results suggest that, in HD, OLB can help in the management of pulmonary radiographic opacities, especially if the radiographic opacities are nodular and the patient's condition is relatively stable.

Comparison of CT scanning, ^{57}cobalt bleomycin scanning and barium swallow in assessment of the mediastinum in lung cancer

CG WATHEN, KM KERR, A MILLAR, AJA WIGHTMAN, JJK BEST, EW CAMERON, NJ DOUGLAS *City Hospital and Royal Infirmary, Edinburgh* Accurate non-invasive assessment of mediastinal lymph node involvement in patients with lung cancer would decrease the need for mediastinoscopy and thoracotomy. Fast breath-hold CT scanning is thought to be the most accurate method (Mintzer *et al, Radiology* 132:653-9) but others have proposed that ^{57}cobalt-bleomycin scanning is superior (Nieweg *et al, Thorax* 1983;38:16-21), although no direct comparison has been done. In Edinburgh mediastinal nodes are traditionally assessed by barium swallow, but no prospective evaluation has been reported. Thirty-one patients with proved tumours have entered a prospective study comparing barium swallow, ^{57}cobalt-bleomycin scanning and GEC 8800 CT scan with enhancement prior to mediastinoscopy and/or thoracotomy with lymph node exploration. Nine had histologically positive mediastinal lymph nodes. The results are:

	Sensitivity	*Specificity*	*Neg Prediction*
CT	78%	58%	83%
^{57}Co-bleo	33%	60%	68%
Ba Swallow	22%	67%	70%

Where neg prediction = true negative ÷ total negative × 100

While CT scanning has the highest sensitivity, if non-invasive assessment is used to select patients to proceed to thoracotomy without mediastinoscopy, these preliminary results show that the negative predictive power of the barium swallow is not significantly worse than that of the more expensive alternatives. ^{57}Cobalt-bleomycin scan seems to have little role in mediastinal staging.

The nutritional status of patients undergoing surgery for lung cancer

Y BASHIR, TR GRAHAM, A TORRANCE, P BUAMAH, GJ GIBSON, CJ HILTON, GN MORRITT, PA CORRIS *Departments of Respiratory Medicine and Thoracic Surgery, Freeman Hospital, Newcastle upon Tyne* Both malnutrition and inadequate perioperative nutritional support have been shown to correlate with increased morbidity in patients undergoing general surgery (*Surg Clin N Am* 1981;61:465-487). Since both malignant disease and chronic airflow obstruction predispose to nutritional deficiency we have assessed the nutritional state of 39 consecutive patients with bronchial carcinoma prior to surgery. Eighteen patients (46%) fell below the 25th percentile for body mass index and for triceps/subscapular skinfold thickness, indicating depleted energy reserves; in 23 patients (59%) the creatinine-height index was below 80% predicted, indicating low static protein reserve. Although mean (SD) albumin level for the group was 40.3 (0.57) g/l and only three patients had subnormal levels, serum transferrin was reduced with a mean (SD) value of 1.77 (0.1) g/l (Ref 2-3 g/l). Moreover sequential measurements of transferrin and prealbumin (which is a circulating protein with a half life of only 24 hours) at 48 hour intervals up to the sixth postoperative day showed progressive depletion of both proteins, suggesting that nutritional support following surgery was inadequate over this period. In this series four patients developed bronchopleural fistulae; all had significant protein-energy depletion preoperatively and two died. We conclude that protein-energy malnutrition occurred commonly in this series of patients undergoing surgery for lung cancer and that routine postoperative feeding failed to prevent further depletion of circulating proteins over the first week. Prospective studies are needed to determine whether preoperative nutritional screening can identify patients at risk of increased morbidity and mortality following surgery for lung cancer.

A radiographic scoring system to assess diffuse pulmonary shadowing in sarcoidosis

MF MUERS, WG MIDDLETON, GJ GIBSON *for BTS Sarcoidosis Subcommittee* A method of radiographic assessment, suitable for serial and between patient comparison of subjects recruited for the BTS Sarcoidosis Study, has been devised and evaluated. Radiographic assessments were made of a) the predominant abnormality (reticulonodular, micronodular, confluent or fibrotic), b) any subsidiary abnormality and c) presence of hilar and mediastinal lymphadenopathy. The extent and profusion of each type of pulmonary abnormality was scored on a four point scale. The method was tested on 169 entry radiographs by two independent readers. Inter-observation variation was 7.6% for predominant abnormality, 16.5% for the presence of

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subsidiary abnormality and 15% for the presence of adenopathy. In 422 comparisons of scores given for extent and profusion a one point discrepancy occurred on 139 occasions (33%) and two point discrepancy occurred on seven occasions (1.6%). Blind comparison of 55 patients in whom the pulmonary abnormality had improved spontaneously at six months and 58 patients with static or worsening pulmonary shadows showed that the latter more often had fibrotic shadowing at presentation (14 vs 2: $p = 0.004$), had a higher total score 10.6 (4.1) vs 8.6 (4.9): $p = 0.023$) and were less likely to have adenopathy (30 vs 40: $p = 0.035$).

Numbers and activity of cells obtained at bronchoalveolar lavage (BAL) from sequential aspirates in sarcoidosis

CA KELLY, C WARD, G BIRD, DJ HENDRICK, EH WALTERS *Department of Medicine, Newcastle General Hospital, Newcastle on Tyne* There is increasing interest in the involvement of a variety of cell types in the pathogenesis of sarcoid. We studied cell numbers and metabolic activity in the separate aspirates (A1, A2, A3) of three sequential 60 ml aliquots of sterile buffered saline introduced into a middle lobe segment in eight patients with biopsy-proved sarcoid and in eight normal controls. Differential and total cell counts were performed prior to centrifugation. Cell pellets were resuspended in medium 199 at a concentration of 5×10^5 cells/ml. After 5% latex stimulation, we measured chemiluminescence (CL) in each of the suspensions using an LKB 1250 luminometer. Luminol was used to enhance neutrophil (PMN) CL, and lucigenin to enhance macrophage (AM) CL. There were significantly more lymphocytes in patients with sarcoid in all three aspirates ($p<0.01$). There were no other significant differences in cell counts between controls and sarcoid patients, although AM numbers rose ($p<0.05$) and PMN numbers fell ($p<0.05$) from A1 to A2 in both groups. Median (range) values for peak CL were;

Luminol CL/10^3PMN	*A1*	*A2*	*A3*
Controls (n = 8)	0.36 (0.1-0.9)	0.25 (0.1-0.7)*	0.29 (0.1-0.7)*
Sarcoid (n = 8)	0.42 (0.1-0.9)	0.64 (0.4-3.2)*	0.58 (0.1-2.4)*
Lucigenin CL/10^6AM	*A1*	*A2*	*A3*
Controls (n = 8)	8 (1-20)	7 (1-30)*	8 (1-30)*
Sarcoid (n = 8)	14 (1-30)	22 (13-100)*	29 (4-70)*

Wilcoxon rank test * $p<0.05$.

Luminometry provides evidence of an increase in both PMN and AM activity in sarcoidosis which is most marked and significant only in A2 and A3, while the increase in lymphocyte numbers in sarcoid appears less specific.

Autologous mixed lymphocyte reactions probe macrophage function in sarcoidosis

M SPITERI, LW POULTER *Departments of Thoracic Medicine and Immunology, Royal Free Hospital and School of Medicine, London* Alveolar macrophages from healthy subjects are poor stimulators of autologous mixed lymphocyte reactions (AMLR) (Lipscomb *et al, J Immunol* 1986;136:497). As sarcoidosis is characterized by a lymphocytosis seen in lavage and the activation of these cells, the question arises as to whether changes in the macrophage or lymphocyte populations present in this disease state are responsible. It is also unknown whether any aberrations in cell-interaction are restricted to the lung. The studies reported here address these questions. BAL and peripheral blood mononuclear cell (PBMC) suspensions were obtained from five sarcoid patients and five healthy volunteers. These two populations were cultured in AMLR either separately or mixed together. In mixtures of BAL and PBMCs, preincubation of one population with mitomycin C was used to create "one way" reactions. All cultures were for four days followed by an 18 hour pulse with tritiated thymidine. Results revealed that, as with normal cells, BAL populations from sarcoid patients exhibited reduced AMLR reactivity when compared with PBMC cultures from the same individual. One-way AMLRs with cross-over mixtures of PBMC and BAL from the same patients showed that the ability of BAL non-lymphoid cells to stimulate PB lymphocytes was also impaired. This result, and a subsequent observation that PBMC treated with mitomycin C are unable to stimulate lavage lymphocytes, suggest that both lymphoid and non-lymphoid cells in sarcoid BAL are compromised.

Expiratory lung crackles in patients with fibrosing alveolitis

MJ WALSHAW, M NISAR, MG PEARSON, PMA CALVERLEY, JE EARIS *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Late inspiratory crackles are a constant and diagnostic feature of fibrosing alveolitis, but the prevalence of expiratory crackles has not been described. To investigate this, lung sounds were recorded in 13 patients (mean age 67 years) with fibrosing alveolitis (10 cryptogenic, three autoimmune). All had restricted PFTs (mean FVC 63%) and a low TLCO (mean 48%) and none produced sputum. Recordings were made at the right lung base during tidal breathing with the patient seated, using a high sensititivy crystal microphone. Airflow was measured with a pneumotachograph. Signals were stored on a FM tape recorder and reproduced on a chart recorder. All patients had late inspiratory crackles in every breath. Expiratory crackles occurred in 12 patients and 84% took place in the last two thirds of expiration. No patient had more than five crackles in any on expiration and 70% contained at least one crackle. Varying the pattern of respiration (deep breathing, breathing to residual volume, measurement after breath holding) did not alter the prevalence or distribution of crackles. The proportion of expirations containing crackles was inversely related to the TLCO ($p<0.05$). Expiratory lung crackles are a common physical sign in fibrosing alveolitis. They are easier to measure than the more numerous inspiratory crackles and appear to be related to disease severity. Further work needs to be done to assess their significance and aetiology.

Airflow obstruction in sarcoidosis: its development in smoking and non-smoking populations

R COATES, E NEVILLE *Department of Medicine, Saint*

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Mary's Hospital, Portsmouth Serial respiratory function tests were examined in smokers and non-smokers with sarcoidosis to study the frequency and progression of airflow obstruction in these populations. Restrictive defects are well described in sarcoidosis, but airways obstruction is increasingly recognised. Large airway obstruction (bronchostenosis) does occur in sarcoidosis, but is fortunately rare, and small airways function has also been studied. However, no longitudinal study has been performed. Thirty patients with histologically proved sarcoidosis have been studied retrospectively over a period between eight months and 21 years (median four years). Chest radiographic abnormalities included eleven (37%) stage I, three (10%) stage II and sixteen (53%) stage III. Of 14 smokers, nine (64%) had FEV/VC $\leqslant$ 70% at the most recent follow up, while five of 16 non-smokers (31%) had a similar obstructive defect. At presentation, only seven had $FEV_1/VC \leqslant 70\%$, and six were smokers. FEV_1 and VC both deteriorated in eight (60%) smokers and seven (44%) non-smokers; FEV_1 alone fell in one smoker and two non-smokers. One smoker and two non-smokers had asthma. Steroid therapy was given to ten smokers and nine non-smokers. We conclude that airflow obstruction is significantly worse and more frequent in smokers presenting with sarcoidosis (43%) than in non-smokers (6%) and becomes more common during follow up (64% and 31% respectively). However, one third of non-smoking patients with sarcoidosis developed airways obstruction during follow-up in this series.

Fine structural changes in idiopathic pulmonary haemosiderosis

B CORRIN, A DEWAR, M JAGUSCH, MF TUNGAKAR, M TURNER-WARWICK, JO WARNER, D EMPEY *Cardiothoracic Institute, Brompton and London Chest Hospitals, London* Lung biopsy specimens from four children and two adults with idiopathic pulmonary haemosiderosis have been examined by transmission electron microscopy. No qualitative differences were identified between the children and the adults but the changes were more severe in the children. In each case the major damage involved the capillary endothelium and its basement membrane. Capillary endothelial swelling, luminal narrowing and platelet aggregation were common. The capillary endothelial basement membrane showed focal thickening, particularly on the thick side of the air/blood barrier, but no electron dense deposits were identified. Degenerative changes in the alveolar epithelium were not so marked as those in the capillary endothelium and the epithelial basement membrane was normal except for haemosiderin deposition. Haemosiderin was also noted on elastin and within intra-alveolar macrophages. Other secondary changes included mild interstitial oedema and fibrosis. These findings indicate that the major site of damage is the alveolar capillary but provide no evidence of the cause of the disease.

Epidermal growth factor ligand binding studies in lung cancer and in normal lung

D VEALE, N KEER, GJ GIBSON, AL HARRIS *Cancer Research Unit, Royal Victoria Infirmary, Newcastle upon Tyne* Epidermal growth factor (EGF_r) binds to a receptor (EGF_r) causing phosphorylation, which in some cell types leads to cell proliferation. The number of EGF_r on tumour cells is related to the staging of squamous lung cancer (Veale *et al, BR J Cancer,* in press). We have therefore investigated the binding of radiolabelled EGF to its receptor in membrane preparations of normal lung and lung tumours. Membranes were prepared by differential centrifugation and EGF_r binding was assayed using ^{125}I-labelled mouse EGF in the presence of increasing concentrations of non-labelled EGF. Binding sites were saturated at EGF concentration of 5nM; at that concentration the number of binding sites was calculated for 22 tumour membranes and five normal lung membranes. There were significantly more binding sites (B_{max}) on the tumours (range 29.9-3181 fmol/mg protein) than on normal lung (16.25-71.8 fmol/mg protein)($p<0.05$, Wilcoxon rank sum test). Using scatchard binding analysis on 19 of the tumours and the five normal lung membranes we found evidence of high and low affinity binding sites. B_{max} for the high affinity sites on tumours was significantly greater (52.6-5185 fmol/mg protein) than for high affinity binding sites on normal membranes (32.8-137.2 fmol/mg protein)($p<0.05$). The mean dissociation constants (K_d) of the high affinity sites on tumours and normal membranes were 2.96×10^{-10} M and 4.1×10^{-10} M respectively (NS). There were no significant differences in the number of binding sites when comparing histological types of tumours or stage by TNM classification. We have therefore shown that lung tumours express more EGF_r than normal lung, which might provide a targetting site for ligand bound cytotoxic drugs.

Ploidy: its significance in operable lung cancer

MH BINT, GA HAWSON, PG PARSONS, PV ZIMMERMAN *Department of Thoracic Medicine, The Prince Charles Hospital, Brisbane, Queensland, Australia* The signficance of cellular DNA content (ploidy) as a prognostic determinant in surgically treated lung cancer was evaluated in 100 patients. Though ploidy of lung cancer has previously been determined, its clinical significance has not been established. Flow cytometric analysis was performed on cells obtained from archival paraffin embedded tumour blocks. Forty-five per cent of tumours were aneuploid and 55% were diploid. Overall, patients with aneuploid tumours had significantly shorter survival ($p<0.0005$) than those with diploid tumours. Patients with diploid tumours, without nodal involvement at surgery (NO), were found to have particularly long survival. Ninety-one per cent of these patients were alive at three years compared with only 51% of patients with aneuploid tumours and NO disease. This subset of patients with such an excellent prognosis has not been previously recognised. Univariate analysis showed ploidy was unrelated to age, sex, type of operation, site of primary

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tumour, histological type or TNM stage. Cox multivariate analysis demonstrated only nodal status and ploidy to be of significance as prognostic indicators. Increasing nodal status was related to shorter survival ($p = 0.0001$). Ploidy was independent of the other variables and was the most important ($p < 0.0005$) prognostic determinant. Hence ploidy should be taken into account in determining management strategy, estimating prognosis, and stratifying patient groups for clinical trials.

Surfactant-containing vesicles in rat lung tissue: a second source of surfactant or vesicles of reuptake?

JHT POWER, TE NICHOLAS, HA BARR *Department of Human Physiology, School of Medicine, Flinders University, Adelaide, Australia* After isolating our normal lamellar body fraction (lb) by isopycnic density gradient ultracentrifugation, we diluted it to 0.25M sucrose and centrifuged first at 8000*g* for 30 min, then at 80000*g* for 60 minutes. Electron microscopy revealed that the first pellet (lbA) contained intact lb (diam:0.7-1.0μm), whereas the second pellet was a mass of small vesicles (diam 0.4μm) without lamellae. Both fractions had similar phospholipid profiles. However, whereas lbA had a mean phospholipid: protein ratio of 6.4 (SD 0.73, n = 12), lbB was 9.2 (SD 2.7, n = 11). Likewise, the fractions differed in marker enzymes with lbB having significantly greater amounts of the plasma membrane marker 5'-nucleotidase, and lbA having a much greater amount of the lysosomal marker β-glycerophosphatase. Following infusion of ^{3}H-choline, the specific activity-time curve of lbA was broader and peaked earlier than that of lbB; there was no apparent precursor-product relationship. Most interestingly, whereas lbA contained a 15 kd protein, lbB contained a 35 kd protein. When the rats swam for 30 minutes in thermoneutral water, a stimulus known to release surfactant, we obtained the following results:

	lbA	*lbB*	*lbA/lbB ratio*
control:	2.4 (0.37) (7)	2.2 (0.46) (7)	1.10 (0.11) (6)
30 min swim:	1.8 (0.37) (8)**	1.3 (0.43) (8)**	1.65 (0.42) (7)*
3hr post swim:	3.3 (0.52) (5)	2.3 (0.58) (5)	1.45 (0.36) (5)
	*p<0.025	**p<0.01	

Results are expressed as mean (SD) (μg DPPC/100g body wt). Hence, although swimming releases both lbA and lbB, lbA was depleted 29% while lbB was depleted 42%. The pattern of recovery also differed. We conclude that there are two distinct organelles containing surfactant in lung, and these can be released differentially.

Pleural mesothelioma of epithelial type and pulmonary adenocarcinoma: an ultrastructural and cytochemical comparison

A DEWAR, M VALENTE, NP RING, B CORRIN *Cardiothoracic Institute, Brompton Hospital, London* Twelve diffuse pleural mesotheliomas of epithelial type have been compared with 20 intrapulmonary adenocarcinomas. All mesotheliomas were negative for epithelial mucin by diastase periodic acid Schiff stains and for carcinoembryonic antigen by immunoperoxidase staining, whereas 17/20 carcinomas stained for epithelial mucin and 15/20 for carcionembryonic antigen. Hyaluronidase sensitive alcian blue positive material was present in 6/12 mesotheliomas and 0/20 carcinomas. Previously described electron microscopic differences were validated, including one which has so far received insufficient emphasis: microvilli making direct contact through basement membrane deficiencies with collagen fibres on the abluminal side of tumour cells were identified in 10/12 mesotheliomas and in 0/20 carcinomas.

Significant intimal abnormalities in the muscular pulmonary arteries of smokers

JM FERNIE, D LAMB *Institute of Occupational Medicine and University Medical School, Edinburgh* Intimal changes in muscular pulmonary arteries in man are a common and variable features of ageing: pronounced intimal abnormality is usually associated with specific disease states. We have found substantial intimal changes, unrelated to ageing, in resected lobes/lungs of 30 smokers without significant respiratory disease (22 males, 8 females; age range 46-74 years: FEV_1% predicted range 47-119%). The area of arterial intima was measured using a digitiser and expressed as a proportion of the area enclosed by the internal elastic lamina (IEL), correcting for constriction (intima index). Arteries were subdivided into four size groups (based on length IEL), and mean intima indices calculated for each. For the smallest size group ($\leqslant 600\mu$m length IEL) the mean intima index (II600) ranged from 0.09 to 0.34. Half the patients had values $\geqslant 0.20$ — i.e. $\geqslant 20\%$ lumen occulusion. Intimal abnormality was unrelated to the presence of tumour or to macroscopic emphysema. II600 values were significantly correlated with microscopic emphysema (expressed as alveolar wall surface area per unit lung volume), smoking (expressed as pack years) and FEV_1% predicted. The latter two factors were also significantly associated with intimal abnormality in arteries measuring 601-1200μm length IEL. Smoking and respiratory function appeared to be the key factors in these relationships.

Ultrastructure of the alveolar wall before and after cardiopulmonary bypass

PS HASLETON, L MCWILLIAM, A WEBSTER, RA LAWSON *Department of Pathology and Surgery, Wythenshawe Hospital, Wythenshawe, Manchester* Ten patients with angina of effort but no evidence of congestive cardiac failure had after informed consent pre and post bypass lung biopsies. The prebypass biopsy specimens were ultrastructurally normal. Post bypass a series of changes were seen. The type I cells showed an increase in micropinocytosis with the formation of numerous vesicles in their cytoplasm. The luminal surfaces developed variable numbers of surface, finger-like protrusions. There was an increase in the mitochondria. In two caes there was focal necrosis of type I cells, leaving a bare basement membrane.

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These latter structures showed some oedema. The endothelial cells showed focal electron lucency suggesting early degenerative change.

A self management plan in the treatment of asthma

CRW BEASLEY, ST HOLGATE *Medicine I, Southampton General Hospital, Southampton* In this open prospective study we have investigated whether routine assessment of peak expiratory flow rate (PEFR) in association with a self management plan based on inhaled corticosteroid use is effective in the management of asthma. Thirty-six consecutive adult asthmatic patients attending an outpatient chest clinic were studied. All patients were treated with inhaled salbutamol and beclomethasone (B) and the dose of B was adjusted to a maximum of 2 mg/day in an attempt to achieve normal lung function. Patients measured PEFR each morning. If PEFR dropped by >30% from predicted normal values or previous baseline (if greater than predicted), the dose of B was doubled until PEFR returned to normal. If PEFR fell by >50% in those patients confident to self administer oral steroids, prednisolone was started at 40 mg/day until PEFR returned to normal, then 20 mg/day for the same number of days. In all patients, if PEFR fell to 150-200 l/min, they contacted emergency medical assistance. In the 30 patients who completed the trial, comparison was made between the six months prior to and the six months following intervention with the self-management plan. There was a significant improvement in predicted FEV_1 (76% (5%) vs 92% (4%), $p<0.001$), reduction in nights woken per two weeks (4.3 (1.0) vs 0.7 (0.5), $p<0.001$) and days lost from work per six months (12.9 (3.1) vs 1.7 (1.0), $p<0.01$). We conclude that routine measurement of PEFR in association with a self management plan based on inhaled corticosteroid use is effective in the management of adult asthma.

Survey of domiciliary nebuliser use on the Isle of Wight

D MURPHY, S HOLGATE *St. Mary's Hospital, Newport, Isle of Wight, and University of Southampton* There is considerable concern over the use and abuse of home nebulisers for the bronchodilator treatment of airways disease. In this study we report the evaluation of domiciliary nebuliser use covering all ages in a well defined population on the Isle of Wight. A questionnaire was administered to 167 known users of nebulisers and all were returned. The indication for nebuliser therapy was asthma (137), bronchitis (32), and emphysema (30). Twenty-three had never had a metered dose inhaler prescribed and, of the others, 13 had never had instruction in its use. One hundred and fifty-three had used the nebuliser within the previous year and, of these, instruction was provided by physiotherapist (87), general practitioner (30), nurse (19) and hospital doctor (6). Nine received no advice. The drugs used comprised mostly salbutamol (140) and sodium cromoglycate (51). Twenty-six mixed medicines for use in the nebuliser and 24 admitted to exceeding the recommended dose. Side effects reported most frequently were tremulousness (44), palpitation (32), throat discomfort (20). Twenty-three patients had a peak flow meter available at home. With treatment failure 108 would call a doctor or report to hospital, while 25 would persist with nebuliser therapy. Thirty-two patients had no help at home in the event of an emergency. While the overwhelming opinion of these patients was that they benefited greatly from nebuliser treatment at home, it is clear that better monitoring of its need, efficacy and safety is advisable.

The use of nebulised salbutamol by ambulance personnel

LS HILL *Warwick Hospital, Warwick* By June 1983 all 46 emergency ambulances of the Warwickshire Ambulance Service were equipped with Inspiron nebulisers, driven by oxygen at six litres per minute. The crews were trained to recognise appropriate indications for the administration of 2.5 mg salbutamol nebules. The first one hundred usages were evaluated by analysis of specially written crew reports, a questionnaire completed during transfer and subsequent hospital records. Ninety-four administrations were for asthma. By arrival in hospital 87% were subjectively improved, 12% unchanged. Only one patient deteriorated (and was ventilated on arrival). Six per cent of administrations were inappropriate (three myocardial infarcations, three LVF). However in no case did the admitting clinician consider that the patient had been adversely affected. The ventilated patient would probably not have survived the eighteen mile journey without bronchodilator and oxygen. Salbutamol nebulised in oxygen appears a simple, safe and effective therapy when administered by trained ambulance personnel. It is particularly appropriate for a service covering a wide rural area with prolonged transfer times. An unexpected but not unsurprising benefit was a considerable improvement in morale and job satisfaction in the crews.

Video education for patients who use inhalers

EMT MULLOY, MK ALBAZZAZ, ARH WARLEY, JE HARVEY *Bristol Chest Clinic, Bristol* The use of pressurised aerosol inhalers is often limited by inadequate patient technique. We therefore investigated whether the viewing of an eight minute educational video improved patients' inhaler technique and understanding of their inhaler therapy. Two groups of patients taking regular inhaled drugs were invited to participate; 64 were attending the Bristol Chest Clinic, 69 were attending their general practitioners. Forty-five chest clinic but only nine general practice patients completed the study. All patients had initial assessment of lung function, inhaler technique and knowledge of their therapy. Half of them (Group A) then saw the video, were re-assessed six weeks later and saw the video a second time before a final assessment at 12-16 weeks. Group B had two baseline assessments six weeks apart before being studied in the same manner as Group A. Both groups of patients showed significant improvements in inhaler technique and comprehension only after seeing the video, with further improvement after a second viewing. There were no significant changes in PEFR, even

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in those with bad initial technique. Recruitment and compliance was poor in general practice patients. Regular showing of educational videos may be a useful addition to a chest clinic.

