Thorax 1988;**43**:219P–264P

Proceedings of the British Thoracic Society

The 1987 winter meeting of the British Thoracic Society was held on 8 and 9 December at Kensington Town Hall, London.

Influence of starting airway calibre on slope of the concentration-response curve to methacholine assessed by partial flow-volume loops

RW HEATON, MK GILLETT, PD SNASHALL *Department of Medicine, Charing Cross and Westminster Medical School, London* In assessment of bronchial responsiveness to inhaled pharmacological agents it is customary to "normalise" the concentration-response curve (CRC) so that the baseline measurement of airway calibre is expressed as 100% and responsiveness given as the concentration of agonist causing a given percentage change. This is valid only if the slope of the CRC relates to starting airway calibre in a consistent manner. Increasing use is being made of partial flow-volume loops in bronchial challenge testing, although the influence of starting flow rates on the slope of the CRC so obtained has not been studied. We have investigated this relationship in 20 CRCs from normal subjects and 19 CRCs from asthmatic subjects. Methacholine was administered by the method of Juniper *et al* (*Thorax* 1978;**33**:705–10). Maximal and partial flow-volume loops were obtained according to the method of Zamel (*Clin Respir Physiol* 1984;**20**:471–5). The concentration of methacholine producing a 40% fall in flow at a lung volume 40% above residual volume on the partial loop (V_{40p}) was determined from the log concentration-response curve and the slope of the curve determined at that point. Similar assessments were made for a 20% fall in FEV_1 derived from the maximal loops. In all subjects there was a significant negative correlation between the starting V_{40p} and the slope of the CRC ($r = -0{\cdot}73$, $p < 0{\cdot}001$). In subgroups of eight asthmatic and six normal subjects whose baseline V_{40p} values overlapped each other's range, there was no significant difference in mean slope between the normal subjects ($-1{\cdot}16$ ($0{\cdot}55$) 1 s^{-1}/mg ml^{-1}) and the asthmatic subjects ($-1{\cdot}99$ ($1{\cdot}2$) 1 s^{-1}/mg ml^{-1}). In contrast, the correlation between starting FEV_1 and slope was much weaker ($r = 0{\cdot}38$, $p < 0{\cdot}05$). We conclude that "normalisation" of the CRC to methacholine using partial flow-volume loops is a valid procedure. Normal and asthmatic subjects cannot be distinguished on the basis of the slope of such curves. The practice of "normalising" the FEV_1 concentration-response curve is less justifiable.

Rebound increase in bronchial reactivity following regular inhaled terbutaline

AS VATHENEN, AJ KNOX, B HIGGINS, J BRITTON, S COOPER, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We have investigated the effect of two weeks' treatment with terbutaline on bronchial reactivity measured at intervals during day 1 and day 14 of treatment and on the day following cessation of treatment, day 15, to determine whether a rebound increase in reactivity occurs after cessation of regular inhaled β agonist therapy. Eight subjects aged 18–45 years with mild asthma received placebo or 750 μg terbutaline via a Nebuhaler at 10, 16 and 22 h for two weeks in a randomised double blind crossover design with a one week run in/washout period preceding each phase. Histamine PD_{20} FEV_1 was measured at 09, 12, 15, 18 and 21 h on days 1, 14 and 15; ΔFEV_1 and ΔPD_{20} following terbutaline were assessed as change from 09 to 12 h and from 15 to 18 h. On both days 1 and 14 terbutaline produced an increase in FEV_1 and an increase in PD_{20} (0·45 1 and 2·9 doubling doses of histamine two hours after the first dose of terbutaline on day 1). ΔFEV_1 after terbutaline did not differ significantly between day 14 and day 1. However, ΔPD_{20} after terbutaline was smaller on day 14 than on day 1 ($p < 0{\cdot}05$). On day 15 both FEV_1 (NS) and geometric mean PD_{20} ($p < 0{\cdot}05$) were lower after cessation of terbutaline than after cessation of placebo. The lowest PD_{20} on day 15 occurred at 21 h (23 hours after the last dose of terbutaline), when the difference between the values following placebo and terbutaline treatment was 1·5 doubling doses of histamine. Thus regular inhaled terbutaline resulted in impaired ability of terbutaline to reduce bronchial reactivity and in a rebound increase in bronchial reactivity following cessation of therapy.

Relationship between bronchial responsiveness and atopy in extended families

COOKSON WOCM, HOPKIN JM *Osler Chest Unit, Churchill Hospital, Oxford* As part of a study into the genetics of atopic asthma we have investigated 94 members of three extended families. The PD_{20} to methacholine was estimated by the method of Yan *et al* (*Thorax* 1983;**38**:760–5) at a maximum dose of 62 μg, which was likely to give a measurable PD_{20} in 50% of subjects (Cookson *et al, Clin Allergy* 1986;**16**:425–32). Atopy was defined on the basis of prick skin tests, total IgE estimations, and RAST responses to 13 common allergens. The sum of an individuals RAST scores was taken as a quantitative measure of atopy (atopic index:ATOPI). In these subjects the distribution of log PD_{20} (LPD_{20}) was bimodal with a median of 7·91 μmol for individuals with measurable reactivity (skewness $-0{\cdot}65$, SE skewness 0·31). As previously reported, atopy was inherited as a dominant trait (Cookson and Hopkin, *Thorax* 1987;**42**:735). The symptoms of wheeze and chest tightness correlated with LPD_{20} ($r = 0{\cdot}33$, $p = 0{\cdot}001$; and $r = -0{\cdot}32$, $p = 0{\cdot}001$ respectively) and with atopi ($r = 0{\cdot}20$, $p = 0{\cdot}026$;

and r = 0·37, p = 0·0001 respectively). Multiple stepwise regression analysis with LPD_{20} as the dependent variable found ATOPI (R^2 = 27%, p = 0·001) and age (additional R^2 = 7%, p = 0·006) to be negatively correlated with bronchial responsiveness. Smoking did not relate significantly to LPD_{20}. No clear pattern of inheritance of non-atopic bronchial hyperresponsiveness could be perceived. The results indicate that bronchial hyperresponsiveness may be inherited as part of the atopic state, and imply that atopy per se is a cause of hyperresponsiveness. Increasing age is also shown to relate to hyperresponsiveness independently of the effects of atopy and smoking.

Do patients with bronchial hyperreactivity attend more frequently with respiratory complaints in general practice?

CJ TRIGG, JB BENNETT, M TOOLEY, NF D'SOUZA, RJ DAVIES *Bartholomew's Hospital, London; and Canbury Medical Centre, Kingston-upon-Thames, Surrey* Recent studies by this department have shown that the prevalence of bronchial hyperreactivity (BHR) in the general population in Kingston is far in excess of the prevalence of asthma: 23% as compared with 5·07% in a systematic sample of the practice population (n = 366) on bronchial provocation testing with methacholine and a tidal breathing method. It has been proposed that these patients have more respiratory symptoms than those who are not hyperreactive. We have carried out a survey of the general practice notes of a sample of these patients to determine whether those with BHR present more frequently to the surgery with respiratory complaints. Random samples of patients in each of three groups were taken from the original 366 cases whose provocation concentration (PC_{20}) values are known: (1) $PC_{20} \leqslant 2$ mg/ml (n = 50); (2) $PC_{20} > 2 < 32$ mg/ml (n = 51); (3) $PC_{20} \geqslant 32$ mg/ml (n = 68). These groups had characteristics similar to those of the whole sample. The notes were analysed for attendance with respiratory complaints over a five year period up to June 1987. Numbers of attendances with respiratory complaints for every individual and attendances with upper respiratory tract and lower respiratory tract symptoms were analysed separately. Logged data were subjected to analysis of variance and Student's *t* test. This showed no significant difference between any of the three groups. This study has shown no relationship between BHR and attendance at the general practitioner with respiratory complaints despite the fact that more than 20% of those with BHR were asthmatic. This suggests that the detection of BHR per se is of little importance in clinical practice.

Relationship of peak flow variability to symptoms of asthma

BG HIGGINS, JR BRITTON, S CHINN, T JONES, PGJ BURNEY, AE TATTERSFIELD *City Hospital, Nottingham, and St Thomas's Hospital, London* We have examined the relationship of PEF variability to symptoms of asthma, as part of the assessment of peak expiratory flow (PEF) recording in epidemiological surveys of asthma. A randomly selected group of 121 subjects and 221 subjects who had experienced wheeze in the last year were asked to record PEF two hourly for seven days, and to complete a symptom questionnaire. Three indices of PEF variability were derived for each subject: amplitude % mean (AM = highest–lowest/mean daily reading); cosinor AM (=amplitude/mean of fitted cosinor curve); and standard deviation % mean (SDM = standard deviation/mean). Increased variability, arbitrarily defined as that lying beyond the 90th centile of the variability distribution in the random sample, was significantly associated with wheeze, cough, dyspnoea, and a diagnosis of asthma (χ^2 analysis, p < 0·0005 for each index), and identified those who had been given a diagnosis of asthma with a sensitivity of 43% and a specificity of 89%. These figures were 50% and 82% respectively if the 85th centile was used. Discrimination between wheezers with a diagnosis of asthma and non-wheezers without a diagnosis of asthma was assessed as described by Armitage (*Statistical Methods for Medical Research*. 1st ed. Blackwell, 1971:436) and was best when AM was used (Δ = 1·57). Correlations of PEF variability with frequency of wheeze (r = 0·477, p < 0·0001) and with severity of dyspnoea (r = 0·351, p < 0·0001) were also best with AM. Thus in a population covering a wide range of respiratory symptoms PEF variability is significantly related to wheeze, and in this context amplitude % mean is the best index for expressing variability.

Effect of azelastine hydrochloride on histamine and allergen induced bronchoconstriction in asthmatic subjects

P RAFFERTY, PJ HARRISON, ST HOLGATE *Immunopharmacology Group, Southampton General Hospital, Southampton* Azelastine hydrochloride is a novel histamine H_1 receptor antagonist that is reported to exhibit antileukotriene activity and to inhibit mast cell mediator release. We have examined the effect of a single dose of azelastine on histamine and allergen induced bronconstriction in 12 patients with mild, atopic asthma. Patients attended the laboratory on four separate days. During the first two visits standardised histamine inhalation challenge tests were performed four hours after azelastine 8·8 mg or matched placebo. During the last two visits patients underwent inhalation challenge tests using five fold increasing concentration of allergen after azelastine or placebo. All drugs were administered double blind and in random order and the allergen challenges were carried out three weeks apart. Azelastine produced significant bronchodilation four hours after administration (p < 0·01). Azelastine increased the concentration of histamine required to produce a 20% fall in FEV_1 from a geometric mean of 0·3 mg/ml to 13·2 mg/ml, a 42 fold geometric mean displacement (p < 0·02). Allergen induced bronchoconstriction was also inhibited by azelastine, increasing the dose of allergen required to provoke a 20% fall in FEV_1 from a geometric mean of 9·3 cumulative breath units (cbu) to 47·9 cbu, a five fold geometric mean displacement (p < 0·05). We conclude that azelastine inhibits allergen induced bronchoconstriction, but from this study we are unable to ascertain whether or not this effect is due to properties other than H_1 histamine blockade.

Lung cancer in lifelong non-smokers

R SANKARAN, S CAPEWELL, D LAMB, M MCINTYRE, MF SUDLOW for the Edinburgh Lung Cancer Group *Department of Respiratory Medicine, City Hospital, Edinburgh* Over 3070 patients with lung cancer were registered by the group in the five years 1981–1985, yet only 99 patients (3%) were classified as lifelong non-smokers (Capewell *et al, Thorax* 1987; **42**:209). We have reviewed the 99 alleged non-smokers. Twenty five were excluded on clinical grounds after review of their case notes; three had other forms of malignancy (one lymphoma, one angiosarcoma, and one mesothelioma); (two breast, one bladder, one prostate), and 18 patients were in fact previous smokers. The remaining 74 non-smokers differed significantly from smokers with lung cancer. Seventy seven per cent were female (v 26%, $p < 0.001$) and the mean age was 75·4 (v 68·0) years. Significantly more were in the worst performance status category (Karnofsky 10–60, 36% v 26%, $p < 0.05$), and fewer underwent surgery (10% v 19%, $p < 0.05$). Stage of disease was comparable and five year survival was equally poor (5%). Histological cell type was known in 59/74 cases. Non-smokers had significantly more adenocarcinoma (33% v 12%) less squamous carcinoma (26% v 49%, $p < 0.01$), and slightly less small cell carcinoma (12% v 24%, $p = 0.08$). However, of all adenocarcinomas seen in the five years, 267/291 occurred in smokers rather than in non-smokers, suggesting that adenocarcinoma is strongly associated with cigarette smoking. Review of the pathological material highlighted several problem areas, however. In seven patients the diagnosis of lung cancer was based principally on pleural biopsy; 5/7 had adenocarcinoma. Two adenocarcinomas were diagnosed on lymph node biopsy alone and in six further adenocarcinomas it was impossible to determine whether the lung tumour was primary or secondary. Furthermore, two patients with squamous carcinoma had a previous carcinoma of cervix. We conclude that lung cancer in a non-smoker is rare (2% of this series) and errors in assessing smoking status are frequently made. The diagnosis should always be questioned, particularly with adenocarcinoma reported on pleural biopsy or with a past history of malignancy elsewhere.

Endoscopic laser treatment for tumours causing complete endobronchial obstruction

PJM GEORGE, MR HETZEL *Department of Thoracic Medicine, University College Hospital, London* Endoscopic laser treatment for patients with tumours causing complete endobronchial obstruction is often not attempted because it is technically difficult and because the clinical value of lung re-expansion is not known. Thirteen patients with complete or partial collapse of a lung have been treated with a neodymium YAG laser under general anaesthesia. Recanalisation was achieved in seven out of 10 patients with main bronchial obstruction and in all three patients with obstruction of intermediate and lobar bronchi. Treatment for two of the seven patients with main bronchial obstruction whose airways had been recanalised could not be regarded as successful, however, as one patient died from pneumonia and the other developed a pneumothorax with no re-expansion after chest drain insertion. In the remaining five patients mean values of forced vital capacity rose from 1·93 to 2·66 litres ($p < 0.05$), in association with significant improvements in arterial blood gases ($p < 0.05$), six minute walking distances ($p < 0.05$), Karnofsky performance indices ($p < 0.05$), and scores of breathlessness ($p < 0.001$) and wellbeing ($p < 0.05$). One patient derived additional clinical benefit from drainage of infected secretions which had become trapped beyond the tumour. Significant improvements in lung function and symptom scores were not seen in the smaller group of patients with more peripheral obstruction. Thus re-expansion of collapsed lungs may lead to a worthwhile physiological and symptomatic improvement, although the value of treatment in patients with more peripheral obstruction is questionable.

Combined laser therapy and endobronchial radiation for relief of tracheobronchial obstruction M J PHILLIPS, S MOKEY, P KLEMPE, F G CAMERON *Departments of Respiratory Medicine and Radiotherapy, Sir Charles Gairdner Hospital, Nedlands, Western Australia.*

Results of endoscopic implantation of radioactive gold grains in patients with recurrent endobronchial carcinoma

SJM LEDINGHAM, P GOLDSTRAW *Department of Thoracic Surgery, Brompton Hospital, London* Between 1985 and 1987 15 patients previously treated by external radiotherapy for inoperable carcinoma of the lower trachea and major bronchi underwent endobronchial insertion of radioactive gold grains as a palliative procedure for relief of symptoms. Fourteen had squamous cell carcinomas and one had adenocarcinoma. Symptoms of stridor or dyspnoea occurred from four to 36 months following deep x ray therapy. Tumour and/or external compression involved the lower trachea, carina, and both major bronchi in three patients; lower trachea and a major bronchus in five patients; and only a major bronchus in seven patients. Two patients had collapse of a lung and six patients had collapse of a lobe. Four patients had previously undergone three or more endobronchial laser resections before being referred. A mean of 1872 MBq activity was inserted into tumour or compressed endobronchial wall under general anaesthesia. Diathermy was used to resect obstructing tumour in four patients. When assessed at one month, 11 patients had been symptomatically improved. Both collapsed lungs and three collapsed lobes had re-expanded. Survival ranges from two weeks to 22 months. One patient with recurrent symptoms after 10 months has undergone a further implantation.

Fine needle aspiration biopsy (FNAB) compared with fibreoptic bronchoscopy (FOB) in the investigation of peripheral pulmonary opacities

CR SWINBURN, D VEALE, ET PEEL, V WADEHRA, ST ELLIOTT, MD SUMERLING, PA CORRIS, GJ GIBSON *Departments of Res-*

piratory Medicine and Radiology, Freeman Hospital, and of Cytopathology, General Hospital, Newcastle upon Tyne, and Preston Hospital, North Shields In the investigation of peripheral pulmonary opacities suspected to be neoplastic the choice of primary diagnostic procedure lies between FNAB and FOB with cytological brushings and washings from the appropriate segment. We randomly allocated 28 such patients (18 M, 10 F, mean (SD) age 65·6 (7·1) y) with a peripheral pulmonary opacity (mean (SD) size 3·6 (1·8) cm) to initial investigation by one or other procedure to assess the diagnostic yield of each. If the first procedure failed to establish a diagnosis the other was then performed. For the purposes of the study a template constructed from a postero anterior bronchogram defined "peripheral" as the area lying beyond segmental bronchi. No adjustment was made for patient size. Lesions inside the template but within 4 cm of the anterior or posterior chest wall on the lateral radiograph were included in the study. FOB was performed routinely with careful brushing and washing of the appropriate segment. FNAB was performed with fluoroscopic screening, a 22 gauge needle being used. A maximum of three passes was made with smears prepared immediately and assessed for adequate cellularity. A diagnosis was established by the first investigation in 14/15 subjects randomised to FNAB and 1/13 randomised to FOB ($p < 0·01$). Twelve patients thus proceeded to FNAB and one to FOB as the second investigation and in these a diagnosis was established in 10 and one respectively. Overall a diagnosis of neoplasia was confirmed in 24/27 patients undergoing FNAB but in only 2/13 undergoing FOB ($p < 0·01$). One of the two patients in whom both tests were negative was subsequently found to have tuberculosis and the other had a carcinoma. In the investigation of peripheral pulmonary opacities, provided that good screening and cytological facilities exist, fine needle aspiration biopsy is more likely to establish a diagnosis than fibreoptic bronchoscopy.

Preoperative oesophageal function studies in patients being evaluated for lung tumour surgery

J OLAK, HR PAYNE, C FORRESTER-WOOD, K JEYASINGHAM There are several anecdotal reports of patients who have undergone lung surgery developing altered oesophageal motility after a variable interval of time. Objective evaluation of oesophageal function before and after lung surgery is lacking in such reports. As part of a prospective study, 101 patients (76 males and 25 females), with a mean age of 65·3 years, underwent upper gastrointestinal endoscopy, manometry, and prolonged pH studies. Forty one of 49 patients who subsequently underwent pneumonectomy had abnormal manometry. The lower oesophageal sphincter tone was subnormal in 15 patients, eight of whom had normal results in pH studies and endoscopies, while five had normal results in endoscopy and one in pH studies. Twenty of these patients also had disordered motor activity in the body of the oesophagus, and 15 showed no response in the lower oesophageal sphincter to an oncoming swallow peristalsis. Of 46 patients who subsequently underwent a lobectomy, 34 had abnormal manometry, 16 of whom had a low tone in the lower oesophageal sphincter which correlated with abnormal pH results in only four patients, three of whom had abnormal endoscopy. Nine patients showed disordered motor activity and 12 showed no response in the lower oesophageal sphincter to an oncoming swallow peristalsis. Among six patients who subsequently underwent segmental or wedge resection of lung, manometry was normal in only one. There was no correlation to results of pH studies, which were normal in five, or of endoscopy, which were normal in four. Overall, 79% (80/101) showed abnormal manometry. Results of prolonged pH studies were abnormal in 16% (12/75) and of endoscopy in 16·3% (13/80). It is concluded that patients being evaluated for lung tumour surgery do appear to have a high incidence of oesophageal motility disorders. The report of postoperative abnormality as resulting from surgery should really be accompanied by appropriate preoperative data in the respective patients. The correlation of manometric, pH, and endoscopic findings is weak in the group under discussion.

Histamine production by bacteria associated with chronic respiratory infection

GDW CROOK, RD MURDOCH, HC TODD, PJ COLE Host Defence Unit *Cardiothoracic Institute, Brompton Hospital,* and *Division of Medicine, Guy's Campus, UMDS, London* Histamine in the sputum of chronic bronchitics is increased during exacerbation. The increase in histamine content during incubation of sputum in vitro at 37°C is abolished by addition of antibiotic. Sheinman *et al* (*Br Med J* 1986;**292**:857–8) showed 7/12 strains of *Haemophilus influenzae* to produce histamine when cultured in histidine enriched broth. We asked whether other bacteria associated with chronic respiratory infection possessed this property. Eleven strains (10 clinical isolates, one NCTC) each of uncapsulated *H influenzae, H parainfluenzae, Streptococcus pneumoniae, Branhamella catarrhalis,* and *Staphylococcus aureus* and 20 strains (nine clinical isolates, one NCTC) each of mucoid and non-mucoid *Pseudomonas aeruginosa* were incubated in broth with added histidine for 18–20 hours at 37°C and the supernatant fluids filtered and stored at −20°C. Identically treated but uninoculated broth was used as control. Samples were extracted by the method of Granerus and Wass (*Agents Actions* 1984;**14**:341–5) and histamine measured using a fluorimetric assay corroborated by HPLC. Control broth contained 65·8 (20·8) ng/ml histamine. The number of strains producing significant amounts ($p < 0·01$) of histamine were 10/11 *H parainfluenzae*, 2/11 uncapsulated *H influenzae*, 1/10 non-mucoid and 3/10 mucoid *P aeruginosa*. Only *H parainfluenzae* (nine strains) produced >140 ng/ml histamine (range 140–2000, mean 738 ng/ml). We consider this result to contribute to the increasing evidence (Rhind *et al, Br Med J* 1985;**291**:707–8) that *H parainfluenzae* may be a pathogen in the respiratory tract.

Variation in histamine synthesis by Gram positive and negative respiratory tract bacteria

JL DEVALIA, D GRADY, Y HARMANYERI, S TABAQCHALI, RJ DAVIES *St Bartholomew's Hospital, London* Recently we

have shown that sputum of patients with acute exacerbations of chronic bronchitis and cystic fibrosis contain large amounts of histamine, which might have an important role in the production of the inflammation and airflow limitation which characterise these diseases. Although we have also recently shown that *Haemophilus influenzae* can synthesise histamine in vitro, this is not the only pathogenic bacterium isolated during infection. The purpose of this study was to determine whether other bacterial pathogens—namely, *Branhamella catarrhalis, Haemophilus parainfluenzae, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae*—isolated from purulent sputum were capable of synthesising histamine in vitro. The Gram negative species *B catarrhalis, H parainfluenzae* and *P aeruginosa* synthesised histamine when cultured in histidine enriched growth medium. Of these *H parainfluenzae* was the most efficient and five out of six isolates produced increases in histamine levels of 128–776% (mean 395%) by 48 hours' incubation, as compared with levels at the beginning of incubation. Similarly five out of seven isolates of *P aeruginosa* produced increases of 169–511% (mean 330%) and six out of eight isolates of *B catarrhalis* produced increases of 120–283% (mean 183%). Differences between histamine levels at times 0 and 48 hours of incubation for all these species were highly significant ($p < 0.05$). Detailed analysis of growth curve characteristics of *H parainfluenzae* and *P aeruginosa* demonstrated that production of histamine was maximal by 24 hours of incubation and corresponded to the stationary phase of the growth curve for both these bacteria. The Gram positive bacteria *Staph aureus* and *S pneumoniae*, however, did not seem capable of synthesising histamine. These results suggest that pathogenic bacteria other than *H influenzae*, and especially the Gram negative species, are capable of synthesising large amounts of histamine and may have an important role in the pathogenesis of the infective lung diseases in which they predominate.

Effect of high dose antibiotics on airway responsiveness in bronchiectasis

CA KELLY, C WARD, FK GOULD, DJ HENDRICK, EH WALTERS *Department of Medicine, Newcastle General Hospital, Newcastle upon Tyne.*

Assessment of the penetration of amoxycillin and ciprofloxacin into the bronchial mucosa

D HONEYBOURNE, R LODWICK, JM ANDREWS, JP ASHBY, R WISE *Departments of Respiratory Medicine and Medical Microbiology, Dudley Road Hospital, Birmingham* We have measured the levels of two antibiotics, amoxycillin and the quinolone ciprofloxacin, in bronchial tissue obtained at fibreoptic bronchoscopy and in venous blood. Nine patients took 500 mg tds of oral amoxycillin for four days prior to bronchoscopy and another 29 patients took 500 mg bd of oral ciprofloxacin for the same period of time. The last dose of antibiotic was taken on the morning of the bronchoscopy and the time noted. In addition to the samples taken for diagnostic purposes three bronchial biopsies were taken from each lung. Venous blood was taken at the same time for assay of the serum level. After ultrasonification the bronchial biopsy specimens were assayed by using *S lutea* for the amoxycillin group and *E coli* for the ciprofloxacin group as indicator organisms, with controls. The mean weight of biopsy specimens per patient was 5·1 (SD 1·5) mg in the amoxycillin (A) group and 6·5 (2·5) mg in the ciprofloxacin (C) group. The mean serum level in A group was 4·1 mg/l (2·4) and 3·0 (1·7) mg/l in C group. The mean bronchial biopsy level was 2·7 (1·2) mg/kg in A group and 4·4 (3·2) mg/kg in C group. The percentage penetration into bronchial tissue was calculated as (bronchial tissue level ÷ serum level) × 100. The penetration in A group was 75% (32%) and in C group was 147% (114); this difference was significant ($p < 0.01$). These results suggest that there is mucosal concentration of the quinolone ciprofloxacin in the lungs.

Stimulation of neutrophil locomotion by bacterial products in vitro

GJ RAS, R WILSON, H TODD, PJ COLE *Host Defence Unit, Cardiothoracic Institute, Brompton Hospital, London* In patients with chronic bronchial sepsis (CBS) a vicious circle of host derived inflammatory damage to the bronchial tree occurs (Cole, *Eur J Respir Dis* 1986;**69**(suppl 197):6–15). Neutrophils travel to the lungs but the stimulus is uncertain (Currie *et al, Lancet* 1987;i:1335–9). We asked whether the products of commonly isolated bacterial respiratory pathogens are chemotactic. Three strains of *Haemophilus influenzae* (Hi), *Haemophilus parainfluenzae* (Hpi), *Diplococcus pneumoniae* (Dp), *Staphylococcus aureus* (Sa), *Pseudomonas aeruginosa* (Pa), (mucoid and non-mucoid), and *Pseudomonas cepacia* (Pc) were isolated from sputum of patients with CBS. Overnight cultures in medium 199 cell culture fluid (supplemented with growth factors if required) were centrifuged and filtered (0·2 μmol/l). Peripheral blood neutrophils were isolated from healthy donors (3×10^6/ml) (>95% pure. A 48 well micro chemotaxis chamber (modified Boyden technique) was used to assess neutrophil locomotion. The table summarises the results ($\bar{x}$ (SD)) for neutrophils per high powered field.

	Filtrate dilutions					
Bacteria	*Neat*	10^{-1}	10^{-2}	10^{-3}	*M199*	*FMLP* 10^{-8}
Hi	45 (14)	70 (16)	63 (24)	25 (10)	25 (8)	67 (12)
Hpi	41 (19)	72 (19)	75 (18)	29 (9)	22 (7)	95 (18)
Dp	41 (10)	47 (7)	70 (10)	57 (8)	9 (4)	59 (4)
Sa	21 (5)	62 (13)	65 (15)	35 (6)	21 (7)	109 (10)
Pa mucoid	42 (9)	93 (12)	70 (15)	50 (15)	24 (4)	101 (11)
Pa non-muc	84 (13)	112 (19)	93 (19)	52 (10)	25 (11)	119 (23)
Pc	33 (15)	95 (15)	91 (17)	50 (12)	14 (2)	97 (6)

The filtrate chemotactic activities were heat stable (100°C for 30 minutes). Purified lipopolysaccharide from Hi and Pa were chemotactic at lower concentrations. We conclude that bacteria release leucoattractants which may stimulate

neutrophil locomotion into the bronchial tree in vivo.

Fungal handling by phagocytic cells from asthmatic patients sensitised and non-sensitised to *Aspergillus fumigatus*

MD ROBERTSON, DM BROWN, WM MACLAREN, A SEATON *Institute of Occupational Medicine, Edinburgh* In order to investigate why people with asthma may develop bronchopulmonary reactions to *Aspergillus fumigatus*, as opposed to many of the other fungi in the atmosphere, the possibility that there may be a defect in the handling of the fungus by such patients has been tested. A comparison of the abilities of phagocytes from asthmatic patients, both sensitised and non-sensitised to *A fumigatus*, and phagocytes from non-asthmatic subjects to bind and kill spores of *A fumigatus*, as well as the non-pathogenic fungus *Penicillium ochrochloron*, has been made. The cell association of spores with phagocytic cells was generally very high. However, compared with the control group (n = 15), monocytes from asthmatic patients sensitised to *A fumigatus* (n = 13) were significantly less efficient at killing spores of *A fumigatus* (opsonised in autologous sera) while their polymorphonuclear leucocytes (PMN) were significantly more efficient ($p < 0.05$)—mean (SEM) of % killed: monocytes 51·4 (5·1), PMN 51·1 (3·6); control group, monocytes 63·3 (4·4) PMN 35·8 (3·9). The results for the non-sensitised asthmatic patients (n = 14) generally fell between the other two groups. No such differences were found for *P ochrochloron*. It thus appears that phagocytic cells from asthmatic patients sensitised to *A fumigatus* do show significant differences in their handling of this fungus. Further work to assess the relevance of this finding in relation to the development of allergy to *A fumigatus* is being carried out. This work is supported by the Asthma Research Council.

A radioisotopic method for monitoring the rate of formation of pleural effusions

GS BASRAN, M SOLANKI, JG HARDY *University Hospital, Nottingham* Pleural effusions result from an imbalance between the rate of formation and the rate of clearance of fluid from the pleural cavity. We describe a radioisotopic method for monitoring the rate of formation of pleural fluid.

Causes of amylase rich pleural effusions

GS BASRAN, B OLDING, JT MACFARLANE *City Hospital, Nottingham*

Median sternotomy in the management of patients with bilateral recurrent pneumothoraces and bullous disease

RR JEFFREY, R AL-KHADIMI, MJ DRAKELEY *Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Liverpool* Patients who are operated on for bilateral recurrent pneumothoraces or bullous disease have traditionally undergone staged thoracotomies a few weeks apart. We report our experience of the surgical management of such patients using a median sternotomy dealing with both sides at one operation. Since 1981 17 patients have been operated on. Twelve have been referred with a persistent pneumothorax and a history of previous contralateral pneumothorax. Five have been referred with evidence of bilateral emphysematous bullae and deteriorating exercise tolerance. These five patients (mean age 52·6, range 29–68 years) had a history of chronic obstructive airways disease, while recurrent pneumothorax was typically seen in a younger age group (mean age 26·2, range 19–40 years). Preoperative pulmonary function tests were not routinely undertaken in those with pneumothorax and a chest drain in situ. At operation each lung was carefully inspected and bullae were either ligated or stapled and a pleurodesis was performed. There was no operative mortality and in those with preoperative radiographic evidence of lung compression, subsequent radiographs have demonstrated re-expansion of these areas. Measured pulmonary function also improved. The advantages of medial sternotomy over bilateral thoracotomies for other procedures have been documented by other authors. We feel that median sternotomy should be considered in suitable patients for the treatment of bilateral bullous disease or recurrent pneumothoraces.

Assessment of suction equipment commonly used for chest drainage

PS THOMAS, JS MILLEDGE *Department of Respiratory Medicine, Northwick Park Hospital and Clinical Research Centre, Harrow* For persistent pneumothorax the ideal suction would maintain a high flow in the face of a large bronchopleural air leak so as to avoid obstructing air drainage from the pneumothorax during expiration. It would not develop a high negative pressure if the leak stopped, otherwise damage could occur to the underlying lung. We bench tested four commonly used pumps (Genitourinary Tubbs, Eschmann Mattburn VP12S, Roberts (Medcalf Bros)) and a low pressure regulator (LPR) (Medishield) on the hospital main suction line. The negative pressure and flow achieved was measured with a chest tube either open or occluded. Measurements were repeated at various pressure settings if available. Only the LPR came close to providing ideal performance. Pumps other than the Tubbs were unable to maintain a negative pressure with the tube wide open and produced undesirably high negative pressure when it was occluded. The Tubbs was intermediate in performance. A survey of six district general hospitals and four teaching hospitals (three with thoracic surgical units) showed that the former all relied on suction pumps; two also used a Tubbs pump. Three of the four teaching hospitals used LPR but only in one case was this used on the wards. We suggest that the LPR on wall suction provides the best suction for underwater seal chest drainage in persistent pneumothoraces.

Differentiation of malignant mesothelioma from reactive pleural tissue by enumeration of nucleolar organiser regions using the AgNOR technique

J CROCKER, JG AYRES, NQ SKILBECK *Departments of Histopathology and Respiratory Medicine, East Birmingham Hospital, Birmingham* Nucleolar organiser regions (NORs) represent areas of ribosomal DNA on certain chromosomes from which ribosomal RNA is formed and their numbers per nucleus reflect nuclear activity. By the use of a simple argyrophilic staining method (the AgNOR technique) which can be used on paraffin sections, several malignancies from various tissues have been shown to have greater numbers of AgNORs per cell than normal, and in lymphomas the number of AgNORs related to the grade of malignancy (Crocker, *J Pathol* 1987;**151**:111–8). We applied this method to sections of pleural tissue in an attempt to differentiate between malignant and reactive conditions of the pleura. The mean (SD) number of AgNORs in 10 examples of normal pleura was 1·04 (0·11) and in 10 reactive examples was 1·75 (0·55) ($p < 0·001$). In the four types of malignant mesothelioma the corresponding values were tubulopapillary ($n = 10$), 5·43 (1·34); undifferentiated ($n = 5$), 5·00 (1·23); sarcomatous ($n = 5$), 7·52 (2·56); mixed histology ($n = 5$), 4·94 (1·25) (all values $p \ll 0·001$ compared with both normal and reactive tissue). We conclude that this technique readily separates malignant from reactive pleural tissue and, for the first time, demonstrates a difference in nucleolar activity in an inflammatory condition.

Role of fibreoptic bronchoscopy in early diagnosis of smoke inhalation injury

CJ CLARK, J KINSELLA, WH REID, D CAMPBELL *Department of Respiratory Medicine, Hairmyres Hospital, and Royal Infirmary, Glasgow* There has been increasing use of fibreoptic bronchoscopy in the critical care setting and recently it has been suggested that direct visualisation of the bronchial tree is essential in diagnosing the extent of inhalation injury. In this study 25 patients underwent fibreoptic bronchoscopy following smoke inhalation. The endoscopic appearances could be graded into four categories on the basis of visual inspection by an experienced bronchoscopist, consisting of normal mucosa ($n = 1$), soot deposits of variable quantity diminishing the light reflex but without visible mucosal inflammatory changes ($n = 3$), inflammatory changes with/without soot but without distortion of endobronchial architecture ($n = 14$), and inflammatory changes consisting of oedema, sloughing, or denudation of mucosa altering the endobronchial architecture ($n = 7$). Bronchoscopy abnormalities showed no correlation with other established criteria of smoke inhalation injury (Clark *et al, Lancet* 1981;i:1332) including clinical score and exposure carboxyhaemoglobin (COHb) concentration. Only patients with severe (category 4) changes had non-viability of the airway requiring early intubation and all seven patients with severe changes had concomitant orofacial burns, indicating that these appearances were due to direct thermal trauma rather than smoke injury. A good yield of particulate debris was obtained in most cases during bronchoscopy with a wide suction channel (Olympus BFIT). This study indicates that fibreoptic bronchoscopy is not necessary for the early diagnosis of pure smoke inhalation injury but should be considered (1) as a diagnostic aid in patients with facial burns injuries affecting "respiratory areas" to allow a decision regarding elective intubation and (2) as a possible *treatment* aid for the removal of retained secretions in patients with severe smoke inhalation.

Bradykinin induced bronchoconstriction: inhibition by nedocromil and cromoglycate

CMS DIXON, PJ BARNES *Department of Clinical Pharmacology, Cardiothoracic Institute, Brompton Hospital, London* Bradykinin is a potent inflammatory mediator which may contribute to bronchoconstriction in asthma. In man bradykinin inhalation causes cough, retrosternal discomfort, and dose dependent bronchoconstriction in asthmatic but not in normal subjects. Bradykinin induced bronchoconstriction is inhibited by inhaled cholinergic antagonists, suggesting that the bronchoconstriction may be due in part to a cholinergic reflex. We have examined the effect of nedocromil and cromoglycate, which are effective in blocking several bronchoconstrictor stimuli which involve neural reflexes. We compared pretreatment with nedocromil (4 mg), cromoglycate (10 mg), and matched placebo on bronchoconstriction induced by inhaled bradykinin in a double blind, randomised study of eight subjects with mild asthma. After baseline measurements of flow at 70% of original vital capacity from a forced partial flow volume manoeuvre (Vp_{30}) the drugs or matched placebo were administered. Vp_{30} measurements were repeated at +5 and +10 min and at 15 min a dose-response to inhaled bradykinin was obtained with doubling concentrations (0·25–8·0 mg/ml). Vp_{30} was repeated 60 and 90 seconds after each concentration until a fall of greater than 40% from control was recorded. The provocative dose of bradykinin causing a 40% fall in Vp_{30} (PD_{40}) was then calculated. Baseline Vp_{30} did not differ on any of the study days and there was no change after drug administration. Geometric mean PD_{40} (95% confidence interval) was 0·035 μmol (0·02–0·07) after placebo, 0·22 (0·11–0·44) after cromoglycate, and 0·37 (0·19–0·72) after nedocromil. Nedocromil and cromoglycate both significantly protected against bradykinin induced bronchoconstriction when compared with placebo ($p < 0·05$). As bradykinin is not known to degranulate mast cells these results confirm that the mode of action of nedocromil and cromoglycate involves mechanisms other than stabilisation of mast cells.

Inhibition of AMP induced bronchoconstriction in non-atopic asthma by sodium cromoglycate and nedocromil sodium

VL SCOTT, GD PHILLIPS, R RICHARDS, ST HOLGATE *Department of Immunopharmacology, University of Southampton* Inhaled adenosine and adenosine 5'-monophosphate (AMP) cause bronchoconstriction in both atopic and non-atopic asthma, probably by potentiating preformed mediator release from bronchial mast cells. Sodium cromoglycate (SCG) and nedocromil sodium (N) are drugs

with stabilising properties against lung mast cells. In this study the effect was observed of prior inhalation of nebulised SCG (7·7 (SD 0·6) mg) and N (7·5 (0·6) mg), administered in randomised, double blind fashion, on AMP induced bronchoconstriction in 11 non-atopic asthmatic subjects, mean age 56·8 (4·1) years. In the first phase of the study the geometric mean (range) provocation doses of methacholine and AMP required to produce a 20% decrease in FEV_1 from post-saline baseline values (PD_{20} FEV_1) were shown to be 2·4 (0·4–60·3) and 28·1 (3·4–780·2) mg/ml respectively, representing a potency difference of 5·2 fold on a molar basis. In the second phase of the study mean PC_{20} FEV_1 values for AMP after preinhalation of nebulised placebo. SCG and N were 4·9 (0·3–54·4), 46·5 (2·2–1123·8), and 107·9 (5·4–1123·8) μmol respectively. Thus, when compared with placebo, SCG and N produced mean shifts to the right of the AMP concentration-response curve of 9·6 ($p < 0·01$) and 22·2 ($p < 0·01$) fold respectively, N being significantly more potent than SCG ($p < 0·05$). These data support the view that SCG and N protect against AMP induced bronchoconstriction by similar mechanisms.

IgG dependent generation of platelet activating factor by normal and "low density" human eosinophils

A CHAMPION, AJ WARDLAW, R MOQBEL, AB KAY *Cardiothoracic Institute, Brompton Hospital, London* Platelet activating factor (PAF) is an inflammatory mediator which has been shown to cause bronchoconstriction and bronchial hyperreactivity. It acts on and is produced by several cell types, including mast cells, basophils, monocytes, platelets, and neutrophils. PAF generation by eosinophils following a physiological stimulus is not well documented. We have compared generation of PAF by normal and low density eosinophils and neutrophils in response to stimulation by IgG coated particles, previously shown in our laboratory to stimulate leukotriene release from these cells (Shaw RJ *et al, Nature* 1985;**316**:150–2). The chemotactic peptide f-Met-Leu-Phe (fMLP) was used to study the effect of IgG (Fc) receptor enhancement. Maximal PAF generation was achieved with the calcium ionophore A23187. Initial observations suggested that all cell types studied generated PAF in a dose and time dependent manner, with a substantial proportion remaining cell associated (37–76%, 41–50%, and 53–96% in normal eosinophils, low density eosinophils, and neutrophils respectively). Amounts of PAF generated and released varied between individuals with values (at the optimal dose and time) in the range 1·8–3·9 ng/10^6 cells for normal eosinophils, 1·5–2·1 ng/10^6 for "low density" eosinophils, and 0·7–1·5 ng/10^6 cells for neutrophils. This variation was reflected in the values of PAF generated with A23187 as a stimulus. The IgG stimulus generated 11·5–20% (normal eosinophils), 12·8–16% ("low density" eosinophils), and 4·7–16·1% (neutrophils) of the PAF generated by A23187. Enhancement by fMLP was observed in some cases, but this was not a consistent finding. We suggest that eosinophils can generate and release PAF in amounts comparable with neutrophils and may in this way contribute to the complex inflammatory changes known to be associated with asthma and other obstructive lung diseases.

Allergen induced generation of a T cell derived neutrophil chemotactic factor

P MAESTRELLI, J-J TSAI, RE O'HEHIR, AB KAY *Department of Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* As part of a series of studies to define the role of cell mediated immunity in atopic asthma we have measured neutrophil chemotactic activity (NCA) in serum free supernatants from human blood mononuclear cells. Initial studies with cells stimulated with the lectin phytohaemagglutinin showed that NCA was eluted as a single major peak of molecular weight 10 kD following gel filtration. The activity was apparently distinct from interleukin-1, interleukin-2, granulocyte/monocyte colony stimulating factor, tumour necrosis factor, and γ interferon. T lymphocytes were identified as a cell source of NCA (LD-NCA) since human peripheral blood mononuclear cells stimulated with anti-CD3 monoclonal antibody (OKT3) also induced the generation of appreciable amounts of 10 kD NCA. Subsequent experiments using long term human T cell lines (CD4+, CD8+) reactive with house dust mite (*Dermatophagoides farinae*) (O'Hehir RE *et al, Immunology*, in press) and human T cell clones (CD3+, CD4+) reactive with influenza virus antigens (Lamb JR *et al, J Immunol* 1982;**128**:233) produced a comparable 10 kD NCA when stimulated with the inducing antigen together with irradiated antigen presenting cells. These findings indicate that the NCA is derived from T lymphocytes, secretion being induced by stimulation of the antigen receptor. The results support the view that allergen derived LD-NCA might have a role in allergic inflammation.