Hospital asthma management: a comparison between general medical units with and without a respiratory input

CE BUCKNALL, C ROBERTSON, RD STEVENSON, F MORAN *Department of Respiratory Medicine, Royal Infirmary, and Department of Mathematics, Strathclyde University, Glasgow* Full details including admitting ward were available for 77% (150) of all asthma admissions in a prospective audit of hospital asthma management. Cases could be subdivided into 64 admitted to general wards with a respiratory input (A) and 86 to similar wards without such specialist interest (B). Cases in A and B were similar in terms of age, previous severity of asthma, previous treatment and initial pulse rate. Fewer cases in B were treated with oral corticosteroids (A 83%, B 67%; $p=0.04$), had regular peak flow recordings made (A 73%, B 42%; $p<0.005$) or review planned (A 92%, B 56%; $p<0.005$) and fewer had their regular inhaled therapy increased after discharge (A 55%, B 28%; $p<0.005$). These differences in management were associated with more cases from B reporting sleep disturbances (A 23%, B 41%; $p=0.03$), morning chest tightness (A 37%, B 55%; $p=0.03$) or wheeze on one flight of stairs (A 34%, B 58%; $p<0.005$) at interview 13 days later. In addition 20% of cases first admitted to B were readmitted within the year compared with 2% for A. The better outcome in cases admitted to A shows that the more intensive management practised in these wards is worthwhile.

Difficulties in establishing a regional adult cystic fibrosis unit

AK WEBB *Monsall Hospital, Newton Heath, Manchester* In 1982 an Adult Cystic Fibrosis Unit was set up at Monsall Hospital to receive adolescents from the two main Manchester childrens' hospitals. By March 1987 approximately 100 CF patients had been referred to the adult clinic from all over the North West. B.T.S recommendations are that there should be a Regional CF Unit. Such units require allocated beds, extra physiotherapists, social workers and specified monies to meet drug costs. Overall financing far exceeds a district budget. Practical regional support is essential but not easily given. The efforts to obtain regional support for an adult CF clinic in the North West are described and may be of assistance to other chest physicians.

Plasma levels of atrial natriuretic peptide in primary pulmonary hypertension

A MORICE, J PEPKE-ZABA, L DAVIES, M BROWN, T HIGENBOTTAM *Clinical Pharmacology Unit, Addenbrookes Hospital, and Respiratory Physiology Laboratory, Papworth Hospital* Atrial natriuretic peptide (ANP) is released into the circulation in response to atrial distension, and plasma levels are elevated in pathological states such as congestive cardiac failure where right atrial pressure is known to be elevated. We have investigated by selective plasma sampling ANP levels in patients with primary pulmonary hypertension (PPH) both at rest and during infusion of prostacycline (PGI). Eight patients (age 32-59 years) with PPH were studied during right heart catheterisation. Right atrial (RA), pulmonary artery (PA), and mean systemic artery pressures (MAP) were recorded using a Swan-Ganz catheter and a Roshe pressure monitor. Plasma ANP was estimated by radioimmunoassay after preliminary acetonitrile extraction. Pulmonary artery pressures were elevated in all patients. Mean (SD) PA pressure was 74.3 (12.7) mm Hg. In contrast MAP was 69.6 (7.5) and RA 8.6 (5) mm Hg and pressures were not significantly altered by PGI infusion (200-600 ng/min): PA 74.2 (15.5), MAP 76.8 (14), and RA 8.1 (5.9). Plasma ANP (NR during rest <10 pmol/l) was elevated in all but one subject: RA 36.9 (21.9), PA 48 (34.7), and systemic artery 36.9 (21.6) pmol/l. Plasma ANP was not significantly changed by PGI infusion. Because RA pressure is not significantly raised in these subjects the cause of their elevated plasma ANP is obscure and it is probable that mechanisms other than right atrial distension are responsible for the increased plasma levels of ANP seen in PPH.

Users, use and usefulness of ventilation-perfusion lung scans in the management of suspected pulmonary embolism

CR SWINBURN, CB CLAYTON *Departments of Medicine and Medical Physics, Royal Victoria Infirmary, Newcastle upon Tyne* Between 150 and 250 ventilation-perfusion ($\dot{V}/\dot{Q}$) isotope lung scans are performed annually at this hospital. To establish the source of requests for these scans, the accuracy of clinical estimates of the likelihood of pulmonary embolism (PE) and the impact of the scan results on management, a questionnaire was prospectively completed by the requesting doctor to accompany all requests for in-patient $\dot{V}/\dot{Q}$ scanning over a six month period. Sixty scans were requested, 49 by physicians and 11 by surgeons. Clinically, PE was thought to be unlikely in 25 and probable in 35 patients. Overall, 44 scans were reported as negative (strongly in 26) and 16 as positive (strongly in 11). The scan result supported the clinical impression of unlikely PE in 23/25 (92%), but in only 14/35 patients (40%) felt on clinical grounds to probably have PE was the scan concordant ($p<0.01$). Surgeons were significantly better ($p<0.05$) in their clinical assessment than physicians, but junior and senior doctors did not differ. Anticoagulants were started in nine and stopped in eight patients because of the scan result. No patient proceeded to angiography. In conclusion, a "near categorical" report was given in 27 patients (62%). Anticoagulation was altered in the light of the report in 17 patients (28%). The results also indicate that clinically (as judged by the scan results) we appear able to confidently predict when PE is unlikely but that we may be inaccurate when we feel PE is clinically probable.

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Abnormalities of pulmonary function in primary pulmonary hypertension (PPH) and chronic thromboembolic pulmonary hypertension (TEPH)

J SCOTT, C COUTTS, J WALLWORK, T HIGENBOTTAM *Papworth Hospital, Cambridge* The diagnosis of pulmonary hypertension is often delayed; breathlessness, a common initial symptom, is commonly attributed to other causes. Pulmonary function tests (PFTs) including gas transfer for carbon monoxide (TLCO) can be normal (CM Burke *et al, Thorax* 1987;**42**:131-135). We have questioned these data, suspecting that patients with advanced disease may be mistaken as having a restrictive ventilatory defect on function testing. Twenty-nine patients are reported, all with clear radiographs; 11 had pulmonary angiographic or histological evidence of thromboembolic disease and 18 had normal $\dot{V}/\dot{Q}$ lung scintigraphy. All patients had mean pulmonary artery pressures above 40 mm Hg.

Mean % predicted (SD)	*FEV_1*	*VC*	*TLC*	*TLCO*
TEPH (n = 11)	86.3 (23.4)	86.1 (20.3)	86.9 (18.4)	62.3 (11.4)
PPH (n = 18)	84.5 (18.8)	89.3 (19.6)	99.4 (12.7)	64.7 (18.0)

There was a general reduction of dynamic lung volumes FEV_1, VC and also TLC; for the latter 50% TEPH and 26% PPH were lower than 1 SD of mean predicted. The TLCO was markedly reduced: 100% TEPH and 84% PPH lower than 1 SD below this mean predicted. Caution must be observed when interpreting PFTs in breathless patients showing reduction in lung volumes and TLCO.

CT determined main PA diameter does not predict PA pressure in pulmonary hypertension

NR MOORE, JP SCOTT, CDR FLOWER, TW HIGENBOTTAM *Departments of Radiology and Respiratory Physiology, Addenbrooke's and Papworth Hospitals, Cambridge* Computed tomography (CT) measurement of main pulmonary artery (PA) diameter has been proposed as a method of assessing PA pressure. We have compared these measurements in two groups of patients with pulmonary arterial hypertension. Ten patients (3 male, 7 female; mean age 37.6 years) had pulmonary vascular disease comprising seven with primary pulmonary hypertension (PPH) and three with thromboemboli and five had chronic obstructive airways disease (COAD). The mean PA pressure of the PPH group (69 mm Hg, SD = 9) was significantly greater than the COAD group (35 mm Hg, SD = 9): $p<0.001$. The CT PA diameters were corrected for body surface area (BSA). There was no difference in the PA diameters (PPH = 36 mm, SD = 6; COAD = 33 mm, SD = 5). Non-parametric analysis showed no correlation between mean PA pressure and PA diameter and no correlation between age and PA diameter for either group. Patients with PVD showed a weak positive correlation between PA diameter and pulmonary vascular resistance (PVR), and a weak negative correlation with cardiac output (CO). There were no correlations in COAD. No relationship was observed between total lung capacity and PA diameter.

Altered lung vascular permeability during the early stages of intermittent haemodialysis

D BELL, M JACKSON, AM MILLAR, JJ NICOLL, R WINNEY, AL MUIR *Departments of Medicine and Medical Physics, Royal Infirmary, Edinburgh* Hypoxia during haemodialysis is associated with complement activation and pulmonary neutrophil margination (*N Engl Med,* 1977;769-774). Although hypoxia is partly due to hypoventilation (*J Appl Physiol,* 1981;259-264), this does not explain the varying hypoxaemia produced by differing dialyser membranes. We used a dual isotope method (*J Clin Invest,* 1980;869-877) to measure pulmonary vascular permeability in eight patients (age 17-61 years) on chronic haemodialysis. Indium (^{113m}In) transferrin was the protein marker. The blood pool marker was technetium (^{99m}Tc) red blood cells. Transient leucopenia developed in all patients. The mean WBC pre-dialysis was 6.49 (SD 2.67) $\times 10^9$/l; it fell maximally 15 minutes after commencing haemodialysis, (1.28 (0.51) $\times 10^9$/l, $p<0.001$) and recovered within 90 minutes. Po_2 fell significantly from pre-dialysis (12.83 (1.72) kPa) compared with the maximal fall during dialysis (10.56 (1.39) kPa, $p<0.001$), which always occurred during the leucopenic phase. During this period, indices of lung permeability and ratio of In/Tc lung increased significantly in all patients (1.13 ± 1.27) compared with pre-dialysis (0.06 ± 1.81, $p<0.05$), as did lung/heart ratio ($1.64 \times 10^{-3} \pm 2.3$) compared with pre-dialysis values (-1.41 (3.39), $p<0.05$), although lung/heart ratio increased in only four patients. These results suggest increased lung permeability during the leucopenic phase of haemodialysis and may further explain the development of hypoxaemia.

Effect of inhaled leukotriene C_4 on cardiopulmonary haemodynamics in man

MK ALBAZZAZ, S SHAKIR, JM REID, HJ DARGIE, KR PATEL *Departments of Respiratory Medicine and Cardiology, Western Infirmary, Glasgow* In animals leukotriene C_4 (LTC_4) causes increase in the mean pulmonary artery (PAP) and pulmonary capillary wedge (PCWP) pressure with decrease in cardiac output (Qp) and oxygen tension (Pao_2) (Ahmed *et al, Am Rev Respir Dis* 1985;**131**:554-558). In asthmatic patients LTC_4 inhalation causes significant arterial oxygen desaturation before bronchoconstrictor response is observed (Albazzaz and Patel, *J Allergy Clin Immunol* 1987;**79**:140). In the present study we have measured the changes in cardiopulmonary haemodynamics and arterial blood gases after LTC_4 inhalation in seven patients undergoing right heart cardiac catheterisation. After baseline measurements, each patient inhaled 10μg of LTC_4 and measurements were repeated at 5, 10 and 15 minutes. The mean Qp fell by 15% (SEM 3.9 $p<0.05$) Pao_2 decreased from 12.7 (1.1) to 8.0 (1.1) kPa ($p<0.01$) and the mean $D(A\text{-}a)O_2$ gradient increased from 2.3 (0.8) to 7.1 (0.6) kPa ($p<0.01$). The changes in mean PAP, PCWP and heart rate were not significant. In two patients given 20μg of LTC_4 the PAP and PCWP increased by 18% and 58% respectively from the baseline. The results suggest that inhaled LTC_4 has a negative inotropic effect and causes significant hypoxaemia. The impaired gas

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exchange may result from LTC_4's effect on pulmonary vasculature and/or increase in peripheral airflow obstruction.

Long term lung function changes in patients with obstructive sleep apnoea during treatment with nasal continuous positive airway pressure

IH YOUNG, M MIHALYKA, L COSTAS, CE SULLIVAN *Department of Thoracic Medicine, Royal Prince Alfred Hospital, Sydney, N.S.W., Australia* Nasal continuous positive airway pressure (CPAP) has been successfully used to reverse obstructive sleep apnoea (OSA) for the last six years. The long term changes in lung function in a group of 29 treated patients with OSA who presented for routine testing from January to June 1986 were followed. Total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) were measured by closed circuit helium dilution while vital capacity (VC), inspiratory capacity (IC), and FEV_1 were measured by spirometry and all expressed in litres (BTPS). Single breath transfer factor for carbon monoxide (TLCO, ml/min/mmHg/l) was also measured. Baseline values were recorded before the start of CPAP and a linear regression model fitted to the per cent change from baseline of each of the tests with respect to time (range four months to five years).

LUNG FUNCTION	*RATE OF CHANGE % Baseline/Year (SEM)*	*p VALUE FOR SLOPE (Rate of Change)*
TLC	−3.68 (1.4)	<0.001
FRC	−6.25 (2.3)	<0.005
RV	−6.02 (2.4)	<0.01

There were no significant changes in VC, IC, FEV_1, or TLCO. The significant falls in TLC, FRC, and RV were more apparent after one year of treatment and those patients who were initially hyperinflated tended to show greater proportional falls in FRC and RV. These results are consistent with changes in respiratory muscle tone rather than any changes in lung compliance or alveolar capillary membrane function.

Criteria for diagnosing abnormal breathing during sleep

GA GOULD, KF WHYTE, MAA AIRLIE, GB RHIND, JR CATTERALL, CM SHAPIRO, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* The sleep apnoea syndrome is usually diagnosed by the number of apnoeas/hours of sleep, without reference to the patient's symptoms, frequency of hypopnoeas, desaturations or arousals. To try to improve on this definition we initially performed sleep studies on 30 normal subjects (21-68 years); all had < 13 apnoeas/hours of sleep, < 14 apnoeas + hypopnoeas (a + h)/hour of sleep with < 2 4% desaturations/hours and < 10 arousals/hour of sleep. We have evaluated the sleep results from 50 consecutive patients (18-70 years, 45 M) found to have abnormal breathing during sleep and referred because of suspicion of the sleep apnoea syndrome. All had at least two of the following clinical features: loud snoring (42), excessive daytime somnolence (45), disturbed sleep (13), morning headache or secondary polycythaemia and ankle swelling for which no other cause is known. Thirty of the 50 patients had > 10 apnoeas/hour of sleep; the remaining 20 were clinically indistinguishable and had numerous hypopnoeas, such that all 50 had > 14 a + h/hour of sleep (range 16-170, mean 63, SD 34 a + h/hour). Forty-six of the 50 had more than five 4% desaturations/hour of sleep, the four others having 0-5 desaturations/hour, mild but significant symptoms and 18-50 a + h with 13-33 arousals/hour of sleep. The results indicate that the occurrence of more than 15 apnoeas + hypopnoeas/hour of sleep is the best definition of symptomatic abnormal breathing during sleep currently available, but that oximeter screening alone will miss a few patients with relatively mild symptoms and slightly abnormal breathing.

Eye movement density during rapid eye movement sleep does not alter ventilation in man

GA GOULD, M GUGGER, J MOLLOY, CM SHAPIRO, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* The most severe nocturnal hypoxia occurs during rapid eye movement (REM) sleep in both the sleep apnoea/hypopnoea syndrome and chronic bronchitis and emphysema. REM sleep is a heterogenous state, which has been divided into phasic REM with frequent eye movements (EMs) and tonic REM with few EMs. There is some evidence in animals (Sullivan, *J Appl Physiol* 1979;**47**:1304-10) and preliminary evidence in man (Millman, *Am Rev Respir Dis* 1986;**133**:308) that ventilation and ventilatory responses may be decreased during phasic REM and that the most severe hypoxia during sleep in bronchitics occurs during phasic REM (George, *Am Rev Respir Dis* 1985;**131**:302). We have thus examined the relationship between the number of EMs/20 second epoch in REM sleep with simultaneous breathing pattern recorded using a face mask (with CO_2 leak detector) and a dead space of 60 ml connected to a Fleisch No. 3 pneumotachograph. Six male normal subjects were studied and a mean of 119 (SD 65) breaths during REM sleep analysed in each subject. In no subject was there a significant correlation between EM density and either minute ventilation or tidal volume. The mean levels of ventilation during epochs with no EMs (6.49 (SD 0.52) l/min) was not significantly different from that during epochs with maximal EM density (6.64 (1.22) l/min). Furthermore, the variability of breathing pattern did not alter with EM density. These results suggest that the heterogeneity of breathing pattern during REM does not relate to eye movement density in man, contrary to preliminary results in which ventilation was measured by surface techniques.

Ventilation and occlusion pressure responses to added resistance during sleep

M GUGGER, GA GOULD, J MOLLOY, CM SHAPIRO, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* The ventilatory

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response to added resistance during sleep is important as airflow resistance increases during sleep not only in normal subjects but also in patients with the sleep hypopnoea syndrome and in patients with nocturnal asthma. Iber *et al (J Appl Physiol* 1982;**52**:607-14) suggested that the ventilatory and occlusion pressure responses to increased resistance were impaired during non-REM sleep, but they studied only five breaths in five subjects. We thus measured the occlusion pressure (P0.1) and ventilatory responses to inspiratory resistive loading (4-10 cm H_2O/l/s) during wakefulness (W) and non-REM and REM sleep in seven normal subjects using a face mask system with a CO_2 leak detector. Both ventilation and P0.1 were measured each breath, using a computer driven occlusion system with rapid off phase. The occlusion pressure increased following the addition of both seven and 10 cm H_2O/l/s resistances during both W (control 0.71 (SE 0.10), 7 cm H_2O/l/s, resistance 0.85 (0.10) cm H_2O; $p<0.05$) and during non-REM sleep (0.71 (0.12), 0.91 (0.14) cm H_2O; $p<0.05$). In the five subjects with REM studies, the same trend was shown but was not significant (0.73 (0.20), 0.87 (0.18) cm H_2O). In each sleep stage the addition of four and seven cm H_2O/l/s did not alter ventilation but in non-REM sleep the 10 cm H_2O/l/s resistance decreased ($p<0.05$) ventilation (6.33 (0.33), 5.94 (0.46) l/min). We conclude that contrary to earlier reports non-REM sleep does not alter the occlusion pressure response to added resistance but that ventilation is decreased by high resistive loads during sleep.

Domiciliary positive pressure ventilation, using a nasal mask, for nocturnal hypoventilation

N CARROLL, MA BRANTHWAITE *Brompton Hospital, London* Nocturnal hypoventilation, associated with respiratory or cardiorespiratory failure, was treated with overnight positive pressure ventilation using a nasal mask. Nine patients (6 male, 3 female), aged 41 to 67, were studied. Seven patients had restrictive chest wall disease with a mean FVC of 27.6% predicted. Two had severe chronic airflow obstruction with a mean FEV_1 of 25.8% predicted. The hypoventilation and consequent respiratory failure had been uncontrolled by protriptyline and/or negative pressure ventilation. A Lifecare PLV 100 ventilator was used overnight for between three and 12 months. Air was delivered through a tightly fitting nasal mask, and ventilation triggered by the patient's own inspiratory effort. Tidal volume, frequency and inspiratory flow rate were determined by overnight monitoring. Six patients were studied overnight. The mean % of total sleep time spent with an oxygen saturation of $\leqslant$ 80% fell from 45% to 3%. Diurnal arterial blood gas tensions also improved. The mean Pao_2 increased from 6.87 kPa (range 5.39 - 9.64) to 8.78 kPa (range 7.55 - 10.14; $p=0.05$). The mean $Paco_2$ fell from 8.2 kPa (range 6.72 - 9.84) to 6.77 kPa (range 5.44 - 7.36; $p=0.05$).

First night effect in middle aged patients

MB ALLEN, K PROWSE *Department of Respiratory Physiology, City General Hospital, Stoke on Trent* The First Night Effect (FNE), which describes changes in sleep architecture which improve on subsequent nights when an individual sleeps in a different environment, is recognised by all. Studies to define the features of FNE used paid, young adults who were monitored by electroencephalogram (EEG) only (HW Agnew, *Psychophysiology* 1966;**2**:263-6). The effect of age on sleep stage is well reported but information on the FNE in middle aged and elderly patients undergoing assessment of airflow, ventilation, oxygen saturation and sleep is lacking. In an attempt to define the features of the FNE we have studied six patients, mean age of 57.6 years (range 51-69), on consecutive nights. All patients were in good health, none took hypnotics and only one reported problems with sleep (insomnia). Airflow, abdomen and chest movements, ECG, oxygen saturation, EEG (four channels), EOG and EMG were recorded by standard, non-invasive methods. Sleep was scored in 20 second epochs and staged according to standard criteria by one observer (MBA). There were significant ($p<0.05$) increases in the time to onset of light and rapid eye movement (REM) sleep, increased time awake and reduced REM sleep and sleep efficiency (time asleep/time in bed) on the first night. REM sleep is the period when ventilation is less stable and arterial desaturation tends to occur. If REM time is short or the sleep efficiency is poor the severity of respiratory problems may be underestimated.

LY171883 as an oral leukotriene D_4 antagonist in non-asthmatic subjects

GD PHILLIPS, P RAFFERTY, ST HOLGATE *Medicine I, Southampton General Hospital, Southampton* Leukotriene D_4 (LTD_4) has been suggested as a pro-inflammatory mediator in the pathogenesis of asthma. We have investigated the inhibitory activity of the oral LTD_4 antagonist LY171883 (1-(2-hydroxy-3-propyl) -4-(4-(1H-tetrazol-5-yl)butoxy)phenyl)ethanone) on LTD_4-induced bronchoconstriction in non-asthmatic subjects, in a double blind, placebo controlled, randomised, cross over study. Twelve subjects, mean age 26.3 (SD 1.7) years, participated. On four separate days, baseline measurements of FEV_1 and maximum flow at 30% of vital capacity above residual volume ($\dot{V}max_{30}$) were performed, following which subjects ingested either 50 or 200 or 400 mg of LY171883, and then undertook a dose-response study with inhaled LTD_4. Measurements of FEV_1 and $\dot{V}max_{30}$ were made at intervals for eight minutes after inhalation of each concentration of LTD_4, and increasing concentrations administered until FEV_1 had fallen by $>20\%$, or the maximum concentration of LTD_4 (1000 μmol/l) had been given. Cumulative dose-response curves were constructed on a logarithmic scale, and the provocation dose of LTD_4 producing a 12% fall in FEV_1 (PD_{12} FEV_1) and a 30% fall in $Vmax_{30}$ (PD_{30} $\dot{V}max_{30}$), determined by linear interpolation. LY171883 caused a dose-related shift to the right of the LTD_4 dose response curve in 10 of the 12 subjects, ranging from 0.7-16.2 fold with a mean of 4.6 (1.3) for PD_{12} FEV_1, and 0.4-20.7 fold with a mean of 6.3 (1.8) for PD_{30} $\dot{V}max_{30}$, after the 400 mg dose. No significant side effects were reported. We conclude that LY171883 is an LTD_4 antagonist in normal man.

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Effect of single and multiple dose therapy with azelastine on leukotriene C_4 (LTC_4) and histamine (H) induced bronchoconstriction in patients with asthma

MK ALBAZZAZ, KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow* Azelastine (AZ) is a new oral agent with antiallergic and anti-histamine properties. In guinea pigs it antagonises the effect of LTC and H. It also modifies allergen induced bronchoconstriction in asthmatic patients (Ollier *et al, J Allergy Clin Immunol* 1986;78:358-64). We have examined the effect of AZ after a single dose (8.8 mg) and 14 days of continuous treatment (8.8 mg BID) on LTC_4 and H induced bronchoconstriction in a placebo controlled double blind cross over study in 10 patients with asthma. LTC_4 and H were inhaled in doubling concentrations from a dosimeter. The results were expresed as cumulative dose (PD_{20}) producing 20% fall in FEV_1 (SEM). The mean pretreatment baseline FEV_1 was comparable on placebo and AZ. A single dose of AZ produced significant bronchodilatation with a mean increase in FEV_1 of 10.3% (0.67, $p<0.05$). The geometric mean PD_{20} - LTC_4 (nmol) was 0.60 and 0.59 after single dose and fortnight treatment with placebo respectively compared to 0.65 and 0.75 after single and fortnight treatment with AZ(NS). In contrast the geometric mean PD_{20} - H(μmol) was 0.51 and 0.54 after single and fortnight treatment with placebo respectively compared with 22.85 ($p<0.001$) and 15.18 ($p<0.001$) after AZ. These results suggest that AZ is a potent H_1 antagonist but has no effect on LTC_4 induced bronchoconstriction. Furthermore, prolonged LTC_4 induced bronchoconstriction and prolonged H_1 receptor blockade in the airways does not modify leukotriene responsiveness in asthmatic patients, suggesting an independent action of H and LTC_4 on the bronchial smooth muscle.

Ketotifen inhibits the cutaneous responses but not the bronchoconstriction and bronchial hyperresponsiveness induced by PAF in man

KF CHUNG, M MCCUSKER, P MINETTE, PJ BARNES *Department of Clinical Pharmacology, Cardiothoracic Institute, Brompton Hospital, London* Ketotifen, an oral antiallergic and antihistaminic drug, is prescribed for the prophlaxis of asthma but there are few data as to its effect on the hyperresponsiveness of asthma. Platelet activating factor (PAF), a potent mediator of inflammation, causes a sustained increase in airway responsiveness to methacholine in man. We have studied the effect of ketotifen on PAF responses in the airways and skin in a double blind, randomised crossover study in six normal subjects. Ketotifen (three doses of 2 mg taken over a 24 hour period prior to PAF) did not alter PAF-induced bronchoconstriction, nor did it prevent the accompanying flushing and coughing. The transient neutropenia (74.5% (SD 4.8%) fall; $p<0.001$) and rebound neutrophilia (104 (55%) rise) induced by PAF were not affected by ketotifen. Airway responsiveness to methacholine increased with PC_{40}, decreasing from 69.2 mg/ml (GSEM 2.69) to 23.3 mg/ml on day three ($p<0.001$); this was not inhibited by ketotifen (PC_{40} on day three = 21.5 mg/ml (2.14)). However, ketotifen reduced the flare areas from 8.1 (3.6) cm^2 (mean (SEM)) to 1.1 (0.3) ($p<0.05$) and the wheal volumes from 0.68 (0.10) cm^3 to 0.45 (0.08) cm^3 ($p=0.02$) induced by 200 ng PAF. There was also significant inhibition of the cutaneous flare ($p<0.002$) and wheal ($p<0.01$) responses to 1 μg histamine. We conclude that the bronchoconstriction and bronchial hyperresponsiveness induced by PAF are not inhibited by ketotifen; in contrast to the effects of PAf in the skin, these are not mediated by histamine.