Metabisulphite induced bronchoconstriction does not involve mast cells

CAROLINE MS DIXON, PHILIP W IND *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Inhaled metabisulphite induces dose dependent bronchoconstriction in atopic non-asthmatic subjects and those with mild asthma but not in normal subjects. This bronchoconstrictor response is completely prevented by prior inhalation of nedocromil sodium, which in vitro inhibits mast cell degranulation. Mast cell involvement in the mechanism of induced bronchoconstriction is supported by an inhibitory action of specific antihistamines. We have investigated the effect of terfenadine, a potent selective H_1 receptor antagonist, on sodium metabisulphite induced bronchoconstriction. We studied six atopic subjects (three with mild asthma, three male) with reproducible bronchoconstrictor responses to inhaled metabisulphite on two study days. In random order, subjects received orally 180 mg terfenadine or matched placebo, three hours before a metabisulphite dose-response curve was obtained. Specific airways conductance (sGaw) was determined as the mean of six readings by computerised body plethysmography. sGaw was measured after inhalation of increasing concentrations of metabisulphite (5–100 mg/ml) from a breath actuated dosimeter, until a fall of greater than 35% from baseline values was recorded. The PD_{35}—that is, the provocative dose of metabisulphite causing a 35% fall in sGaw—was cal-

culated by interpolation in each case. Terfenadine had no significant effect on metabisulphite induced bronchoconstriction. The metabisulphite PD_{35} geometric mean (95% confidence interval) after placebo was 28·1 (10·4–75·8) μmol and 23·4 (10·6–51·8) μmol after terfenadine. These results do not support the involvement of histamine in metabisulphite induced bronchoconstriction and suggest a non-mast cell stabilising action for nedocromil in vivo.

Contractile activities of lipoxin A4 and B4 on guinea pig airways

CAJ JACQUES, BW SPUR, AE CREA, TH LEE *Department of Medicine, Guy's Hospital, London* Lipoxin A4 (LxA4) and lipoxin B4 (LxB4) are arachidonic acid derived metabolites produced through an interaction between the 5- and 15-lipoxygenase pathways. The compounds have been prepared by total chemical synthesis and their isometric contractile activities for guinea pig lung tissue were evaluated over the concentration range of 10–8 to 10–5 mol/l. LxA4 contracted guinea pig lung parenchymal strips but not tracheal spirals and the concentration eliciting 50% of the maximum histamine response was 3 × 10–6 mol/l. The LxA4 dose-response curve was parallel to that of leukotriene D4 (LTD4), LxA4 being approximately 10 000 fold less potent than LTD4. The time course of the contraction elicited by LxA4 was similar to that of LTD4 and it was slow in onset and did not plateau for 20 minutes. Preincubation of parenchymal strips with 1 × 10–6 mol/l to 3 × 10–5 mol/l FPL 55712 inhibited LxA4 activity in a dose dependent manner. The displacement of the LxA4 dose response curve by FPL 55712 occurred throughout all the active concentrations of LxA4 studied, whereas FPL 55712 inhibited the contractile response of parenchymal strips only to 10–9 mol/l LTD4. Preincubation of tissues with 1 × 10–6 mol/l and 1 × 10–5 mol/l L 651392, a 5-lipoxygenase inhibitor, or 1 × 10–5 mol/l indomethacin, a cyclo-oxygenase inhibitor, did not affect the contractile activity of LxA4. LxB4 did not constrict parenchymal strips or tracheal spirals.

Functional capacity of macrophages and lymphocytes in the bronchial inflammation of bronchiectasis

JRL SILVA, JAH JONES, PJ COLE, LW POULTER *Host Defence Unit, Cardiothoracic Institute, Brompton Hospital and Department of Immunology, Royal Free Hospital School of Medicine, London* We have previously shown that in bronchiectasis the bronchial epithelium and lamina propria contain increased numbers of lymphocytes which are of cytotoxic/suppressor CD8+ve phenotype. We now report the expression of functionally relevant molecules on these cells and on non-lymphoid mononuclear cells in bronchiectasis. Lymphocytes and macrophage like cells in frozen sections of biopsy material from 15 bronchiectatic patients and four non-bronchiectatic controls have been examined by using monoclonal antibodies selected to identify functionally relevant molecules as activation markers on lymphocytes and acid phosphatase activity in macrophage like cells. Most lymphocytes were T cells, of which >60% were CD8+ve. These cells were found associated with the epithelium and in clusters deeper in the lamina propria, and they expressed a phenotype of CD8+ve, CD7+ve, RFT10+ve, CD25−ve, SN130−ve, RFDR±. Of these cells only 30% were CD5+ve. These results suggest that most of the CD8+ve population was immunologically committed (SN130−ve) and activated (RFT10+ve, CD7+ve), although only a minority expressed IL2 receptors. The expression of HLA-DR was difficult to assess owing to intense DR reactivity throughout the section. Most of the macrophage like cells identified with RFD1 were negative for acid phosphatase (ACP) while more RFD7+ve cells were ACT+ve. A population of ACP+ve cells negative for both markers was seen, possibly representing monocytes. These results support the hypothesis that the inflammatory reaction in bronchiectasis results at least in part from a cell mediated immune response.

Suppression of cytotoxic lymphocyte function by pulmonary surfactant

ML WILSHER, DA HUGHES, PL HASLAM *Cell Biology Unit, Cardiothoracic Institute, London* Alveolar natural killer cells (NKC) obtained by bronchoalveolar lavage (BAL) function poorly compared with those obtained from blood or lung interstitium. Having established that pulmonary surfactant suppresses lymphocyte responses to mitogens and alloantigens we sought to determine if surfactant has a similar effect on cytotoxic function. Surfactant lipids were purified from the BAL fluid of normal volunteers. Peripheral blood lymphocytes were obtained from 10 young adult volunteers and cultured overnight in the presence or absence of surfactant (0·2 mg/ml). Standard NKC assays were performed with a K562 tumour cell line, and antibody dependent cytotoxicity (ADCC) testing with Chang liver cells. Both NKC and ADCC activity was significantly depressed in the surfactant cultured lymphocytes (NK 68% (25%), control (SD), $p = 0{\cdot}01$; ADCC 68% (17%), $p < 0{\cdot}01$). These effects were seen at all effector to target cell ratios and were dose dependent. Further studies using pure phospholipids (phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylglycerol (PG) instead of surfactant were performed in six subjects. No effect was seen with PC preincubated cells, whereas PG suppressed and PE enhanced both NKC and ADCC functions. These results suggest that in normal circumstances pulmonary surfactant may suppress cytotoxic responses in the alveolus and that imbalances in its phospholipid profile might affect this immunoregulatory activity. (Supported by the Wellcome Trust, Medical Research Council of New Zealand and the Chest, Heart and Stroke Association.)

Release of IL-1 and TNF by alveolar macrophages from patients with bronchial carcinoma

AP GREENING, FS DI GIOVINE, JA SYMONS, NE WOOD, GW DUFF *Respiratory and Rheumatic Diseases Unit, Northern General Hospital, Edinburgh* Interleukin 1 (IL-1) and tumour necrosis factor (TNF) are cytokines thought to have

an important role in host defence through their effects on inflammatory and immune responses. These peptides are produced by macrophages and their production may be induced by several different stimuli. We tested whether the presence of tumour altered alveolar macrophage release of these cytokines in vitro. Alveolar macrophages (AM) were obtained by bronchoalveolar lavage from nine patients with bronchial carcinoma and 12 patients with no carcinoma (three with no active pulmonary disease; four with interstitial lung diseases; five with recent pneumonia). AM were enriched by plastic adherence and cultured at 1×10^6 cells/ml in RPMI 1640 with or without *Escherichia coli* lipopolysaccharide (LPS) at 10 ng/ml or 100 ng/ml. After 24 hours, cell free culture supernatants were removed and stored at $-20°C$ until tested for cytokine content. IL-1 activity was measured in the EL4/CTLL conversion assay and TNF activity was measured in the conventional L929 cytotoxicity assay. All tests were performed in triplicate and pooled results (mean (SEM)) are given in the table.

	Controls (ng/ml)		*Bronchial carcinoma (ng/ml)*	
	IL-1	*TNF*	*IL-1*	*TNF*
Unstimulated	2·7 ± 0·8	7 ± 3	2·4 ± 1·4	0·6 ± 0·2
+ LPS10 ng	14 ± 4	90 ± 34	3·0 ± 1·0	13 ± 7
+ LPS100 ng	21 ± 10	89 ± 35	5·0 ± 1·4	33 ± 19

Unstimulated and LPS stimulated TNF release and LPS stimulated IL-1 release were all significantly lower in the bronchial carcinoma group. Although the control group was heterogeneous, these results suggest a defect in alveolar macrophage cytokine production in bronchial carcinoma.

Lymphocyte subsets in bronchoalveolar lavage (BAL) fluid in asthma

CA KELLY, CS STENTON, C WARD, G BIRD, DJ HENDRICK, EH WALTERS *Department of Medicine, Newcastle General Hospital, Newcastle upon Tyne* We have previously reported an increase in BAL lymphocytes in asthmatics. Bronchial responsiveness to methacholine (PD_{20} FEV_1) was assessed in 22 asthmatic patients five days prior to BAL. A PD_{20} FEV_1 could not be attained in 20 matched controls with normal pulmonary function. BAL was performed in all subjects, 3×60 ml aliquots being introduced into a segment of the middle lobe and immediately aspirated into siliconised glassware at 4°C. Cells were counted, and the cell pellet was resuspended in medium 199. Cytospin slides were prepared and a differential cell count was performed. Lymphocyte subsets were identified by labelling further slides with monoclonal antibodies against T3, T4, T8, and B cell markers. The mean (SD) lymphocyte counts are shown as cells $\times 10^8$/l.

	Total	*T3*	*T4*	*T8*	*B*
Asthmatics	0·34* (0·3)	0·25 (0·3)	0·16 (0·2)	0·12* (0·1)	0·02 (0·02)
Controls	0·19* (0·1)	0·14 (0·1)	0·08 (0·09)	0·06* (0·05)	0·02 (0·02)

*$p < 0.05$.

The mean T4/T8 ratio was similar in asthmatics (1·51) and controls (1·45). Log PD_{20} FEV_1 correlated positively with total lymphocyte counts ($r = 0.44$, $p < 0.05$) and with total T8 counts ($r = 0.50$, $p < 0.05$). The correlations between bronchial responsiveness and T3 ($r = 0.36$), T4 ($r = 0.29$), and B ($r = 0.17$) lymphocyte numbers all failed to reach significance, and there was no correlation with T4/8 ratios. The increase in BAL lymphocyte counts in asthma appears to be due to an absolute increase in T cell subsets, and is greatest in patients with mild asthma.

Early alveolitis in patients with primary biliary cirrhosis

MA SPITERI, MA JOHNSON, O EPSTEIN, S SHERLOCK, SW CLARKE, LW POULTER *Department of Thoracic Medicine, Medical Unit, and Department of Immunology, Royal Free Hospital and School of Medicine, London* Subclinical alveolitis may occur in patients with primary biliary cirrhosis (PBC) with no clinical or radiological evidence of pulmonary involvement. It is as yet unknown whether this phenomenon is controlled by similar immunopathological mechanisms as PBC, thus representing an early stage of granulomatous disease of the lung in this disease. To investigate this question bronchoalveolar lavage (BAL) was performed on 10 patients with PBC but with no symptoms of chest disease. Seven of these patients showed evidence of pneumonitis (raised total lymphocyte count 1.7×10^9 cells, lymphocytosis 30%). The lymphocyte populations of these patients were analysed with McAbs to determine phenotype and potential immunocompetence. The results were compared with those from groups of normal controls and patients with established granulomatous disease of the lung. Our results revealed raised proportions of CD4+ T cells (12% of total mononuclear cells) in six of seven patients; this was lower than in patients with established sarcoidosis (20% of total mononuclear cells). In one patient with lymphocytosis CD8+ cells predominated. In all seven cases, however, over 80% of the BAL T cells expressed signs of activation (HLA.DR+, UCHL1+, SN130−). This phenotype suggests that these cells are actively involved in local immunological reactions. Our data support the hypothesis that alveolitis in PBC is consistent with that found in granulomatous interstitial lung disease. However, this suggestion does not exclude the possibility that other factors may cause alveolitis in PBC patients.

A model of lung injury in man

GM ROCKER, MS WISEMAN, D PEARSON, DJ SHALE *Respiratory Medicine Unit and Department of Medical Physics, City Hospital, Nottingham* Lung injury follows various precipitants, which probably initiate common inflammatory pathways, leading to loss of integrity at the capillary-alveolar barrier and the adult respiratory distress syndrome (ARDS). Direct and indirect lung injury sustained at oesophagectomy was studied in nine subjects. Pulmonary vascular permeability, determined as the accumulation in the lung of transferrin (Rocker *et al, Thorax* 1987;**42**:620–3) was significantly increased eight hours after surgery, with return to

baseline by 24–48 hours. Significant and progressive reduction in oxygenation (Pao_2:Fio_2) occurred from 8 ($p = 0.003$) to 48 hours. Plasma lactoferrin concentration was maximal at 8 hours ($p = 0.001$), returning to baseline by 48 hours, while the absolute neutrophil count rose significantly at 8 hours ($p = 0.005$) and remained so up to 48 hours. This suggests that by 24 hours fewer circulating neutrophils were activated. The peripheral platelet count was reduced by 8 hours ($p = 0.024$) and remained so up to 48 hours. Maximum reductions in the absolute lymphocyte and eosinophil counts occurred at 8 and 24 hours respectively ($p < 0.001$ and $p = 0.016$). Postoperatively these patients exhibited reported features of ARDS, including hypoxaemia, neutrophil activation, thrombocytopenia, and increased pulmonary vascular permeability. Most studies of inflammatory mechanisms in lung injury have been carried out in animal models or established ARDS in man and have not provided information leading to early diagnosis or effective treatment. Patients at risk have rarely been studied owing to the difficulties of timing changes in relation to the original insult. Study of patients experiencing a defined surgical event provides an opportunity for the investigation of the initial inflammatory mechanisms underlying lung injury in man.

Prospective study of lung function abnormalities in human immunodeficiency virus (HIV) infected patients with and without pneumonitis

DM MITCHELL, RJ SHAW, C ROUSSAK, CM STONEHAM, SM FORSTER, JRW HARRIS, AJ PINCHING *St Mary's Hospital, London* Pulmonary function was measured in 169 male patients seropositive for HIV. Symptom free patients and patients with persistent generalised lymphadenopathy (PGL) had normal (>83% predicted) diffusing capacity for carbon monoxide (TLCO). Patients with AIDS related complex (ARC), non-pulmonary Kaposi sarcoma (non-pulm KS), and non-pulmonary, non-Kaposi sarcoma AIDS (non-pulm AIDS) had mean (SD) reductions in TLCO to 77% (18%), 70% (17%), and 70% (10%) of predicted values respectively ($p < 0.05$, < 0.01, < 0.01). Further reductions to 50% (19%) and 63% (16%) predicted were seen during acute and recovery phases of *Pneumocystis carinii* (PCP) pneumonia ($p < 0.001$, < 0.001); reduced values were also seen in AIDS patients with lung mycobacterial infection or lung Kaposi sarcoma. Tests were repeated on patients at three monthly intervals. No reductions in TLCO occurred in symptom free patients over nine months or in PGL patients over 12 months. A gradual decline in TLCO in ARC patients was seen over nine months (77% (18%) →63% (13%; $p < 0.05$). Following PCP the TLCO improved from 50% (19%) to 79% (18%) at six months ($p < 0.01$), whereas patients who had already recovered from an episode of PCP when first tested had no improvement over 6 months (63% (16%) → 61% (21%). Non-pulm KS patients also failed to improve over 9 months (70% (17%) → 71% (24%). These results show abnormalities of TLCO in pulmonary AIDS, ARC, and non-pulmonary AIDS, emphasising the need to interpret lung function data in HIV related disease in the clinical and radiological context of the individual patient. TLCO improves in those who recover from PCP. It is unlikely that abnormalities seen in ARC and non-pulmonary AIDS are due to subclinical pulmonary infection at the time of testing as the follow up study showed no further significant deterioration.

Lung ^{99m}Tc DTPA transfer in patients with lung infections

MJ O'DOHERTY, CJ PAGE, DN CROFT, NT BATEMAN *Departments of Nuclear Medicine and Chest Medicine, St Thomas's Hospital, London* Lung ^{99m}Tc DTPA transfer is substantially altered in patients who are HIV antibody positive with *Pneumocystis carinii* pneumonia (PCP). We have extended our previous study (MJ O'Doherty, *et al, Genitourinary Med* 1987;**63**:268–70) and found in 12 patients with PCP that the DTPA transfer curve becomes biphasic and the first component is rapid with a T_{50} (or half time transfer value) of two minutes. Ten patients with bacterial lung infections were studied—six had mycobacterial infections (one patient was HIV antibody positive), two pneumococcal pneumonia, one staphylococcal pneumonia, and one legionella. The transfer curves and times were examined over all lung regions and over the regions abnormal on chest radiographs. One patient (legionella) had a single area in which there was a curvilinear plot but with no fast initial component (T_{50} 20 min). All T_{50} values were greater than 20 minutes in these infections. It is probable that PCP and bacterial infections can be distinguished by the DTPA transfer technique.

Trends in bronchoscopic diagnosis of lung disease in AIDS: implications for management

DR BUCHANAN, ND FRANCIS, D COLEMAN, RJ SHAW, D ROBINSON, AW BOYLSTON, AJ PINCHING, D MITCHELL *St Mary's Hospital, London* One hundred and seventy five consecutive bronchocoscopic examinations were carried out on 161 HIV positive patients from June 1983 to August 1987. All were homosexual or bisexual men, 21–52 (mean 38) years. Bronchoscopy was performed to exclude opportunistic lung infection on the basis of respiratory symptoms, radiographic shadowing, and carbon monoxide transfer factor <60% predicted. The mean Pao_2 breathing air was 65 mm Hg (range 49–100 mm Hg) and TLCO 54% (7%) predicted. The numbers of bronchoscopic examinations have substantially increased over four years, from five bronchoscopies in 1983 to 15 per month in August 1987. One hundred and twenty eight paired biopsy and cytology samples of 118 patients were reviewed. The sensitivity of bronchoscopy specimens for diagnosing *Pneumocystis carinii* pneumonia was 79% for transbronchial touch preparations, 66% for transbronchial biopsies, and 34% for bronchial lavage. There was no significant difference between transbronchial touch preparations and biopsy in diagnosing *Pneumocystis carinii* pneumonia (PCP) ($p > 0.1$). Twenty four per cent of patients had multiple infections or Kaposi's sarcoma (KS). Biopsy was more useful than cytology in the diagnosis of simple bacterial or mycobacterial infections or Kaposi's sarcoma, with positive cytological correlation in only six of the infections. Complications included haemoptysis, significant post-biopsy bleeding (>50 ml) in 3% patients, fever, and

infection. The incidence of pneumothorax is 8%, over half requiring intercostal tube drainage. With the incidence of AIDS and HIV infection increasing in the general hospital population, the number of bronchoscopic examinations is doubling yearly. Clinical and laboratory work load considerations should take account of the need for early and accurate diagnosis by bronchoscopy with biopsy and cytology, especially in those conditions which mimic and coexist with PCP.

Pneumonia in patients with AIDS: is empirical treatment justified?

AB MILLAR, RF MILLER, IVD WELLER, SJG SEMPLE *University College and Middlesex School of Medicine, London* It has been suggested that "high risk" patients presenting with respiratory symptoms suggestive of *Pneumocystis carinii* pneumonia (PCP) may be empirically treated with cotrimoxazole, and only require fibreoptic bronchoscopy (FOB) if clinical improvement does not occur within five to seven days (AL Pozniak *et al, Br Med J* 1987;**291**:797–9). We have studied 58 consecutive male patients (antibody positive for the human immunodeficiency virus) presenting with respiratory symptoms, to determine the outcome of such a policy. Patients were assigned to either group A (typical history, examination, arterial blood gases, and chest radiograph (CXR)—empirical treatment appropriate), or group B (atypical history, examination, blood gases, or CXR—require FOB to elucidate diagnosis). Subsequently, all patients were to undergo FOB with bronchoalveolar lavage and transbronchial biopsy. Four patients were excluded, one refused, and three were too ill for FOB. In group A there were 37 patients: 33 (89%) had PCP (in one case as a copathogen with *Staph aureus*). Four cases were not PCP, one had *Strep pneumoniae*, one lymphoid interstitial pneumonitis (LIP), one upper respiratory tract commensals. In one case FOB was negative, but a clinical and radiographic response occurred with co-trimoxazole treatment, suggesting that the patient had PCP. In group B there were 17 patients: four had PCP alone (24%), one had PCP with *M tuberculosis*; in six patients FOB was negative, and in the remainder various bacterial pathogens were isolated which indicated the appropriate therapy. The institution of an empirical treatment policy would have resulted in five errors in group A; two patients with LIP and with PCP with a copathogen (*Staph aureus*), would have undergone FOB after five to seven days owing to lack of clinical improvement. Two remaining patients had respiratory infections that were treated satisfactorily with co-trimoxazole, although at a greater dose and duration than is usual. One case had probable though unproved PCP. Institution of empirical treatment as suggested would have avoided 37 (68·5%) of initial bronchoscopies. We conclude that this approach is justified in these patients.