Inhibition of PAF-acether induced neutrophil and eosinophil chemotaxis by the gingkolide-derived PAF antagonist (BN 52021)

K KURIHARA, AJ WARDLAW, R MOQBEL, AB KAY *Department of Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* PAF-acether has been shown to be a very effective chemotactic agent for human granulocytes and may be partially responsible for the inflammation associated with asthma and other lung diseases. We have attempted to inhibit PAF-acether induced *in vitro* chemotaxis of human eosinophils and neutrophils by BN 52021, a specific PAF-acether receptor binding antagonist derived from the Chinese tree *Gingko biloba*. Chemotaxis was assayed using a 64 well microchamber (Boyden technique). Normal density human eosinophils were obtained by metrizamide separation of leucocytes from eosinophilic subjects (7-32%). Drug was added either to the lower compartment or both compartments of the chemotaxis chamber and PAF-acether (10^{-6} ML^{-1}) to the lower compartment. Mean chemotaxis counts (10 hpf) in the absence of drug were 686 (SD 108) eosinophils, 1534 (118) neutrophils, <18 (5) background. BN 52021 resulted in significant dose dependent inhibition of eosinophil and neutrophil chemotaxis to PAF-acether (eosinophils 10^{-4} M — 10^{-7} M IC_{50} 5×10^{-6} M, n=9; neutrophils 10^{-4} M — 10^{-5} M IC_{50} 5×10^{-5} M, n=13). Specificity of BN 52021 was demonstrated by its inability to inhibit LTB_4 (10^{-7} M) induced neutrophil chemotaxis. Sodium cromoglycate and nedocromil sodium, two drugs which inhibit granulocyte activation, were unable to inhibit PAF-acether induced eosinophil or neutrophil chemotaxis. This study demonstrates that BN 52021 might be effective *in vivo* at inhibiting PAF-acether induced inflammatory responses.

Eosinophils and eosinophil-derived proteins in allergic asthma

SR DURHAM, S DUNNETTE, D LOEGERING, GJ GLEICH, AB KAY *Cardiothoracic Institute, Brompton Hospital, London, and Mayo Clinic, Rochester, U.S.A.* Blood eosinophils (Eos) and peripheral concentrations of the eosinophil-derived proteins, major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil peroxidase (EPO) and eosinophil cationic protein (ECP) were measured in 12 atopic asthmatics and 23 normal controls. The same measurements were performed in six asthmatics with previously documented dual (early + late)

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asthmatic responses after inhalation challenges with methacholine and allergen. Eos ($p<0.001$), MBP ($p<0.01$), EDN ($p<0.01$) and ECP ($p<0.03$) were elevated in the asthmatics compared with the controls, whereas EPO ($p<0.01$) concentrations were reduced (unpaired *t* test). There were no significant differences between baseline measurements of FEV_1, Eos, MBP, EDN, EPO or ECP on the methacholine and allergen challenge days. When the changes in these variables after allergen were compared with the corresponding changes after methacholine, there were no significant differences at 0-60 minutes or at three hours, whereas EDN ($p<0.025$), EPO ($p<0.05$) and ECP ($p<0.025$) were relatively increased at 6-12 hours and accompanied the late falls in FEV_1 ($p<0.001$) (paired *t* test). Eos ($p<0.025$) were elevated at 24 hours, when there was a small relative increase in MBP ($p<0.05$). Eosinophils appear to be "acivated" in allergic asthmatics and further activation may occur during late asthmatic responses.

The effects of dietary supplementation with fish oil on neutrophil biochemistry and function, and the natural history of bronchial asthma

JP ARM, CE HORTON, NM EISER, TJH CLARK, B SPUR, TH LEE *Department of Medicine, Guy's Hospital, London* The effects of dietary supplementation with fish oil on neutrophil biochemistry and function and the natural history of bronchial asthma have been studied. Twenty subjects with mild asthma were studied. Twelve subjects received 3.2 g of eicosapentaenoic acid (EPA) and 2.2 g of docosahexaenoic acid (DCHA) daily, and eight subjects received olive oil for ten weeks in a double blind fashion. Bronchial response to histamine and exercise, diurnal peak flow readings, symptom scores, bronchodilator usage, neutrophil fatty acid composition, neutrophil leukotriene (LT) B_4 and B_5 generation and neutrophil chemotactic responses to f-met-leu-phe and LTB_4 were assessed. Following dietary supplementation with fish-oil, EPA increased from being undectable to comprising 2.5% (0.73%) (mean (SEM)) of total neutrophil fatty acids. There was a 50% inhibition of total LTB (LTB_4 + LTB_5) generation by ionophore stimulated neutrophils ($p<0.01$) and neutrophil chemotaxis was markedly depressed. Neutrophil function remained unchanged in the placebo group. No significant changes in the clinical indices of severity of asthma were found in either group of subjects. Airways histamine reactivity and morning and evening peak-flow readings were 0.32 μmol (geo.mean), 485 (25) l min^{-1}, and 490 $\pm$ 27 l min^{-1} respectively before and 0.37 μmol, 490 (27) l min^{-1}, 490 (27) l min^{-1} after fish oil. In subjects with mild asthma, a fish-oil enriched diet attenuates neutrophil function without changing the severity of asthma.

Heart-lung transplantation in patients with end-stage lung disease

ARL PENKETH, J WALLWORK, TW HIGENBOTTAM *Departments of Respiratory Physiology and Surgery, Papworth Hospital, Cambridge* Combined heart and lung transplantation was initially used to treat patients with primary pulmonary hypertension or pulmonary hypertension secondary to cardiac disease. We have treated seven patients with "end-stage" primary lung diseases. All were severely disabled and their disease had a poor prognosis. The underlying conditions were cystic fibrosis, bronchiectasis, sarcoidosis, cryptogenic fibrosing alveolitis, histiocytosis X and emphysema (2). Six patients are well, six months to three years after transplantation. One patient died after 44 days from a primary cytomegalovirus infection transmitted from the donor. Lung function of the six survivors improved progressively over four to six months to reach near normal predicted volumes for the recipient. All survivors have a normal exercise tolerance and have either returned to work or are fit to do so. The major complications have been opportunistic infections, cytomegalovirus (3) and tuberculosis (1). One patient has had a rejection episode, which responded to treatment. Heart and lung transplantation offers a treatment for suitably selected patients with "end-stage" chronic lung disease.

Diagnosis of rejection after unilateral lung transplantation

JR PEPPER, JA READER, GJ PARFETT, JA KIRBY *Department of Immunology, St. George's Hospital Medical School, London* A series of left unilateral lung allografts were performed between inbred PVG ($RT1^C$ donor and Lewis ($RT1^l$) recipient rats; the ischaemic time ranged between 32 and 50 minutes with 70% of the recipients surviving surgery. On the basis of examination at post mortem and *in situ* chest radiograph, the lungs appeared to consolidate between four and five days after transplantation. This rejection was more rapid than that observed for heterotopic cardiac allografts performed using the same rat strain combination; such grafts lost function a mean 5.9 days after transplantation. Bronchoalveolar lavage of the lung allografts on day four gave a yield of 7.3 (4.8) $\times 10^6$ (mean (SD); n=9) leucocytes, of which a mean 43% were lymphocytes. These cells were found to proliferate rapidly in response to brief culture with recombinant IL-2, suggesting *in vivo* activation, and to lyse ^{51}Cr-loaded donor cells without the need for *in vitro* pre-activation, suggesting the presence of specific cytotoxic cells within the bronchoalveolar space. Limiting dilution analysis of the frequency of donor reactive cytotoxic lymphocytes has shown a similar frequency (1/781 — 1/1283) of such cells within both the bronchoalveolar population and that released from the parenchyma of the lung. This suggests that immunological analysis of the leucocytes derived by lavage of lung allografts can provide an accurate measure of the parenchymal events underlying acute rejection.

Comparison of techniques for lung preservation prior to transplantation in dogs — use of bronchoalveolar lavage (BAL)

TJ LOCKE, G JACKSON, RT PEASTON, P. MCARDLE, CGA MCGREGOR, PA CORRIS *Department of Respiratory Medicine and University Department of Surgery, Freeman Hospital, Newcastle upon Tyne* The early function of a

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transplanted lung is critically dependent upon satisfactory preservation during the ischaemic period. We have compared two current methods of lung preservation in a dog model. Seven beagle dogs underwent unilateral left lung transplantation following six hours ischaemia. In four the donor lung was preserved by topical cooling (TC) and stored at 4°C. In three it was preserved by flush perfusion using modified Euro-Collins solution and prostacyclin (EC) and stored at 4°C. All donor animals received methyl prednisolone 250 mg iv 15 minutes prior to excision of the lungs. Thirty minutes following transplantation, the contralateral right main bronchus and pulmonary artery were ligated and animals maintained on positive pressure ventilation at fixed settings until death or sacrifice at 24 hours. F_IO_2 was maintained at 40% and arterial blood gases regularly sampled. Immediately following death, the transplanted lung was lavaged with 60 ml saline and samples taken for cell count, cell differential and albumin levels. Control lavage specimens were taken immediately following resection of the recipients left lung prior to transplantation and all results expressed per unit volume of lung fluid using serum and lavage urea concentrations and a simple dilution equation. The results (meas (SD)) were:

	Neutrophils ($\times 10^9 l^{-1}$)	*Albumin* ($g\ l^{-1}$)	*A-aDo_2 at 1 h Post Transplant (kPa)*	*Survival (h)*
Control n=7	0.11 (0.09)	1.5 (0.9)		
EC n=3	0.26 (0.23)	6.4 (1.9)	5.7 (3.7) All sacrificed at 24 h	
TC n=4	0.65 (0.30)	10.5 (2.4)	22.2 (5.8)	3.2 (1.9)

Lung vascular injury following transplantation was characterised at BAL by neutrophil sequestration and high lung fluid albumin concentrations. Although the numbers are small, injury was much less in the group where lungs were preserved by EC and these animals showed improved early function and survival.

Transbronchial lung biopsy is effective in the diagnosis of rejection and opportunistic infection in heart-lung transplantation

ARL PENKETH, S STEWART, T HIGENBOTTAM, J WALLWORK *Papworth Hospital, Cambridge* Most of the long term complications of heart-lung transplantation appear to be pulmonary. It was initially incorrectly believed that by combining heart with lung transplantation, rejection would be monitored by endomyocardial biopsy. We have used transbronchial lung biopsy with fibreoptic bronchoscopy to provide a repeatable method of obtaining material for the histological diagnosis of opportunistic infection and rejection of the lung. Transbronchial biopsies were performed on 40 occasions in 18 patients. All but six routine biopsies were performed because of respiratory symptoms and reduced lung function. Histological criteria for rejection were perivascular infiltrates and mucosal inflammation (Youseman *et al, Hum Pathol* 1985;16:911-923). *Cytomegalovirus* pneumonia and *Pneumocystis carinii* pneumonia were diagnosed by their typical histological appearance. From 18 episodes of rejection, confirmed by a symptomatic and physiological response to augmented immunosuppression, 16 positive sets of biopsy specimens were obtained. Two biopsies were falsely positive and two falsely negative. Overall sensitivity was 88% and specificity 71%. For opportunistic infection sensitivity of the biopsy was 61% and specificity 100% from a total of eight episodes of infection and 15 sets of biopsies.

Immunomodulation by colophony, an agent causing occupational asthma

RT CULLEN, P JOHNSON, G BROWN, CA SOUTAR *Institute of Occupational Medicine, Edinburgh* Published clinical studies have so far failed to find evidence of specific immune responses to this agent. However, we have found that injection of saline suspensions of Portuguese colophony can modulate leucocyte function in C57 BL/6 mice. The *in vitro* production of hydrogen peroxide by peritoneal macrophages seven days after an intraperitoneal injection of colophony was significantly greater ($p<0.02$) increased (2.35 (SD 0.31) nmol/10^6 cells/hour) than that of control macrophages (1.21 (0.37) nmol). The ability of colophony-induced macrophages to spread on glass was also significantly ($p<0.001$) enhanced: saline 13.41 (7.20) μm, colophony 18.98 (8.03) μm. In further experiments we found that intraperitoneal injection of 2 mg colophony, two days before a subcutaneous injection of Keyhole limpet haemocyanin in Freund's complete adjuvant, affected the ability of draining lymph node cells to proliferate *in vitro* in response to this antigen seven days later. Some variation in this result may be related to the colophony preparation, and is being studied further. The mechanism of this immunomodulation is not known but may be related to the observed activation of macrophages by colophony.

Occupational asthma: the effect on health

DC WEIR, AS ROBERTSON, S JONES, PS BURGE *Department of Occupational Lung Disease, East Birmingham Hospital, Birmingham* We have followed up 45 patients (34 male, 11 female) with occupational asthma from a variety of causes for one to five years after presentation. Patients were identified from positive bronchial provocation tests and work related peak flow records held in the unit. Symptoms were assessed by a modified MRC questionnaire and spirometry performed. The age at follow-up ranged from 21 to 72 (mean 48.5) years; 35 patients were taking regular prophylactic treatment at follow-up and eight patients were still exposed to the causative agent. The FEV1 of the group had improved significantly from (as % predicted (SD)) 72 (24) at presentation to 77 (22) at follow up ($p<0.02$) and the FVC from 85 (21) to 94 (18)($p<0.01$). However 41% of patients complained of frequent wheezing, and 61% of significant breathlessness. Fifty-nine per cent of patients fulfilled MRC criteria for chronic bronchitis. Patients unemployed as a result of developing occupational asthma had significantly lower spirometry at presentation and follow-up and were significantly more breathless than those still employed. Complaints of wheezing, cough and sputum were similar between employed and unemployed groups at follow-up. Those patients with continued exposure had similar lung function

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and symptoms to the non-exposed group. Initial lung function was higher in the non-exposed group, but did not show the significant improvement at follow-up.

Estimated prevalence and relative risks of respiratory and allergic symptoms in wool textile workers

RG LOVE, TA SMITH, CA SOUTAR *Institute of Occupational Medicine, Edinburgh* A recent report (*Thorax* 1987;42:208) has demonstrated a clear relationship between respiratory symptoms and current exposure to inspirable wool mill dust in 2151 wool textile workers. We now present the estimated prevalences and relative risks of persistent cough and phlegm (chronic bronchitis), rhinitis and conjunctivitis and grade three breathlessness in this population in relation to dust concentration for men and women of European and Asian origin, smokers and non-smokers. Estimated prevalences have been calculated from logistic regression models, which included terms on age, sex, ethnic group, language used at interview, smoking habits and dust concentration. A rapid rise in prevalence is predicted over the dust concentration range from 0-5 mg/m^3 and a slower increase at higher concentrations up to 20 mg/m^3 and above. The highest relative risks in non-smokers were in European women and were, in relation to non-dust exposed, non-smoking women aged 40, 2.47 for rhinitis, 2.77 for chronic bronchitis, 3.56 for conjunctivitis and 6.20 for breathlessness at concentrations of 10 mg/m^3, the current nuisance dust limit. Other groups of workers have lower relative risks than these. These data can be helpful in decisions on an airborne dust standard for the wool textile industry.

Course and determinants of diffuse pleural thickening after crocidolite asbestos exposure

WOCM COOKSON, NH DE KLERK, AW MUSK, JJ GLANCY *Osler Chest Unit, Churchill Hospital, Oxford, and the Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia* The serial plain chest radiographs of 280 claimants for compensation for asbestosis among former crocidolite miners and millers at Wittenoom Gorge, Western Australia, were examined side by side by two independent observers for evidence of pleural disease using the 1980 ILO criteria for classification of radiographs for pneumoconiosis. Each subject had an average of 10 radiographs extending over a median period of 14 years. Observer one found that 163 patients (58%) and observer two found that 135 subjects (48%) showed evidence of pleural disease at some time. The median time to onset of diffuse pleural thickening was 23 years from first exposure to asbestos. The latent period to the onset and the risk of contracting diffuse pleural thickening was unrelated to total cumulative exposure to asbestos (fibres cc^{-1} year), site of work at Wittenoom (i.e. mining or milling of asbestos), or age at first exposure. Once established, pleural thickening progressed more rapidly in millers than in miners but there was no effect of estimated total cumulative exposure to asbestos on the rate of progression. No regression of pleural thickening was observed in any subject. Diffuse pleural thickening was observed rather than localized pleural plaques: in most cases the thickening was initially less than 5 mm in thickness but extended for more than 50% of the length of the lateral chest wall.

Respiratory changes in laryngeal dimension in patients with chronic airflow limitation (CAL)

W KELLY, A TULLY, A BRANCATISANO, LA ENGEL *Thoracic Medicine Unit, Westmead Hospital, Sydney, Australia* To study the respiratory function of the larynx in patients with CAL, we measured the glottic and supraglottic lateral diameters (Dg and Dsg) at mid-tidal inspiration (i) and expiration (e) in 13 patients with an FEV_1 of 36% (4%) predicted. Real dimensions were obtained from fluoroscopic images recorded on videotape with the use of known skin markers. Synchronous recordings of flow and volume were derived from a pneumotachograph. Five to six breaths were analysed during quiet breathing (QB) on application of 10 cm H_2O continuous positive airway pressure (CPAP) and during hyperoxic hypercapnia (RB) after ventilation ($\dot{V}E$) and expired Co_2 concentration ($FeCo_2$) had increased.

Mean (SEM):	*$\dot{V}E$ (l/min)*	*$FeCO_2$ (%)*	*Dgi (mm)*	*Dge (mm)*	*Dsgi (mm)*	*Dsge (mm)*
QB	12.3	4.8	7.7	4.2*	12.2	8.5*
n=13	(1.3)	(0.3)	(0.4)	(0.5)	(1.0)	(1.0)
CPAP	15.4	4.8	8.7	5.6*	14.6	11.2*
n=8	(1.5)	(0.3)	(0.5)	(0.6)	(1.3)	(1.2)
RB	20.7	7.8	8.5	3.0*	12.7**	8.6
n=8	(1.5)	(0.1)	(0.9)	(0.5)	(1.0)	(1.1)

*p<0.02 (relative to Di); **p<0.02 (relative to QB). Mean ± SE.

Thus, unlike in normal subjects (England *et al, J Appl Physiol* 1982), in CAL the expiratory glottic narrowing is not reduced during hyperpnoea. Similarly, unlike in acute asthma (Collett *et al, Am Rev Respir Dis* 1986), CPAP does not widen glottic diameter in patients with CAL. Our results are consistent with a persistent and stable pattern of laryngeal braking of expiratory flow in CAL.

Valve closure in the Nebuhaler in patients with low expiratory rates of flow

WOCM COOKSON, RM HIGGINS *Osler Chest Unit, Churchill Hospital, Oxford* We have previously shown poor bronchodilator response in patients with severe COAD using the Nebuhaler tube spacer device. The function of the valve in the mouthpiece and inspiratory and expiratory flows through the Nebuhaler were measured in 12 patients (mean age 67.2 (SEM 2.6), mean FEV_1 0.76 (SEM 0.09) litres, mean peak expiratory flow (PEF) 106.8 (SEM 10.7) litres/min. Using a compressed air source, the valve in a Nebuhaler mouthpiece was found to close when flow past it reached 42.6 (SEM 4.6) litres/min (mean of 10 measurements). Whilst breathing according to the manufacturer's instructions (deeply and slowly) through a Nebuhaler, seven of the 12 subjects (mean PEF 87.0 (SEM 17.8) litres/min) were unable to close the mouthpiece valve.

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The mean volume exhaled through the spacer chamber in the subjects who did not close the valve was 0.21 (SEM 0.08) litres, with a range up to 0.59 litres. This air exhaled through the spacer chamber may allow any aerosol suspended in the chamber to be lost. The full 0.75 litres volume of the Nebuhaler was not inhaled by 10 of the subjects (overall mean volume inhaled 0.47 (SEM 0.07) litres) whilst using the Nebuhaler, so they would not be expected to receive all the aerosol suspended throughout the spacer chamber. In its present form, the Nebuhaler may not be suitable for some patients with severe COAD.

A comparison of high dose inhaled with oral corticosteroids in corticosteroid trials in chronic airflow obstruction (CAO)

RI GOVE, AS ROBERTSON, PS BURGE *Department of Respiratory Diseases, East Birmingham Hospital, Birmingham* One hundred and twenty-one patients with adult onset CAO completed a double blind randomised crossover trial of inhaled and oral corticosteroids. Three two week phases of treatment with a two week washout period consisted of 1) prednisolone 40 mg/day and a placebo inhaler, 2) beclomethasone dipropionate (BDP) 500 μg inhaled tds and placebo, 3) both preparations as placebo. A response was a change $\geqslant 20\%$ in FEV_1, FVC or mean PEFR during the second week of treatment as compared with baseline. A change $\geqslant 15\%$ in any one measurement or $\geqslant 10\%$ in any two measurments was labelled an equivocal response. Patients with clinical asthma were excluded. There was a significant effect of order on the response to placebo, but not on the other two treatments (log liklihood ratio test; $\chi^2 = 20.4$, $2p < 0.001$). Because of this responses were compared with baseline values, or placebo only if the placebo period came first. Forty-eight patients (40%) had a full response, and 10 patients (8%) an equivocal response. Nineteen of the responders responded to both active treatments, 23 patients responded only to prednisolone and six only to BDP. Significantly more patients responded to prednisolone (McNemar's test; $2p < 0.025$). Of the 23 prednisolone responders nine had an equivocal response to BDP; of the six BDP responders one had an equivocal prednisolone response. The mean percentage change from baseline in the responders' FEV_1 and FVC were similar after prednisolone and BDP, but the changes in mean PEFR were greater following prednisolone ($2p < 0.001$). The BDP only responders had significantly greater cigarette consumption and reversibility in response to ipratropium bromide than the other responders. Prednisolone is more effective than BDP in inducing a corticosteroid response in CAO, although some patients with a different pattern of airflow obstruction may respond better to the inhaled drug.

Mood, attitudes to health and respiratory impairment in redundant shipyard workers

B KING, JE COTES *Respiration and Exercise Laboratory, Department of Occupational Health, Medical School, Newcastle upon Tyne* In patients with disabling bronchitis Morgan and colleagues (*BMJ* 1983;286:171-3) found that attitudes and beliefs contributed more to the description of the 12 minute walking distance than mood and ventilatory capacity. We have examined the relationships of these factors to lung function and performance on a cycle ergometer, the latter expressed as maximal O_2 % of reference value. The 161 shipyard workers had a mean age of 56 years (range 27-71 years) and forced expiratory volume (FEV_1) of 2.69 l (range 0.3-4.8 l). The scores for anxiety, depression and attitudes to health were highly inter-correlated. After allowing for age, stature and smoking history, scores for anxiety or depression contributed significantly to the descriptions of FEV_1, forced vital capacity, peak expiratory flow and transfer factor. Dichotomous scores explained rather more of the variance than continuous scores and anxiety more than depression. Lung function was also related to attitudes to health but not to breathlessness. Both mood and attitudes contributed to grade of breathlessness; FEV_1 and wheeze also contributed, obesity and smoking did not. Exercise capacity was significantly correlated with attitudes to breathlessness and general health, and also with anxiety but not depression. Anxiety was associated with shallow breathing during exercise. These results confirm the association between mood, attitudes to health, respiratory impairment and disability. They suggest that anxiety and depression result from negative attitudes to health, which in turn are probably aggravated by respiratory impairment and disability.

Intermittent humidification influences occurrence of humidifier fever

K ANDERSON, AD WATT, D SINCLAIR, G BOYD *Department of Respiratory Medicine, Royal Infirmary, Glasgow, and Employment Medical Advisory Service, Glasgow* Humidifier fever has been described as an illness of clearly defined periodicity (Finnegan and Pickering, *Clin Allergy* 1986;16:389). Recognition of this pattern probably relies on continuous use of contaminated humidifiers maintaining airborne antigen at a high level. Two factories are described where the humidifiers (cold water spray and ceiling mounted spinning disc) were used on an intermittent basis and only when relative humidity was less than 45%. This would occur commonly in winter, when air intake required warming and humidification more continuously than in the other seasons, when the external air temperature was above 10°C. Symptoms occurred irregularly in 40 out of 250 workers in one factory and 17 out of 50 in the other until two more classical episodes of humidifier fever occurred during summer periods when humidification of air intake was necessary. Symptoms were particularly common in night shift workers who had changed from day shift, suggesting altered exposure to antigen from humidifiers operating more often at night in response to cooler nocturnal air intake. We conclude that the nature and form of humidifier fever is altered by intermittent use of humidifiers.

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Serology of farmer's lung, following a dry and a wet summer in south-west Ireland

CP BREDIN, D KERINS, BV FOLEY *Departments of Respiratory Medicine and Microbiology, Regional Hospital, Wilton, Cork, Ireland* In a retrospective study, the positive serology rate and other characteristics of farmer's lung antibodies were compared over two years, from October 1 1984 to September 30 1985 following a low rainfall summer, compared with the same period one year later following a high rainfall summer. Serology was considered positive if antibodies were detected by either counter-immunoelectrophoresis (C.I.E.P.) or enzyme linked immunosorbent assay (E.L.I.S.A.). Four out of 20 sera were positive in the first year (1984-85); 23 out of 61 were positive in the second year (1985-86) — an expected increase after the wet summer. There were positive antibodies to *Micropolyspora faeni* in 26 patients, and to *Thermoactinomycetes vulgaris* in 11 patients. All positive sera were detected by E.L.I.S.A. and only one by C.I.E.P.. The peak period of positive sera occurred in June of each year. This is a later peak than in Finland and Britain, and may be due to variation in local farming methods.

Pulmonary eosinophilia with and without bronchopulmonary aspergillosis

S CAPEWELL, BJ CHAPMAN, F ALEXANDER, R GIBSON, AP GREENING, GK CROMPTON *Respiratory Unit, Northern General Hospital, Edinburgh* Sixty-five patients with pulmonary eosinophilia (PEo) presenting to one respiratory unit have been reviewed. All had fleeting chest radiographic abnormalities and a peripheral blood eosinophilia $> 500 \times 10^6/l$. Eighteen had one episode and 47 patients had recurrent episodes of PEo during a mean follow-up period of 13.8 years. Thirty-three/65 (51%) patients were considered to have PEo associated with bronchopulmonary aspergillosis (BPA) on the basis of skin tests, serum precipitins and sputum culture of *A fumigatus* (at least 2/3 tests positive). BPA patients differed from non-BPA patients. BPA patients were more frequently male (58% vs 28%; $p<0.01$), had a higher incidence of asthma (97% vs 81%, $p<0.05$) with an earlier age of onset (15.6 vs 26.0 years; $p<0.01$) and more commonly had radiographic evidence of bronchiectasis/fibrosis (54% vs 12%, $p<0.001$). During episodes of PEo non-BPA patients had a greater incidence of associated systemic features (fever, night sweats, weight loss, arthralgia, rash, anaemia, cardiovascular involvement)(44% vs 9%; $p<0.005$) and a higher mean (SEM) eosinophil count (2858 (516) vs 1406 $(224) \times 10^6/l$; $p<0.01$). Pulmonary eosinophilia associated with BPA appears a distinct clinical syndrome which results in greater permanent radiological abnormality but which is associated with fewer systemic symptoms and lower peripheral blood eosinophilia.