Pulmonary complications after cardiac transplantation

R FREEMAN, PA CORRIS, K GOULD, CGA MCGREGOR *Regional Cardiothoracic Centre, Freeman Hospital, Newcastle* We have reviewed early and late pulmonary complications of orthotopic cardiac transplantation in the first 20 patients undergoing this operation at Freeman Hospital. There were 16 men and four women and all had cardiomyopathy of ischaemic heart disease. None had evidence of pulmonary infiltrates immediately prior to surgery and all received narrow spectrum flucloxacillin prophylaxis alone over the perioperative period. Immunosuppression comprised cyclosporin A, azathioprine, and prednisolone, with 10 patients receiving additional prophylactic antithymocyte globulin in the week. Ten patients developed radiographic opacities prior to first discharge and a definitive diagnosis was made in all cases, samples for bacteriology and cytology being obtained by transtracheal aspiration, bronchoalveolar lavage, or percutaneous needle aspiration. In nine patients shadowing developed in the lower lobe (six left, three right) and was due to upper respiratory tract flora. All developed within the first four days and shortly (mean 10 hours) after extubation and were probably due to aspiration. The remaining patient developed a rounded opacity in the left upper lobe, which was proved to be due to aspiration of cyclosporin A. There were five late episodes of pneumonia in five patients occurring 77–645 days following transplantation. Four were due to pneumococcal infection and one to haemophilus. It was noteworthy that five of the 20 patients developed serological evidence of cytomegalovirus infection (CMV) shortly after transplantation and of these, three subsequently developed pneumococcal pneumonia, whereas only one of the remaining 15 patients with no evidence of CMV infection developed this complication ($p = 0.05$). We conclude that early episodes of pneumonia may be due to aspiration following extubation and that late episodes of pneumococcal pneumonia may be related to previous CMV infection. To date none of the patients have developed opportunistic lung infections and the simple nature of the organisms encountered support the concept of narrow spectrum prophylaxis. Nine of the first 10 patients are surviving more than one year after transplantation.

Abnormal distribution of IgG subclasses in the lung of bone marrow transplant recipients with pneumonitis

HJ MILBURN, JE GRUNDY, RM DUBOIS, PD GRIFFITHS *Department of Thoracic Medicine and Virology, Royal Free Hospital, London* Although all subclasses of IgG are represented in the normal lung, recent evidence has suggested that only IgG_4 is produced locally (Merrill *et al, Am Rev Respir Dis* 1985;**131**:584–8), raising the possibility that this subclass plays an important role in the lower respiratory tract. Bone marrow transplant (BMT) recipients are systemically immunosuppressed, however; and in a recent report to this society we have demonstrated that these patients can produce large amounts of total and virus specific IgG in the lung. Despite this local antibody production, this group is susceptible to pulmonary infections, possibly owing to defect in the production of a particular subclass of IgG in the lungs of these patients. We have studied 32 BMT recipients with pneumonitis and five normal volunteers and have measured the levels of IgG subclasses in bronchoalveolar lavage (BAL) fluid and serum by radial immunodiffusion using albumin measurements to correct for

serum leakage. All our controls showed significant local production of IgG_4 only, with the exception of one individual who also had evidence for local production of IgG_1. In the 32 BMT recipients, however, 26 were producing local IgG_1, 12 were producing IgG_2, 22 were producing IgG_3, and 25 were producing IgG_4 in the lung. IgG_4 could not be detected in lavage fluid from one patient with cytomegalovirus (CMV) pneumonitis, one with CMV and *Pneumocystis carinii*, and five patients with fungal or bacterial infections. Thus most BMT recipients appeared to be able to produce local IgG of all subclasses and not just IgG_4. IgG_4 was not produced by some patients with bacterial and fungal infections and the levels of this subclass were generally higher in patients with viral infections than in those with bacterial and fungal infections.

Long term prospective study of pulmonary function after bone marrow transplantation for chronic myeloid leukaemia

JMB HUGHES, TG SUTEDJA, JF APPERLEY, VR ABER, JM GOLDMAN *Departments of Medicine and Medical Physics and MRC Leukaemia Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London* This study extends previous reports (*Thorax* 1985;**40**:233; 1986;**41**:726) on the effects of bone marrow transplantation (BMT) for chronic myeloid leukaemia (CML) in chronic phase on spirometry and single breath diffusing capacity (TLCO and KCO). Thirty four patients were followed at three monthly intervals for 12 months after BMT, 16 of whom were studied up to 24 months. All patients received similar treatment before BMT with daunorubicin, cyclophosphamide, and total body irradiation (TBI), and after BMT prednisone and cyclosporin. Pre-BMT pulmonary function was in general normal (values <75% predicted occurred for vital capacity (three cases), TLCO (9), KCO (1)) and no different for survivors versus non-survivors or smokers (n = 8) versus non-smokers). Spirometric values and TLCO was significantly reduced six months post BMT but significant recovery of function had occurred at 24 months. As % predicted TLCO fell the most, from 87 (SD 4) initially to 65 (SD 4) at six months recovering to 73 (SD 3) at 24 months (n = 16). Airflow obstruction developed in only one case. With stepwise multiple regression analysis at 0, 6, and 12 months a significant correlation ($p < 0.005$) was found between transplantation with T cell depleted bone marrow (n = 29) and a higher dose of TBI (12 Gy as against 10 Gy) (n = 23) and a greater fall in KCO and a rise in the FEV_1/VC ratio (suggesting pulmonary fibrosis). The presence of acute (n = 13) or chronic (n = 16) graft versus host disease (GVHD) was also associated with significantly greater loss of function. GVHD and the higher dose of TBI (12 Gy) pose additional problems for the lung after BMT, but long term impairment of function is not serious.

Trial of the effect of inhaled corticosteroids on bronchoconstrictor and bronchodilator responsiveness in middle aged smokers

A WATSON, TK LIM, H JOYCE, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith, London* Inhaled corticosteroids attenuate bronchial hyperresponsiveness (BHR) to constrictor drugs in asthmatic subjects but there is little information on their effects in smokers with BHR. We have compared the effects of three months' of treatment with inhaled budesonide (BUD) 600 μg bd and three months' treatment with placebo (PLAC) on baseline FEV_1 and bronchial responsiveness to inhaled histamine and to a combination of inhaled salbutamol (5 mg) and ipratropium bromide (0·5 mg) in a crossover trial. Responsiveness to inhaled histamine was assessed by the concentration (mg/ml) reducing FEV_1 by 20% (PC_{20}). Assessments were made at monthly intervals. Compliance with treatment was checked by weighing aerosol canisters, and by measuring plasma BUD and metabolites; active treatment was associated with a small but significant fall in total blood eosinophils. Comparing the complete set of measurements over each month showed no significant change in FEV_1 (BUD mean 2·38 (SEM 0·17) l *v* PLAC 2·42 (0·19) l),vital capacity (BUD mean 3·69 (0·17) l *v* PLAC 3·70 (0·19) l or in bronchodilator responsiveness (mean increase over baseline FEV_1, BUD 9·8% (2·6%) *v* PLAC 9·3% (3·7%). Though there were small increases in histamine PC_{20} in the second and third months of BUD treatment, these did not differ significantly from the placebo values at any interval and geometric mean PC_{20} values for all six months (BUD and PLAC) were all within the range 3·5–4·5 mg/ml. Overall there was no consistent change in bronchoconstrictor or bronchodilator responsiveness over the three months of BUD treatment. Larger trials will be required to establish whether (1) a subgroup of smokers show a useful response, (2) improvement of BHR can be obtained after a longer period of treatment.

Assessment of reversibility in chronic airways obstruction (COPD)

M NISAR, MJ WALSHAW, JE EARIS, PMA CALVERLEY, MG PEARSON *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Clinical trials of bronchodilator treatment are frequently performed on patients with stable COPD but it is unclear which is the best test, what criteria constitute reversibility, and what percentage of older patients respond. We studied 80 patients (52 male, aged 42–77 years, mean FEV_1 0·95 SD 0·3 l) before and after 200 μg salbutamol via MDI (IS), 5 mg nebulised salbutamol (NS), and 30 mg prednisolone for two weeks (PN). Fifty seven patients (71%) improved their FEV_1 by more than 15% over baseline in response to one or more agents but some absolute changes were very small. Moreover, some non-responders showed a fall in FEV_1 of up to 200 ml. We revised our response criteria to accept a 15% rise in FEV_1 only if it exceeded 200 ml and found that 47 patients (59%) still had significant rises in FEV_1. All the responders were detected with NS but IS missed 19 responders to NS and six who later responded to PN. Only 17 (21%) showed a PN response. Mean FEV_1 increases in the 47 responders after NS (0·35 (SD 0·15 l)) were significantly greater than after IS (0·25 (0·21 l)) ($p = 0.006$). Among the responders to salbutamol and PN increase in FEV_1 following NS was 0·39 (0·2 l), not significantly different from the 0·33 (0·11) in those responding to NS alone and significantly less than the 0·77 (0·63 l) increase which PN produced in this steroid responsive group.

The mean daily PEF changes after PN correlated only weakly with FEV_1 responses because of their high SD. With our modified criteria airflow limitation can be improved in over half of COPD patients. Use of nebulised salbutamol is the best method of detecting this and its routine use can reduce the number of unnecessary steroid trials.

Clinical and laboratory correlates of reversibility in chronic airways obstruction

M NISAR, MJ WALSHAW, JE EARIS, MG PEARSON, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Reversible airflow limitation is a feature of some patients with COPD but there are few clinical or laboratory data on the accompanying features. Eighty patients (52 male, mean (SD) FEV_1 0·95 (0·36 l) with stable COPD had symptoms, signs, and spirometry recorded before and after both 5 mg nebulised salbutamol and 30 mg prednisolone (PN) for two weeks. Additional baseline tests included lung volumes, blood eosinophils, IgE, and RAST and skin tests. Thirty three patients (group 1) failed to respond to either drug, 30 (group 2) responded to salbutamol alone while 17 (group 3) responded to both drugs. There were no differences in age, smoking habits or atopic history between the groups but men were more likely to respond (67% *v* 43%, $p = 0·04$). Group 2 and group 3 patients were more likely to produce sputum ($p = 0·03$) and to complain of continuous or nocturnal wheeze ($p = 0·005$). Neither morning symptoms nor clinically audible wheeze were helpful. Group 3 patients had a higher eosinophil count (533 (SD 570) $\times 10^9$/l) than group 1 (122 (163) $\times 10^9$/l) or group 2 (213 (299) $\times 10^9$/l) ($p = 0·002$). Skin prick tests, IgE levels, and RAST tests were similar in the three groups, as were also baseline FEV_1 volumes and KCO. However, group 2 patients were more hyperinflated than either group 1 or 3: mean TLC 6·0 (SD 1·4) l RV 3·6 (1·2) l in group 2 compared with TLC 5·0 (1·1) l, RV 3·1 (0·9) l ($p = 0·05$). The improved FEV_1 in group 3 was accompanied by improved symptoms: less cough ($p < 0·5$), less wheeze ($p = 0·002$), and less sputum ($p < 0·003$) after treatment with PN. In contrast there was no symptomatic benefit in group 1 or group 2 subjects with PN. In conclusion, although no combination of clinical features predicts bronchodilator response with absolute certainty the presence of nocturnal or continuous wheeze favours response to some therapy, a high eosinophil count points to steroid responsiveness while those with marked hyperinflation are more likely to improve with β agonists alone.

Bronchiolar size and shape in relation to alveolar surface area loss

D LAMB, A MCLEAN, GA GOULD, P WARREN, W MACNEE, DC FLENLEY Bronchiolar size and shape was measured in 30 lobectomies (23 of them men) aged 51–71). Lobes were fixed at inflation with formal saline and cut into 1 cm parasagittal slices. Sic (180 mm^2) random blocks of tissue were taken from each of the first two lateral subpleural slices, embedded in GMA, cut at 3 μm, and stained H and E. All bronchioles were located and their ellipticality (maximum:minimum diameter) was measured. The 30% most elliptical were rejected as probable tangential sections. In the remainder bronchiolar size–mean minimum diameter (0·36–0·78 mm) measured area (0·19–0·87 mm^2) and a circular theoretical lumen area (0·42–1·56 mm^2) based on lumen circumference, and the mean interalveolar attachment distance—IAAD– (0·13–0·24 mm) of radial peribronchiolar attachments—were measured. Mean AWUV—airspace wall surface area per unit lung volume—(8·8–25·4 mm^2/mm^3) was also measured. Neither minimum diameter nor measured lumen area related to loss of AWUV or increased IAAD. Rather theoretical lumen area increases with loss of AWUV and increased IAAD. Importantly, a highly significant proportion of the variation in bronchiolar-ellipticality (R^2 = 62%) was explained by AWUV and IAAD. We conclude that changes in bronchiolar shape are related to alveolar/airspace loss whereas loss of bronchiolar size is not. Indeed, indications are that bronchiolar size increases. The measured alteration in bronchiolar shape is related to increased closing volume – CV/VC%– ($r = 0·66$ $p < 0·001$) and decreases in FEV_1 % predicted ($r = 0·35$ $p = 0·028$).

Physiological changes during external negative pressure ventilation in hypercapnic chronic obstructive airways disease

CB COOPER, ND HARRIS, P HOWARD *University Department of Medicine, Royal Hallamshire Hospital, Sheffield* External negative pressure ventilation (ENPV) is effective in respiratory failure with normal lung mechanics. Using an airtight jacket (Pneumosuit) and vacuum pump (Newmarket) we applied ENPV to 10 patients with clinically stable hypercapnic ($Paco_2 > 6·0$ kPa) chronic obstructive airways disease (COAD): mean (SD) age 63 (11) y, weight 70·6 (17·8) kg, FEV_1 0·9 (0·10) l, % l predicted FEV_1 23 (4), FVC 1·45 (0·53) l, Pao_2 6·4 (1·4) kPa. Ventilation was recorded with a light emitting turbine transducer (PK Morgan). Measurements were made at rest and then during ENPV with pressures of -20 cm H_2O and -40 cm H_2O. The ventilator rate was fixed at 16 min^{-1}. Subjects were judged to have regained equilibrium when mixed expired gas fractions became constant. The effects on minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) were compared with those in 10 normal subjects: age 29 (9) y, weight 71·8 (5·7) kg, FEV_1 4·50 (0·72) l, FVC 5·47 (0·93) l; and 10 patients with normocapnic ($Paco_2 < 6·0$ kPa) chronic obstructive airways disease: age 67 (8) y, weight 62·4 (14·0) kg, FEV_1 0·88 (0·28) l, % predicted FEV_1 36 (14), FVC 1·71 (0·46) l, Pao_2 9·5 (1·0) kPa, $Paco_2$ 4·9 (0·4) kPa. In hypercapnic patients $\dot{V}E$ increased from 9·7 to 12·4 l min^{-1} ($p < 0·02$) and $\dot{V}CO_2$ did not change. In normocapnic patients $\dot{V}E$ increased from 11·5 to 17·1 l min^{-1} ($p < 0·001$) and $\dot{V}CO_2$ increased from 0·23 to 0·26 l min^{-1} ($p < 0·05$). In normal subjects $\dot{V}E$ increased from 8·6 to 22·9 l min^{-1} ($p < 0·001$) and $\dot{V}CO_2$ increased from 0·25 to 0·39 l min^{-1} ($p < 0·001$). There were no changes in $\dot{V}O_2$. Serial arterial blood samples were obtained in eight hypercapnic patients. Pao_2 increased during ENPV from 6·8 to 8·2 kPa ($p < 0·005$) while $Paco_2$ decreased from 6·8 to 5·8 kPa ($p < 0·005$). The increase in ventilation in the hypercapnic patients was associated with an increase in physiological deadspace. Improvements in ventilation and

gas exchange may be achieved with ENPV of only −20 cm H_2O in patients with chronic obstructive airways disease.

Symptomatic benefit of oxygen in hypoxaemic patients with chronic obstructive airways disease

CR SWINBURN, H MOULD, TN STONE, PA CORRIS, GJ GIBSON *Department of Respiratory Medicine, Freeman Hospital, Newcastle upon Tyne* Patients with chronic airways disease (COAD) often claim symptomatic relief from supplemental oxygen, and attempts to remove this may be resisted. The purpose of this study was to investigate the extent to which this may be a placebo effect. We studied 12 patients (seven male, mean (SD) age 59. 8 (9·1) y) with stable but advanced COAD (mean (SD) FEV_1 0·66 (0·2) l; FVC 1·10 (0·6) l), all of whom claimed a reduction in breathlessness from supplemental oxygen. Mean blood gases breathing air were Pao_2: 6·7 (1·7) kPa and $Paco_2$ 6·3 (1·1) kPa. The patients were seated upright in a chair. They received either 28% oxygen or air via a facemask at identical flow rates, each gas being given for two periods of 10 minutes in a randomised and double blind sequence separated by five minute washout periods breathing room air. Arterial oxygen saturation (SaO_2) was measured by oximetry. In 10 patients ventilation ($\dot{V}E$) was measured over the last five minutes of each of the four gas breathing periods using two pairs of magnetometers (AP rib cage and abdomen) calibrated by the isovolume method. At the end of each period the patients were asked whether the gas helped their breathing and to grade their breathlessness on a visual analogue scale (VAS). SaO_2 was increased breathing oxygen (air: 85·1% (8·1%); oxygen: 93·1% (4·8%); $p < 0·001$). The patients stated that air helped their breathing on 15/24 occasions and oxygen on 22/24 occasions ($p > 0·05$). VAS scores, however, were lower during oxygen breathing (mean VAS: air 45·5 (20·5); oxygen 29·6 (15·4); $p < 0·02$). $\dot{V}E$ and tidal volume (VT) were also lower on oxygen ($\dot{V}E$; air 9·3 (3·4) l/min, oxygen 8·2 (3·1) l/min: $p < 0·01$; VT: air 0·44 (0·19)l, oxygen 0·38 (0·1) l; $p < 0·01$. There was no change in respiratory rate. We conclude that although supplemental air had a placebo effect of oxygen in relieving breathlessness was significantly greater and was associated with reductions in tidal volume and minute ventilation.

Type 1 muscarinic receptors and the control of bronchomotor tone in normal subjects

JFJ MORRISON, SB PEARSON *Pulmonary Function Laboratory, Killingbeck, Leeds* Animal studies have revealed that M_1 (ganglionic) receptors are important in the control of bronchomotor tone. We have studied the effect of M_1 blockade with pirenzepine on airway calibre and lung mechanics in seven normal subjects and compared this to non-selective muscarinic receptor blockade with atropine. The study was double blind and placebo controlled. Subjects were studied fasting and tea and coffee were not allowed for 12 hours before each study session. Baseline measurements of specific airways conductance (sGaw), maximum flow-volume loops, and lung volumes were made in a body plethysmograph. Resting pulse was recorded. Subjects attended on five occasions and randomly received oral pirenzepine 50, 100, or 150 mg, oral placebo, or intravenous atropine 30 μg/kg. Measurements were repeated two hours after the oral drugs and 5–15 minutes after atropine. All the subjects showed significant bronchodilation following atropine. Two of the seven subjects showed no response to pirenzepine but the remaining five showed a dose-related bronchodilation in measurements of large airway function (PEF, sGaw, FEV_1) and small airway function (FEF 25–75% VC). 150 mg of pirenzepine produced the same degree of bronchodilation as 30 μg/kg of atropine. Lung volumes were unaffected by both pirenzepine and atropine. Pirenzepine had no significant effect on pulse rate. We conclude that M_1 receptors are important in the control of bronchomotor tone in most normal subjects.

Tissue culture of airway smooth muscle from rabbit trachealis: intracellular calcium store

CHC TWORT, C VAN BREEMEN *Department of Pharmacology, University of Miami Medical School, Miami, Florida, USA* We have developed a novel preparation of airway smooth muscle, saponin skinned monolayers of cultured cells, in order to investigate the intracellular calcium (Ca^{2+}) store in airway smooth muscle (an important source of cytoplasmic Ca^{2+} for the activation of contraction). Cells enzymatically dispersed from rabbit trachealis were cultured in monolayers, and confirmed as airway smooth muscle by positive immunocytochemical staining against actin and myosin. The retention of functional surface receptors in cultured cells was demonstrated by stimulation of efflux of intracellular Ca^{2+} from ^{45}Ca labelled (unskinned) cells in response to bronchoconstrictor agonists (control Ca^{2+} loss, 43 pmol $Ca^{2+}/10^6$ cells/min; + 10 μM serotonin, 71 pmol $Ca^{2+}/10^6$ cells/min; + 10 μM carbachol, 60 pmol $Ca^{2+}/10^6$ cells/min (mean, n = 3–4). Uptake of Ca^{2+} into the intracellular store, measured in saponin skinned monolayers loaded for varying durations (0–20 min) by a ^{45}Ca labelled 1 μM free Ca^{2+} containing solution, was dependent on the presence of MgATP (steady state uptake at 20 min: + 3·15 mmol/l ATP, 1·12 nmol/l $Ca^{2+}/10^6$ cells; − ATP, 0·17 nmol $Ca^{2+}/10^6$ cells (mean, n = 6). Uptake was unaffected by the mitochondrial inhibitor sodium azide (5 mmol/l) at varying ambient free Ca^{2+} concentrations (0·1–1 μM Ca^{2+}), so identifying the store as sarcoplasmic reticulum. Addition of inositol 1, 4, 5-trisphosphate (IP_3) for 1 min to Ca^{2+} loaded skinned cells reduced the Ca^{2+} content of the store: maximally effective IP_3 (30 μmol/l) released 87% of the MgATP dependent Ca^{2+} uptake; ED_{50} for IP_3 was 500nmol. This supports a role for IP_3 as the "second messenger" which links surface receptor activation to release of intracellular Ca^{2+} in airway smooth muscle.