Aspergillus fumigatus counts in the beds of asthmatics with and without bronchopulmonary aspergillosis

IJ GORDON, CC EVANS *Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Liverpool* Bronchopulmonary aspergillosis (B.P.A.) affects 1% of asthmatics and the role of environmental factors or host susceptibility is unknown. Patients spend up to one third of their lives in bed and the mattress contains stuffing rich in fungi and bacteria. Ten patients with B.P.A., six asthmatics with aspergillus positive skin prick tests but no other criteria for B.P.A. and nine asthmatics with negative skin prick tests to aspergillus were studied. Each was visited at home every three months for one year and bed dust was collected using a portable vacuum cleaner and filter. The dust was filtered, weighed and spread onto Sabourauds medium in equal aliquots. The number of aspergillus colonies were counted after 48 hours' incubation and the number of colonies per square metre of bed was calculated. No seasonal rhythm in aspergillus counts was detected, nor was there any significant difference in counts between any of the groups, although very high counts were occasionally recorded.

Smoking cessation in patients with smoking-related diseases

IA CAMPBELL FOR BTS RESEARCH COMMITTEE *Sully Hospital Cardiff* From October 1984 to June 1986 sixty-seven physicians entered 1415 new out-patients into the Second B.T.S. Smoking Withdrawal Study. Patients were randomised to physician's advice alone (Group I) or to physician's advice reinforced by a signed agreement, two visits by a health visitor and repeated postal encouragement (Group III). Clinic follow-up was at six months, when non-smoking claims were validated by COHb and thiocyanate measurements. Of 710 Group I patients 105 denied smoking and blood was taken from 94, among whom 70 claims were supported. In Group II the corresponding figures were 705 entered, 164 claimed non-smoking status, 147 blood tests performed and 95 claims supported. Thus 13.5% of Group II and 9.9% of Group I were not smoking at six months, χ^2_c 4.1, $p=0.04$. Males did better than females, 14.8% compared to 7.0%. Follow-up continues to 12 months: if the difference is maintained physicians will have, for the first time, a means of increasing cessation above the rate achieved by advice alone.

BCG SYMPOSIUM PAPER

Protective effect of BCG vaccination in newborn Asians: a case-control study

GE PACKE, JA INNES *Birmingham Chest Clinic, Birmingham* BCG vaccination has been routinely offered to newborn Asian children in Birmingham since 1965. We conducted a case-control study to assess the protective effect of this scheme. One hundred and eight Asian children aged under 13 years and born since 1965 were included in the analysis; they were notified as suffering from tuberculosis on objective evidence other than a positive tuberculin test. Asian children notified with tuberculosis only on the evidence of a positive tuberculin test were not included, nor were those given BCG as contacts or at any time other than the newborn period. For each case, four controls were selected from vaccination records, matched to the case by month and year of birth, sex, and ethnic origin. Cases and controls were all born in Birmingham. Of

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the cases, 57% (62/108) had received BCG, and of the controls, 78% (336/432) had received BCG. The estimated protective efficacy of vaccination was 64% (95% confidence limits, 43% and 77%), indicating useful protection against the development of tuberculosis in childhood.

Contribution of histamine to benzalkonium chloride-induced bronchoconstriction in asthma

K MISZKIEL, R BEASLEY, P RAFFERTY, ST HOLGATE *Medicine I, Southampton General Hospital, Southampton* We have presiously shown that benzalkonium chloride (BAC), a preservative present in some nebuliser solutions, is a bronchoconstrictor agonist. The ability of BAC to cause histamine release from rodent mast cells *in vitro* suggests that its adverse airways effect may be secondary to histamine release. To investigate this possibility 12 atopic asthmatic subjects underwent inhalation challenge with BAC or histamine (H) three hours after treatment with terfenadine 180 mg or placebo. On four occasions concentration-response studies were undertaken to determine the concentration of each agonist required to cause a 20% fall in FEV_1 (PC_{20} FEV_1). On four further occasions, FEV_1 was measured for 45 minutes after inhalation of the PC_{20} FEV_1 agonist concentration. Terfenadine caused significant displacement to the right of the H and BAC concentration-response curves. The geometric mean PC_{20} FEV_1 concentrations (mg/ml) for H and BAC were 0.61 and 3.98 after placebo, and 39.3 ($p<0.001$) and 10.28 ($p<0.01$) after terfenadine respectively. Compared with H the bronchoconstriction provoked by BAC was slower in onset and more sustained. Terfenadine inhibited the first 15 minutes of bronchoconstrictor response due to H by 92.2% (17.0%) ($p<0.001$) and that due to BAC by 22.7% (16.0%) ($p<0.05$). Almost identical results were obtained with the chemically unrelated H_1-antagonist astemizole. We conclude that, although part of the bronchoconstriction induced by BAC is mediated through the release of histamine within the airways, it represents a small component of the overall response.

The optimum aerosol size and dose of salbutamol in the treatment of asthma

MA JOHNSON, R BLOOM, S NEWMAN, SW CLARKE *Department of Thoracic Medicine, Royal Free Hospital, London* It has been suggested that adrenergic receptors predominate in the small airways and that β_2 agonists should therefore be targeted to the small airways to ensure high concentrations at their site of action. This study examines the effect of aerosol size on bronchodilation with nebulised salbutamol using much smaller doses than conventionally used (to avoid saturation of the adrenoreceptors) and administered in a dose response fashion. Eight patients with moderate asthma were studied on two occasions in a randomised single blind crossover study. On each visit they each received 250, 250, 500 and 1000 μg of salbutamol, nebulised to dryness, at 35 minute intervals delivered via two different types of nebuliser with different compressed gas flow rates to generate an aerosol size of 3 μm (MMD) and an aerosol size of 7 μm (MMD). The bronchodilator response was assessed by change in FEV_1, FEV, PEFR, $\dot{V}max_{25}$, $\dot{V}max_{50}$. There was significantly greater increase in all measurements following 3 μm aerosols. The increase in FEV_1 following 1,000 μg was 52.9% for the 3 μm aerosol and 39.9% for the 7 μm aerosol ($p<0.02$). In addition there was no significant further bronchodilation following 1000 μg of salbutamol delivered via either aerosol. These results suggest that aerosol size is important when administering β_2 agonists and that the optimum dose of salbutamol may be much smaller than that presently used.

Theophylline increases salbutamol induced hypokalaemia and tachycardia

KF WHYTE, C REID, R WHITESMITH, GJ ADDIS, JL REID *Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow* Salbutamol and adrenaline cause hypokalaemia by stimulating membrane bound Na^+/K^+ ATPase linked to β_2-adrenoreceptor (Whyte *et al, Brit J Clin Pharmacol* 1987;23:65-71). Theophylline enhances adrenaline induced hypokalaemia (Whyte *et al, Eur J Respir Dis* 1987; in press). In a single blind placebo controlled study in 14 normal subjects we have examined the effects of therapeutic theophylline levels on the haemodynamic changes and hypokalaemia following salbutamol infusion ($4\ \mu g\ kg^{-1}$ over five minutes and then $8\ \mu g\ kg^{-1}\ h^{-1}$ for 55 minutes). Potassium levels fell during the salbutamol infusion on both study days but this fall was significantly greater on the theophylline limb (mean (SD) 3.9 (0.3) to 2.6 (0.3) mmol l^{-1} compared with the placebo limb (4.0 (0.3) to 3.0 (0.3) mmol l^{-1}, $p<0.05$; repeated measures analysis of variance (ANOVA)). Baseline heart rate was higher on theophylline than placebo (78 (12) and 72 (7) beats min^{-1} respectively) and the rise in heart rate during the salbutamol infusion was greater on theophylline ($p<0.05$, ANOVA). Salbutamol infusion resulted in similar changes in diastolic and systolic blood pressure on both treatments. We conclude that theophylline significantly increases salbutamol induced hypokalaemia and tachycardia. Intensive bronchodilator therapy with salbutamol and theophylline in acutely ill, hypoxic asthmatics may increase the risk of cardiac dysrhythmias.

Can pursed-lip breathing prevent hyperventilation-induced asthma?

JM WARDLAW, RJ FERGUSSON, PM TWEEDDALE, GJ MCHARDY *Respiratory Unit, Northern General Hospital and Pulmonary Function Laboratory and Department of Medicine, Western General Hospital, Edinburgh* As a result of a personal observation by one of the authors that breathing through pursed lips (PLB) could prevent the development of exercise-induced asthma (EIA) a study was performed to investigate the value of this manoeuvre in blocking bronchoconstriction induced by isocapnic hyperventilation (IH). Ten subjects (five male) with a

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history of EIA underwent three separate IH tests breathing cold, dry air at a "target" minute volume (MV) for six minutes (Tweeddale *et al, Thorax* 1981;36:598-9). FEV_1 and FVC were measured before and at 1, 5, 10 and 15 minutes after each test. On the first visit (test one) a standard mouthpiece and noseclips were used. On the two subsequent visits, the subjects used a large, air-tight face mask breathing either through a wide open mouth (OM) or with pursed lips. The order of these two tests was randomised. Pre-test FEV_1 and FVC and MV did not differ significantly between visits. The mean maximum fall in FEV_1 from pre-test values after test one and OM breathing was virtually identical (1.37 l (0.52) and 1.35 l (0.54) respectively). Bronchoconstriction was significantly reduced by PLB when compared with test one and OM (mean fall in FEV_1, 0.68 (0.65) l, $p<0.01$ using both parametric and non parametric tests). PLB is a simple manoeuvre which may be of practical benefit to some patients with EIA, but the mechanism of the effect requires further investigation.

A comparison of intravenous with nebulised salbutamol in the treatment of acute severe asthma

B CHEONG, S REYNOLDS, KG RAJAN, MJ WARD *Department of Thoracic Medicine, Llandough Hospital, Nr. Penarth* Previous studies have claimed IV and nebulised bronchodilator to produce similar bronchodilatation. This study was designed to have adequate power to detect a true 15% difference in PFR response. Seventy-one patients with acute severe asthma were admitted to hospital in whom the PFR remained below 50% predicted 30 minutes after 5 mg nebulised salbutamol were randomised to receive either further nebulised or IV salbutamol. In the nebulised group ($n=34$) 5 mg was repeated to a total dose of 15 mg in two hours. In the IV group ($n=37$) 12.5 μg/minute was given for four hours. No other bronchodilator was given. The PFR and pulse rate were monitored for four hours. Both groups were well matched for age, sex and severity of attack. The admission mean PFR in the NEB and IV groups was 111 and 91 l/min. The % increase in PFR was greater in the IV group reaching statistical significance three hours after admission (IV = 20.7% vs NEB = 12%, $p<0.025$, and IV = 25.5% vs 14.3%, $p<0.01$, after four hours). Tachycardia was more prominent in the IV group, becoming significant at 1.5 hours. An intravenous β agonist may be useful in severe asthma.

Bronchodilator efficacy of nebulised salbutamol and ipratropium sequentially and in combination in acute asthma

QA SUMMERS, RA TARALA *Respiratory Medicine Unit, Royal Perth Hospital, Perth, Western Australia, Australia* It has been suggested that nebulised antimuscarinic bronchodilators, alone or in combination with adrenoceptor agonists, may be useful in the treatment of acute asthma. We have undertaken a double blind, randomised trial of nebulised ipratropium and salbutamol in acute asthma. We studied 64 patients with acute asthma. Each received two nebulised preparations, at time 0, and at 60 minutes, containing salbutamol 5mg (S) and ipratropium 0.5mg (I): Group (A) — S followed by I; (B) I followed by S; or (C) S combined with I, followed at one hour by normal saline. Peak flow (PEFR) was measured before the first treatment (at time 0), then at 15 and 60 minutes after nebulisation was completed; and at the same intervals after the second treatment (75 and 120 minutes). There was a significant rise in PEFR after each treatment — in Group A ($n=23$) between A0 and A15, A60 and A75, and A75 and A120 ($p<0.001$ for each value); in group B ($n=18$) between groups B0 and B15, and B60 and B75 ($p<0.005$); in group C ($n=23$) $p<0.001$ between C0 and C15, and $p<0.005$ between C60 and C75. There was no evidence of an order effect, in that the improvement after each agent was similar, irrespective of whether the drug was given first or second. The effect of I after S did not differ from the effect of placebo given after S/I combined. The combination of S/I was not superior to S alone at one hour. These results do not suggest a substantial therapeutic effect from the routine use of ipratropium added to salbutamol, either sequentially or in combination, in the immediate treatment of acute asthma.

The effect of house dust mite (HDM) avoidance measures on adult atopic asthma

AJ DORWARD, MJ COLLOFF, NS MACKAY, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow, and Department of Zoology, University of Glasgow* Twenty-one adult asthmatics, skin-test positive to *D pteronyssinus,* were randomised to a control group or to a group which performed HDM avoidance measures including initial application of liquid nitrogen to mattresses and bedroom carpets to kill the HDM population. Histamine airway responsiveness was measured by PC_{20} FEV_1, symptom scores, peak flow rates (PFR) and HDM numbers were measured during the two week pre-trial and eight week trial periods. Nine patients in each group completed the study. There was a significant reduction in live mites in the avoidance group by the end of the study but not in the control group. The avoidance group showed a significant improvement in symptom scores, number of hours wheezing and PFR. These changes were not found in the control group. The PC_{20} FEV_1 increased significantly in the avoidance group at eight weeks while there was no change in the control group. Four out of the nine avoidance group patients had a greater than four times increase in PC_{20} FEV_1. These results demonstrate that HDM avoidance when combined with an initial kill of the mites by liquid nitrogen diminishes airway responsiveness over an eight week period in adult asthmatics with HDM allergy.

Intermittent positive pressure hypoventilation and inotropic support in severe acute asthma

SG BREAR, JD EDWARDS *Wythenshawe Hospital, Manchester and University Hospital of South Manchester, Manchester* As a last resort treatment of acute severe

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asthma, intermittent positive pressure ventilation is lifesaving in the majority of patients. However, the mortality remains high (in most units of the order of 30%) and complications secondary to the high inflation pressures and internal positive end-expiratory pressures generated are frequent. During 10 episodes in eight patients requiring intermittent positive pressure ventilation we have compared the clinical and haemodynamic responses of patients during initial "conventional" intermittent positive pressure ventilation and subsequent intermittent positive pressure hypoventilation with inotropic support (IPPH/IS). One patient died of adult respiratory distress syndrome secondary to gastric aspiration. All other patients survived with no episodes of pneumothorax, mediastinal or surgical emphysema. The mean peak inspiratory pressures fell from 96.4 in the intermittent positive pressure ventilation group to 57.6 in the IPPH/IS group. The mean cardiac index rose from 2.0 in the intermittent positive pressure ventilation group to 4.6 in the IPPH/IS group, the overall effect being to markedly improve tissue oxygen delivery.

Comparison of the efficacy of preservative-free ipratropium bromide and Atrovent ipratropium bromide nebuliser solution in asthmatic subjects

P RAFFERTY, R BEASLEY, ST HOLGATE *Southampton General Hospital, Southampton* Isotonic Atrovent nebuliser solution has been reported to produce paradoxical bronchoconstriction in asthmatic subjects and we have recently demonstrated that this is due to the preservatives benzalkonium chloride and EDTA present in the solution (Beasley *et al, Br Med J* 1987, in press). In this double blind study we have compared the airway response to inhalation of Atrovent nebuliser solution with that to preservative-free ipratropium bromide (PFIB). Thirty asthmatic subjects (21M, 9F, mean (SEM) age 55 (3) years, mean (SEM) FEV_1 59% (5%) predicted) inhaled 2 ml of Atrovent nebuliser solution or PFIB and airway calibre measured as FEV_1 before and for 45 minutes after inhalation. Atrovent provoked a fall in FEV_1 of 20% in five (17%) subjects whereas this did not occur following PFIB. Inhalation of PFIB resulted in greater bronchodilation than following Atrovent with mean (SEM) increases in FEV_1 of 29.2% (3.6%) and 18.5% (2.8%) respectively ($p<0.001$). We conclude that PFIB is safer and more effective as a bronchodilator in asthma than the currently available Atrovent solution.

Effects of salbutamol and ipratropium bromide on intraocular pressure in chronic bronchitis with glaucoma

L KALRA, H KAZMI, MF BONE *Department of Medicine, Russells Hall Hospital, Dudley* A controlled double blind crossover study of ocular complications associated with nebulised ipratropium bromide and salbutamol therapy for respiratory distress was undertaken in 46 chronic bronchitics (14 open angle glaucoma, 12 narrow angle glaucoma, 20 controls). There was no significant rise in intraocular pressure or change in anterior chamber angle in patients with open angle glaucoma, narrow angle glaucoma, or controls following treatment with either drug. However, when the two drugs were used in combination intraocular pressure rose by a mean of 5.8 (SD 0.3) (range 4-7) mm Hg at 90 minutes in patients with narrow angle glaucoma but not in patients with open angle glaucoma or controls ($p<0.05$). Transient angle closure was seen in five of these patients. Intraocular pressures did not rise when swimming goggles were used to protect the eyes or when antiglaucoma treatment was continued. Nebulised bronchodilator therapy is safe in non-glaucomatous patients and those with open angle glaucoma. Ocular complications can follow combined ipratropium bromide and salbutamol nebulisation in patients with narrow angle glaucoma but can be prevented by using the drugs separately, protecting the eyes, and ensuring continued antiglaucoma measures.

Warm-up exercise inhibits exercise induced asthma (EIA)

DB REIFF, N CHOUDRY, HA JONES, PW IND, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London* Although refractoriness in EIA is well recognised there has been little work on the effect of different exercise regimes. Seven mild asthmatics (five male), aged 16-32 years, with a history of EIA were excercised on two study days, in random order, within five days. On one day standard treadmill exercise (EX1), six km/hour at 15% gradient for six minutes, was performed and repeated after 45 minutes (EX2). Heart rate (HR) was continuously monitored and minute ventilation ($\dot{V}$) was measured. On another day, the same exercise test (EX3) was repeated 29 minutes after a 30 minute "warm-up" run of six km/hour at 3% slope. There was no significant difference between baseline mean FEV_1 on the two study days (80 (SEM 8) and 79 (7)% pred). These subjects were refractory with a mean maximum fall in FEV_1 of 1.52 l (46% baseline) after EX1 and 0.56 l (19%) on EX2 and also felt less wheezy. Environmental conditions, HR and $\dot{V}$ did not differ significantly during EX1, EX2, EX3. After warm-up most subjects developed slight bronchoconstriction with recovery to $FEV_1 > 85\%$ baseline prior to EX3. During EX3 they were refractory (mean maximum fall in FEV_1 of 0.63 l 21% baseline) with less wheeze on visual analogue score. Thus refractoriness was equivalent to that induced by EX1 though work output ($\dot{V}O_2$) on warm-up was 3-4 fold greater. Preliminary warm-up exercise can induce refractoriness without itself producing marked E.I.A. This has implications for asthmatics participating in sport and also for understanding the mechanisms of E.I.A.

Serum neutrophil chemotatic activity (NCA), plasma histamine and catecholamines in asthma induced by hypertonic saline (HS) and exercise (EX)

N BELCHER, R MURDOCH, N DALTON, PJ REES, TJH CLARK, TH LEE *Departments of Medicine and Respiratory Medicine, Guy's Hospital, London* In nine subjects with exercise induced asthma NCA and plasma histamine concentrations have been measured following asthma induced by EX and

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HS on two separate occasions. In each subject HS and EX produced a similar fall in FEV_1. Venous plasma histamine and catecholamines were measured by radioenzymatic assays and NCA was assayed by a microchemotactic method on 0.25, 0.5, 1.0 and 5.0% serum dilutions. At optimal serum concentrations for analysis there were significant time dependent increases in NCA at five and 15 minutes following both EX (mean (SD) % 183 (61), 246 (825), $p<0.05$, $n=9$) and HS (206 (103), 137 62, $p=0.02$, $n=9$). NCA released after EX and HS had a molecular weight of approx. 700 kd. There was a significant increase in plasma histamine from a baseline of 4.7 (1.2) to 9.1 (3) nmol/l ($p<0.05$, $n=9$) at 15 minutes following EX but not following HS. There was a 110% (25%) ($p=0.02$) and 3% (1%) (NS) increase in basophil counts after EX and HS respectively. There was no significant rise in plasma adrenaline following EX or HS ($n=7$); there was a rise in noradrenaline following EX from a baseline of 1.8 (0.29) to 3.15 (0.53) and 2.1 (0.33) nmol/l ($p=0.02$, $p=<0.05$, $n=7$) at five and 15 minutes respectively but this was not seen following HS.

Nocturnal asthma: role of snoring and obstructive sleep apnoea (OSA)

CS CHAN, AJ WOOLCOCK, CE SULLIVAN *Department of Medicine, University of Sydney, N.S.W., Australia* Many mechanisms have been proposed for nocturnal asthma attacks. We report the effect of nocturnal nasal continuous positive airway pressure (nCPAP) on six patients (M:F 5:1) who have a combination of persistent nocturnal asthma attacks and recurrent upper airway obstruction (UAO). These patients had common symptoms of heavy snoring, nocturnal choking, excessive daytime sleepiness and frequent sleep arousals. All night sleep studies confirmed mild OSA in five patients and partial UAO in one patient. All snored heavily. Peak Expiratory flow rates (PEF) were recorded in three intervals of two weeks before, during, and after cessation of nocturnal nCPAP therapy. The morning and evening prebronchodilator PEF (mean (SEM) of 14 days), expressed as a percentage of the predicted PEF, is as shown in the table. During the period of nCPAP therapy no patient had symptoms of nocturnal asthma, snoring, or nocturnal choking. These results suggest that recurrent UAO and snoring are important triggering mechanisms of nocturnal asthma attacks. Treatment of patients with dominant nocturnal asthma attacks and recurrent UAO with nCPAP may improve not only the symptoms of OSA but also the severity of the asthma.

	Am	*p*	*Pm*	*p*
Control	40 (6)	<0.02	49 (7)	<0.02
nCPAP	52 (8)	<0.02	60 (9)	<0.05
Control	44 (6)		55 (9)	

Is cosinor analysis an appropriate model for diurnal variation in asthma?

CK CONNOLLY *Friarage Hospital, Northallerton, North Yorkshire* Diurnal variation in asthma is frequently called morning "dipping", which implies deviation from a maximum. Characteristic patterns may be described qualitatively (CK Connolly, *Brit J Dis Chest* 1979;73:357), supported by simple calculation. Cosinor analysis is more sophisticated, potentially able to avoid observer bias and detect rhythms in "noisy" data. It requires a computer and assumes oscillation about a mean, rather than a fall from a baseline. Four hundred and seventy-six subjects with airway obstruction (376 asthmatics) recorded their peak flow rate four hourly during the day. Pattern analysis with simple calculation and cosinor analysis were compared. Consistent variation was demonstrated in 332 subjects by pattern and in 253 subjects by cosinor analysis ($p<0.01$ approximating to 95% confidence limits of acrophase $\pm$ three hours). Only 18 of these did not show a characteristic pattern, and 95% of subjects within each pattern group showed an acrophase within $\pm$ three hours of the median, corresponding to lowest PEFR at 0520 for morning dippers and 0245 hours for double dippers. Calculated mean was highly correlated with cosinor mesor ($r=0.999$), as was cosinor amplitude with simply calculated "amplitude" ($r=0.935$) and morning dip ($r=0.86$). Pattern with simple calculation is a closer model of dipping than cosinor analysis and, as the latter gives no more information, the computer should be abandoned in favour of the eye, pending the discovery of a more appropriate sophisticated mathematical model.

Acute asthma in the Grampian Region, 1976-85: hospital admissions and GP survey

PP SUTTON, ER ALEXANDER, G RUSSELL, JG DOUGLAS, JAR FRIEND, JS LEGGE, SJ WATT *Departments of Respiratory Medicine, Community Medicine and Paediatrics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen* Hospital admissions from acute asthma (ICD code 493) were examined for the Aberdeen hospitals serving the Grampian Region (1984 population 497272) during 1976 to 1985. There was a 105% increase in total admissions during this period and the mean stay fell from 9.4 to 6.1 days. The increase was prominent in the young: 0-14 302%, 15-44 48%, over 45 years 10%. These changes persisted following corrections for population changes and comprised both new and return patients. It is unlikely that altered prevalence or diagnostic accuracy could explain these recent changes and therefore a postal survey of all general practitioners in this region was conducted to study attitudes towards assessment, treatment and supervision of acute asthma. Two hundred and eighteen detailed replies were received from 293 questionnaires (74%). Ninety-eight per cent used peak flow meters during asthma supervision but only 45% thought them useful in acute domiciliary episodes. Eighty-five per cent used nebulised bronchodilators in treating acute severe asthma with steroids (57-79%) and aminophylline (52%) — although in

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57% of adults and 64% of children the steroid regimen was suboptimal. There was strong support for self-medication (87%), self-referral (75%) and shared-care schemes. Questions on preventive treatment indicated considerable scope for further prophylaxis in both adults and children.