Effect of challenge of sensitised rats on permeability of the tracheal lumen in life

F CARSWELL, S MUKHERJEE, P HEAP *Respiratory Research Group, Department of Child Health, and Department of*

Anatomy, University of Bristol Aerosol challenge of sensitised rats leads to an apparent increase in permeability of the fixed trachea (*Clin Exp Immunol* 1986;**65**:647). The present study was undertaken to show that this increased permeability occurs because of increased porosity of the luminal surface in life. Rats were sensitised with DNP_{19} ovalbumin (DNP-OA) or saline. They were exposed to an aerosol of DNP-OA plus lanthanum nitrate for one hour. Tracheas were processed immediately after challenge. The elemental lanthanum concentration was measured by *x* ray microanalysis with KeVex 5000 A/6000 spectrometers. The lanthanum penetrated between the cells. Its concentration was greatest at the airway surface and decreased progressively towards the cartilage. More lanthanum was present in the epithelium of six DNP-OA sensitised rats (42·9 (SD 6·0) counts/100 s) than for six controls (11·9 (1·5) counts/100 s), $p < 0·01$, Mann-Whitney). The DNP-OA sensitised group showed a more severe response on body plethysmography. There is an increase in permeability of the luminal surface of the trachea on challenge with aerosol antigen, probably as a result of the opening of the intercellular junctions. (This work was supported by the Wellcome Trust.)

Nasal potential difference: effect of aerosol challenge of varying tonicity and ionic content

AM WOOD, TW HIGENBOTTAM *Department of Respiratory Physiology, Addenbrooke's Hospital, Cambridge* Physical challenges—for example, inhaled ultrasonically nebulised aqueous solutions of high or low tonicity—may initiate bronchoconstriction in asthma by inducing a change in epithelial permeability. Nasal mucosal potential difference can be easily and reproducibly measured (Alton EW *et al, Thorax* 1985;**40**:704) and provides an assessment of integrity of the epithelial surface. In this study we examined the effects of five aerosols of varying tonicity and ionic content delivered from a DeVilbiss 65 ultrasonic nebuliser on separate days in random order to 10 normal subjects. The aerosols of distilled water (DW), 0·9% saline, 5% dextrose (dex), 3·6% saline, and 20% dextrose were each inhaled through the nose for one minute. Maximum potential difference values (PD_{max}) were measured one minute post-challenge and compared with baseline readings (Base). The results were analysed by the method of non-parametric multiple comparisons.

Results

	Aerosol					
	Base	*DW*	*NaCl 0·9%*	*Dex 5%*	*NaCl 3·6%*	*Dex 20%*
Mean PD_{max} (mV)	17·5	9·6	16·4	16·5	16·1	16·4
Mean % drop from base		45·1	6·45	5·75	8·15	6·05
Range of response (%)		18–83	0–13	0–12·5	5–13	0–12

Only the distilled water aerosol significantly reduced potential difference ($p < 0·05$). This implies that over the range of tonicity studied only distilled water can alter epithelial permeability when applied by aerosol. The ionic content of the aerosol was not important. This technique can be readily adapted as a means of studying physical airway challenges, other than aerosols, such as those involved in exercise induced asthma.

Comparison of the efficiency of methylcellulose and cromoglycate in the prevention of exercise induced asthma

CF STANFORD, MG SCOTT, A LEE Exercise induced asthma (EIA) is thought to be induced by the loss of water vapour during exercise (Anderson, *J Allergy Clin Immunol* 1984;**73**:660–5). Sodium cromoglycate (SCG), a hydroscopic substance, may conceivably act by reducing water vapour loss rather than by its known activity on mast cells (Cox, *Br J Dis Chest* 1971;**65**:189–204) or on sensory "c" fibres (Dixon *et al, Br J Pharmacol* 1980;**70**:11–3). Since methylcellulose (MC) is a very hydroscopic substance, we have compared its effect on EIA with that of SCG. Eight subjects with proved EIA were randomly allocated in a double blind study to receive lactose 20 mg, SCG 20 mg, or MC 150 μg in 19·85 mg of lactose. All were inhaled as dry powder 12 minutes before exercise. All subjects were exercised on a treadmill for eight minutes to achieve a pulse rate of 80% maximum predicted and the exercise took place at the same time of day for each patient. Peak flow rates (l/min) were measured at two minute intervals. The results were expressed as means and SEM. Immediately before exercise there was no significant difference ($p > 0·05$) between the peak flow rates (PEF) on any of the three days. With placebo the maximum percentage drop in PEF was 31·8 (8·4). With SCG the maximum fall was 8·1 (3·6). This difference was significant ($p < 0·05$). With MC the maximum fall was 9·5 (7·7). This was significantly different for lactose ($p < 0·05$). There was no significant difference between SCG and the MC ($p > 0·05$). In five additional subjects each tested on five occasions we have demonstrated that MC is significantly better ($p < 0·05$) than lactose. Although MC may have an independent mode of action in EIA, the present preliminary results are consistent with the hypothesis that SCG acts by reducing drying of the respiratory mucosa.

Increase in bronchial blood flow (Doppler) in conscious sheep via H_1 receptor stimulation produced by histamine

GH PARSONS, A VILLABLANCA, R HOWARD (sponsored by CE Cross) *Department of Medicine, University of California, Davis, California* Histamine aerosol increases bronchial blood flow ($\dot{Q}$br) in anaesthetised sheep, an effect reportedly blocked by H_2 receptor antagonists. We chose to study intravenous (IV) histamine effects on $\dot{Q}$br in conscious sheep. At prior thoracotomy a 2 or 3 mm diameter 10 MHz continuous wave ultrasonic Doppler flow probe was placed around the common bronchial branch of the bronchoesophageal artery to allow continuous recording of Doppler shift in KHz, proportional to blood velocity (vel). In nine awake adult sheep restrained in a sling, a bolus of histamine base 0·1 μg/kg was given intravenously while bronchial blood velocity, heart rate, and systemic pressure were continuously recorded. This dose of histamine caused a rapid onset transient (15–20 s) increase in $\dot{Q}$br without a change in heart rate or blood pressure. Three sheep given 10 bolus injections of histamine over one hour did not demonstrate tachyphylaxis. Following an H_1 receptor blocker diphenhydramine (2 mg/kg IV) or chlorpheniramine (2 mg/kg IV) histamine was given at 3, 10, 20, and 30 min. On another day

each animal was given histamine before and after an H_2 receptor blocker—cimetidine (5 mg/kg LV), metiamide (3 mg/kg IV), or ranitidine (2 mg/kg IV.)

	$\dot{Q}br$—increase in doppler shift (KHz)								
	H_1 Blocker					H_2 Blocker			
	Base	3	10	20	30	Base	3	10	20
Mean	2·4	0·5*	0·5*	0·9*	1·0*	2·4	2·2	2·4	2·5
SD	1·1	0·3	0·4	0·6	0·6	0·8	0·8	1·6	0·9

*$p < 0.05$ compared with baseline.

In five additional sheep the H_1 blocker chlorpheniramine (2 mg/kg) failed to block the histamine effect at 60 min. However, continuous infusion of chlorpheniramine (2 mg/kg/h) did block the histamine response at 1 hour. Intravenous histamine increases $\dot{Q}br$, an effect blocked by H_1 but not H_2 receptor antagonists. It is possible that aerosol histamine increases $\dot{Q}br$ by a different mechanism.

Airway blood flow distribution and oedema after histamine infusion in sheep

CE CROSS, DC LINDSEY, C-H WU, S MERTENS, LA RUSSELL, GC KRAMER *Departments of Medicine, Pathology, and Physiology, University of California, Davis, USA* Histamine release from airway mast cells occurs in acute allergic asthma and may occur in various non-allergic conditions characterised by airway injury, infection and/or inflammation. Histamine infusions are known to increase airway blood flow ($\dot{Q}aw$) and extravascular lung water. In the present study the distribution of $\dot{Q}aw$ and lung airway liquid was measured during a two hour histamine infusion (2 μg/kg a minute) in unanaesthetised sheep. With the use of radioactive microspheres, the distribution of $\dot{Q}aw$ to trachea and to tracheal cartilage, smooth muscle and mucosa/submucosa was determined along with measurements of $\dot{Q}aw$ to different sized airway segments and to distal lung parenchyma. Tissue liquid content was measured gravimetrically and correlated with histological findings. $\dot{Q}aw$ increased from 1·7% (SEM 0·13%) of cardiac output to 3·2% (0·5%) and 2·9% (0·8%) after 15 min and 2 h of histamine infusion respectively. Histamine increased blood flow to medium size airway (5–10 mm diameter) to 5–10 × baseline flow, while in airways of 3–5 mm diameter the increase was 10–15 ×. Blood flow in tracheal mucosa/submucosa increased 6 ×, but in tracheal muscle increased only 3 × and in cartilage remained at baseline. Cardiac output and most other organ blood flows were unchanged by this level of histamine infusion. The liquid content of trachea and main stem bronchi was increased after histamine. Histopathological findings after histamine infusions included congestion and oedema of airways. The results indicate that histamine is a potent and selective vasodilator of $\dot{Q}aw$ and particularly affects blood flow to medium sized and peripheral airways and to airway mucosa/submucosa. Although the cellular transducing system(s) for this selective effect of histamine are uncertain, it is probable that interrelationships with airway neurohumoral and mast cell systems contribute to this effect.

Nasal disease in adult cystic fibrosis

DW MORGAN, K PEARMAN, PM SHENOI, D STABLEFORTH *Departments of ENT and Thoracic Medicine, East Birmingham Hospital, Birmingham* The extent and severity of nasal disease was studied in 26 adults with cystic fibrosis (11 male, 15 female) ages 14–31. Forty four per cent had childhood sinusitis, but none underwent radical sinus surgery; 4% of adults had sinusitis, although 14% had unrelated headaches and facial pain. All sinus radiographs were opaque and therefore of little use in diagnosing sinusitis in the absence of a fluid level. Thus the frequency of sinusitis decreases with age and should be managed conservatively. Twenty eight per cent had childhood polyposis and 25% underwent polypectomies; 20% had small unilateral polyps, none of which required removal. All had multiple allergies on skin testing but normal IgE levels. Thus the incidence and severity of polyposis decreases with age. Eighty per cent complained of perennial nasal obstruction, 74% of rhinorrhoea, and 26% of hyposmia. Eighty one per cent had hyperaemic nasal mucosa and 74% non-purulent mucus strands; 74% had grossly enlarged inferior turbinates causing nasal obstruction. On investigation of the symptom free patients (20%), all had negative skin test responses, normal IgE levels, and negative *Aspergillus fumigatus* precipitin reactions. Of the patients with rhinitis, 85% had multiple positive skin test reactions (including *Aspergillus fumigatus*), 80% positive *Aspergillus fumigatus* precipitins, and 70% elevated IgE levels up to 2720. Thus perennial rhinitis in adult cystic fibrosis appears to be related to the atopic state.

Microsomal drug metabolism in cystic fibrosis

B SALH, K WEBB, JM BRAGANZA, LR SANDLE *Royal Infirmary and Monsall and Park Hospitals, Manchester* The accelerated clearance of drugs by patients with cystic fibrosis (CF) is generally regarded as being due to aberrant renal function. We have explored another possible explanation—namely, hyperactivity of microsomal drug metabolising enzyme systems in cells, since the target organs in CF happen to be rich in these (JM Braganza, *Medical Hypoth* 1986;**20**:233). Phase I metabolism was explored by following the elimination of an intravenous dose of theophylline (DW Acheson *et al, Clin Chim Acta* 1985;**153**:73), and phase II metabolism by measuring the eight hour urinary excretion of D-glucaric acid (LN Sandle, JM Braganza, *Clin Chim Acta* 1987;**162**:245).

	Controls (median (range))	*CF*	*Significance (Mann-Whitney)*
Theophylline clearance (ml/kg/h	59 (45–81) (n = 13)	76 (42–187) (n = 22)	p = 0·03
D-glucaric acid excretion (mmol/mol creatinine)	2·9 (0·4–4·8) (n = 22)	4·1 (2·1–16) (n = 21)	p = 0·007

There was no correlation between theophylline clearance and D-glucaric acid excretion, but the results show acceleration of

both phase I and phase II metabolism in microsomes. Since these enzyme systems are largely located in the liver, the corollary is that hepatic metabolism contributes to the enhanced drug elimination by CF patients.

Ototoxicity in adult cystic fibrosis: relationship to aminoglycoside blood levels, total dosage, and duration of treatment

DW MORGAN, K PEARMAN, PM SHENOI, D STABLEFORTH *Departments of ENT and Thoracic Medicine, East Birmingham Hospital, Birmingham* Twenty six adults (11 male, 15 female) aged 14–31, originating from a number of centres, were studied. Seventy per cent had normal hearing, 30% bilateral sensorineural loss greater than 30dB, and 23% vertigo following aminoglycoside therapy. Thirty per cent had been using nebulisers for up to 18 years. Of these, half had normal hearing and all were on colomycin nebulisers. Half had hearing loss following the use of neomycin nebulisers in early childhood. Half were using nebulisers and having intermittent courses of aminoglycosides. Of these, 70% had normal hearing following colomycin or gentamycin nebulisers for up to 12 years and intermittent courses of aminoglycosides up to 148 days and 43·2 g. The average blood levels were below the accepted toxic range. Thirty per cent had hearing loss. Hearing loss dated from single occasions when toxic blood levels were recorded. Twenty three per cent had vestibulotoxicity following single episodes of toxic blood levels. However, repeat electronystagmography and audiometry showed no abnormality by six weeks. Thus 40% had ototoxicity. Of the affected patients, 45% had deafness, 27% had a combination of deafness and vestibulotoxicity, and 28% pure vestibulotoxicity. Long term colomycin nebulisers do not cause ototoxicity but neomycin is associated with deafness. Intravenous aminoglycoside ototoxicity is related to high blood levels rather than total drug dosage or duration of treatment. Vestibular dysfunction is a short term problem and full compensation occurs within six weeks.

Shwachman's syndrome in adults

J WIGGINS, DM GEDDES *Brompton Hospital, London* Shwachman's syndrome is a rare disorder whose main features are pancreatic insufficiency and bone marrow dysfunction (Shwachman, *J Pediatr* 1964;**65**:645). The usual haematological abnormalities are varying degrees of leucopenia, neutropenia, and thrombocytopenia, which may be either constant or cyclical. The syndrome, which may be confused with cystic fibrosis, causes considerable morbidity in childhood, particularly from recurrent respiratory infections. However, while most patients survive into later life, information about the syndrome in adults is limited. We therefore report the details of six older patients (four male; mean age 27·2 years, range 19–32). Recognised clinical features persisting into adulthood include pancreatic insufficiency (all patients), short stature (5/6), advanced dental caries (3/6), and impaired glucose tolerance (2/6). The chest radiograph was normal in all. Lung function tests showed mild restriction in three patients (FEV_1/FVC% 82–94) and obstruction in two (FEV_1/FVC 59 and 63). All patients were cyclically leucopenic (nadir count 2·1–3·3 × 10^9/1) and neutropenic (nadir count 0·4–1·2 × 10^9/1); 4/6 were thrombocytopenic (nadir count 65–102/nl) and three had persistent immunoglobulin deficiencies (two low IgA and IgM, one low IgM). Neutrophil function tests showed normal phagocytosis in all patients, impaired chemotaxis in 4/6, and an abnormal nitrobluetetrazolium test in 1/6. Despite these abnormalities, only two patients had recurrent respiratory infections (one of whom died from bone marrow aplasia) and both produced leucocytosis in response to infection. In conclusion, although Shwachman's syndrome is associated with low respiratory morbidity, many of the recognised features persist into adult life, and may cause diagnostic difficulty.

Randomised control trial of six months' versus nine months' chemotherapy in pulmonary tuberculosis

F HOWELL, R O'LAOIDE, P KELLY, J POWER, L CLANCY *Peamount Hospital, Newcastle, Co Dublin* We report the first trial in the Republic of Ireland to look at chemotherapy for tuberculosis. This management trial, carried out in a single unit, which treats a third of all tuberculosis in the Republic of Ireland, compared the effectiveness of a three drug nine month regimen (rifampicin (R), isoniazid (H) supplemented with ethambutol (E) for the first two months = RHE9) with a four drug/six month regimen (R, H supplemented with E and pyrazinamide (Z) for first two months = RHEZ6). The cooperation of the community services was essential and the brand of rifampicin used was Orifam. Two hundred and eighty eight patients in whom a clinical decision to treat for tuberculosis had been made were entered into the trial. One hundred and forty five were not valid for analyis at completion of therapy for the following reasons: presumed tuberculosis 41, drug intolerance 35, death 23, non-compliance 19, diagnosis not tuberculosis 10, drug resistance seven, extra pulmonary disease four, consent withdrawn three, MOTT three. Of the remaining 143, 76 were in the RHE9 group and 67 in the RHEZ6. There was no significant difference between those withdrawn and those not, and neither was there a significant difference in patient characteristics between those remaining for analysis in the two groups. Of the 143 patients valid for analysis, all were culture negative at the end of chemotherapy. However, by the end of the third month, significantly more patients in the RHEZ6 regimen (98%) were culture negative than the RHE9 regimen (88%). Overall drug intolerance was seen in 35 (12%) patients, with no significant difference for hepatitis between the two regimens. The degree of toxicity from pyrazinamide was minimal. All patients are being followed for a further two years to monitor relapse rates. These data confirm the effectiveness and safety of pyrazinamide in our population and we now recommend the inclusion of pyrazinamide as a standard antituberculous agent.

Interrelationship between compliance, drug regimen, and relapse in tuberculosis

LP ORMEROD *Chest Clinic, Blackburn Royal Infirmary* Nine hundred and eighty nine patients treated for tuberculosis

(all forms) during 1978–86, were assessed. Compliance was judged from physicians' comments and health visitors' reports. Relapse was taken as recurrence of disease within 36 months of cessation of treatment. Good and fair compliance were more common in the white ethnic group; poor compliance was similar in the ISC (Indian subcontinent) and white ethnic groups. Compliance has been better since 1981, when shorter regimens were introduced. Relapses have also been significantly lower, 22/444 patients *v* 3/340 1981–3 (χ^2 10·34, 0·01 > p > 0·001). Relapse was highly correlated with compliance, occuring in 14/39 with poor compliance, in 5/139 with fair compliance, and in 6/811 judged to have good compliance, but was unrelated to ethnic group. Short course six month regimens had excellent compliance and no relapses. Compliance with the six month regimens was significantly better than regimens of nine to 12 months' duration. Pyrazinamide containing regimens had a significantly lower relapse rate than other regimens from 1978–83 (χ^2 5·82 0·05 > p > 0·01). Pyrazinamide containing regimens allow a shorter treatment period, and a major factor in the success of these regimens is shown to be better patient compliance.

Improvement in perception of breathlessness during exercise in asthmatics produced by physical training

LM COCHRANE, CJ CLARK *Department of Respiratory Medicine, Hairmyres Hospital, Glasgow, and University of Glasgow* There has been increasing recognition that breathlessness can be alleviated even in the absence of improvements in the underlying condition (A Woodcock *et al*, *Br Med J* 1981;**283**:343). In this study we have investigated the effects of physical training on the perception of breathlessness in 36 patients with moderate asthma. Subjects were randomly allocated into trainers and controls. Sequential evaluation consisted of baseline dynamic spirometry and progressive incremental exercise testing. A categorical scale (modified Borg) was used to assess breathlessness during exercise. Following three months' physical training, during which frequency, intensity, and duration of exercise were recorded, there was a highly significant reduction in breathlessness at each work rate ($\dot{V}O_2$) in the trainers with no change at any level in the control group. The training group showed a significant increase in $\dot{V}O_2$ max (23·00 (SD 4·7) to 28·41 (6·0) ml/min/kg, $p < 0·001$) and a reduction in $\dot{V}EO_2$ (38·14 (4·3) to 34·94 (4·03), $p < 0·01$) with no significant change in the controls. However, there was no correlation between the reduction in breathlessness during exercise and changes in cardiovascular fitness ($\dot{V}O_2$ max), $\dot{V}EO_2$, or baseline lung function (FEV_1). In conclusion, physical training produced a highly significant improvement in the perception of breathlessness during exercise across a spectrum of work loads equivalent to a wide variety of daily activities. This was not dependent on achievement of major changes in cardiovascular fitness, thus indicating that similar benefits may also be available to more severely disabled asthmatics. Alleviation of breathlessness by physical training should be considered as an important objective in improving the quality of life in asthmatic patients.

Inhaled β agonists relieve breathlessness without controlling asthma

CR HORN, GM COCHRANE *Department of Respiratory Medicine, Guy's Hospital, London* The prominence of different symptoms of asthma varies widely between individual patients. Specific symptoms may possibly be relieved to varying extents by different therapeutic agents. In a prospective study of the value of inhaled therapy for the control of asthma the differential effect of inhaled β agonist alone or in combination with inhaled steroids on a variety of indices of morbidity has been determined. Sixty five adults with airflow obstruction were prospectively treated with salbutamol in doses increasing to 2000 μg qds over nine months. Two thirds of the patients also received up to 1000 μg bd of beclomethasone (BDP). Asthma morbidity was assessed both subjectively (visual analogue scales and continuous domiciliary symptom scores) and objectively (spirometry, the incidence of acute attacks, and domiciliary PEF). All patients reported compliance with their prescribed regimen. Regular β agonists abolished breathlessness in two thirds of patients, but they continued to experience intrusive symptoms, acute attacks of asthma, and marked airflow obstruction. In contrast, early introduction of BDP not only reduced breathlessness but also abolished symptoms in general and eliminated acute attacks of asthma with significant improvement in PEF. Beta agonists relieve breathlessness without controlling asthma in general; complete suppression of asthma is totally dependent on the use of inhaled steroids. It is possible that breathlessness has a different pathogenesis from that of other symptoms of asthma and may be less associated with airway inflammation.

Falls in blood eosinophils parallel the late asthmatic response and associated changes in airway responsiveness

SR DURHAM, WOCM COOKSON, CF CRADDOCK, MK BENSON *Osler Chest Unit, Churchill Hospital, Oxford* Fourteen asthmatic patients underwent inhalation challenges with allergen and allergen diluent in random order with an interval of 14 days. Blood eosinophils (EOS) were measured before challenge and at 3, 9, 24, and 48 hours and two weeks. Changes in EOS were compared with the size of the late asthmatic response (LAR) and changes in histamine PC_{20}. The previously reported (*Thorax* 1987;**42**:724 issue) association in seven subjects between changes in histamine PC_{20} and LAR were confirmed. There were decreases in histamine PC_{20} at 3 h ($p < 0·01$), 24 h ($p < 0·01$), and 48 h ($p = 0·02$), which correlated with LAR (3 h $r = 0·69$, $p = 0·007$; 24 h $r = 0·63$, $p = 0·015$). When compared with those in controls EOS were decreased at 9 h ($p = 0·005$) and increased at 24 h ($p = 0·05$) and at 48 h ($p = 0·006$). The decrease in EOS at 9 h correlated with LAR ($r = 0·72$, $p = 0·003$) and with the decreases in histamine PC_{20} at 3 h ($r = -0·55$, $p = 0·044$) and 24 h ($r = -0·82$, $p = 0·0001$). All variables had returned to baseline at two weeks. These results demonstrate a decrease in blood eosinophils which occurred at the time of development of the late response and which correlated with the size of the late response and with the associated changes in histamine responsiveness. They suggest that eosinophil

recruitment to the lung may be a common underlying mechanism in the development of the late response and associated increase in airway responsiveness.

Mast cells and eosinophils in the bronchial mucous membrane in asthma

S LOZEWICZ, E GOMEZ, H FERGUSON, RJ DAVIES *Department of Respiratory Medicine, St Bartholomew's Hospital, London* We have counted the numbers of mast cells and eosinophils in bronchial biopsies from seven atopic asthmatic patients (mean age 23·3 years) and nine healthy non-atopic volunteers (mean age 27·6 years). None of the asthmatic patients was receiving inhaled/oral corticosteroids and inhaled salbutamol was stopped 12 hours before bronchial provocation. Bronchial reactivity to methacholine was measured in all subjects between 1300 and 1500 hours with a De Vilbiss 646 nebuliser and tidal breathing method as previously described (J Bennett, RJ Davies, *Br J Dis Chest* 1987;**81**:252–9). Between 0930 and 1030 hours on the following day fibreoptic bronchoscopy was performed under local anaesthesia and mucosal biopsy specimens taken from the right upper and middle lobe carina with cup forceps. Biopsy specimens were fixed in Carnoy's solution and serial sections stained separately with toluidine blue and with the α-ASD chloroacetate esterase reaction for mast and basophil cells. Further specimens were fixed in 10% buffered formalin prior to staining of eosinophils with chromotrope 2R. Significantly more ($p < 0·02$) metachromatically staining (mast/basophil) cells but not eosinophils were counted in the lamina propria of specimens from asthmatics than of normal volunteers (medians of 86 and 24 cells/mm^2 respectively). There was no correlation between the numbers of mast cells or eosinophils in the epithelium or lamina propria and airway hyperreactivity expressed as the PC_{20} FEV_1 for methacholine. These results are compatible with the proposed role of mast cells in allergic asthma but do not support a direct involvement of mast cells or eosinophils in the pathogenesis of bronchial hyperreactivity.

Airway inflammation in fatal asthma

PW JOHNSTON, PP SUTTON *Department of Pathology, University of Aberdeen, and Department of Thoracic Medicine, Aberdeen Royal Infirmary, Aberdeen* Fatal asthma is rare and usually occurs outside hospital. We have examined clinical and pathological features in 20 patients (12 female, eight male), mean age 37 years (range 1–64 years), who died from asthma from 1975 to 1987: 17 died at home and three were dead on arrival at hospital. Although all were known asthmatics, only six were prescribed inhaled steroids and four had been taking steroids orally at the time of death. Classical postmortem appearances of asthma (MS Dunnill, *Pulmonary pathology*. 2nd ed. Churchill Livingstone, 1987)—namely overinflation, mucus plugging, focal collapse and oedema, thickening of bronchial epithelial basal lamina, and smooth muscle hypertrophy—were ubiquitous. In addition, bronchi showed marked inflammatory cell infiltration in all cases: this comprised eosinophils in superficial layers, and, furthermore, in the muscle and adventitia lymphocytes and plasma cells which were predominant there in 17 cases. Interstitial parenchymal chronic inflammatory cell infiltration was present in 16 cases. The findings show that in fatal asthma airway inflammation is more intense than has been recognised previously. This emphasises that treatment of acute severe asthma must include specific therapy directed towards reducing airway inflammation.

T lymphocyte activation in acute severe asthma: implications for disease pathogenesis and management

CJ CORRIGAN, A HARTNELL, AB KAY *Department of Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* Lymphocytes (LC) are conspicuous in the bronchial inflammatory cell infiltrate in patients with asthma. We have tested the hypothesis that cell mediated immunity has a role in the pathogenesis of acute severe asthma (ASA) by examining the peripheral blood LC from patients with ASA for markers of activation. Venous blood was withdrawn from 11 patients with ASA on days 1, 3, and 7 of admission. At corresponding time points comparison was with a control group of normal subjects and patients with mild asthma, coryzal symptoms, and chronic obstructive airways disease. Blood mononuclear cells were separated on Ficoll-Paque, labelled with fluorochrome conjugated monoclonal antibodies to LC surface markers, and analysed by flow cytometry with FACS Analyser/Consort 30 system. LC phenotypic markers (CD3, CD4, CD8) and T-LC activation markers (class II histocompatibility (Ia), interleukin-2 receptor (IL-2R), and "very late activation" antigen [VLA-1]) were studied. Irrelevant antibodies were used as controls. Double labelling allowed analysis of LC subsets. There were no significant differences in CD4, CD8, and the CD4:CD8 ratio between asthmatics and controls. Significantly elevated levels of all three activation markers were found on LC from patients with ASA on day 1 of admission when compared with controls ($p < 0·05$ in each case). IL-2R and VLA-1 levels remained significantly elevated on days 3 and 7. There was a trend downwards in the levels of these markers in the ASA group from days 1 to 7 as the patients improved clinically, although this did not reach statistical significance. These changes were not observed in those with mild asthma. These results provide strong evidence that T-LC activation is a feature of ASA and may provide an objective assessment of asthma severity and response to treatment.

The symptoms of pigeon breeders' disease (PBD)

S BOURKE, K ANDERSON, J BOYD, S KING, P LYNCH, G BOYD *Centre for Respiratory Investigation, Royal Infirmary, Glasgow* Two hundred and eighty seven pigeon fanciers completed a doctor administered questionnaire of symptoms and had antibody to pigeon gammaglobulin measured by an ELISA technique. Eighty five (29·6%) fulfilled the criteria (*Thorax* 1986;**41**:274) for diagnosis of PBD and had sensitisation to pigeon gammaglobulin. Thirty one (36·5%) had severe acute symptoms requiring them to come away from

the pigeons. The frequency and spectrum of acute and delayed (4–8 hours after exposure) symptoms were studied. It was found that 28·2% of patients with PBD compared with 12% of those without PBD ($p < 0·05$) had chronic bronchitis as defined by MRC criteria (*Lancet* 1965;i:775) despite being non-smokers, having no other chest disease, and having no occupational exposure to dusts; 8·4% of non-smokers from the total population surveyed had symptoms of chronic bronchitis without any delayed symptoms of PBD. Acute, delayed and bronchitic symptoms all increased in frequency as level of sensitisation to pigeon gammaglobulin increased. Current textbook descriptions of PBD, which focus only on delayed symptoms, give an incomplete picture of the disease. Acute symptoms are common and troublesome. Chronic bronchitis is a feature of the disease and may occur in fanciers without delayed symptoms and may therefore go unrecognised.

Value of repeat bronchoalveolar lavage in pulmonary sarcoidosis

NM FOLEY, K TUNG, AP CORAL, DG JAMES, NMCI JOHNSON *Middlesex and Royal Northern Hospitals, London* We have studied the correlation between changes in bronchoalveolar lavage (BAL) fluid cell counts and changes in radiological, radionucleotide, and pulmonary function parameters in sarcoidosis. Thirty four patients with biopsy proved sarcoidosis were studied (19 female, 15 male, 11 caucasian, 15 black, eight Asian; mean age 40·6 years, mean disease duration 3·6 years). All patients had bronchoscopy and BAL at the beginning of the study period. Standard chest radiographs were performed and films described by means of Chretien's modification of the standard Silzbach staging, ILO profusion score, and also a newer method of scoring chest films in sarcoidosis (BH Miller, CE Putman, *Sarcoidosis* 1985;**2**:85–90). Gallium-67 lung scanning was performed in all patients, the film being taken 48 hours after injection of isotope. A computer based system of counting activity on gallium scans was used, in which a region of interest was drawn on the film, excluding the hila, and counts per pixel converted into an activity score. The above investigations were repeated in all patients 4–20 (mean 8·6) months after the initial assessment, except for gallium lung scanning, which was repeated in 25 patients. On both initial and follow up visits all investigations were performed within a four day period. We have found a significant correlation between change in percentage of lymphocytes (ΔLC) in BAL fluid and change in FVC over the same period ($r = 0·33$, $p < 0·05$). There is also a significant correlation between ΔLC and change in activity score on Gallium scan ($r = 0·43$, $p < 0·05$). There is no significant correlation between change in lymphocyte count and change in chest radiographs on the basis of Chretien staging or either of the quantitative methods. However, changes in ILO and Miller/Putman scores do correlate ($p < 0·05$). Change in percentage neutrophils correlates with ΔLC ($r = 0·35$, $p < 0·05$), but not with any other parameter studied. Our results suggest that serial BAL does demonstrate changing activity in sarcoidosis, as lymphocyte count changes correlate with changes in FVC and gallium scan; but it is doubtful whether BAL adds to the clinical management of patients with sarcoidosis.

Clinical and immunological effect of inhaled corticosteroids in patients with pulmonary sarcoidosis

MA SPITERI, SW CLARKE, RM DUBOIS, LW POULTER *Departments of Thoracic Medicine and Immunology, Royal Free Hospital and School of Medicine, London* Ten symptomatic patients with grade III chest radiographs and restricted ventilatory defects (mean % predicted TLCO 65%) were treated with inhaled budesonide (Draco, Astra Pharmaceuticals), 800 μg twice a day, administered via a nebuhaler for four months. A placebo group included 10 healthy volunteers and five sarcoid patients with similar features to the treated group. Bronchoalveolar lavage (BAL) was performed before and after therapy, as was chest radiography and lung function tests. All 10 treated patients reported an improvement in their symptoms of cough and dyspnoea; in addition, a significant improvement in their lung function was found after treatment (mean % predicted TLCO 77%). Seven of the 10 patients also showed significant resolution of the parenchymal shadowing on their radiographs. Using BAL and blood mononuclear cells of the above subject groups, autologous mixed lymphocyte reactions (AMLR), were set up; in addition McAb studies using RFD1 and RFD7 were performed on all BAL cell cytospins. In those patients treated with inhaled budesonide there was an increase in RFD7+ macrophages (mean 17% increase), at the expense of the RFD1+ cells (mean 14% reduction). These changes resulted from a reduction in cells expressing both D1 and D7 epitopes. In addition, when AMLR in BAL fluid and blood were analysed after treatment, there was no change in reactivity in lavage AMLR, while a slight rise in the blood reactivity of the same patients occurred. However, when BAL cells were mixed with peripheral blood a dramatic increase in AMLR was seen after treatment. Such an increase also occurred with the mitomycin treated BAL fluid being used to stimulate blood lymphocytes. This suggests that the effect of inhaled steroids may be on the stimulator macrophage like cells. Interestingly, mitomycin treated blood mononuclear cells were also able to cause an eight fold increase in BAL AMLR, implying that some change had also occurred in the blood inducer macrophage population. No similar changes were seen either in the healthy volunteers or in untreated sarcoid patients.

Value of soluble immune proteins in the assessment of interstitial pulmonary disease

SP REYNOLDS, ED JONES, KP JONES, BH DAVIES *Asthma and Allergy Unit, Sully Hospital, South Glamorgan* In this study we set out to evaluate the cellular and soluble immune components of lavage fluid taken from patients with exposure to pigeon antigens (18 symptomatic, seven asymptomatic), sarcoidosis (10 high and six low intensity alveolitis), idiopathic pulmonary fibrosis (IPF) (19), and "normals" (5). Differential cell counts, lymphocyte subsets, interleukin-1 (IL1), interleukin-2 (IL2), and fibronectin levels were measured in all samples. These values were correlated with clinical and radiological staging of disease. Five symptomatic pigeon breeders underwent subsequent lavage six months later (three of these had decreased antigenic exposure), and

the above mediators were re-evaluated. Our results show that total lymphocyte numbers and lymphocytes expressed as a percentage of other cells (% lymphocytes) were significantly higher in the sarcoidosis and pigeon breeder groups than in our "normals" ($p < 0.001$). However, 4/8 ratios did not differ significantly between any groups. Furthermore, the interstitial diseases could not be differentiated on the basis of soluble immune mediator levels. [For IL1 pigeon breeders 2·6 (SD 2·1) $\times 10^3$, sarcoidosis 2·4 (2·1) $\times 10^3$, IPF 2·0 (1·0) $\times 10^3$, "normals" 2·0 (0·7) $\times 10^3$ ½ max units/ml of epithelial lining fluid.] There was little difference in lavage profiles in those pigeon breeders undergoing subsequent lavage according to whether or not they decreased their antigenic exposure.

Systemic features in patients with pulmonary eosinophilia

S CAPEWELL, BJ CHAPMAN, AP GREENING, GK CROMPTON *Respiratory Unit, Northern General Hospital, Edinburgh* Sixteen of 65 (25%) patients with pulmonary eosinophilia (PEo) presenting to one respiratory unit manifested systemic features during one or more PEo episodes. Twelve patients had fever, five night sweats, three arthralgia, three vasculitic rashes, and two weight loss. Anaemia, myalgia, peripheral neuropathy, mononeuritis, pericardial effusion, and photosensitive skin rash were also recorded. Four patients had allergic bronchopulmonary aspergillosis (ABPA). Three of 12 non-ABPA patients had Churg-Strauss syndrome/polyarteritis nodosa. The 16 patients with systemic symptoms differed from the remaining 49 patients in terms of associated asthma (69% *v* 96%; $p < 0.02$), allergic bronchopulmonary aspergillosis (25% *v* 59%; $p < 0.05$), and maximum recorded eosinophil counts (mean (SEM) $\times 10^6$/l: 4666 (936) *v* 2329 (435); $p < 0.02$). Steroid therapy achieved a good clinical response and radiological clearing in most patients. Only 3/16, all of whom had ABPA, developed persistent radiographic abnormalities. There was no long term decline in FEV_1 (% predicted mean (SEM)): initial 78 (9), follow up 76 (10) or VC (initial 79 (7), follow up 85 (9)). The median follow up was 11·1 years; 15/16 received "long term" prednisolone (mean (SEM): dose 8·5 (1·0) mg/day; duration 5·5 (1·3) years). Currently 4/16 are off all steroids and 6/16 receive < 5 mg/day. Despite sometimes dramatic clinical presentations most patients with PEo associated with systemic manifestations of disease are steroid responsive and have a good long term prognosis.

Steroid treatment and prognosis in pulmonary eosinophilia

S CAPEWELL, BJ CHAPMAN, F ALEXANDER, AP GREENING, GK CROMPTON *Respiratory Unit, Northern General Hospital, Edinburgh* We have reviewed the 247 responses to steroid therapy and long term outcome for 65 patients with pulmonary eosinophilia (PEo). Twenty four episodes of PEo were observed during a mean follow up period of 13·1 years. Ninety two of 247 (37%) occurred during long term prednisolone therapy, but only 10/92 when the daily dose was > 10 mg. One hundred and eighty six of 247 (75%) PEo episodes were treated with prednisolone or increased doses of prednisolone (67% receiving ≥ 20 mg/day). Complete clearing of chest radiographic infiltrates occurred in 161/247 (65%) (31/247 (12%) despite no steroid therapy), partial clearing in 61/247 (25%), and no response in 23/247 (9%). Eosinophil counts were followed during 185/247 episodes; they returned to normal in 134/185 (72%) (24/185 (13%) despite no steroid therapy), reduced in 35/185 (19%), but remained elevated in 16/185 (9%). Thirty three of 65 patients had allergic bronchopulmonary aspergillosis (ABPA) and 32/65 non-ABPA PEo. Long term prednisolone (LTPRED) was given to 28/33 ABPA patients (mean 7·4 mg/day × 11 years) and 29/32 non-ABPA patients (mean 8·1 mg/day × 4·6 years). Evidence of fibrosis or bronchiectasis occurred in 20/33 ABPA patients (4/5 receiving no LTPRED 10/15 receiving > 7·5 mg prednisolone/day) and 7/32 non-ABPA (1/3 receiving no LTPRED, 1/12 receiving > 7·5 mg prednisolone/day) ($p < 0.005$). Initial pulmonary function between PEo episodes was worse for ABPA than non-ABPA patients (% predicted, mean (SEM): FEV_1 57 (4) *v* 83 (5) ($p < 0.001$); VC 76 (4) *v* 88 (4)). There were no differences in pulmonary function between asthmatic and non-asthmatic non-ABPA patients. Thirty two of 33 ABPA patients had asthma. On long term follow up neither the ABPA nor the non-ABPA group displayed further decline in FEV_1 or VC. The prognosis for PEo associated with ABPA appears worse overall despite long term prednisolone therapy.

One year survival in patients with primary pulmonary hypertension

J PEPKE-ZABA, T HIGENBOTTAM, N CAINE, J WALLWORK *Papworth Hospital and Department of Community Medicine, University of Cambridge* Primary pulmonary hypertension (PPH) is a fatal disease with a reported 10 year survival of less than 25% (Fuster *et al, Circulation* 1984;**70**:580–7). Long term infusion of prostacyclin (PG12) improves the quality of life (Jones *et al, Br Heart J* 1987;**57**:270–8) but heart-lung transplantation (HLT) possibly offers the chance of improving survival (Burke *et al, Lancet* 1986;i:517–9). We have treated 36 patients (19 female and 17 male) with PPH. Long term PG12 infusion was given if acute vasodilatation occurred with PG12 at cardiac catheterisation. HLT was performed in patients who failed to respond acutely, or in the long term, to PG12 administration. The median follow up period was 390 days (range 5–1675). Survival at one year was less among those patients with mixed venous oxygen saturation ($S\bar{v}O_2$) < 63% (n = 31; mean survival 58% (SEM 9%)) than those with greater values (n = 5, survival 75% (21%)). There was no significant difference in one year survival of patients with $S\bar{v}O_2$ < 63% who received long term PG12 (n = 19; survival 60·5% (11%)) and in those who did not (n = 12; survival 56% (15%)). One year survival in patients who were transplanted (n = 8; survival 86% (13%) was greater than in those who were not (n = 28; survival 53% (10%) $p = 0.07$). These preliminary figures suggest that HLT significantly improves median term survival in PPH, while PG12 infusion, as shown in our previous work, improves the quality of life.

Changes in deadspace and physiological shunt during exercise and during acute vasodilation in pulmonary hypertension

BA OTULANA, TW HIGENBOTTAM, J WALLWORK *Departments of Respiratory Physiology and Surgery, Papworth Hospital, Cambridge* Hypoxaemia is a major factor in exercise intolerance of patients with pulmonary hypertension (Nadel *et al, Am J Med* 1968;**44**:16–24). Ventilation-perfusion ($\dot{V}/\dot{Q}$) imbalance is thought to contribute minimally to the hypoxia (Dantzker *et al, J Clin Invest* 1979;**64**:1050–5). We have studied eight patients (six male, two female, mean age 32 (SD 8) y), five with primary pulmonary hypertension and three with recurrent thromboembolic disease. The mean pulmonary artery pressure (PAP) was 66·54 (22·3) mm Hg and mean cardiac output ($\dot{Q}$) 3·5 (0·71)/min. Spirometry was normal in all but one who had mild obstruction, but TLCO was reduced (54% (16·4%) pred). The physiological deadspace (vd/vt, 0·46 (0·11)) and shunt (qs/qt, 15·2% (9·0%)) were higher than normal at rest according to the three compartment model (Riley *et al, J Appl Physiol* 1949;**1**:825–47). There was significant hypoxaemia (Pao_2 60·3 (12·4) mm Hg), widened alveolar-arterial oxygen difference (A–aDo2, 52 (15·4) mm Hg), and low mixed venous oxygen tension (Pvo_2, 27 (2·7) mm Hg). During supine exercise cardiac output increased (4·8 (0·2) l/min) but with a significant fall in $P\bar{v}o_2$ and Pao_2 and widening of A–aDO2. Small, but insignificant, changes occurred in vd/vt (0·50 (0·11)) and qs/qt (17·2% (15·1%)). Vasodilation with intravenous prostacyclin caused 21% (0·5%) increase in cardiac output and a rise in $P\bar{v}o_2$. The Pao_2 also increased (mean 84·4 (8·0) mm Hg) but the vd/vt (0·48 (0·11)) and qs/qt (12·5% (7·4%)) remained elevated above normal with no significant change. We have shown that $\dot{V}/\dot{Q}$ imbalance together with a low $P\bar{v}o_2$ causes the hypoxaemia in these patients. Improvement in cardiac output with prostacyclin does not affect the $\dot{V}/\dot{Q}$ mismatch but raises the Pvo_2 and thus the Pao_2.