Asthma mortality and drug therapy in Northern Ireland

SC WRIGHT, AE EVANS, D SINNAMON, J MACMAHON *Chest Unit, Belfast City Hospital; Department of Medicine, Coleraine Hospital; Department of Community Medicine, Queen's University, Belfast* We have investigated asthma deaths in Northern Ireland during 1981-84. The following death certificates issued in Northern Ireland during this period were extracted. 1) Asthma listed as the main cause of death. 2) Asthma listed as the supplementary diagnosis. 3) Airflow obstruction suggested by the listed diagnosis (age $\geqslant 55$ excluded). Further information was obtained from questionnires to each general practitioner, interviews with a close relative or associate of the deceased, hospital charts, and necropsy reports. Two chest physicians then decided which of the 382 deaths were due to asthma. Although the death certification of asthma was not accurate, the total number of deaths confirmed by the panel differed little from the total registered in each year. The registeed yearly totals are therefore useful in the assessment of trends in asthma mortality. Since 1960, two "peaks" were identified — from 1964 to 1969 and from 1979 to 1985. During the period 1977-1985, prescriptions for simple β agonist inhalers rose from 77000 to 234000. Theophyllines rose from 33000 to 135000. Steroid inhalers increased from 15000 to 46000. Prescriptions for nebulised β agonists rose from one in 1980 to 7200 in 1985. Of the patients investigated 82.5% were on inhaled β agonists, 33.7% were on oral β agonists, 60.4% were on theophyllines, 13.6% were on ipratropium, 30.2% were on inhaled corticosteroids and 35.3% were on oral corticosteroids. Only 5.9% were on nebulised β agonists. The use of nebulised β agonists does not appear to have been a major factor in overall asthma mortality.

Asthma mortality in the Republic of Ireland 1970-1984 and analysis of hospital deaths in a single year

P MANNING, E MURPHY, L CLANCY, B CALLAGHAN *Peamount Hospital, Newcastle, Co. Dublin* Mortality from asthma since the 1960s epidemic has remained static in the Republic of Ireland over the period 1970-1984. We reviewed asthma mortality in Ireland and obtained copies of all death certificates with asthma recorded as the cause of death for 1981. In 28 of these patients the primary cause of death recorded on the death certificate was not asthma. Eighty per cent of the remaining 104 deaths were in-patients over 50 years of age. Fifty-four patients died in status asthmaticus/acute asthma (28 in hospital; 26 at home). Patients who died at home from acute asthma were younger than those dying in hospital, 26 patients had asthma for over five years, 20 patients had three or less acute exacerbations in the last year. Six patients had no previous hospitalisation. Twenty patients had exacerbations of symptoms for less than one week (<24 hours in nine cases). Death occurred within 72 hours of admission in 19 cases. We found that the nine patients dying within 24 hours of admission had little or no steroid therapy. Twelve patients were given supplemental oxygen. Four patients were given sedation shortly before death. In only four cases were objective assessments of bronchial obstruction recorded on admission or subsequently. Twenty-three patients had chest radiographs. We found no single reason to account for the majority of asthma hospital deaths. Most patients were elderly and infection was a contributing factor.

FEV_1, age and smoking in working men aged 18-64

NM FARRER, KM VENABLES *Department of Occupational Medicine, Brompton Hospital, London* Working populations may include young adults. Some published regression models which account for the increase and plateau of FEV_1 with age are complex. A cross-sectional survey of industrial workers measured FEV_1 (Vitalograph). Four hundred and sixty-seven technically satisfactory traces from white males were analysed. Mean age was 41 years (range 18-64). Fourteen per cent were under 27, at which age FEV_1 appeared maximal. Log_e(age) was included and height (m) was squared (Cole *J R Statist Soc A* 1975;**138**:297-337). Residual standard deviation (RSD) of the regression was 0.538 l. Smoking is often a confounding variable. Pack-years (PY) of smoking and PY.year since stopped smoking (up to a maximum of five years) (PY.Ex) were additional significant predictors of FEV_1 (RSD 0.522). The final equation was: $(0.680.\log_e(\text{age}) - 0.029.\text{age}) \text{height}^2 - 0.010.\text{PY} + 0.002(\text{PY.Ex})$. In separate regressions for non-, ex- and current smokers (n = 125, 138, 204), FEV_1 difference with age was -32, -39 and -48 ml/year estimated at mean age and height. It was not a stepwise regression, so did not explore all possible forms and interactions, but showed (1) a simple curvilinear term allows one equation for the whole working age range; (2) smoking terms in the regression do not wholly explain the greater age-related FEV_1 difference in smokers, who may require separate analysis (Oldham *Thorax*, 1987;**42**:161-4).

Asthma and chronic bronchitis: mortality and hospital discharge patterns in the West Midlands

G BENFIELD, DE STABLEFORTH *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* Deaths from asthma in England and Wales now exceed 2000 per annum, with a continuing rise in older age groups. This may not be a true reflection of the asthma death problem because of the diagnostic confusion presented by chronic bronchitis and emphysema (CB/E). In the West Midlands the overall asthma mortality rate (MR) increased from 1.7 to 3.3 per 10^5 population between 1974 and 1984, mainly attributable to a steep rise in the 65+ age group. However, in the most diagnostically accurate 15-44 age group there was no increase in mortality, whereas asthma hospital discharges for the group increased from 35.2 to 67.4 per 10^5, with deaths per thousand discharges

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decreasing from 6.9 to 2.7. Over the period the CB/E mortality rate has fallen from 50 to 30 per 10^5, predominantly because of to a change in the 65+ age group, and the discharge rate has decreased from 42 to 26 per 10^5 over the same period. In the diagnostically less accurate 45-64 and 65+ age groups asthma discharge rates have increased in a diametrically opposite fashion to that of CB/E. Asthma mortality in the 15-44 group has not increased in the West Midlands despite markedly increased admissions, which possibly reflect altered admission criteria. The contrasting patterns of asthma and CB/E mortality and hospital discharges rates suggest possible changes in diagnostic attitudes, particularly in older patients, which may significantly influence our view of trends in deaths from asthma.

Dominant inheritance of atopic trait

WOCM COOKSON, JM HOPKIN *Osler Chest Unit, Churchill Hospital, Oxford* Twenty sets of parents of a random sample of atopic asthmatics aged <25 were compared with 14 sets of parents of controls. Ninety-five per cent of asthmatics had at least one atopic parent. The proportions of atopic and non-atopic parents in marriages were as follows:

Atopic:	*Both*	*One*	*Neither*
Parents of Asthmatics	8(40%)	11(55%)	1(5%)
Parents of Controls	1(7%)	7(50%)	6(43%)

The proportions expected from a randomly distributed trait with a prevalence of 33% are not different from the findings in controls ($\chi^2=0.18$), but are significantly different from parents of asthmatics ($\chi^2=10.08$, $p<0.005$), indicating a major genetic component to atopy. Three extended families (140 subjects) were studied, showing a simple vertical transmission of the trait through affected individuals from one generation to the next, so that, of 29 matings producing atopic children, only on three occasions did neither parent fulfil the criteria for atopy. In the largest family (110 individuals), 55% of children were atopic if one parent was affected, and 83% were atopic if both parents were affected. The results suggest an autosomal dominant inheritance of a single gene locus predisposing to atopy, the fundamental cause of which may be investigated by molecular genetic linkage analysis.

Measurement of peak expiratory flow rate variability in a community population

BG HIGGINS, T JONES, S CHINN, JR BRITTON, PJ BURNEY, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham and Department of Community Medicine, St. Thomas' Hospital, London* Serial peak expiratory flow (PEF) measurement is widely used in the diagnosis of asthma and may offer a means of estimating asthma prevalence in epidemiological surveys. However, there is no adequate description of the range of PEF variability in a random population, and it is not clear which index best expresses this variability. We have analysed PEF recordings made two hourly over seven days in 121 subjects selected at random from a large general practice register, and in 221 subjects selected because of wheeze in the last year. PEF variability was expressed for each subject as absolute amplitude (highest — lowest reading each day); amplitude % mean; amplitude % mean for a fitted cosinor curve; and morning dip. In the random sample, PEF variability followed a skewed distribution for all these indices, the 90th centiles being 70 litres/minute, 19%, 13% and 34 litres/minute respectively. The proportion of subjects with wheeze lying beyond the 90th centile was similar for each index, varying from 25% to 34%. Amplitude % mean and cosinor amplitude % mean had the highest intra-class and correlation coefficients in the random sample, and appear to be the most informative indices of PEF variability between subjects.

Inpatient care of respiratory patients in one region

MJB FAREBROTHER *Medway Hospital, Gillingham* For the fifteen districts of South East Thames Region the HAA data base was used to examine admissions with respiratory diseases (by ICD code) under thoracic physicians and under all physicians and geriatricians during 1985. For all physicians and geriatricians 15.8% (range for districts 13.3-18.9%) of all admissions were for respiratory diseases with admission rates of 4.7 (range 3.2-6.4) per 1000 acute catchment population. Twelve per cent (range 1-24%) of all admissions, but 23% (range 7-42%) of respiratory admissions, were under thoracic physicians; but 59% of asthma, 52% of lung cancer and 34% of respiratory tuberculosis patients were not admitted under thoracic physicians. Thirty per cent (range 15-80%) of admissions under thoracic physicians were for respiratory disease, highest where there were physicians wholly in thoracic medicine, but in some districts no higher than for all physicians. Therefore in all districts only a minority of patients with respiratory disease are admitted under thoracic physicians, and in some districts there is little specialisation of physicians with an interest in thoracic medicine for in-patient work.

Attendance of asthmatic children at accident and emergency departments

S O'HALLORAN, DP HEAF *Royal Liverpool Children's Hospital, Alder Hey, Liverpool* Hospital admissions for childhood asthma have increased markedly in recent years, despite advances in treatment. In 1986, 820 children made 1389 visits to the AED at RLCH Alder Hey for acute asthma. To investigate reasons for repeated attendance, those who came twice or more in 12 months were assessed by questionnaire and, in those > five years, interval lung function tests (LFTs), and compared with a control group of OPD asthmatics who had not needed emergency treatment for at least 12 months. LFTs showed lower mean FEV_1 (79% vs 84%, $p<0.05$), $Vmax_{75-25\%}$ VC (48% vs 59%, $p<0.01$), $Vmax_{25\%}$ VC (56% vs 70%, $p<0.05$) and $FEV_1/FVC\%$ (75% vs 79%, $p<0.005$) in AED children. Mean change in PEFR was greater on exercise (39% vs 33%, $p<0.05$) and bronchodilator (31% vs 26%, $p<0.02$)

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and the lability index was higher (47% vs 38%, $p<0.02$) in the AED group. Usual attacks were of equal severity, but AED children had worse "worst ever" attacks (34% blue vs 14% OPD, $p<0.05$). There were no differences in treatment; 97% AED, 99% OPD had a bronchodilator at home; 73% AED, 68% OPD took prophylaxis and 11% AED and 12% OPD had a home nebuliser. Parental knowledge was similar. Seventy-three per cent of AED and 71% of OPD parents thought asthma could be fatal, but 71% of AED vs 56% OPD had feared their own child might die ($p<0.05$), and would seek medical help sooner ($p<0.005$). Repeated attendance for asthma is related to greater severity of disease and parental concern, but not to differences in treatment, ignorance or social disadvantage.

Is asthma becoming more severe?

H REA, M SEARS, E MITCHELL, J GARRETT, J MULDER, R ANDERSON *Department of Respiratory Medicine, Green Lane Hospital, Auckland, New Zealand* In 12 of 15 countries studied, asthma mortality (5-34 years) was higher in 1982-84 than in 1979-81. Hospital admissions for asthma are rising and in Auckland Accident and Emergency Department (A and E) use for asthma has doubled in the last decade. These trends may indicate increase in prevalence, severity, or changes in management, e.g. a shift from community to hospital care. If increased hospital use is due to the latter, those reaching hospital now should have less severe disease on arrival. In Auckland with both paediatric admissions and in the A and E department, pulse and respiratory rate are recorded by a nurse as the patient arrives and before any treatment is given. Records have been reviewed. The mean pulse in 182 patients arriving at the A and E department in a 2 month period in 1986 was 114 and the mean respiratory rate 28.7. Corresponding figures for 1979 were 108 ($p=0.076$) and 33 ($p=0.051$). Asthma admissions in 5-14 year olds tripled between 1977 and 1981. Mean pulse (p) and respiratory rates (rr) for all European children admitted were: 1970 — $n=73$, $p=122$, $rr=35$; 1978 — $n=119$, $p=123$, $rr=36$; 1985 — $n=135$, $p=125$, $rr=35$. Since severity on presentation to hospital is unchanged and since the pattern of change with time is so similar in the admissions, A and E department use, and mortality for all races, we believe that our data point to a real increase in the number of severe asthma attacks. Presumably a ubiquitous factor has increased severity.

Mortality rates and hospital activity analyses as performance indicators for a regional thoracic service

PDO DAVIES *Llandough Hospital, Penarth, South Glamorgan* Mortality rates and hospital discharges and deaths by district health authorities are published annually in the *Monitors* of the Office of Population Censuses and Surveys. Data from these publications for Wales for the years 1981 to 1984 have been extracted to provide a measure of extent or respiratory diseases. Comparisons have been made with thoracic consultant staffing in each district to determine how staffing might be made more efficient. For the nine health districts of Wales, mortality rates for respiratory diseases showed a significant correlation with hospital deaths and discharges by place of residence ($r=0.69$, $p<0.02$). Mortality rates were generally higher in districts with a higher ratio of population per chest physician. Mortality rates were also higher in districts where hospital deaths and discharges per chest physician were higher ($r=0.72$, $p<0.05$, one district with no chest physician excluded). Districts where respiratory diseases, as measured by mortality and hospital deaths and discharges, are more prevalent, generally have *fewer* chest physicians per 1000 population. These findings suggest a need for an increase in consultant thoracic staffing in certain districts. Mortality rates and Hospital Activity Analyses gave a similar picture in terms of distribution of respiratory diseases and relevant staffing structures within Wales.

Interaction between phenytoin and antituberculous drugs

D O'REILLY, GS BASRAN, B HOURIHAN, JT MACFARLANE *Department of Thoracic Medicine, City Hospital, Nottingham* In epileptics the interactions between phenytoin and anti-TB drugs are confusing: isoniazid causes potentially fatal phenytoin toxicity in slow acetylators whilst rifampicin increases phenytoin clearances in both slow and fast acetylators. We present the clinical and biochemical data from two cases to remind clinicians of this complex problem and recommend a practical scheme of management to avoid these interactions. The first case was an epileptic stabilised on 300 mg of phenytoin daily who developed progressive drowsiness during the first week of triple therapy with isoniazid, rifampicin and ethambutol. He had a toxic phenytoin level (table) and slowly recovered on withdrawal of this drug. He was subsequently stabilised on only 200 mg of phenytoin daily. On the basis of this experience, when a second stable epileptic was started on triple chemotherapy his dose of phenytoin was intentionally reduced from 300 mg to 200 mg daily. However, three days later he developed seizures and his blood phenytoin levels were low. He required a final dose of 400 mg of phenytoin daily to control his fits and on this dose the blood level was in the therapeutic range. Determination of the acetylator status in each case helped to explain the contrasting pictures.

	Phenytoin dose (initial; mg/d)	*Phenytoin level mg/l*	*Acetylator status*	*Phenytoin dose (final; mg/d)*
Case 1	300	46.1	Slow	200
Case 2	300	8.0	Fast	400

Case one was a slow acetylator (hence isoniazid-induced phenytoin accumulation occurred) whilst case two was a fast acetylator (presumably rifampicin induced phenytoin clearance predominated). To avoid these serious complications in epileptics stabilised on phenytoin the acetylator status should be determined before starting isoniazid.

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Reduced paediatric notifications for tuberculosis: the effect of the introduction of chemoprophylaxis in a high incidence district

LP ORMEROD *The Chest Clinic, Royal Infirmary, Blackburn* In the Blackburn Health District in 1978-81, children accounted for 136/642 (21.2%) of all notified cases of tuberculosis. Following the introduction in November 1981 of prophylactic chemotherapy, paediatric tuberculosis has fallen significantly. Isoniazid (10 mg/kg) and rifampicin (10 mg/kg) were given for a duration of nine months from 1981-83, and for six months from 1984 onwards, to children with Grade three or four positive tuberculin tests seen as new immigrants, contacts, or from school screening. Paediatric cases fell to 55/418 (13.15%) of total cases notified in 1982-86, a fall which is highly significant (χ^2 11.04, $p<0.001$). This effect is due to reduced notifications in the Indian Subcontinent (ISC) ethnic group (χ^2 10.41, $p<0.001$), who made up 80.2% of the children given chemoprophylaxis. The notifications in the white ethnic group were not affected by the introduction of chemoprophylaxis (χ^2 0.59). Few side effects have occurred, and only two of the 339 children given chemoprophylaxis later developed clinical tuberculosis (0.6%). Prophylactic chemotherapy is shown to play an important part in the management of paediatric tuberculosis in a high incidence district. The combination of rifampicin and isoniazid may allow chemoprophylaxis to be given for less than six months.

Changes in tuberculosis notification rates in the white ethnic group in England and Wales between 1953 and 1983

VH SPRINGETT, AJ NUNN, I SUTHERLAND, JH DARBYSHIRE *MRC Cardiothoracic Epidemiology Group, Brompton Hospital, London* Since the early 1960s notification rates for tuberculosis in England and Wales for the whole population have been influenced by high rates in some immigrant groups. Using data by ethnic group from the MRC surveys in 1983 and 1978/79 and by country of birth from the BTS survey in 1971, information on the rates in the white population have been calculated and compared with published rates for the total population for 1953, when only a very small proportion of the population was born abroad. Between 1953 and 1983 the notification rate for the white ethnic group fell from 122.2 to 11.3 per 100 000 for the males, a mean annual rate of decline of 7.7%, the corresponding rates for the females being 90.1 and 5.8, an annual decline of 8.8%. In both sexes the most rapid decline occurred in young adults (age 15-24 years), becoming less with increasing age. Between 1978/79 and 1983 the annual rate of decline was 6.9% for males and 7.3% for females, less than the decline over the whole period 1953-1983, but greater than that for the period 1971 to 1978/79 (5.1% for both sexes). A more rapid fall in notifiction rates in young adults than in the older age groups has led to a different pattern of annual notification rates by age. Thus in 1953 the highest rates occurred in young adults in both sexes. In contrast, in 1983 the highest notification rates were in the oldest age groups. There is no evidence of any cohort showing an increase in notification rate with increase of age.

Is the hyperventilation syndrome simply a manifestation of occult bronchiectasis?

LS HILL, Z THOMPSON, WJ ADAMS *Warwick Hospital, Lakin Road, Warwick* Fifteen patients with classical hyperventilation syndrome were studied prospectively (8M; 7F; ages 17-72, mean age 44). All were non-smokers and non-atopic and had normal full physical examination, plain chest radiography, blood count, biochemistry screen, thyroid function, FEV_1, FVC, carbon monoxide transfer, total lung capacity, and KCO. There was no evidence of asthma on peak flow charts or reversibility studies. The mean resting minute volume from a sixty second tidal trace (wet spirometer) was 14.5 l/minute (range 10.2-18.6 l/minute). Voluntary hyperpnoea reproduced symptoms within twenty five seconds, gave respiratory alkalosis on blood gas analysis, and provoked paradoxical dyspnoea rather than apnoea. All breathed irregularly from the upper chest and did not produce sputum. At bronchography all had bronchiectasis, bilaterally in twelve and in the lingula and left lower lobe in three. Four had involvement of four or more lobes. Although conventional clinical examination failed to detect the pathology, palmar palpation (akin to cardiac thrill detection) was positive in all cases. Conclusions: 1) Hyperventilation may be a manifestation of occult bronchiectasis. 2) Should palmar palpation be adopted as part of the routine examination of the chest as it was the only method of clinical detection of pathology?

How should lung disease be assessed in cystic fibrosis (CF)?

DP HEAF, PR STUTCHFIELD, H DAVIES, DJ MATTHEW, J STROOBANT *Royal Liverpool Children's Hospital, Alder Hey, and Hospital for Sick Children, London* Lung disease is the predominant factor responsible for prognosis in cystic fibrosis. A trend towards regional CF clinics and shared care increases the need for objective assessment of lung disease to compare patients and monitor treatment. Methods of assessing lung disease were compared in 21 CF patients (age 6-15 years) during a clinical trial (Group A) and 24 CF patients (age 5-19 years) during routine clinic assessment (Group B). Lung disease was assessed using Chrispin Norman X-ray score, $\dot{V}/\dot{Q}$ lung scans*, PEFR, FVC, FEV_1/FVC ratio, $\dot{V}max_{25}$*, RV/TLC*, weight/age, height* age and weight/height (*Group A only). In Group A there was a highly significant correlation between X-ray score, $\dot{V}/\dot{Q}$ scan and lung function indices but a poor correlation between these and measurements of weight and height. X-ray and $\dot{V}/\dot{Q}$ scan correlated best with FVC ($r=-0.84$, $p<0.00001$; $r=0.82$ $p<0.0001$) and FEV_1 ($r=-0.84$, $p<0.00001$; $r=0.79$ $p<0.0001$). In Group B there was less significant correlation between radiograph and lung function measurements (FVC $r=-0.49$, $p<0.02$; FEV_1 $r=-0.63$, $p<0.001$). Group A had repeat four-monthly assessments over 18 months. No significant correlations were found between four-monthly changes in X-ray score, $\dot{V}/\dot{Q}$ scan, lung function and weight, but there was a significant correlation between 18 month change in X-ray score and FVC ($r=0.53$, $p<0.05$), and $\dot{V}/\dot{Q}$ scan and FEV_1 ($r=0.78$, $p<0.01$). X-ray score and simple

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spirometry but not weight and height can be used to assess severity of lung diseases in CF patients over five, but may not predict acute changes.

Knowledge of their disease in adults with cystic fibrosis in the Trent region

JC TYRRELL, EJ HILLER, DJ SHALE *Departments of Paediatrics and Respiratory Medicine, City Hospital, Nottingham* In 1986, 102 adults with cystic fibrosis (CF), median age 19 years (range 16-44), were identified in the Trent Region. Of these 86 were interviewed (JT), using a standard questionnaire, about their knowledge and attitudes towards CF. Only 7/86 did not know why they had CF, whilst 43 understood the genetics and were able to quote the correct recurrence risk of their parents having another affected child. In answer to the question "What is cystic fibrosis?" only 19 knew CF could affect more than "the lungs and digestive system". While 74 knew why they took pancreatic supplements only 46 knew why vitamin supplements were necessary. Within this group 42 (21 male, 21 female) were unaware that males are likely to be infertile, including eight men over the age of 20. The effect CF might have on a woman's reproductive ability was unknown to 57/86. Only 11 regarded themselves as too sick to work, with 63 either still in full time education or employment. As more patients survive into adult life in reasonable health it is important that they are given accurate facts about their condition. This study of adult CF patients has demonstrated relatively good knowledge of the basic disease, but a serious deficit regarding fertility in both sexes.

Measurement of nasal potential difference

EWFW ALTON, JO WARNER, DM GEDDES *Brompton Hospital, London* We have previously reported measurements of nasal potential differences (PD) amongst patients with cystic fibrosis (CF) in comparison to normal or "diseased" controls (*Thorax* 1985;**40**:704). The former group show markedly more negative PD than either of the latter, raising the possibility of its use in the diagnosis of CF. We have further modified the technique allowing for easy and rapid measurements in children as well as adults, and greatly increased our experience in terms of patient numbers and diseases. PD was measured along the floor of the nasal cavity using a fine rubber catheter containing electrolyte cream, into which was placed a silver/silver chloride electrode connected to a high impedance voltmeter. Voltages were recorded with reference to a surface electrode placed on the forearm, following abrasion of the epidermal surface with a hand-held skin burr (patent pending for above technique). One hundred and twenty-two normal or "diseased" controls with mean age 34 years (range 3-73) showed a mean PD of -19 mv (-2 to -30 mv) in comparison to 54 patients with CF of mean age 17 years (2-37) and PD -46 mv (-33 to -77mv). Of the above, 29 CF children aged 2-16 showed a mean PD of -47 mv and eight asthmatic children aged 2-16 a mean of -21 mV. We conclude that with the above improvements this technique is now easily applicable to children as well as adults. The investigation retains the discrimination previously reported following a total of 176 subjects tested, and may have a place alongside established techniques in the routine testing of CF.

The radiographic features of pneumonia in the community

MA WOODHEAD, JT MACFARLANE, JS MCCRACKEN, DH ROSE *Departments of Thoracic Medicine and Radiology, City Hospital and Department of General Practice, University of Nottingham* From 1 October 1984, for one year, 236 adults with pneumonia (defined as a lower respiratory tract infection associated with new focal signs on chest examination) presenting to 29 general practitioners were studied in detail. An acute chest radiograph was performed in all but two cases (96% within seven days of initial consultation). Ninety-two per cent were performed in the hospital radiology department and 8% by domiciliary visit. Fresh radiographic shadowing (FRS) was present in 93 (39%). Only two without FRS developed such changes on later radiographs. Of those with FRS the right lung (59%) was affected more often than the left (41%), with one lobe affected in 81%, two lobes in 17% and three in 2%. FRS was usually patchy (62%). Extension of FRS occurred in only eight (9%) and radiographic complications were uncommon, with pleural effusion in six collapse in six and cavitation in one. A number of clinical and laboratory features were significantly associated with FRS, but only leucocytosis, neutrophilia, lymphopenia and a CRP level > 100 mg/l remained after stepwise discriminant analysis. Radiographic clearing was slow with 66% still showing changes at two and 32% at six weeks. FRS in patients with pneumonia in the community is seldom extensive and usually uncomplicated, but slow to clear.

Antibody response to Bordetella pertussis antigens

PC SEDDON, P NOVOTNY, CA HART, CS SMITH *Departments of Child Health and Microbiology, Royal Liverpool Children's Hospital, Alder Hey, and Wellcome Biotech Laboratories, Kent* We have conducted a prospective survey of 46 consecutive cases of pertussis-like illness in children admitted to the Royal Liverpool Children's Hospital, Alder Hey. Routine clinical and laboratory data were collected. In addition acute (within two weeks of onset of coughing) and convalescent (after two weeks of illness) sera and salivary samples were collected. Using an enzyme linked immunoassay (ELISA) we have measured antibody levels (IgM, IgG, IgA) to four *Bordetella pertussis* antigens (LPF — lymphocytosis promoting factor; LPS — lipopolysaccharide; 69 kilodalton protein; and FHA — filamentous haemagglutinin). Ten patients had pertussis confirmed by culture. Of these, six had both acute and convalescent sera taken: all showed rising IgG antibody titre, and four showed acute IgM antibody, to one or more antigens. Seven culture positive cases had saliva collected, four showed IgA antibody to one or more antigens. Twenty-nine patients had pertussis diagnosed clinically. All 13 where acute and convalescent sera were available showed

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rising IgG antibody titre to one or more antigen. Ten of 21 saliva samples showed IgA antibody to one or more antigens. It appears that the measurement of salivary IgA antibody to *Bordetella pertussis* antigens may prove a useful tool for studying the sero-epidemiology of pertussis.