Transmission emission scanning of pulmonary oedema

DJ SEDDON, BA BRIGGS, PD SNASHALL *Departments of Medicine and Nuclear Medicine, Charing Cross Hospital, London* Transmission emission scanning of the thorax with the use of ^{99m}Tc labelled autologous red blood cells and diethylenetriaminepenta-acetic acid (^{99m}Tc-DTPA) allows measurement of total thoracic tissue thickness and blood and interstitial fluid volume per pixel of the gamma camera image. Volume of blood or interstitium per pixel divided by pixel area gives the apparent transthoracic thickness of these compartments. We have previously validated this technique and demonstrated increased interstitial thickness in alveolar fibrosis (Briggs *et al, Clin Sci* 1987;**73**:319–27). In eight symptomatic patients with radiologically apparent partially treated cardiogenic pulmonary oedema and eight normal individuals we measured total thoracic thickness (T_t), blood thickness (T_{bl}), and interstitial fluid thickness at the base of the right lung. Anterior and posterior chest wall thickness (T_{cw}), measured on a lateral chest radiograph, when subtracted from T_t gives lung tissue thickness (T_l). Mean (SD) values in centimetres are:

	T_t	T_{cw}	T_l	T_{bl}	T_{in}
Normal	9·0 (0·6)	5·6 (0·3)	3·4 (0·5)	2·0 (0·3)	1·0 (0·5)
Pulmonary oedema	15·0 (3·8)	6·1 (1·6)	8·9 (3·2)	2·0 (1·1)	1·3 (0·5)

We assume that the substantial increase in T_l in the oedema group is due to increased lung water but this is not significantly labelled with ^{99m}Tc-DTPA at the time of scanning (five minutes after intravenous injection). We believe that this is because the majority of the oedema is within the alveolar air space or in slowly exchanging extra-alveolar compartments such as peribronchial and perivascular cuffs or pleural fluid. Rapid exchange of ^{99m}Tc-DTPA probably occurs only in alveolar septal interstitium. In conclusion, to label pulmonary oedema it will be necessary to use longer scanning times and/or a lipid soluble tracer molecule.

The von Willebrand Factor: a potential marker of endothelial cell injury?

DAR BOLDY, JG AYRES, PE SHORT, FGH HILL *Department of Respiratory Medicine, East Birmingham Hospital, and Department of Haematology, Birmingham Children's Hospital* von Willebrand factor (vWF) is synthesised in endothelial cells and megakaryocytes, and has an important role in primary haemostasis. It has also been suggested that vWF acts as an acute phase protein and that it may be used as a marker of pulmonary endothelial cell damage, since higher plasma levels are observed in critically ill patients with severe acute lung injury than in critically ill patients without lung injury (Carvalho *N Engl J Med* 1982;**307**:1113–9). In a community study of patients with acute bronchitis (AB) vWF antigen (vWF:Ag) (ELISA) and C-reactive protein (CRP) were measured on presentation and two and six weeks later in 39 individuals. The mean (SEM) vWF:Ag on presentation was 1·51 (0·15) V/ml (normal range 0·5–1·5 V/ml), falling to 1·06 (0·11) u/ml at two weeks and 1·12 (0·15) V/ml at six weeks (0–2 and 0–6 weeks $p < 0·0001$). vWF:Ag exceeded the normal range in 11 (28%) cases on presentation. CRP was slightly elevated in five cases (normal range <4 mg/l; values 4, 5, 7, 8, and 12 mg/l) and greatly increased in one case (84 mg/l). There was no correlation between vWF:Ag and CRP. Current and lifelong non-smokers had similar vWF:Ag levels but ex-smokers had significantly higher levels on presentation ($p < 0·0001$). We conclude that vWF:Ag is raised in AB, but that this is not an acute phase response. Our results are similar to the reported changes in vWF:Ag levels in acute bronchiolitis in infants, but less marked than in patients with acute respiratory failure. Further work is needed to identify whether pulmonary endothelial cells are the source of vWF:Ag and whether vWF:Ag is released by active secretion or cellular damage.

Bronchial blood flow (Doppler) following pulmonary embolism in conscious sheep

GH PARSONS, A VILLABLANCA (sponsored by CE Cross) *Department of Medicine, University of California, Davis,*

California Pulmonary artery obstruction reportedly causes an increase in bronchial blood flow (Q̇br) to the affected lung. We chose to study the magnitude and duration of change in Q̇br over four weeks in conscious sheep following pulmonary microembolism. At prior thoracotomy a 2·0–3·0 mm diam 10 MHz continuous wave (ultrasonic) or a 20 MHz pulse Doppler flow probe was placed around the common bronchial branch of the broncho-oesophageal artery to allow continuous recording of Doppler shift in kHz, proportional to blood velocity. In seven awake adult sheep restrained in a sling Sephadex beads 40–120 μm diam (3·1 (1·0) g, mean (SD)) were infused intravenously over 2–4 hours to achieve a two fold increase in mean pulmonary artery pressure (15·4 (4·8) to 39·4 (7·6) mm Hg). Before and following microembolism and at 2, 4, 6, 14, 21, and 28 days, Q̇br (kHz Doppler shift), arterial, pulmonary artery, and pulmonary artery wedge (Paw) pressures, arterial blood gases, and cardiac output were measured. By day 4 post embolism mean arterial pressure, mean pulmonary artery pressure (P_{PA}), Paw, and arterial P_{O_2}, P_{CO_2}, and pH had returned to baseline values. Cardiac output was never significantly different from before embolism. However, the Doppler shift of the common bronchial branch increased at days 7, 14, and 21.

	Days post embolism						
	Base	*2*	*4*	*7*	*14*	*21*	*28*
Q̇br Mean	2·4	2·6	2·9	3·7*	3·4*	3·5*	2·7
(kHz) SD	0·8	1·7	1·6	1·6	0·9	1·4	1·0
P_{PA} Mean	15·4	26·4*	20·1	17·6	17·7	16·5	13·8
(mm Hg) SD	4·8	8·5	5·1	3·4	5·5	2·1	1·0

*$p < 0·05$ compared with base.

The increased Q̇br at days 7, 14, and 21 cannot be explained by increased driving pressure, changes in P_{PA}, or altered arterial blood gases. We speculate that at 28 days new pulmonary channels have developed, reducing the requirement for Q̇br.

Atrial natriuretic peptide (ANP) levels in decompensated and treated cor pulmonale

JB NEILLY, J DOYLE, RD STEVENSON *Department of Respiratory Medicine, Royal Infirmary, and MRC Blood Pressure Unit, Western Infirmary, Glasgow* We sought to examine the relationship between atrial natriuretic peptide and oedema formation in cor pulmonale. ANP levels together with concomitant haemodynamic measurements were determined in 10 patients with oedematous cor pulmonale. Right atrial pressure (RAP) and pulmonary artery pressure (PAP) were both elevated (12 (SD 4) mm Hg and 43 (11) mm Hg respectively) but pulmonary capillary wedge pressure (PCWP) was normal (9 (3) mm Hg). The results were compared with those obtained in 12 patients with stable cor pulmonale (control), but with normal right and left atrial pressures: RAP 3 (2) mm Hg; PCWP 9 (3) mm Hg; PAP 33 (9) mm Hg. Arterial ANP levels were significantly increased in the patients compared with controls (271 (268), control 62 (33) pg/ml; $p < 0·02$), although four patients with oedema had ANP levels within the normal range (5–50 pg/ml). Six patients were restudied during convalescence when the oedema had cleared and both RAP and PAP had decreased (9 (3), 27 (4) mm Hg respectively). ANP levels were lower than at the time of admission in five of the six patients (mean 118 (131) pg/ml). A correlation ($r = 0·56$) was observed between ANP levels and RAP. The findings of this study support a role for right atrial distension alone in the secretion of ANP.

Breath carbon monoxide and the influence of smoking on the antibody response in pigeon fanciers

K ANDERSON, S BOURKE, S MORRISON, G BOYD *Department of Respiratory Medicine, Royal Infirmary, Glasgow* Cigarette smoking is known to alter the immune response (PG Holt, *Thorax* 1987;**42**:241) and seems particularly relevant in individuals susceptible to the effects of organic antigen inhalation (McSharry *et al, Clin Allergy* 1985;**15**:487). Other groups have made similar observations but we are unaware of any study using an objective marker of cigarette exposure. A group of 86 volunteer pigeon fanciers donated a serum sample for circulating specific anti-pigeon IgG and also used a hand held carbon monoxide (CO) meter which immediately indicated the end expired CO. Although there was no direct correlation between CO and specific IgG, a significant difference was found in antibody levels between smokers and non-smokers ($H = 7·3$, $p = 0·007$) and in antibody levels for subjects with ≥ 10 and < 10 parts per million CO ($H = 8·2$, $p = 0·004$). The smoking history obtained appeared accurate in 65/66 non-smokers and 15/19 smokers. A tendency towards lower CO levels in the smokers who had detectable circulating antibody was noted. This study reinforces previous conclusions drawn from observations made without benefit of a marker of cigarette smoking and suggests that cigarette smokers who have detectable circulating antibody are exposed to less smoke than those who do not.

Pulmonary abnormalities in Crohn's disease (CD)

JB NEILLY, C MCSHARRY, A MAIN, RI RUSSEL *Departments of Respiratory Medicine and Gastroenterology, Royal Infirmary, Glasgow* Abnormalities of pulmonary function and various lung disorders have been described in Crohn's disease. So that the relation could be examined more closely, 29 patients with biopsy proved Crohn's disease and 29 control subjects matched for age, sex, and smoking history underwent detailed respiratory assessment, including pulmonary function studies. Crohn's disease activity was assessed by the modified Crohn's disease activity index (CDAI) (RF Harvey, JM Bradshaw, *Lancet* 1980;i:514). A history of asthma (10%, control 14%) and chronic bronchitis (14%, control 20%) was reported with similar frequency in patients and controls. Vital capacity (CD 89% (SD 17%) predicted, control 96% (13%); $p < 0·01$) and FEV_1 (CD 84% (21%), control 94% (16%); $p < 0·05$) were significantly lower in patients than in controls but features of airways obstruction were present with equal frequency in the two groups (CD 31%, control 28%). Total lung capacity (CD 97% (19%) control 102% (12%); NS) was normal but two patients (no control subjects) had a restrictive ventilatory defect. None had radiological

features of diffuse pulmonary fibrosis. The single breath carbon monoxide diffusing capacity (transfer factor, TLCO) was significantly less in the patients than in controls (CD 100% (17%), control 113% (25%); $p < 0.05$). CDAI (6·4 (5·0)) was positively correlated with the residual volume ($R = 0.44$, $p < 0.02$) but with no other parameter of lung function. There was a weak inverse correlation between Crohn's disease duration and the TLCO ($R = 0.36$, $p < 0.05$). In conclusion, we did not confirm the increased incidence of airways obstruction in Crohn's disease reported by others. (RV Heatley, *et al, Q J Med* 1982;**203**:241–50.) Restrictive ventilatory abnormality is more common in Crohn's disease than normal and defects in gas transfer are related to duration of illness.

Community acquired pneumonia in West Africa: seasonality, outcome, and usefulness of lung aspiration

P NUNN, RN'JIE, K MANNEH, AJP CROWDEN, S GOODISON *Royal Victoria Hospital, Banjul, Gambia* Three hundred and six patients with acute community acquired pneumonia were admitted to the adult medical wards of the Royal Victoria Hospital from September 1983 to August 1985, representing 10% of all medical admissions. This figure excludes those who also had pneumococcal meningitis or a diagnosis of tuberculosis made within the following six months, or whose pneumonia was secondary to a cerebrovascular accident, malignancy, or tetanus. Admission was significantly more likely in the dry season ($p < 0.001$). Thirty five patients (11%) died, 14 within 24 hours of admission. A further 11 (3·5%) developed an important complication: seven had an effusion requiring more than one aspiration or surgical drainage, three empyema, two multiple pulmonary abscesses, and one a solitary lung abscess. Standard initial treatment was with parenteral penicillin. Thirty two of the 35 deaths occurred during the initial treatment. A further 34 patients failed to respond to first line treatment and required a change in antibiotic, including three of those with complications. Only three of these subsequently died. Of the 32 initial non-responders, 20 unselected patients with persistent consolidation only underwent percutaneous lung aspiration, including two immediately after death. No haemoptysis or pneumothorax occurred following the procedure. Penicillin resistant organisms were isolated from 50%: *Klebsiella pneumoniae* (5), *K pneumoniae* var *oxytoca* (1), *Bacteroides fragilis* (2), one in association with a non-haemolytic streptococcus, *S aureus* (1) and *Actinobacter* sp (1). The remaining cultures were sterile. We conclude that community acquired pneumonia is a substantial drain on scarce resources in West Africa. Of those who die many present too late. Three quarters of the patients responded to initial treatment. Outpatient treatment may be appropriate for most cases if those likely to develop complications can be identified. Lung aspiration is a useful technique for identifying persistent infections. It is not clear whether the organisms so identified were primary or secondary infections.

An audit of inpatient oxygen usage

AA JEFFREY, S RAE, NJ DOUGLAS *Department of Respiratory Medicine and Chest Unit, City Hospital, Edinburgh* We have audited how accurately oxygen therapy is being prescribed for and received by patients in the two respiratory units in our hospital. Inpatient oxygen usage has been assessed by comparing prescribed oxygen therapy with that actually being received by the patient at random checks at varying times in the day over a two month period in the two units. One hundred and sixty of 626 patients (25·6%) were prescribed and/or receiving oxygen therapy. Only two patients were receiving oxygen by mask; the remainder were prescribed or using nasal prongs. Seventy seven patients (48·1%) were receiving their prescribed method and flow of oxygen with the oxygen delivering device correctly in place on the face. One patient was receiving oxygen by a delivery device which was not that prescribed and 16 (10·8%) were receiving oxygen which had not been prescribed at all. Twenty six patients (16·3%) had valid oxygen prescriptions but the oxygen was switched off and the nasal prong removed. Forty two patients (26·3%) had oxygen available but the delivery device displaced off their faces. In 51 of the cases (31·9%) in which a defined oxygen flow rate was prescribed, the flow rate was wrongly set (error > 1 l/min). Thus over half the patients in these specialist respiratory units were not receiving their prescribed oxygen. The principal problems were wrongly set flow meters and lack of patient compliance despite the dominant use of nasal cannulas, which are generally more acceptable to patients than masks (Green, *Br Med J* 1967;iii:593).

Epidemiology of tuberculosis in the Republic of Ireland 1980–85

F HOWELL, P KELLY, L CLANCY *Peamount Hospital, Newcastle, Co Dublin*

Rifater without ethambutol or streptomycin in short course chemotherapy of pulmonary tuberculosis

P KELLY, P CORCORAN, L CLANCY *Peamount Hospital, Newcastle, Co Dublin* The role of ethambutol/streptomycin in short course chemotherapy of pulmonary tuberculosis is uncertain if the organism is fully sensitive. We treated 29 consecutive patients (11F, 23M; mean age 51·2 (SD 19·3) y) with culture positive pulmonary tuberculosis using Rifater (combination of rifampicin 120 mg, isoniazid 50 mg, pyrazinamide 300 mg; Merrell Dow). Patients received Rifater for two months followed by rifampicin and isoniazid for a further four months. All patients achieved a culture negative status. The mean time to negative culture was 4·5 (SD 2·66) weeks (range 1–9). The median time to negative direct smear was seven weeks. All patients have been followed for a minimum of six months following completion of therapy; all remain culture negative. Eleven patients developed abnormal liver function and four required temporary cessation of therapy because of hepatitis. Although 27 patients had raised serum uric acid levels, none developed clinical gout. One patient underwent a psychotic mood change secondary to isoniazid. It is concluded that Rifater alone seems effective in the management of pulmonary tuberculosis; the time taken to become culture negative is comparable to that seen with ethambutol and streptomycin

containing regimens. Moreover, drug toxicity was no different than that seen in other regimens, and compliance may be better because of the single species of tablet prescribed.

May the second World War and not AIDS be the cause of the recent arrest in the decline of tuberculosis notifications in England and Wales?

PDO DAVIES *Department of Medicine, Llandough Hospital, Penarth, S Glamorgan* Over the past five years there has been a decrease in the rate of decline of tuberculosis notifications in England and Wales. Notifications for 1986 show a slight increase over 1985. It has been suggested that HIV infection and AIDS may be responsible for the apparent arrest in an otherwise downward trend. We have conducted an analysis of the most recent figures published for tuberculosis notifications available from the Office of Population Censuses and Surveys (*OPCS Monitor* MB2). Between October/December 1982 and April/June 1986 notification rates declined from 16·6 to 14·2/100 000 in males and 11·7 to 11·4 in females. The smallest decline was in women aged 55 or more, with a slight increase in women aged 65–74 (11·8 to 11·9). The decline was most marked in males and females under the age of 25. In particular, men aged 20–24 showed a decline from 14·2 to 8·1/100 000 and those aged 25–34 from 17·2 to 15·4, probably the group most at risk from HIV infection. It is likely that patients aged 55 and over incurred infection during teenage or early adult life, a period around or during World War II. At this time there was a considerable increase in tuberculosis notification and therefore presumably in infection as well. World War II is a more probable cause of the recent slowing in the decline of tuberculosis than is HIV infection.

Initial evaluation of a new method of measuring compliance with antituberculous therapy

N DE SOUZA, S PEAKER, KRM HAIGH, M GREENSTONE, NK COOKE, M FEELY *Departments of Medicine and Respiratory Medicine, General Infirmary, Leeds* A new method of assessing patient compliance with drug therapy, with low dose phenobarbitone (PB) as a pharmacological indicator, has been described recently (*Br J Clin Pharmacol* 1987;**24**:77). It was, however, unclear whether this method could be applied in tuberculosis (TB) because rifampicin is one of the few drugs which stimulates the metabolism of barbiturates (*Clin Pharmacol Ther* 1977;**21**:470). We gave PB tablets, 2 or 7·5 mg daily, to six inpatients being treated for TB. Subsequently, in 10 cases followed for up to 30 weeks as outpatients we used a preparation incorporating PB 4 mg in the same capsule as therapeutic doses of rifampicin and isoniazid. Plasma levels of PB were measured at regular intervals and compliance was assessed by calculating the PB level (mg/l) to dose (mg/kg) ratio (LDR). PB LDRs were substantially lower (by ~40%) in patients having antituberculous therapy than in volunteers and interindividual variation in LDR was greater. However, the PB LDRs showed a negative correlation with rifampicin dose ($r = -0.571$, $p = 0.021$, $n = 16$). Furthermore, PB levels approached steady state after only five to seven days of antituberculous therapy and levels obtained from inpatients showed that intraindividual variation in LDR was slight. As a result of these latter findings, outpatient PB levels provided a clear indication of compliance. Two of the 10 outpatients showed evidence of poor compliance; one admitted this and the other was an Asian speaking little English whose LDR decreased dramatically on leaving hospital.

Effect of fenbufen on the quality of life of patients with pain from squamous cell carcinoma of the bronchus

A JAVAID, MF BONE, CS STANLEY *Russells Hall Hospital, Dudley, West Midlands* Non-steroidal anti-inflammatory drugs are effective in relieving cancer pain of non-neural origin (*Clin Pharmacol Ther* 1975;**17**:784–89). We investigated the effect of fenbufen as an adjunct in improving quality of life in patients with squamous cell carcinoma of bronchus by relieving pain and so reducing the necessity for more powerful analgesia. This study was a double blind, parallel group comparison of fenbufen 900 mg/day with a matched placebo. Treatment was for four weeks and patients were assessed on quality of life, on the basis of a 10 point visual analogue scale and severity of pain prior to the study and at weekly intervals. Patients were provided with adequate escape analgesia—namely, pethidine tablets 25 mg as required; the number of pethidine tablets taken each week was noted. Twenty two patients were studied, 10 in the fenbufen group and 12 in the placebo group. The groups were matched for age, presence of secondaries, severity of pain, and the number of pethidine tablets taken per week prior to study. In patients having active treatment the mean pethidine requirement changed from 8 (SEM 2) to 10 (6), whereas in the placebo group it increased from 11 (2) to 25 (8) ($p < 0.05$). The feeling of well being improved in the fenbufen group, the score falling from 52·8 (5·8) to 38·4 (9·7), whereas in the placebo group the score increased from 40·8 (5·2) to 46·1 (9·1) ($p < 0.05$). Severity of pain in the fenbufen group fell from 2·6 (0·2) to 1·9 (0·2) and in the placebo group it fell from 2·8 (0·3) to 2·2 (0·4) ($p < 0.05$). No significant differences were found between the two groups regarding level of anxiety, ability to perform, level of activity, social activities, appetite, mood, or nausea. We concluded that fenbufen is a useful adjunct in improving the quality of life by controlling pain and in reducing the requirement for more powerful analgesia such as opiates.