Are enteric-coated microspheres of pancreatin more effective than non-enteric-coated pancreatin with cimetidine in cystic fibrosis?

RJ STEAD, I SKYPALA, ME HODSON *Brompton Hospital, Fulham Road, London* Inactivation of pancreatin by low pH contributes greatly to persistent malabsorption in cystic fibrosis (CF). Enteric-coating reduces inactivation, enteric-coated microspheres of pancreatin (ECMP) being more effective than standard enteric-coated pancreatin. Alternatively intraluminal pH may be increased by H_2 receptor blockade. In an open, randomised cross-over study, ECMP (Creon) were compared with non enteric-coated pancreatin (NECP, Pancrex V capsules) combined with cimetidine (400 mg taken 40 minutes before the three main meals), over two consecutive 28 day periods. Fourteen adults with CF were studied. Lipase intake equalled their previous needs and remained constant throughout. Patients compared diary cards daily, and 72 hour faecal collections at the end of each period. One patient withdrew owing to inability to stabilse her dose of ECMP. Comparing ECMP with NECP/cimetidine, bowel actions were less frequent on ECMP (1.7 vs 2.4/day; $p<0.001$) and stool character was improved ($p<0.001$). Mean daily faecal weight on ECMP (319g) tended to be less than on the combination (451g; $p=0.06$) as did daily faecal fat excretion (20g vs 28g; NS), whereas percentage fat absorption (82% vs 72%; $p=0.06$) tended to be greater. Mean body weight increased 0.3 kg on ECMP and fell 0.1 kg on the combination (NS). The data indicate that ECMP are at least as effective as the combination of NECP and cimetidine in CF and are probably more effective. They are certainly more convenient.

Multiresistant Pseudomonas aeruginosa in patients with cystic fibrosis

CD SHELDON, ME HODSON *Department of Cystic Fibrosis, Cardiothoracic Institute, Brompton Hospital, London* We have followed the clinical progress of 40 patients with cystic fibrosis (CF) whose sputum cultures on one or more occassions grew *Pseudomonas aeruginosa* resistant to ceftazidine, azlocillin, carbenicillin, ticarcillin and piperacillin. Twenty-seven patients had sputum cultures persistently growing a multiresistant *P aeruginosa* over several months and 13 patients had positive sputum cultures once only. At first isolation neither group showed any statistically significant change in PEFR, FEV_1, FVC or body weight when compared with the mean out-patient values over the previous 12 months. Cough, sputum volume and general well-being showed no significant change in either group when compared with the symptoms recorded at the out-patient visit before first isolation of a multiresistant organism. The group whose sputum cultures persistently grew a multiresistant *P aeruginosa* showed no significant difference in the number of days spent as an in-patient in the 12 months before or after infection. There was no significant change in the mean out-patient values for PEFR, FEV_1, FVC or body weight during the period when a multiresistant organism was isolated when compared with the mean out-patient values over the previous 12 months. In these patients with CF, isolated or persistent culture of *P aeruginosa* resistant to β lactam antibiotics was not associated with clinical deterioration.

Pyocyanin from *Pseudomonas aeruginosa* stimulates airway mucus secretion *in vivo*

M SOMERVILLE, P RICHARDSON, H TODD, R WILSON, G TAYLOR, P COLE *Host Defence Unit, Cardiothoracic Institute, Brompton Hospital, London, Department of Physiology, St. George's Hospital Medical School, London, Department of Clinical Pharmacology, RPMS, Hammersmith Hospital, London* *Pseudomonas aeruginosa* may colonise the respiratory tract of patients with cystic fibrosis or severe bronchiectasis, in whom there is a marked increase in mucus production. Wilson *et al* showed that *P aeruginosa* phenazine pigments slowed ciliary beating *in vitro* (*J Clin Invest* 1987;**79**:221) and also noted mucus secretion. We have studied the effect of pyocyanin on mucus secretion in the cat trachea *in vivo*, using ^{3}H-glucose and ^{35}S-sulphate to label glycoproteins (Gallagher *et al, Proc R Soc Lond B* 1975;**192**:49-76). Pyocyanin stimulated the output of radiolabelled glyco-proteins in a dose-dependent manner between the concentrations of 15 and 150 μm. At 50 μm, there was a 50% (SD 6.5%) increase in ^{3}H-labelled glycoproteins ($p<0.001$ cf. control) and a 20.5% (9.8%) increase in ^{35}S-labelled glyco-proteins ($0.1>p>0.05$). The increases at 150 μm were 348% (32%) ($p<0.001$) and 119% (33.8%) ($p<0.02$) respectively. As concentrations of pyocyanin similar to the above have been found in sputum sols from the respiratory tract of patients with cystic fibrosis (Wilson *et al, J Clin Invest* 1987;**79**:221), these results suggest that pyocyanin may have a significant role in stimulating mucus production in the respiratory tract of patients colonised by *P aeruginosa*.

Assessment of the efficacy of intramuscular and intravenous replacement therapy in patients with adult onset hypogammaglobulinaemia

ND GARBETT, DC CURRIE, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* Patients with hypogammaglobulinaemia suffer from chronic and/or recurrent acute sinopulmonary infection. In order to reduce the incidence and severity of these infections, patients are given immunoglobulin (Ig) replacement therapy. Although it is now generally believed that intravenous (IV) replacement is superior to intramuscular (IM), there is no proof of this. An important purpose of substitution therapy is to enhance the opsonic activity of the patient's serum, since opsonisation is necessary for efficient phagocytosis. We have used an *in vitro* neutrophil chemiluminescence

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(CL) assay to follow the *in vivo* replacement of Ig via both IV (Intraglobin-F, Biotest; 300mg/kg/4 weeks) and IM (Lister, Elstree; 25mg/kg/week) routes in 10 patients. The opsonic activity for *Haemophilus influenzae* (non-capsulated) and *Streptococcus pneumoniae* of sera obtained pre-treatment and after six months' regular replacement was measured. Results were expressed % CL of that obtained with control pooled serum. There was no significant difference between IM(mean 42 (SEM 5); 66 (5)) and four-weekly IV(48 (7); 68 (7)) replacement. However, in a subgroup of patients treated IV at three-weekly intervals there was a significant improvement in opsonisation of both organisms ($p<0.01$). This difference was even more significant in sera collected one and two weeks post-infusion. We conclude that IV infusions of Intraglobin F produce significant *in vivo* opsonic activity, the magnitude depending on the interval between infusions. These results support the view that IV replacement is superior to IM.

Culture of bronchopulmonary samples in the diagnosis of legionella pneumonia

J DORCA, J BOADA, G RUFI, R VERDAGUER, F GUDIOL, F MANRESA *Hospital de Bellvitge. Universitat de Barcelona. Spain* Since July 1985 selective culture medium for *Legionella pneumophila* (BCYE-alfa) has been available in our hospital. During this time, *L pneumophila* pneumonia has been diagnosed in 48 cases, either by culture, serology or both. The purpose of this study was to analyse the reliability of the culture of different respiratory samples in the diagnosis of these patients. Among the 48 cases, 34 were community acquired, and 14 nosocomial. In 19 cases the patient was considered to be severely immunosuppressed. The results obtained by the different techniques are shown:

SAMPLE	*COLLECTED IN*	*POSITIVE IN*
*Sputum or tracheal aspirate culture	33/48	22(66.6%)
*Transthoracic needle aspiration culture	35/48	27(77.1%)
*Bronchoscopic samples culture	13/48	8(61.5%)
*Pleural fluid culture	3/48	2(66.6%)
*Serology	33/48	31(93.9%)

At least one sample was cultured in 45 cases, and *L pneumophila* was isolated in 40 (88.8%). Lung aspirates appeared to be the most reliable way to isolate *L pneumophila,* but it is important to point out that a less invasive approach (sputum or tracheal aspirate culture) was successful in 66.6% of cases. A complete serology could only be obtained in 33 of our 48 patients, and was positive in 31 (93.9%). The culture of respiratory samples is a highly reliable method, and should be the diagnostic procedure of choice in high risk patients.

Amoxycillin and amoxycillin and probenecid treatment in patients with bronchiectasis

MB ALLEN, R FITZPATRICK, A BARRAT, RB COLE *City General Hospital, Stoke on Trent* High dose amoxycillin (3g bd) is effective in the management of patients with daily purulent sputum due to bronchiectasis, improving general well being and spirometry while reducing sputum elastase concentrations. Long term treatment may prevent disease progression but would be relatively expensive, approximately £1540 per patient, per annum. Probenecid is a cheap drug which blocks renal amoxycillin secretion and produces a two-four fold increase in serum antibiotic concentration (R Barbhaiya, *Brit J Venereal Dis* 1979;55:211-3). Probenecid used in conjunction with a smaller dose of amoxycillin may produce the same pharmacological and clinical benefit but reduce the cost by £524 p.a. To determine the efficacy of such a regimen five patients, mean age 51.3 years (range 40-74), with long standing daily purulent sputum were studied. Each received in a randomised double blind, cross over design, with a one week washout period, either amoxycillin 3g bd (as capsules) (Regimen A) or amoxycillin 1g bd plus probenecid 1g bd (Regimen B). After one week's treatment they were assessed clinically and blood was taken for amoxycillin bioassay. Both regimens produced symptomatic benefit, with reduction in volume and purulence of sputum, although two patients felt nauseated when taking probenecid. Pharmacokinetic profiles for each regimen, calculated from the serum amoxycillin levels, were similar. Mean trough A = 1.73 μg/ml, B = 2.72 μg/ml and mean half life A = 2.3 hours, B = 2.96 hours. Both regimens were effective clinically and pharmacologically; thus the use of probenecid allows a saving of £1000/patient p.a.

Chest wall mechanics and pattern of breathing during exercise hyperpnoea during induced bronchoconstriction

W KELLY, D DODD, D COTTON, J WHEATLEY, LA ENGEL *Thoracic Medicine Unit, Westmead Hospital, Sydney, Australia* To determine the manner in which patients with bronchial asthma meet the increased ventilatory demands of exercise, we studied six asthmatics immediately after exercise (Ex) at 50% of the predicted maximal work rate on a bicycle ergometer, before and during bronchoconstriction (BC) induced by aerosolised histamine. Inspiratory muscle pressures (Pmus) were measured by relating oesophageal pressure during 5-6 breaths to the chest wall relaxation curve. Maximal inspiratory muscle pressures (Pmax) were measured at different lung volumes. End-expiratory lung volume (FRC) was inferred from inspiration to total lung capacity (TLC) after each run.

	FEV_1 (%P)	$\dot{V}_E$ (l/min)	VT (l)	FRC (%TLC)	Pmus/ Pmax	Ti/ Ttot	TT Pmus
Ex	81.0	29.8	2.01	53.0	0.12	0.460	0.05
(mean (SD))	(5.0)	(2.7)	(0.22)	(2.9)	(0.02)	(0.01)	(0.01)
ExBC	38.0	30.4	1.01	71.5	0.34	0.380	0.13
(mean (SD))	(2.0)	(2.7)	(0.16)	(3.3)	(0.05)	(0.03)	(0.02)
	*	NS	*	*	*	*	*

*$p<0.02$.

On ExBC the ratio of inspiratory to total cycle duration (Ti/Ttot) was lower and FRC increased by 5% TLC above resting value. The pressure-time index (TTPmus = Pmus/Pmax. Ti/Ttot) was substantially elevated during ExBC. Our results indicate that in severe induced asthma increased

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ventilatory demands of exercise are met by hyperinflation and relatively rapid, shallow breathing with reduction of the duty cycle. Nevertheless, the high Pmus/Pmax and TTPmus levels suggest that inspiratory muscles may be exposed to fatiguing loads.

Prevention of abnormal pulmonary mechanics in the postmortem guinea pig lung

AM REYNOLDS, RD MCEVOY *Department of Thoracic Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia* A phenomenon of severe postmortem bronchoconstriction has been shown previously in guinea pig lungs and linked to pulmonary blood loss during exsanguination (*J Appl Physiol* 1984;**56**:308-314). We have reexamined this phenomenon by measuring postmortem airway function in 46 anaesthetized, open-chest guinea pigs following circulatory arrest. In control (C) animals the lungs were immediately removed and allowed to deflate and relaxation gas volume (Vrx) determined. The remaining animals were ventilated for 15 minutes postmortem with different gases: Group 1 (Gr1) room air; Gr2 5%CO_2 in air (dry, room temp); Gr4 5%CO_2 in air (heated and humidified). Airway pressure was continuously monitored to calculate dynamic compliance (Cdyn). After 15 minutes Vrx and wet to dry weight ratios (W:D) were determined. The results (mean (SEM)) were as follows:

Gr	*n*	*% ΔCdyn (15 min.)*	*Vrx/g dry lung*	*W:D*
C	6	—	2.42 (0.42)	5.09 (0.08)
1	10	−50 (5)*	4.07 (0.42)**	4.88 (0.10)
2	10	−45 (3)*	5.05 (0.39)**	5.07 (0.22)
3	10	−31 (3)*	2.51 (0.38)**	4.58 (0.11)
4	10	−8 (2)	2.95 (0.20)	5.22 (0.11)

*p<0.05 cf Gr4; **p<0.05 cf C.

The addition of CO_2 to the inspirate prevented gas trapping and attenuated the fall in Cdyn. Lung cooling and dehydration may also contribute to the fall in Cdyn seen in Gr3. When the inspirate was conditioned (Gr4) the fall in Cdyn was almost eliminated. We conclude that marked abnormalities in airway function occur postmortem in air ventilated lungs. These changes occur in the absence of pulmonary blood loss and appear to be due mainly to airway hypocarbia.

Flow limitation and mechanisms of hyperinflation in bronchial asthma

JR WHEATLEY, PD PARE, LA ENGEL *Thoracic Medicine Unit, Westmead Hospital, Sydney, Australia* To study the mechanism of hyperinflation in bronchial asthma we induced bronchoconstriction in five asthmatics in remission who inhaled methacholine aerosol until their FEV_1 reached $< 50\%$ of the control value. We measured inspiratory pulmonary resistance (R_L) during tidal breathing, followed by a forced expiration from tidal end-inspiration to residual volume and an inspiration to total lung capacity (TLC). We compared the flow at mid-tidal volume during quiet breathing (V_T) with the isovolumic maximal flow (Vmax), and calculated the hyperinflation (ΔFRC) by reference to TLC. From an assumed respiratory system compliance (0.125 l/cm H_2O) and the R_L we calculated the respiratory time constant in each subject, predicted the time (T_p) for passive expiration of the tidal volume, and compared it with duration of expiration (T_E). At a mean R_L of 41 (SD 15) cm H_2O/l/s (at 0.5 l/s) and an FEV_1 of 45% (11%) predicted, Δ FRC was 1.1 (0.2) l but V_T/Vmax was only 0.73 (0.10) and the T_E/T_p ratio was 2.7 (0.6). The results indicate that in severe induced asthma substantial hyperinflation may be present without expiratory flow limitation and with adequate time for passive lung deflation. We conclude that other mechanisms, e.g. persistent inspiratory muscle activity and/or expiratory glottic braking, must determine the degree of hyperinflation even in severe induced asthma.

The effect of indomethacin on the hyperinflation induced by continuous positive airway pressure breathing (CPAP) in man

CJ DUGGAN, R SIMMUL, N BEREND *Department of Thoracic Medicine, Royal North Shore Hospital, St. Leonards, N.S.W., Australia* We have previously shown in dogs that the cyclooxygenase inhibitor Indomethacin (I) reduces the hyperinflation produced by positive end expiratory pressure breathing (PEEP) (*Am Rev Respir Dis* 1982;**126**:646). We hypothesized that PEEP induced release of a prostaglandin which dilated alveolar ducts. Administration of cyclooxygenase inhibitors has recently been shown to be beneficial in an animal model of ARDS (*J Clin Invest* 1983;**72**:63). However, since the improvement in oxygenation following PEEP in patients with ARDS is directly related to the increase in functional residual capacity (FRC), administration of I may be counterproductive. We therefore examined the effects of CPAP and I on lung volume in man. Ten normal subjects had FRC determined in a constant volume plethysmograph by the Boyle's law method. CPAP at 5 and 10 cm H_2O was then applied via a bias flow system for five minutes each. At the end of each five minute period, FRC was remeasured without removing CPAP. After a further five minutes off CPAP the measurements were repeated. The subjects then took I 75 mg tds for three days after which the above protocol was repeated. One week or more later the protocol was repeated for a third time. The mean (SEM) FRCs (l) are shown below.

	Baseline	*5cm CPAP*	*10cm CPAP*	*Post CPAP*
Day 0	4.0 ± 0.2	5.3 ± 0.2	5.8 ± 0.4	3.9 ± 0.2
Day 3	4.0 ± 0.2	5.0 ± 0.3	5.1 ± 0.3*	3.9 ± 0.3
Day 10+	4.2 ± 0.1	5.0 ± 0.3	5.2 ± 0.3*	3.8 ± 0.1

*Significantly different from Day 0, p<0.01.

We conclude that I reduces the hyperinflation induced by CPAP breathing in man and this needs to be considered when such treatment is advocated for ARDS.

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The non-invasive assessment of the acute effects of oxygen breathing in patients with hypoxaemic chronic obstructive pulmonary disease (COPD)

JM HUNT, RJ PIERCE, CE BARTER, PD ROCHFORD *Department of Thoracic Medicine, Repatriation General Hospital, Heidelberg West, Victoria, Australia* In patients with hypoxaemic COPD receiving long-term domiciliary oxygen, those who demonstrate a brisk fall in pulmonary artery pressure (PAP) in response to *acute* oxygen (O_2) breathing have a distinct survival advantage over those who do not. To be able to predict this survival advantage non-invasively has important clinical implications. The effects of a acute O_2 breathing were assessed by both invasive and non-invasive means in 17 patients with severe stable hypoxaemic COPD with the following baseline characteristics (mean (SD)): age 69 (6) years, FEV_1 26% (10%) predicted, Pao_2 53 (4) mm Hg, $Paco_2$ 45 (9) mm Hg. The non-invasive measurements (dead space/tidal volume ratio (Vd/Vt), effective pulmonary capillary blood flow estimated by re-breathing and single-breath soluble gas uptake ($\dot{Q}_{RB}$, $\dot{Q}_{SB}$), left ventricular ejection fraction (LVEF), and echocardiography) were comapred with right heart catheter measurements of PAP, thermodilution cardiac index ($\dot{Q}_{TD}$) and pulmonary vascular resistance (PVR). The group changes were as follows (mean (SD)):

	AIR	*100% O_2 for 20 min*	*28% O_2 for 24 hours*
PAP (mmHg)	28.8 (8.1)	24.1 (7.5)*	24.9 (7.6)*
PVR dyne/sec/cm^5	415 (179)	389 (170)**	376 (184)
$\dot{Q}_{TD}$ (l/m^2)	2.78 (0.54)	2.43 (0.46)*	2.61 (0.68)
$\dot{Q}_{RB}$ (l/m^2)	1.74 (0.49)	1.43 (0.39)*	1.50 (0.36)*
$\dot{Q}_{SB}$ (l/m^2)	1.44 (0.39)	1.18 (0.60)	1.64 (0.70)
Vd/Vt	0.58 (0.07)	0.62 (0.06)*	0.58 (0.05)

*Denotes significant change from baseline: ($p<0.05$; **$0.1>p>0.05$)

LVEF did not change significantly. Coefficients of variability for $\dot{Q}_{TD}$, $\dot{Q}_{RB}$, $\dot{Q}_{SB}$ and Vd/VT were 4.8, 17.3, 31.0 and 3.0% respectively. Following 100% O_2 the fall in PAP was significantly correlated with the fall in Q_{RB} but not with the fall in $\dot{Q}_{SB}$ or the rise in Vd/VT. We have determined that cardiopulmonary responses to acute O_2 breathing can be measured non-invasively. The variability of these tests in severe COPD may limit their ability to predict long term survival in individual patients receiving domiciliary O_2 therapy.

Effect of gas compression artefact on forced expiratory flows

RE HYATT, MJ KROWKA, PL ENRIGHT, JR RODARTE (SPONSORED BY N PRIDE) *Division of Thoracic Diseases, Mayo Clinic, Rochester, MN, U.S.A.* The American Thoracic Society recommends that the largest one second forced expiratory volume (FEV_1) be reported from a set of forced expiratory vital capacity manoeuvres. However, increased expiratory effort can decrease the FEV_1. Peak expiratory flow rate (PEFR) was evaluated as an index of expiratory effort and was positively correlated with effort estimated by an oesophageal balloon. We then measured the difference ($dFEV_1$) between the largest FEV_1, using ATS standards, and the FEV_1 from the manoeuvre with the highest PEFR in 10 normal subjects and 10 patients with mild to moderate airway obstruction. The mean $dFEV_1$ was 110 ml in normals and 200 ml in patients. We also reviewed 9471 spirometry sessions from outpatients and found $dFEV_1$ to be greater than 50 ml in 26% of this population and greater than 151 ml in 7%. We conclude that FEV_1 is inversely dependent on effort. Maximal effort decreases FEV_1 because of the effect of thoracic gas compression on lung volume. We recommend that values from manoeuvres with submaximal effort (decreased PEFR) be discarded. The flow-volume curve display of superimposed efforts facilitates the recognition of submaximal efforts.

Gas exchange and oxygen cost of breathing in patients with chronic airways obstruction

C LANIGAN, J PONTE, J MOXHAM *Departments of Thoracic Medicine and Anaesthesia, Kings College School of Medicine and Dentistry, London* The work of breathing in patients with severe chronic airways obstruction (CAO) is increased even at rest, and might translate into higher resting total oxygen consumption values ($\dot{V}o_2$). Few published data exist on the magnitude of this increase in $\dot{V}o_2$. We measured resting $\dot{V}o_2$, carbon dioxide production ($\dot{V}co_2$) and respiratory quotient (RQ) over 10 minutes by an open canopy system (Hughes *et al, J Physiol* 1985;371:233P) in 13 patients with CAO (mean FEV_1 0.78 l, VC 2.1 l, % predicted values = 30.9% and 61.9%) and 13 age, weight and height matched controls. Mean RQ values were identical in the two groups; average $\dot{V}o_2$ and $\dot{V}co_2$ were higher in patients, and statistically different when corrected for body surface area (BSA) (see table). The severity of airflow obstruction was poorly correlated with gas exchange data. We conclude that the average increase of 11% in $\dot{V}o_2$/BSA in patients reflects the burden imposed on their respiratory muscles and their increased oxygen cost of breathing at rest.

	$\dot{V}O_2$	$\dot{V}CO_2$	*RQ*	$\dot{V}O_2$/BSA*
Controls	205 (30.9)	169 (29.9)	0.82 (0.03)	119 (12.5)
Patients	223 (49.1)	184 (43.2)	0.82 (0.04)	132 (17.7)**

*Mean (SD) $\dot{V}O_2$, $\dot{V}CO_2$ ml min^{-1} STPD; BSA m^2. **$p<0.05$

Dose-dependent fall in trapped gas volume in "irreversible" chronic obstructive airways disease treated with oral theophylline

H CHRYSTYN, BA MULLEY, MD PEAKE *Pontefract General Infirmary and University of Bradford, W. Yorks* We have shown that in chronic obstructive airways disease (COAD) trapped gas volume (VT_rG, i.e. the *difference* between total lung capacity measured by body plethysmography and helium dilution) falls acutely after theophylline administration (Chrystyn *et al, Thorax* 1986;41:722). In the present study 33 patients (mean age 61.2 years) with COAD and $\leqslant$ 15% improvement in forced expiratory volume in one second (FEV_1) after inhaled bronchodilators were treated for four randomly ordered eight week periods with placebo and three different individualised doses of oral

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theophylline, the highest giving a steady state serum concentration of 18.3 (0.39) mg/l (mean (SEM)). FEV_1, forced and slow vital capacities (FVC, SVC), peak expiratory flow rate (PEFR), VT_rG and six-minute walking distance (WD) were measured before and after each treatment. There were significant ($p \leqslant 0.01$) dose-dependent improvements in all the variables. Comparison of values at the end of the placebo period with those at the end of the highest dosage period showed the changes to be as follows:- FEV_1 +0.13 l (13%), FVC +0.33 l (13.5%), SVC +0.62 l (24.5%), PEFR +17.7 l/min (12.5%), VT_rG −1.16 l (63%) and WD +57 m (20%). Thus large falls in the VT_rG and improvements in WD (and SVC) can occur in COAD following chronic theophylline therapy despite minor improvements in FEV_1 and PEFR.

Changes in regional lung ventilation may explain the hypoxaemia of histamine induced bronchoconstriction

KF WHYTE, M IP, AL MUIR, DC FLENLEY *Rayne Laboratory, Department of Respiratory Medicine, University of Edinburgh, City Hospital, Edinburgh* In 10 chronic stable asthmatics (9M, 1F; 27-61 years, initial FEV_1 54-97% predicted) we measured FEV_1, Sao_2, tidal volume (Vt), functional residual capacity (FRC) and minute ventilation ($\dot{V}e$) before and during bronchoconstriction induced by inhaled histamine (Yan *et al, Thorax 1983;***38:**760-765) so as to reduce Sao_2 by 4% or FEV_1 by 30%. We simultaneously measured regional Vt and regional FRC in three zones (upper, middle and lower) of each lung by a respiratory gated ^{127}Xe ventilation scan as changes in lung geometry during tidal breathing were corrected by recording of ^{99m}Tc counts from labelled MAA previously lodged in lung capillaries (Muir *et al, Nuc Med Com* 1985;**6:**127-139) whilst the subject breathed into a computer linked closed circuit spirometer. Regional ventilation was measured over six minutes before and immediately after histamine challenge. FEV_1 fell 0.45-1.87 l as Sao_2 fell by 0-4%, $\dot{V}e$ rose in seven subjects but fell in three, whereas FRC rose in all with histamine. The variability in regional Vt/regional FRC of the six zones within each subject was exaggerated in every patient by the histamine challenge. The bronchoconstriction induced by histamine inhalation in chronic asthmatics is not uniform throughout the bronchial tree, even within the same subject. This variable change in regional ventilation in response to histamine will increase $\dot{V}/\dot{Q}$ variance and may cause hypoxaemia following histamine, if this is not overcome by an increase in overall alveolar ventilation.

Interactions between swallowing and respiration in normal man

J MOORE-GILLON, P WILKINSON, V MOORE-GILLON, R RUDD *The London Chest Hospital, London; *Professorial Unit, Royal National Throat, Nose and Ear Hospital, London* There is little information regarding the relationships between swallowing and breathing in normal adults. We investigated eight healthy subjects (four male, four female), all unaware of the purpose of the study. Respiration was monitored by repiratory impedance plethysmography and swallows by bursts of activity recorded by electromyographic electrodes placed submentally. Subjects were seated reading, in a quiet room. After a 10 minute run-in period swallowing and respiration were recorded for 20 minutes. One hundred and twenty-three spontaneous swallows were recorded. Only 10 (8%) occurred during inspiration; after swallowing these breaths were terminated and followed by expiration rather than resumption of inspiration. Forty-seven swallows (38%) occurred during expiration and were followed by completion of expiration. Sixty-six swallows (54%) occurred at end expiration, and were followed by a pause at FRC before the next inspiration was initiated. Spontaneous swallowing occurs predominantly during expiration or at end expiration; whatever the phase of the respiratory cycle, swallowing appears never to be followed immediately by an inspiratory effort. We suggest this may help protect the tracheobronchial tree against aspiration of residual matter in the hypopharynx.

How often does response to salbutamol go unobserved in chronic airflow limitation?

D ROGERS, MDL MORGAN *East Birmingham Hospital* Although the value of the knowledge of the bronchodilator response in chronic airflow limitation (CAL) may be questioned, it is often sought by repeating the FEV_1 FVC or PEFR after a few minutes. To understand how often a significant response may go unobserved by this practice we have examined the incidence and distribution of bronchodilator response in 132 patients with CAL on eight measurements derived from the flow volume loop, 15 minutes after 5 mg of nebulised salbutamol. These measurements were FEV_1 FVC, PEFR, $\dot{V}_{50}$, $\dot{V}_{75}$, MMEFR (maximum mean expiratory flow rate derived from area under expiratory F/V curve ÷ by FVC), PIFR, MMIFR (area under inspiratory curve ÷ IVC). In addition three flow/volume loops from 10 subjects without CAL were examined for reproducibility and to set a level for significance. The coefficient of variation in the non-CAL subjects ranged from 1.2% ± 0.9 (FEV_1) to 10.0% ± 5.3 (MMIFR). One hundred and thirteen (86%) patients with CAL had an improvement of $\geqslant$ 20% in one or more measurements after salbutamol, including 11 patients who only had an inspiratory response. We conclude that a response to salbutamol can be demonstrated by flow/volume loop in most patients with CAL. However, only 29 (25.7%) of these would be identified if the FEV_1 and FVC were used and only 29 (25.7%) if the PEFR were used alone.

Gas transfer in diabetes mellitus

DC WEIR, PE JENNINGS, MS HENDY, AH BARNETT, P SHERWOOD BURGE *Department of Thoracic Medicine and Academic Department of Diabetes, East Birmingham Hospital, Birmingham* There is conflicting evidence about the effect of diabetes mellitus (DM) on lung function. Recent evidence suggests that gas transfer is reduced in insulin

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dependant diabetes (Sandler Metal *Am Rev Respir Dis* 1987;135:223-229). The reduction was not correlated with the presence of complications of diabetes elsewhere. We have examined this by comparing lung function in a group of uncomplicated diabetics with a matched group of complicated diabetics. Complications were defined as proliferative retinopathy, or maculopathy, or proteinuria or background retinopathy plus an increased urinary albumin excretion rate. Nine pairs (six male, three female) matched for age and sex were assessed. All were current non-smokers and had no unrelated cardiorespiratory disease. Spirometry and single breath carbon monoxide gas transfer were measured on all subjects. Helium dilution lung volume estimations were performed on 16 subjects. (Two complicated subjects refused). The transfer factor was corrected for haemoglobin concentration. There was no significant difference in FEV_1, FVC, total lung capacity, residual volume or functional residual capacity between pairs. The TLCO, however, showed significantly lower levels in complicated subjects (as % predicted mean (SD): uncomplicated 111.7 (10.2); complicated 103.9 (15.5) ($p<0.05$). The absolute value of TLCO/VA (KCO) showed a similar reduction: uncomplicated 1.75 (0.21); complicated 1.55 (0.18) mmol min^{-1} $kPa^{-1}.1^{-1}$ ($p<0.02$). The results suggest that lower measures of gas transfer in diabetics are associated with complications elsewhere.

Diaphragm weakness in Charcot Marie Tooth disease

CM LAROCHE, J MOXHAM, NN STANLEY, RJ COURTENAY-EVANS, M GREEN *Lister Hospital, Stevenage, Herts, Mayday Hospital, Croydon, Surrey, and Brompton Hospital, London* Charcot Marie Tooth disease refers to a group of inherited neuropathies, usually associated with a normal life span. Respiratory muscle weakness has not been described. We report two men with this disease who developed severe diaphragm weakness. Both had a severe generalised, mainly motor, neuropathy affecting all four limbs, with some loss of touch and vibration sense in the legs. They had become moderately breathless on exertion, associated with paradoxical abdominal motion and discomfort lying flat. Chest radiograph showed progressive elevation of both hemidiaphragms. Lung function tests showed a restrictive defect with a reduced total lung capacity, normal residual volume, reduced TLCO but normal KCO. Resting blood gases were normal. Inspiratory mouth pressures were very low (24% and 34% predicted), whereas expiratory mouth pressures were only moderately reduced. Transdiaphragmatic pressure (Pdi) was very low during a maximal inspiration against a closed airway (22.5 and 15 cm H_2O, normal >44), and during a maximal sniff without a noseclip (17.5 and 23.5 cm H_2O, normal >100). We conclude that diaphragm weakness can occur in Charcot Marie Tooth disease but, because of the motor disability, dyspnoea is only apparent when the patient is lying supine or when diaphragm weakness is particularly severe. Clincally unsuspected diaphragm weakness in these patients may predispose them to respiratory complications.

Respiratory pressure partitioning during quiet inspiration in unilateral and bilateral diaphragmatic weakness

DR HILLMAN, KE FINUCANE *Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Nedlands, Western Australia* To compensate for diaphragm (D) weakness, intercostal/accessory (I/A) muscles (mm) may be recruited in inspiration and/or abdominal mm in expiration with relaxation during subsequent inspiration. These changes should increase the ratio of abdominal to pleural pressure change during quiet inspiration ($\Delta Pab/\Delta Ppl$ (qi)), which is normally <-1. To examine the relationship between degree of D weakness and $\Delta Pab/\Delta Ppl(qi)$, we measured (erect) Ppl, Pab and transdiaphragmatic pressure (Pdi) (balloons) during quiet inspiration (qi), maximum inspiration (mi) and maximum inspiratory effort at FRC in 10 subjects with bilateral and eight with unilateral D weakness. Δ Pdi during mi (ΔPdi(max)mi) was low in all subjects (12.4 (10.2) cm H_2O (mean (SD)), normal >25), as was Δ Pdi during maximum inspiratory effort at FRC (ΔPdi(max)FRC) (27.4 (19.3) cm H_2O, normal >60). Δ Pab/Δ Ppl was increased in all subjects (0.28 (0.7), normal <-1) and was closely correlated with both Δ Pdi(max)mi ($r=-0.89$, $p<0.001$) and Δ Pdi(max) FRC ($r=-0.76$, $p<0.001$). There was extensive overlap in the data between unilateral and bilateral D weakness. The ratio of Δ Pdi during quiet inspiration to Δ Pdi(max)FRC was 0.16 (0.11) and no subject exceeded 0.31. The results suggest that $\Delta Pab/\Delta Ppl$ is a useful index of the degree of D weakness and that unilateral weakness has functional implications for quiet inspiration not rigidly separable from bilateral weakness. That the ratio of Δ Pdi during quiet inspiration to Δ Pdi (max)FRC was always less than the threshold for fatigue (0.4) suggests that recruitment of I/A and abdominal muscles allows ventilation to be maintained without development of diaphragm fatigue.

Effect of lung inflation on airway function after induced bronchoconstriction in normal and asthmatic subjects

JR WHEATLEY, PD PARE, LA ENGEL *Thoracic Medicine Unit, Westmead Hospital, Sydney, Australia* To study the bronchodilating influence of a deep inspiration (DI) on airway function, we induced bronchoconstriction with doubling doses of methacholine in five normal subjects and five asthmatics in remission. At each dose pulmonary resistance (R_L) was measured during tidal breathing followed by a partial (p) forced expiration from end-inspiratory volume to residual volume (RV_1), inspiration to total lung capacity and complete (c) forced expiration to RV (RV_2). Isovolumic maximal expiratory flow ($\dot{V}max$) was measured at each dose during the partial ($\dot{V}max_p$) and complete ($\dot{V}max_c$) expirations. Both groups of subjects reached an R_L of 6-11 cm H_2O/l/s (at 0.5 l/s) and $\dot{V}max_c$ of 0.15-0.70 l/s, allowing comparison of flows and RVs.

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Mean (SD):	$Vmax_p$ *(l/s)*	$\dot{V}max_c$ *(l/s)*	RV_1*(%)*	RV_2*(%)*
Normals	0.49 (0.11)	1.86 (0.22)*	132 (8)	105 (1)*
Asthmatics	0.57 (0.09)	0.92 (0.13)* **	126 (7)	116 (3)**

*p 0.05 relative to $\dot{V}max_p$ or RV_1; **p 0.02 relative to normals. RV_1 and RV_2 as % of RV_2 baseline.

For equivalent R_L values, maximal flows were similar for normals and asthmatics and both groups had a DI bronchodilating effect. The amount of gas trapping was also similar in the two groups. However, in normals this was fully reversed by a DI, whereas in asthmatics the DI had no significant effect. Our results suggest a relatively smaller degree of reversibility of the peripheral airways in response to a deep inspiration in asthmatics.

The role of the parasympathetic nervous system in nocturnal asthma

JFJ MORRISON, SB PEARSON *Pulmonary Function Laboratory, Killingbeck Hospital, Leeds* Increased vagal tone at night has been implicated in the aetiology of nocturnal asthma. In this study vagal activity was blocked using intravenous (iv) atropine at the time of maximal bronchoconstriction (4 a.m.) in 10 sleeping asthmatics (diurnal variation in PEFR > 20%). A dose-response study revealed the optimal dose of iv atropine to be 30 μg/kg. Subjects were admitted for one day's acclimatisation, and were studied at 4 a.m., immediately after being awoken, and at 4 p.m. on two successive days being randomly given atropine or placebo 30 minutes prior to PEFR measurements. Inhaled beta-agonists or anticholinergic drugs were omitted eight hours prior to the study. Plasma adrenaline was sampled immediately before PEFR measurement.

Mean (SEM)	*ADRENALINE (nmol/l)*		*PEFR (l/min)*	
	AM	*PM*	*AM*	*PM*
PLACEBO	0.13 (0.02)	0.36 (0.08)	266 (44)	403 (42)
ATROPINE	0.14 (0.03)	0.37 (0.03)	393 (48)	438 (45)

There was a significant diurnal variation in PEFR ($p<0.01$) and in plasma adrenaline ($p=0.02$). Atropine did not alter plasma adrenaline levels. Atropine reversed the fall in PEFR at night ($p<0.01$) increasing it to PM placebo values; however the PEFR after 4 p.m. atropine was higher than after 4 p.m. placebo ($p<0.05$) and 4 a.m. atropine ($p<0.01$), implying that other factors such as low circulating adrenaline may also be important in the nocturnal fall in PEFR. In conclusion increased vagal tone appears to be an important aetiological factor in nocturnal asthma.

Selective histamine blockade in childhood asthma: the effect of terfenadine on resting bronchial tone and exercise induced bronchospasm (EIB)

PI MACFARLANE, DP HEAF *The Respiratory Unit, Royal Liverpool Children's Hospital, Alder Hey, Liverpool* Histamine is an important mediator of bronchoconstriction but conventional antihistamines only weakly antagonize its effects at bronchial muscle H_1 receptors; they are not therapeutically beneficial because of side effects. Terfenadine is a non-sedative potent selective H_1 antagonist. We have investigated the effects of terfenadine on resting bronchial tone and EIB in a randomized double blind placebo controlled trial. Twenty children (5.5-14.8 years) were studied on two days 48 hours apart, by PEFR and FEV_1 measurements for three hours after oral placebo or terfenadine 60 mg, followed by a free running exercise test. Baseline values were the same on each study day. Terfenadine induced significant bronchodilatation within one hour of ingestion when compared with placebo and a 32% improvement in FEV_1 by three hours ($p<0.00001$), increasing FEV_1 from a baseline mean % predicted 69% to 84% by three hours. Bronchodilatation showed a significant inverse correlation with baseline FEV_1 ($r=-0.81$, $p<0.00005$). After exercise challenge terfenadine significantly inhibited EIB (terfenadine 21.5% fall PEFR, placebo 32% fall, $p=0.037$), but when the exercise test values were normalised to the placebo baseline to eliminate the effect of prior bronchodilatation, no such protective effect was evident. Selective H_1 blockade using terfenadine has an acute bronchodilator effect, suggesting that asthmatic children have significant resting "histamine tone". Partial inhibition of EIB is a non-specific effect of bronchodilatation rather than a separate effect on bronchial reactivity.

Mechanism of metabisulphite-induced bronchoconstriction in atopic non-asthmatic subjects

ER CHILVERS, CMS DIXON, PW IND *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Sodium metabisulphite (MBS) is a widely used preservative which is increasingly recognised to cause bronchocontstriction after ingestion. Inhaled MBS has been the subject of few studies in asthmatics and none in atopics. We have investigated the mechanism of MBS-induced bronchoconstriction by examining the effect of (i) nedocromil sodium, (N) and (ii) cholinergic receptor blockade with oxitropium bromide (OB). In non-asthmatic subjects inhaled MBS produced dose related bronchoconstriction in 8/8 atopics but in 0/6 non-atopics. We studied six atopic non-asthmatics pre-treated with inhaled OB 200 μg, N 4 mg, or placebo (P), 30 minutes before nebulisation of a previously determined dose of MBS, in a randomised, double blind design. Specific airways conductance (sGaw, mean of six readings) determined by computerised body plethysmography was recorded for 20 minutes after MBS inhalation. Baseline sGaw did not differ significantly on the three study days. sGaw increased after OB but this was not significant compared to P or N. After MBS sGaw fell by 59% (9%) and (47) (16%) (mean (SEM)) one and five minutes after P and by 35% (20%) and 27% (12%) after OB ($p<0.05$). Nedocromil prevented any significant fall in sGaw ($p<0.05$). Bronchoconstriction, measured by the area under the curve of sGaw with time, was significantly reduced by nedocromil ($p<0.05$). These results may be

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interpreted as suggesting that MBS induces bronchoconstriction by mast cell degranulation but SO_2 liberation is not excluded.

Muscarinic autoreceptors inhibit cholinergic neurotransmission in human airways *in vivo* and *in vitro*

PA MINETTE, PJ BARNES *Department of Clinical Pharmacology, Cardiothoracic Institute, London* Prejunctional muscarinic receptors which inhibit acetylcholine release from cholinergic nerves have been demonstrated in intestine bladder and, recently in guinea-pig airways *in vivo* (Faulkner *et al, Br J Pharm* 1986;**88**:181-7). We have investigated whether these receptors exist in human airways, *in vitro* and *in vivo*. Human bronchi obtained at surgical lobectomy were mounted in an organ bath and stimulated by electric field stimulation (EFS), that elicited a contractile response which was inhibited by atropine and tetrodotoxin. Pilocarpine, a selective agonist of presynaptic muscarinic receptors, increased basal tone and reduced EFS contractile response in a dose-dependent manner. This effect was inhibited by gallamine. We have further investigated whether pilocarpine inhibits cholinergic reflex bronchoconstriction using sulphur dioxide (SO_2) challenge in eight healthy subjects (five atopics and three non-atopics). In a double blind, randomized fashion, they were pretreated with pilocarpine and histamine on separated days. The drugs increased the airway resistance measured by a forced oscillation technique (Rrs) by 24.6% 2.4% and 22.5% (2.6%) (mean (SEM)) respectively. Then the subjects inhaled a concentration of SO_2 which had been shown previously to give a similar increase of Rrs (27.0 (7.0)). After SO_2, Rrs further increased from 22.5% to 31.8% (6.0%) after histamine, while it decreased from 25.2% to 18.6% (5.3%) after pilocarpine (paired t = 2.96). These data support the idea that inhibitory muscarinic receptors exist on cholinergic nerves in human airways.

Modulation of cholinergic neurotransmission in human airways by β_2-receptors

KJ RHODEN, LA MELDRUM, PJ BARNES *Department of Clinical Pharmacology, Cardiothoracic Institute, London* Cholinergic neurotransmission in isolated canine bronchial smooth muscle is inhibited by catecholamines, probably via prejunctional β-receptors (*J Appl Physiol* 1979;**46**:789-91). Human airway smooth muscle has no functional adrenergic innervation but in asthmatics β-blockers induce a bronchoconstriction which is prevented by anticholinergic drugs. We have examined the effects of catecholamines on the responses of isolated human bronchi to electrical field stimulation (EFS) and exogenous acetylcholine (ACh). Bronchial rings were obtained from patients undergoing lung resection for carcinoma and were suspended in Krebs-Henseleit solution at 37°C, bubbled with 95% O_2-5% CO_2. Contractile responses to EFS (4-32 Hz, 1 ms, 40v) and to ACh (1μM-1mM) were measured isometrically. Isoprenaline and adrenaline inhibited responses to EFS with mean concentrations causing 50% inhibition (IC50) at 4Hz of 48 nM and 398 nM respectively. Both drugs had significantly less effect on comparable responses to ACh, with IC50s of 4μM and 3μM respectively. Noradrenaline was less potent, with an IC50 of 56μM on EFS. The effects of isoprenaline on EFS were inhibited by 1μM propranolol and by 0.1μM ICI118,551 (a β_2-blocker) but not by 0.1μM betaxolol (a β_1-blocker). Thus, we conclude that catecholamines have an inhibitory action on cholinergic neurotansmission in human airways, probably via prejunctional β_2-receptors.

Adrenoceptors decrease during activation of protein kinase C in airway smooth muscle

BM GRANDORDY, KJ RHODEN, PJ BARNES *Department of Clinical Pharmacology, Cardiothoracic Institute, Brompton Hospital, London* Carbachol stimulates breakdown of phosphoinositides (PI) in airway smooth muscle, leading to formation of diacylglycerol (DG), an activator of protein kinase C. We have investigated whether carbachol (CCh) and activation of protein kinase C by phorbol esters (phorbol 12-myristate 13-acetate, PMA) could affect β-receptor density and function. β-receptor density was assessed by (^{125}I) cyanopindolol (ICYP) binding to membranes prepared from chopped bovine airway smooth muscle pre-incubated with CCH (100 μM), PMA (1 μM) or 4-phorbol 12,13-didecanoate (PD, an inactive phorbol). There was a decrease in receptor density after CCh and PMA vs control of 80 fmol/mg protein, $p<0.05$). The displacement of ICYP specific binding by isoprenaline (ISO) in control and PD-treated, but not in PMA and CCh -treated membranes was sensitive to GTP, indicating that coupling of β-receptors to adenylate cyclase (AC) was reduced by protein kinase C activation. ISO-induced cyclic-AMP accumulation was decreased after PMA and CCh treatment ($EC_{50}=56$ μM and 73 μM respectively vs 5.1 μM in control; $p<0.05$). After PMA treatment and contraction by 30 mM KCl, the ISO relaxation curve did not differ from that after KCl alone. We conclude that CCh and PMA (probably via protein kinase C activation) decrease β-receptor number and coupling to AC, although this does not affect ISO-induced smooth muscle relaxation. Combined or prolonged effect of several inflammatory mediators could impair airway β-adrenergic function in asthma, however.

Evidence for a dual effect by beta-adrenoceptor antagonists on post-exercise airway calibre

KE BERKIN, G WALKER, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow* The effect of selectivity of β-adrenoceptor antagonists on resting and post-exercise airway calibre in normal subjects was examined using tests believed to distinguish between effects on central and peripheral airways. Eight normal subjects were given atenolol 50 mg, propranolol 80 mg and placebo orally, in random order, double blind. Specific airways conductance (sGaw) and flow at 25% of VC from partial flow volume curves ($\dot{V}_{25}$(p)) were recorded before, two hours after drug administration and after exercise.

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Neither drug had a measurable effect on sGaw or $\dot{V}_{25}$(p) at rest. After exercise on placebo, $\dot{V}_{25}$(p) increased from 1.97 (0.11) to 2.38 (0.18) l/s (mean(SEM)). This increase was inhibited ($p<0.01$) by propranolol; $\dot{V}_{25}$(p) was 1.81(0.16) before and 1.79(0.17) l/s after exercise. The β_1- selective atenolol allowed an increase in $\dot{V}_{25}$(p) from 1.87(0.14) to 2.24(0.26) l/s, comparable to that seen on placebo. After exercise on placebo, sGaw increased slightly from 1.56(0.18) to 1.69(0.19) $s^{-1}kPa^{-1}$, whereas on atenolol, post-exercise sGaw fell from 1.49(0.20) to 1.23(0.11) and on propranolol from 1.55(0.16) to 1.29(0.13) $s^{-1}kPa^{-1}$ ($p<0.05$). These results suggest that β-adrenoceptor antagonists may have a dual effect on airway calibre. Firstly, a direct effect on the β_2- receptors in airway smooth muscle may occur. Secondly, in the central airways, β-adrenoceptor blockade may inhibit vagal pre-junctional β_1- receptors which normally inhibit acetylcholine release at the nerve ending, thereby permitting vagally induced airway narrowing.

β-receptor stimulation does not inhibit human alveolar macrophage activation

G O'MALLEY, AJ BAKER, J MACDERMOT, RW FULLER *Clinical Pharmacology, Royal Postgraduate Medical School, London* Alveolar macrophages (AM), the most numerous airway cells, may contribute to airway inflammation by the release of mediators following activation by phagocytosis and IgE-dependent mechanisms. We have examined the role of the β-receptor agonist isoprenaline (ISO) and the phosphodiesterase inhibitor RO20-1724 (RO) on AM release of thromboxane B_2 (TXB_2) and *N*-acetyl glucosaminidase (NAG) following activation with both opsonised zymosan (Z) and IgE/anti-IgE complexes (IgE). Z increased TXB_2 and NAG release by a mean (SD) of 63% (59%) (n = 18) and 33% (48%) (n = 13). IgE increased TXB_2 and NAG release by 430% (729%) (n = 14) and 705% (674%) (n = 11). ISO (10μM) plus RO (250μM) increased adenylate cyclase activity by 96% and intracellular cyclic AMP by 103%. Preincubation with ISO (1nM-10μM) (n = 17) or RO (50nM-50μM) (n = 9) or the combination of RO (250μM) with ISO (10nM-10μM) (n = 10) had no effect on AM release of TXB_2 or NAG when stimulated with Z or IgE. Alveolar macrophage activation is not inhibited by β-receptor agonists. This may explain the lack of anti-inflammatory action of these drugs in the lung.

Investigation of the mechanism of methoxamine-induced bronchoconstriction in asthmatic airways

A MATTHEWS, S COOPER, J BRITTON, A TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Methoxamine, an alpha adrenoceptor agonist with mild beta antagonist activity, causes bronchoconstriction when inhaled by subjects with asthma. Whether this action results from alpha agonism or beta blockade, or alternatively from an unrecognised non-specific irritant activity is not clear. We have determined the relative importance of these effects by comparing airway reactivity to methoxamine with reactivity to a beta adrenoceptor antagonist (propranolol) and to a non-specific irritant (histamine), and by assessing the effect of an alpha antagonist (prazosin) on methoxamine and histamine reactivity in 20 subjects with mild asthma. On five separate days in a randomised double blind design, subjects took oral prazosin (1 mg) or placebo one hour before inhaling either methoxamine or histamine, or alternatively took placebo one hour before inhaling propranolol. The inhaled drugs were given in doubling concentrations by nebuliser at five minute intervals, measuring the response as the PC_{35} for specific airways conductance. Log PC_{35} values for methoxamine did not correlate significantly with values for either histamine ($r = -0.097$) or propranolol ($r = 0.416$) when these drugs were given after placebo. After prazosin, mean PC_{35} for methoxamine was increased by 1.4 doubling doses relative to placebo ($p<0.01$), whilst PC_{35} for histamine was unchanged. These findings indicate that methoxamine-induced bronchoconstriction is mediated by alpha receptors.

Bronchial muscarinic receptor hypersensitivity after heart-lung transplantation (HLT)

M JACKSON, T RASHDI, J WALLWORK, T HIGENBOTTAM *Papworth Hospital, Cambridge* After HLT, patients develop increased bronchial responsiveness to inhaled methacholine (NR Banner *et al, Thorax* 1987;**42**:239). It is unclear whether this enhanced sensitivity of muscarinic receptors results from vagal denervation or mucosal inflammation secondary to infection or rejection of the transplanted lung. To test for vagal reinnervation we have studied reflexly induced cough using inhalation of ultrasonically nebulized distilled water "fog" (Godden DG *et al, Clin Sci* 1986;**70**:301-304) and the bronchoconstriction response to "fog" (TW Higenbottam *et al, Br Med J* 1983;**286**:1012-1014) and compared these with the mechacholine response. All patients had concurrent bronchial mucosal and transbronchial lung biopsies. Six patients were studied (age range 21 to 47 years) who had HLT three to 14 months earlier. No patient coughed with "fog," supporting the idea of vagal denervation, and no patient developed bronchoconstriction after a cumulative exposure to "fog" of 30 minutes. The provocative concentration of methacholine at which the FEV_1 fell by 20% (P_C20M) ranged from 1.75 to 4 mg/ml. Two patients had mucosal inflammation on biopsy and their P_C20M was 3 and 3.5 mg/ml respectively. These observations support the view that vagal denervation is responsible for muscarinic receptor hypersensitity following HLT.

De novo beta-adrenoceptor synthesis in adult rat lung: an *in-vivo* study

RJD WINTER, KEJ DICKINSON, RM RUDD, PS SEVER, *Hammersmith Hospital, St. Mary's Hospital, and London Chest Hospital, London* We sought to determine the rate of synthesis of beta-adrenoceptors in adult rat lung. Male Wistar rats were treated with either

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bromoacetylalprenololmenthane (BAAM) 25 mg/kg intraperitoneally (n = 20) or ethanol/saline vehicle (n = 18). BAAM links covalently with the beta-adrenoceptor forming an irreversible bond (*Biochem Pharmacol* 1986;35:857-864). At intervals after injection (range 5-500 hours) animals were killed, lungs removed, and membranes prepared as previously (*Clin Sci* 1986;70:159-165). Beta-adrenoceptor density was determined by measuring the binding of ^{125}I-iodocyanopindolol (Radiochemical Centre, Amersham) at six concentrations (range 10-500 pM). Specific binding, defined using 200 μmol/l isoprenaline, was 85%. In the control group mean binding site maxima, Bmax, was 346.9 SEM 37.7 fmol/mg protein; mean dissociation constant, Kd, 24.7 SEM 4.1 pM. BAAM caused significant reduction in receptor density at five and 15 hours (mean Bmax 155.5 SEM 44.8, n = 4; 231.5 SEM 32.7 fmol/mg, n = 4, respectively; $p < 0.05$ both times) without change in Kd. Recovery to control value, reflecting *de novo* receptor synthesis, took about 300 hours. If airway adrenoceptors do not differ in their pharmacological properties from those at other sites in lung, these data suggest that synthesis occurs slowly. This contrasts with the rapid (30 minutes) *in vivo* alteration in cell surface receptor density after agonist exposure (*Endocrinology* 1984;115:1392-1400).

Cimetidine prevents histamine tachyphylaxis in asthmatic subjects

PJ MANNING, P JACKSON, PM O'BYRNE *Department of Medicine, McMaster University, Hamilton, Ontario, Canada* Histamine tachyphylaxis develops with repeat inhalation of histamine in mild asthmatic subjects, due to the release of prostaglandins. The purpose of this study was to determine whether histamine tachyphylaxis occurs through stimulation of H_2 receptors in the airway. Seven mild asthmatic subjects were studied on two days separated by at least one week. On both days, three histamine inhalation tests were performed, separated by one hour, as described by Cockcroft *et al* (*Clin Allergy* 1977;7:235-43). The response was expressed as the provocative concentration of histamine causing a 20% fall in FEV_1 (histamine PC_{20}). Before each study day subjects were pretreated with placebo or cimetidine (300 mg bid) for three days, in a double blind randomized fashion. The baseline FEV_1 was similar before each histamine test on each study day. Cimetidine pretreatment had no effect on baseline histamine PC_{20} ($p > 0.2$). After pretreatment with placebo, histamine tachyphylaxis occurred in all subjects; the PC_{20} increased from 3.01 mg/ml (%SD 1.44) to 4.88 (%SD 1.68) and to 6.85 mg/ml %SD 1.68). Cimetidine pretreatment prevented histamine tachyphylaxis; the histamine PC_{20} was 2.72 mg/ml (%SD 1.77), 3.02 mg/ml (%SD 1.73) and 3.56 mg/ml (%SD 1.59) with repeated tests, which differed significantly from the placebo values ($p < 0.01$ for the second and $p < 0.0005$ for the third histamine test). This study demonstrated that cimetidine pretreatment prevents histamine tachyphylaxis and suggests that the release of inhibitory prostaglandins in response to histamine inhalation occurs through stimulation of airway H_2 receptors.

Effector functions of bronchoalveolar leucocytes from rats exposed to coalmine dust by inhalation

K DONALDSON, GM BROWN, MD ROBERTSON, J SLIGHT, A SEATON *Institute of Occupational Medicine, Edinburgh* Bronchoalveolar leucocytes are considered to have a central role in tissue injury arising during long-term inflammation and in subsequent fibrosis in the alveolar region of the lung. We therefore assessed key effector functions of bronchoalveolar leukocytes lavaged from control rats and rats exposed for 45 days to airborne dust (50 mg/m^3) collected from a British colliery. The bronchoalveolar population from dust-exposed rats comprised (mean (SEM) × 10^6 per rat; n = 4) 15.6 (3.5)macrophages and 15.2 (2.4) neutrophils; control bronchoalveolar cells were 8.0 (0.1) macrophages and 0 (0) neutrophils. Control and dust-exposed bronchoalveolar cell populations showed different activities in degrading radiolabelled extracellular matrix components: figures for fibronectin degradation (mean (SEM) cpm released; n = 4), control cells 1308 (65), dust exposed cells 7010 (69) ($p < 0.01$). Cells from dust exposed rats also caused marked detachment injury to cells of an alveolar epithelial cell line *in vitro* while control cells were inactive: (mean (SEM) of ^{51}Cr cpm in cells detached following co-culture with bronchoalveolar cells; n = 4) medium 3722 (336), medium + control cells 3518 (441) (NS); medium 5047 (267), medium + dust-exposed cells 11375 (154) ($p < 0.05$). The activated status of the coalmine dust-exposed bronchoalveolar leucocytes was confirmed by their increased microbicidal activity against spores of *Aspergillus fumigatus*:- (mean (SEM) % spores killed; n = 4), control cells 11.85 (5.5), dust exposed cells 30.6 (2.3) ($p < 0.01$).

Production of alveolar macrophage chemotaxins by the action of pathogenic mineral dust on serum from control rats and rats with inflammation

K DONALDSON, J SLIGHT, PP JOHNSTON, RE BOLTON, A SEATON *Institute of Occupational Medicine, Edinburgh* We have investigated the ability of the pathogenic dusts chrysotile asbestos and quartz, and the inert dust titanium dioxide (TiO_2), to generate chemotaxins for alveolar macrophages in HAN and PVG rat serum. Both quartz and chrysotile asbestos, but not TiO_2, generated substantial amounts of migration-inducing activity in the serum of both rat strains. By using a modified "checkerboard" technique to assess chemokinesis we calculated which proportion of the total cell movement was due to chemotaxis in serum activated by the three mineral dusts; this revealed that the percentage of cell movement that was true chemotaxis varied depending on the dust: asbestos 81.1%; quartz 54.3%; TiO_2 23.3%. HAN serum yielded the following measures of chemotaxis on treatment with 5 mg/ml of dust (given as mean (SD) cells per high power field): TiO_2 5.4 (1.5); quartz 15.9 (3.2); chrysotile asbestos 25.1 (4.8). In the second part of the study serum from control PVG rats and PVG rats with inflammation caused by intrapertoneal injection of *Corynebacterium parvum* were compared as to their ability to be activated by the mineral dusts. Serum from

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"inflammatory" rats was much more amenable to production of chemotactic factors (results given as mean (SD) cells per high power field): (i) control rat serum — chrysotile treatment 5.7 (3.4), quartz treatment 2.2 (1.3); (ii) "inflammatory" rat serum — chrysotile treatment 13.3 (7.9), quartz treatment 8.1 (3.9).

Neutrophil chemotactic activity from cultured blood mononuclear cells in acute severe asthma

DR BUCHANAN, P FITZHARRIS, O CROMWELL, AB KAY *Cardiothoracic Institute, Brompton Hospital, London* We previously reported that neutrophil chemotactic activity (NCA) was elevated in serum from patients with acute severe asthma (ASA) and that this reverted to control/baseline values after treatment (*J Allergy Clin Immunol* 1986;77:183). In the present study we have attempted to determine the cell source of NCA by culturing blood mononuclear cells (MNC) for varying intervals of time. MNC from acute severe asthma (nine), mild asthma (six) and normal controls (six) were cultured for 24, 48 and 72 hours in the presence or absence of phytohaemagglutinin (PHA). With PHA no differences were observed in NCA when ASA was compared to mild asthma (MA) and normal controls (N) at 24, 48 and 72 hours. In contrast baseline unstimulated NCA was significantly raised in ASA compared with MA and N at 24 hours ($p<0.02$) and 48 hours ($p<0.05$). There was also a significant decrease in NCA of ASA when day 0 (on admission to hospital) was compared with seven days of treatment ($p<0.05$). Preliminary experiments using fast protein liquid chromatography gel filtration suggest that the MNC-derived NCA of ASA is heterogeneous in respect of molecular size. These experiments suggest that MNC might be a source of the NCA of ASA.

Relationship of pathological changes to bronchial hyperreactivity and bronchoalveolar lavage (BAL) fluid in mild asthma

PK JEFFERY, AJ WARDLAW, FC NELSON, JV COLLINS, AB KAY *Departments of Lung Pathology and Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* The pathological basis of asthma, particularly in its early stages, is still poorly understood. We have investigated bronchial biopsies and BAL in 11 non-smoking mild atopic asthmatics and 10 non-asthmatic volunteers (five hay fever, five non-atopic). Seven of the asthmatics had evidence of active disease with increased bronchial hyperreactivity ($PC_{20}<4$ mg/ml methacholine). Four of these were symptomatic requiring daily inhaled β_2 agonists. We report here the histological changes measured in semi- and ultra-thin plastic sections and the correlation with symptoms and BAL data. Symptomatic asthmatics had increased loss of epithelium ($p<0.01$) and an increased proportion of irregular lymphocytes in their submucosa ($p_{\chi 2}<0.001$). The degree of epithelial loss in all subjects correlated with the degree of airway reactivity ($r_s \equiv \pm 0.60$, $p<0.01$). Hyperreactive asthmatics had a significantly thickened basement membrane ($p<0.01$), which did not correlate significantly with PC_{20} ($r_s = -0.35$, $p=0.12$). There was no difference between groups in the numbers of goblet cells, intraepithelial nerves, subepithelial inflammatory cells, mast cells or platelets. Although there were increased numbers of epithelial cells, eosinophils and mast cells in the BAL fluid there was no significant correlation with the findings in biopsy specimens. The results indicate that epithelial fragility and basement membrane thickening are early changes in asthma which may contribute to the pathogenesis of bronchial hyperreactivity.

Rapid cessation of neutrophil influx after intrapulmonary instillation of the chemotaxin C5a des arg (C5a) in rabbits

C HASLETT, GS DOWNEY, HENSON PM *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital and National Jewish Centre for Immunology and Respiratory Medicine, Denver, U.S.A.* Differences in control of neutrophil (PMN) influx may explain why a single intrabronchial dose of bleomycin induces chronic inflammation and injury, while C5a results in self-limited inflammation. 5×10^7 indium-III labelled rabbit PMN (In.PMN) were given intravenously to 23 rabbits 0.5, 2, 6, and 12 hours after 20 μg C5a was instilled into the right upper lobe (RUL) with left upper lobe (LUL) as control. PMN influx was assessed 20 hours after PMN injection by quantitative external γ camera scintigraphy ("ext."), γ count of bronchoalveolar lavage (BAL) and tissue counts of dissected lungs ("tis.") and results expressed as ten thousandths (mean (SEM)) of original In.PMN infusate:

Hours	*0.5 (n=6)*	*2 (n=5)*	*6 (n=7)*	*12 (n=5)*	*LUL (control)*
BAL	33 (8.1)	3.6 (0.6)	5.3 (1.5)	2.1 (0.2)	0.2 (0.08)
Tis.	218 (54)	16.6 (2)	20 (5)	5.7 (0.3)	4.7 (0.9)
Ext.	250 (28)	105 (8)	105 (7.3)	101 (10)	96 (8.6)

All three methods revealed a dramatic fall in PMN influx at two hours after C5a, with low grade influx detectable at 12 hours by BAL and tissue counts, but not by the external γ camera, which may be less sensitive because of the marginated PMN pool background. In summary, the bulk of PMN influx had occurred within two hours after C5a, in marked contrast to the effects of bleomycin, where influx may persist for three weeeks.

Exposure to cigarette smoke does not enhance bleomycin induced lung injury

JG HAY, TE BETTS, PL HASLAM, ME TURNER-WARWICK, GJ LAURENT *Department of Thoracic Medicine, Cardiothoracic Institute, London and Department of Thoracic Medicine, Fazakerley Hospital, Liverpool* Bleomycin is an important chemotherapeutic agent which unpredictably causes acute severe lung injury. An active species is formed when bleomycin complexes with iron and oxygen and DNA is damaged by the release of free radicals. Hydrogen peroxide is able to regenerate this active species. Exposure to cigarette smoke has been shown to

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stimulate the production of hydrogen peroxide by pulmonary cells (DB Drath *et al, J Cell Physiol* 1978;**95**:105-115), and might therefore be expected to enhance the pulmonary toxicity of bleomycin. We have previously shown that the administration of intravenous bleomycin (5 mg) to male Lewis rats causes no evidence of acute lung injury, yet when combined with hyperoxia or excess iron, severe injury follows (JG Hay *et al, Thorax* in press). In this study rats were exposed to the smoke of 10 cigarettes over a period of 200 minutes on four consecutive days beginning two days prior to (Group 1) or simultaneous with (Group 2) intravenous saline or bleomycin. The effect of exposure to smoke on one session increased the carboxyhaemoglobin concentration from < 1% to 9%. Lung injury was measured as the total pulmonary extravascular albumin space 72 hours following bleomycin; this is the ratio of ^{125}I albumin in the lungs to that in 1 ml of plasma 24 hours following an intravenous bolus injection of ^{125}I albumin.

	Group 1		*Group 2*	
Bleomycin	0.14 (0.03)	NS	0.16 (0.04)	NS
Saline	0.13 (0.01)		0.14 (0.01)	

In conclusion, exposure to smoke in this manner does not increase the pulmonary toxicity of intravenous bleomycin.

Serum human neutrophil elastase is increased in patients with active Wegener's granuloma

CG WATHEN, D BELL, DJ HARRISON, M JACKSON, J DAWES *Departments of Medicine and Pathology and Blood Transfusion Service, Royal Infirmary, Edinburgh* The neutrophil has been implicated in the pathogenesis of vasculitis, including Wegener's granuloma (Leavitt and Fauci, *Am Rev Respir Dis* **134**:149-66). Elevated levels of human neutrophil elastase (complexed to α_1 antiprotease) are associated with neutrophil activation and degranulation. We therefore measured human neutrophil elastase by radioimmunoassay, in patients with active Wegener's granuloma known to have neutrophil anticytoplasmic antibodies present in their sera (de Woude *et al, Lancet* 1985;i:425-9). Sera were studied from 10 patients (age 35-63 years, mean 46) with active Wegener's granuloma and 20 control subjects (22-46 years) mean 31). All patients with Wegener's granuloma had anticytoplasmic antibodies present and detectable by immunofluorescence at dilution of $\geq$1:64. Serum human neutrophil elastase was significantly increased in patients with active Wegener's granuloma (894 (SD668)) ng/ml) compared with controls (81 (50) ng/ml, $p<0.001$). In three patients the level fell after the commencement of treatment of the condition. These data support the view that neutrophil activation and the release of neutrophil products may have a role in the pathogenesis of Wegener's granuloma and that human neutrophil elastase may provide the means of monitoring disease activity and response to therapy.

Human alveolar macrophages release more H_2O_2 in response to increasing environmental hypoxia

AP GREENING, MH BAIN, W SCOTT, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, Edinburgh* Extracellular release of oxidants by macrophages and neutrophils is thought to contribute to acute and chronic lung injury. Alveolar macrophages (AM) differentiate from their monocyte precursors in an aerobic environment and display an active oxidative metabolism. Since patients with chronic bronchitis and emphysema have areas of relative pulmonary hypoxia, we questioned whether the oxidative functions of AM from these areas might be influenced by the "hypoxia". We have studied, *in vitro*, the effects of different degrees of environmental hypoxia on AM obtained from seven patients by bronchoalveolar lavage. AM were purified by plastic adherence and cultured overnight in sandwich boxes "gassed" to give O_2 concentrations of 21%, 10% and 2.5%. H_2O_2 release from the AM, following stimulation, was assayed fluorometrically. Culture in hypoxic environments resulted in enhanced release of H_2O_2 by the AM.

Culture O_2 (%)	*H_2O_2 release (nmol/10^6 cells/h) (mean (SEM))*	
21	12.75 (3.6)	
10	18.6 (5.8)	$p<0.05$
2.5	21.2 (5.3)	$p<0.05$

We conclude that increasing environmental "hypoxia" results in increasing extracellular H_2O_2 release by AM. This may provide a mechanism for progressive oxidant mediated tissue damage.

Transferrin accumulation in the lung and evidence of neutrophil degranulation in the adult respiratory distress syndrome (ARDS)

GM ROCKER, MS WISEMAN, D PEARSON, DJ SHALE *Respiratory Medicine Unit, University of Nottingham, and Departments of Medical Physics, City Hospital, Nottingham* Neutrophil degranulation may be causally linked to increased pulmonary vascular permeability in ARDS. Of 27 patients with widespread pulmonary infiltrates undergoing a double isotope determination of transferrin accumulation in the lung 15 met the criteria of ARDS (Petty *et al, Chest* 1982;**82**:98-103). Simultaneously neutrophil degranulation was assessed as plasma beta-glucuronidase (bG) activity and lactoferrin (Lf) concentration. Nine healthy subjects were also assessed for evidence of degranulation. Lf in ARDS (median 2.8 mg/l, interquartile range 2.5-3.5) and non-ARDS (2.5, 2.2-3.2) was greater than in controls (1.4, 1.3-1.4) $p<0.01$ (Kruskal-Wallis test), but not significantly different from each other. bG activity was not significantly different between groups. The absolute neutrophil count was lower in ARDS (8.3×10^9/l, 6.7-8.7) than non-ARDS patients (11.3, 11.2-14.4; $p<0.01$), but both were significantly greater than the controls (3.1, 2.8-3.1). Transferrin accumulation was significantly greater in ARDS than non-ARDS patients (2.33×10^{-3}/min, 1.67-2.39 vs 0.55, 0.43-0.71; $p<0.01$).

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In established ARDS there was no relationship between transferrin accumulation and neutrophil degranulation. Degranulation occurred in non-ARDS subjects, who did not develop ARDS, though at risk. These findings bring into question the primary role of the neutrophil in ARDS.

A comparison of conventional chest radiography and a double isotope method for lung accumulation of transferrin in pulmonary oedema

GM ROCKER, DH ROSE, AR MANHIRE, D PEARSON, DJ SHALE *Respiratory Medicine Unit, University of Nottingham, and Department of Radiology and Medical Physics, City Hospital, Nottingham* Conventional chest radiography was reported to identify pulmonary oedema associated with high and low capillary permeability states. (Milne *et al, Am J Roentgen* 1985;144:879-94). Twenty-five patients with radiographically detectable pulmonary oedema were studied (seven non-cardiac (ARDS), 10 renal and eight cardiac). Transferrin accumulation (PAI) in the lung was determined using a double isotope method. Chest radiographs were scored according to Milne's criteria with weighting of the scores in favour of a high (HC) or low (LC) capillary permeability cause. Two radiologists unaware of the diagnosis carried out the scoring and agreed a final category for each patient.

	ARDS	*RENAL*	*CARDIAC*
PAI	2.52 (1.5-3.2)	0.72* (-0.1-1.1)	0.79* (0.5-1.9)
HC score	17 (12-22)	0* (0-4.5)	1.5* (0-15)
LC score	0.5 (0-4.5)	7.5* (3.9-9.5)	7.5* (0.8-11)

*Critical value < 0.05, Mann Whitney U test.
Results are median and (interquartile range).

Scores did not differentiate between cardiac and renal pulmonary oedema, but capillary pulmonary oedema (ARDS) was identified with certainty at a time when there was evidence of increased pulmonary permeability to proteins.

The effect of cigarette smoking on polymorphonuclear leucocyte (PMN) retention in the lungs

W MACNEE, BA MARTIN, AS BELZBERG, BJ WIGGS, JC HOGG *UBC Pulmonary Research Laboratory, St. Paul's Hospital, Vancouver, B.C., Canada* Cigarette smoking is thought to recruit PMNs into the lungs. To assess the effect of smoking on the movement of PMNs through the pulmonary vasculature, we have measured PMN retention and subsequent washout from the lungs in healthy smokers ($n = 15$, age 40 (SD 10) years) and non-smokers ($n = 6$, age 38 (7) years). We have related PMN retention in the lungs to blood velocity as measured by red blood cell (RBC) transit time (TT), following i.v. bolus injections of ^{99m}Tc labelled RBCs and Indium-III labelled PMNs using a gamma camera/computer system. The retention of PMNs in the lungs at 10 minutes post-injection (but not the first pass retention) correlated with RBC TT ($r = 0.83$, $p < 0.005$) in both non-smokers and smokers who were not smoking during the study. PMN retention and washout from the lungs was similar in these two groups. Inhalation of cigarette smoke shortened RBC TT in the lungs of smokers ($TT = 6.1 + 1.6$s) compared with non-smokers ($TT = 8.9$ (SD 1) s (1.0) s, $p < 0.001$) but increased 10 minute retention. Analysis of the PMN washout curves using the equation $y = A + Be^{-cx}$ showed that this difference was due to slower washout (c) ($p < 0.001$) rather than the total washout (B) or the concentrations of PMNs present at the end of the experiment (A). We conclude that cigarette smoking produces a transient delay in the passage of PMNs through the lungs in spite of the decrease in RBC TT. Since smoking activates PMNs and inactivates α_1Pi this delay in PMN transit could result in focal areas of intravascular protease/antiprotease imbalance which may be important in the pathogenesis of emphysema.

Plasma elastin derived peptide levels in normal and emphysematous subjects

G MCLENNAN, R WALSH, T DILLON, J MARTIN, R ANTIC *Departments of Thoracic Medicine, Royal Adelaide Hospital, and the Adelaide Childrens Hospital and Department of Clinical Chemistry, Institute of Medical and Veterinarary Science, Adelaide, South Australia* Pulmonary elastin breakdown results in pulmonary emphysema. Elastin breakdown by elastases results in soluble elastin fragments. One method of assessing elastin breakdown is to measure these elastin fragments which may be circulating in the plasma. Assays for elastin derived peptides (EDP) have been performed on human plasma using an Elisa assay. Assays were performed in triplicate and results calculated using a standard curve. The intra-batch coefficient of variation is 4.3% at 0.4 ng/ml and the inter-batch coefficient of variation is 5.2% at 0.4 ng/ml. EDP levels from disease free children ($n = 24$, aged 1-14 years), disease free adult non-smokers ($n = 24$), smokers ($n = 10$), reformed smokers ($n = 14$), (aged 20-50 years) and adults with established pulmonary emphysema ($n = 10$) have been determined. The levels in children were 0.02-0.28 ng/ml (0.155 (SEM 0.017)); in non-smoking adults 0.93-2.67 (1.967 (0.371)); in smoking adults 0.68-3.93 (1.924 (0.349)); in reformed smokers 0.58-5.13 (1.93 (0.318)); and in subjects with emphysema 21.3-90.8 (40.36 (6.35)). The levels in children were significantly lower ($p < 0.001$) than those from normal non-smoking adults. The levels from adults with emphysema were significantly higher ($p < 0.001$) than those from the other adult groups. We conclude that patients with established emphysema have elevated levels of EDPs and that children have low levels. This assay may be useful to evaluate premature or rapid elastin breakdown.

Pleural complications of fatal acute pancreatitis: an necropsy study

M WILKINSON, K ROBSON, GS BASRAN *Departments of Thoracic Medicine and Histopathology, City Hospital, Nottingham* Amylase-rich pleural effusions are

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recognised complications of pancreatitis; however, the significant of their size and relationship to sub-diaphragmatic pathology has not been highlighted. Moreover the mechanism by which these exudative effusions accumulate remain unexplained although direct transdiaphragmatic communications have been postulated. We have analysed the necropsy data on 19 patients who had a clinical and pathological diagnosis of pancreatitis and in whom adequate post-mortem histology was available. Eight of these cases had encapsulated sub-diaphragmatic fluid collections (pancreatic psuedocysts or abscesses) and seven of these had large pleural effusions (volume 500-2000 ml). The fluid was serous in four and blood stained in three. The distribution was bilateral in five and right sided in two. Of the remaining 11 cases only three had pleural effusions and these were small (less than 200 ml; two bilateral, one right sided). Contrary to findings in clinical studies none of our patients had unilateral left sided effusions. Apart from one patient with pleural fat necrosis and another with diffuse alveolar damage no gross pleural or lung pathology was seen. Thus all the patients with large pleural effusions had encapsulated subdiaphragmatic fluid collections. However, the postulated transdiaphragmatic communications which could have explained the formation of the effusions were not seen in any of our cases. The observed subdiaphragmatic inflammatory pancreatic masses could provide alternative explanations: impaired lymphatic drainage through reduced diaphragmatic movement and retrograde flow of fluid through trans diaphragmatic lymphatics.

Alveolar macrophage procoagulant activity is increased in acute hyperoxic lung injury

DA CAMPBELL, PG TIPPING, NW BOYCE, SR HOLDSWORTH *Queen Elizabeth Hospital, Adelaide, and Monash University Department of Medicine, Prince Henry's Hospital, Melbourne, Australia* This study demonstrates that alveolar macrophage (AM) procoagulant activity (PCA) is increased in acute hyperoxic lung injury in rats and indicates that AM are activated early in the development of this disease. AM-PCA has been implicated in fibrin deposition and subsequent fibrosis in chronic interstitial lung disease (Chapman *et al, Clin Invest* 1985;75:2030). AM may also have a role in tissue injury in adult respiratory distress syndrome and in pulmonary oxygen toxicity in animal models (JD Crapo, *Ann Rev Physiol* 1986;48:721). Hyperoxia-induced lung injury was assessed at 24, 48 and 60 hours in rats exposed to > 95% O_2 and compared with controls. Lung injury was assessed histologically (including fibrin deposition by immunofluorescence) and functionally by the assessment of pulmonary capillary permeability (125I-albumin lung permeability index (LPI) and lung weight-body weight ratio (LBW). Inflammatory cell accumulation and differential cell count was assessed by bronchoalveolar lavage (BAL). AM-PCA was measured by a one-stage clotting assay (SR Holdsworth, PG Tipping *J Clin Invest* 1985;76:1367). Pulmonary capillary permeability increased progressively with increased hyperoxia exposure ($p<0.01$ at 24 hours); however inflammatory cell accumulation in BAL fluid was not seen until 60 hours ($p<0.005$), when the proportion of neutrophils was increased ($p<0.01$). AM-PCA was increased at all times in the hyperoxia-exposed groups ($p<0.01$). AM-PCA was dependent upon coagulation factors V and VII and largely independent of factors VIII and XII; thus it has the characteristics of tissue factor. This model provides insights into the contribution of AM-PCA to fibrin deposition in interstitial lung diseases.

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