Small cell lung carcinoma in the elderly: the case for chemotherapy

P KELLY, A O'BRIEN, P DALY, L CLANCY *Peamount Hospital, Newcastle, Co Dublin* Lung cancer is said to be more rapidly progressive in elderly patients (Rossington, *Am Rev Respir Dis* 1982;**126**:771). The average age in series treated with combination chemotherapy is 57–59 years (Aisner J*et al*, *Cancer* 1980;**46**:2543; Nixon *et al*, *Cancer* 1975;**36**:867–72). A retrospective analysis of 48 elderly patients with small cell lung cancer (SCLC) seen during 1979–86 is presented. The

median age was 74 (range 65–83) years with 28 patients older than 70 years. The male/female ratio was 3:2. Mean performance score (Karnofsky) was 80 (60–100). Thirty four patients were treated with combination chemotherapy, six patients received single agent chemotherapy plus or minus radiotherapy, four patients were moribund at diagnosis, and four patients refused treatment. Median survival was 25 weeks for combined chemotherapy; 10 weeks for single agent therapy; three weeks for the moribund group and eight weeks for those who refused treatment. The 34 elderly patients who received combination chemotherapy were compared with 62 patients younger than 65 years (median age 57, range 33–64 years). Overall median survival in the elderly group was 25 weeks (36/13 for limited/extensive stage) and in the young 27 weeks (39/20 for limited/extensive stage). There were two long term survivors (> 2 yr) in the elderly and three in the younger group. We plotted survival probabilities for both elderly and young treated with chemotherapy (Kaplan-Meier). There was no statistical difference in survival between the two groups or between the sexes. We conclude that age itself is not a contraindication to therapy and that outcome is determined by initial stage of disease and initial performance status. We could show no difference in survival between men and women.

Bronchography in patients with collapsed lungs: demonstration of "reversible bronchiectasis"?

PJM GEORGE, D EDWARDS, MR HETZEL *Departments of Thoracic Medicine and Radiology, University College Hospital, London* Endoscopic laser treatment for tumours causing complete endobronchial obstruction tends to be unsuccessful. Plain chest radiographs do not provide information on the extent of tumour and patency of the distal airways, with the result that the operator may needlessly subject patients with very extensive tumours to treatment, while abandoning treatment prematurely in some patients whose lungs are salvageable. To overcome this problem, we have developed a bronchographic technique in which an arterial catheter is passed beyond the tumour, allowing contrast to be injected into the distal airways. This method has successfully demonstrated patent distal airways in five out of six patients with collapsed lungs. The airways distal to the obstruction were in all cases abnormally dilated; in one patient the bronchiectatic changes were sufficiently severe for a decision not to attempt recanalisation. Laser resection successfully recanalised airways in three out of five patients. Treatment was unsuccessful in the patient whose distal airways could not be demonstrated bronchographically and in another whose bronchogram suggested extensive endobronchial obstruction (approximately 4 cm). Bronchography was repeated in one patient, two weeks after re-expansion of the collapsed lung, and revealed a considerable reduction in the dilatation of the airways. Bronchography was performed in two additional patients whose lungs had been collapsed but had recently expanded (one spontaneously and one after radiotherapy); in both cases the airways were of normal calibre. Preliminary experience with this new technique thus demonstrates its potential to identify patients with patent distal airways who are suitable for laser treatment. Bronchiectasis in patients with collapsed lungs may be reversible and therefore should not be regarded as a contraindication to treatment.

Testing new drugs in untreated small cell cancer may prejudice the efficacy of standard treatment: a phase II study of oral idarubicin in extensive disease

SR SMITH, MH CULLEN, GFA BENFIELD, CM WOODROFFE *Queen Elizabeth Hospital, Birmingham* The results of standard chemotherapy treatment in small cell cancer are poor, with virtually no long term survivors. Several chemotherapeutic agents, in combination, can, however, provide effective short term palliation and extension of survival. Conventionally, new drugs are tested in patients who have failed with standard treatment and thus, by definition, have multi-drug resistant tumours. It is quite possible that potentially valuable agents will not be identified in this setting. Thus some investigators have tested new drugs in previously untreated cases, reverting to standard treatment in those who fail to respond. We have evaluated the orally active anthracycline idarubicin (40 mg/m^2 in divided doses over 24 h) in 21 patients with extensive stage small cell lung cancer, and report the results of subsequent intravenous therapy (CVE—cyclophosphamide 1000 mg/m^2, vincristine 1 mg/m^2, etoposide 120 mg/m^2 intravenously day 1; etoposide 250 mg/m^2 orally in divided doses on day 2), as well as those of the phase II study. Of 21 treated patients, three (14%) responded with two complete remissions. Patients failing to respond promptly and relapse cases were treated with CVE. Seven patients did not receive CVE for the following reasons: early death four, early CNS disease two, refusal one. Fourteen cases did receive CVE. Of 12 idarubicin failures, eight progressed with CVE, three achieved partial remission and one complete remission. Two idarubicin responders who had CVE achieved partial remission and complete remission. The median survival (MS) of all 21 patients is six months. For those with WHO performance scores of 0 or 1 the MS is 6·2 months and for the rest it is 2·6 months. Despite a strictly applied policy of instituting standard intravenous therapy promptly in static or progressive disease, these results are inferior to those seen in our centre with standard treatment from the start, in extensive small cell cancer, especially in those with poorer performance status. We believe that patients with extensive small cell cancer often require a rapid and more guaranteed response to their first treatment and may not be suitable for experimental therapy.

Clinical significance of disordered haemostatis in small cell lung cancer

R MILROY, JT DOUGLAS, GDO LOWE, R CARTER, CD FORBES, SW BANHAM *Department of Respiratory Medicine and University Department of Medicine, Royal Infirmary, Glasgow* Disorders of haemostasis and altered platelet activity have been well documented in patients with malignant disease but their relationship to prognosis and response to treatment are not known. We report our experience in a study of 37 patients with small cell lung cancer (30 with limited and seven with extensive disease). Estimations of fibrin formation, plasmin

mediated fibrinolysis, and platelet α granule release were obtained by measurement of plasma levels of fibrinopeptide A (FPA), Bβ15–42 antigen (Bβ), and β thromboglobulin (BTG) levels respectively. There was evidence for considerably increased fibrin formation and fibrinolysis in all patients. Median FPA (pmol/ml) was 13·2 (interquartile range 5·3–65·5; normal <4); median Bβ (pmol/ml) was 5·6 (interquartile range 3·6–8·7; normal <3). In addition, most of our patients (57%) showed evidence of increased platelet α granule release. Median BTG (ng/ml) was 50 (interquartile range 33–73; normal <50). There was no correlation between these haemostatic parameters and disease extent. Twenty six of these patients completed induction chemotherapy and were evaluable for response: 14 complete responders, seven partial responders, and five non-responders. There was a significant correlation between increased thrombin generation and fibrin formation (FPA levels) and lack of response to chemotherapy ($p < 0.01$, Mann-Whitney U test), and non-responders had evidence of an increased ratio of fibrin formation to lysis ($p < 0.05$, Mann-Whitney U test). This is the first study to document a relationship between increased fibrin formation in cancer patients and lack of response to chemotherapy.

The responder lymphocyte as the target for the immunosuppressive effects of pulmonary surfactant

ML WILSHER, DJ PARKER, PL HASLAM *Cell Biology Unit, Cardiothoracic Institute, London* Pulmonary surfactant has recently been shown to have immunosuppressive properties and may exert these effects at the level of antigen presentation. We have sought to clarify in vitro whether surfactant exerts its effects on stimulator monocytes (Mo) or responder lymphocytes (Ly). Peripheral blood monoclear cells were obtained from eight adult volunteers. They were separated into two populations, monocytes and T cells, by stepwise adherence, rosetting, and nylon wool passage. Purity was determined by non-specific esterase (NSE) staining and monoclonal antibodies (Mab), with a flow cytometer. Both populations of cells were cultured overnight in the presence (+) or absence (−) of surfactant lipids purified from the bronchoalveolar lavage fluids of normal volunteers (0·2 mg/ml). Mo were then added to Ly culture in a ratio of 1:5 in the presence of optimal phytohaemagglutinin. Suppression of the proliferative response occurred only in the Ly + Mo− and Ly + Mo+ cultures (61% (SEM 4%), 61% (7%) lipid free control phytohaemagglutinin response). No effect was seen in the Ly − Mo+ cultures. The suppressive effect could not be washed off prior to addition of mitogen and was not seen if the lipids were added to culture 24 hours after the mitogen. These results suggest that surfactant exerts its effects at the early inductive phase of the T lymphocyte response rather than on antigen presenting cells. (Supported by the Wellcome Trust, the Medical Research Council of New Zealand, the British Lung Foundation, and the Percy Bilton Charity.)

Expression of MHC class II encoded molecules by pulmonary epithelial cells in chronic lung diseases

PL HASLAM, PJ TOWNSEND, DJ PARKER, A DEWAR *Cell Biology Unit and Department of Electron Microscopy, Cardiothoracic Institute, London* T helper lymphocytes recognise foreign antigens only in association with self MHC class II molecules on the surface of antigen presenting cells. Normally, class II expression is mainly restricted to dendritic cells, macrophages, B cells, and activated T cells. However, in studies of lung biopsy specimens from patients with cryptogenic fibrosing alveolitis (CFA) using immunocytochemical methods, we and others have recently reported class II molecules on both alveolar and bronchial epithelial cells. It is known that mediators released during cellular immune responses can induce aberrant class II expression in some cell types. Cellular immunity is suspected to play a part in some chronic inflammatory lung diseases. We have examined 15 open lung biopsy specimens from patients with sarcoidosis, extrinsic allergic alveolitis, and CFA. We have used monoclonal antibodies to HLA-DR, DQ, and DP and demonstrated epithelial cells expressing these class II antigens in all the specimens. To obtain confirmatory evidence that class II expression relates to epithelial cells and not infiltrating dendritic cells or macrophages, we have extracted cells from eight lung biopsy specimens and double stained them with a monoclonal antibody to cytokeratin (epithelial cells) and with anti HLA-DR. We have detected the presence of double labelled cells using two colour flow cytometry and confirm that most cytokeratin positive cells express HLA-DR. We have also sorted and further examined these cells by electron microscopy. Whether these cells function to amplify and maintain the local immune response in these chronic inflammatory lung diseases needs to be established. (Supported by the Clinical Research Committee in National Heart and Chest Hospitals, the British Lung Foundation, and the Percy Bilton Charity.)

Tumour necrosis factor release by pulmonary alveolar macrophages

NM FOLEY, AB MILLAR, GAW ROOK, NMCI JOHNSON *Departments of Medicine and Microbiology, Middlesex Hospital, London* Tumour necrosis factor (TNF) is a macrophage secretory product which causes fever, weight loss, and endothelial cell necrosis. Tuberculosis and sarcoidosis are conditions in which there is massive production of γ interferon and enhanced vitamin D 1-hydroxylase activity, both of which prime macrophages for TNF release. We have performed a preliminary study on the ability of macrophages obtained by bronchoalveolar lavage (BAL) to produce TNF in response to stimulation with staphylococcal endotoxin lipopolysaccharide (LPS). Eight patients undergoing bronchoscopy and BAL were studied: (mean age 47·7 (SD) 17·4) y, six female; two sarcoidosis, two tuberculosis, four controls—patients with normal bronchoscopy and negative cytology appearances and ZN staining of BAL fluid). Patients with neoplastic disease were excluded from this study. BAL was performed with prewarmed, buffered saline in the right middle lobe. Macrophages were harvested by an adherence method and cultured in RPMI with 10% fetal calf serum. The cells were incubated with increasing concentrations of LPS for four hours, and the supernatants collected. TNF was assayed by the enzyme linked immunosorbent assay (ELISA). Production of TNF was significantly

different in macrophages from patients with tuberculosis and sarcoidosis from that in controls. After stimulation with LPS, the mean TNF concentration in these patients was 245·6 IU/ml while that in controls was 39·7 IU/ml ($p < 0·05$, Student's t test). Baseline TNF (without LPS stimulation) was also much higher in tuberculosis and sarcoid macrophage supernatants (mean 225·4 IU/ml) than in controls (mean 41·2): $p < 0·05$. Our results suggest that macrophages from patients with tuberculosis and sarcoidosis produce significantly more TNF than those from (non-neoplastic) controls, both in vivo and after stimulation with LPS.

H_2O_2 release from alveolar macrophages of patients with sarcoidosis and fibrosing alveolitis

AP GREENING, NE WOOD, M GORDON, GK CROMPTON
Respiratory Unit, Northern General Hospital, Edinburgh
Release of reactive oxygen intermediates (ROI), such as hydrogen peroxide (H_2O_2), by macrophages is one indicator of the state of cell activation. ROI can exert both pro-inflammatory and anti-inflammatory effects, both by causing tissue damage or inactivation of mediators locally and by affecting secretory responses of adjacent cells or lymphocyte function. In the interstitial lung disorders pulmonary macrophages may have a central role in modulating the inflammatory responses. We have examined the release of H_2O_2 from alveolar macrophages (AM) of patients with sarcoidosis and fibrosing alveolitis. AM were obtained by bronchoalveolar lavage from 13 control subjects (no active lung disease), nine sarcoiodosis patients, and 11 fibrosing alveolitis patients. The cells were purified by plastic adherence and overnight culture in medium 199 supplemented by 5% fetal calf serum. At 24 h H_2O_2 release was measured fluorimetrically after stimulation of the AM with phorbol myristate acetate. There were no differences in H_2O_2 release between the control and fibrosing alveolitis groups (mean (SEM), nmol/10^6 cells/h: controls 9·8 (2·1), fibrosing alveolitis 11·95 (1·4) but sarcoidosis AM displayed a substantial enhancement of H_2O_2 release (17·1 (2·5)) compared with both other groups ($p < 0·01$). On the basis of ROI generation as a marker of cell activation, sarcoid AM appear to have been primed, in vivo, to a greater extent than fibrosing alveolitis AM. The general lack of long term tissue damage in sarcoidosis implies that in this disease enhanced release of ROI by pulmonary macrophages may be immunoregulatory rather than tissue toxic.

Ultrastructural features of developing Kveim test granulomas

E SHEFFIELD, DN MITCHELL, B CORRIN, BJ ADDIS, A DEWAR
Brompton Hospital, London
Sequential Kveim biopsies provide a unique opportunity to study the development of epithelioid cell granulomas in man. We present a controlled prospective ultrastructural study of such developing epithelioid cell granulomas. Two Kveim tests were performed simultaneously on 132 patients being investigated for possible sarcoidosis. One test site was biopsied at 28 days to assess Kveim reactivity: 49 patients showed a positive response. The other test site was biopsied after a varying interval to study the development of the lesion. Controls were provided by biopsies of injection sites performed at variable intervals on a further 12 patients following simultaneous tests with Kveim and normal spleen suspensions. Additionally, a group of apparently healthy subjects were tested similarly. In the developing Kveim reaction, perivascular collections of undifferentiated mononuclear cells are seen from 24 hours. Phagocytosis of Kveim material by histiocytes is seen within one to two days. This is, however, a short lived phenomenon. Features of mononuclear cell activation are seen from three days. Interactions between lymphocytes and monocytes become most frequent at five to seven days. Monocytes develop prominent rough endoplasmic reticulum, which in some areas dilates to form clear vesicles. The Golgi apparatus increases in size and lysosomal and secretory type membrane limited vacuoles appear. Large numbers of bristle coated vesicles develop, many closely relating to cytoplasmic filaments, indicating increased intracellular transport of protein. Activated monocytes show cytoplasmic projections containing prominent filaments. Maturing epithelioid cells develop junctions in relation to subplasmalemmal densities. Endocytosis is seen, particularly in developing epithelioid cells. Mature epithelioid cells are seen at seven to 10 days and contain large numbers of secretory vacuoles. Thus during development epithelioid cells switch from a phagocytic to a full blown secretory pathway of the type seen in exocrine cells.

Functional deterioration in sarcoid patients with bronchoalveolar lavage fluid collagenase

CM O'CONNOR, K WARD, C POWER, MX FITZGERALD
Department of Medicine, University College Dublin and St Vincent's Hospital, Dublin
Collagenase is thought to have a role in the development of fibrosis in several interstitial lung diseases. In a previous study we noted an association between bronchoalveolar lavage (BAL) collagenase and chronic, prolonged disease in sarcoidosis. We also noted that a higher proportion of patients with BAL collagenase required that corticosteroid treatment shortly after lavage than patients without BAL collagenase. In the present study disèase progress was monitored in a group of 28 untreated sarcoid patients over a period of 12–24 months. BAL, performed at the beginning of the study, indicated that nine patients had elevated collagenase levels (collagenase + ve) and 19 patients undetectable collagenase levels (collagenase − ve). At time of BAL pulmonary function profiles for the collagenase + ve and collagenase − ve groups were similar, only two patients in each group displaying impaired function (as determined by FVC% or TLCO% values < 80% predicted). On follow up, TLCO% levels decreased significantly in the collagenase + ve group ($p < 0·05$, paired t test), and a further four patients displayed impaired function. No significant improvement in pulmonary function (as assessed by an increase of > 10% in FVC% or TLCO%) was noted in any patient from this group. By contrast, no decrease in TLCO% was noted for the collagenase − ve group and only one patient developed impaired function on follow up. In addition, pulmonary function improved significantly in five patients from this group. These results indicate that sarcoid patients with BAL collagenase are more likely to exhibit functional deteriora-

tion over time than patients without BAL collagenase. (This work was supported by the Health Research Board of Ireland.)

Luminol amplified chemiluminescence (CL) as a marker of neutrophil metabolic activity in asthma

C WARD, CA KELLY, SC STENTON, M DUDDRIDGE, DJ HENDRICK, EH WALTERS *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne* Bronchoalveolar lavage (BAL) cells from a normal area of lung in five non-asthmatic subjects undergoing diagnostic bronchoscopy were pelleted (1000 rpm, 4°C) and resuspended in medium 199 (Gibco) to 5 × 10^5 cells/ml. The differential cell counts were 97–98% macrophages (AM), 0–1% neutrophils (PMN), and 0–2% lymphocytes. Two hundred and fifty thousand cells were stimulated with 5% w/v latex particles. Allogenic blood leucocytes (PMN) were obtained by separation on a Ficol gradient (≥95% PMN) and stimulated with latex as above. Maximum luminol amplified CL was measured:

	Mean (SEM) counts/second	
n = 5	*≥ 95% PMN*	*≥ 97% AM ≤ 1% PMN*
Mean luminol Amplified CL	47·3 (± 11·1) × 10^4	2·1 (± 0·9) × 10^4

In a previous report (*Clin Sci* 1987;**73**:33–P) the relationship between luminol amplified CL and PMN was studied by replacement of AM with blood PMN. Final concentrations of PMN were 10%, 20%, 40%, 50%, and 70%. Luminol CL increased linearly ($r = 0{\cdot}996$, $p < 0{\cdot}001$) and the regression passed through the origin. In this study the relationship between PMN count in BAL fluid and luminol amplified CL has been studied in mixed aliquots of 250 000 cells obtained from asthmatic ($n = 22$) and non-obstructed ($n = 20$) control subjects. There was again a linear correlation in each group (asthma $r = 0{\cdot}82$, $p < 0{\cdot}001$; control $r = 0{\cdot}83$, $p < 0{\cdot}001$), with a y intercept indistinguishable from the origin. However, comparison of the two regressions showed a significantly greater slope in the asthmatic subjects than in the controls ($p < 0{\cdot}01$). These results confirm that luminol amplified CL exclusively reflects PMN activity in BAL specimens and show that in asthmatic subjects airway PMN function is uniformly increased.

Enhanced neutrophil leukotriene B_4 generation by a T cell derived product

J-J TSAI, P MAESTRELLI, O CROMWELL, R MOQBEL, AB KAY *Department of Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* Leukotrienes are potentially important proinflammatory mediators in asthma and related conditions. We have previously reported that human mononuclear cell (MNC) culture supernatants can enhance neutrophil activity in terms of increased leukotriene generation (J-J Tsai *et al J Allergy Clin Immunol* 1987;**79**:167). We now report that the activity was associated with a protein of about 35 000–40 000 daltons and an isoelectric point of 5·1–5·5. Human peripheral blood MNC were obtained from patients undergoing leucapheresis, and stimulated with phytohaemagglutinin. Leukotriene release enhancing activity (LREA) was progressively purified with gel filtration and chromatofocussing. The activity appears to be distinct from recognised cytokines, including interleukins 1 and 2, γ interferon, tumour necrosis factor, and granulocyte/monocyte colony stimulating factor. The specific activity of the LREA was increased 50 fold as judged by its ability to enhance leukotriene B_4 generation by neutrophils stimulated with IgG coated agarose beads. LREA appeared to have other activities towards neutrophils in vitro, producing increases in the expression of complement receptors (CR3), and both dose dependent increases in the adherence to nylon wool and the cytotoxic capacity of the cells against the opsonised schistomula of *Schistosoma mansoni*. LREA also possessed minimum neutrophil chemotactic activity. LREA may be important in modulating the activity of neutrophils and in this sense provides a further association between granulocyte derived mediators and cell mediated immunity.

Effect of corticosteroid treatment on the ability of phagocytes from asthmatic patients to kill *Aspergillus fumigatus*

MD ROBERTSON, A SEATON *Institute of Occupational Medicine, Edinburgh* Treatment with high dose corticosteroids renders people more susceptible to infection with the opportunistic fungus *Aspergillus fumigatus*. To determine whether maintenance dose levels of corticosteroids affect phagocytic cell association and killing of *A fumigatus*, blood was obtained from 13 asthmatic patients who were skin test positive for *A fumigatus* (eight of whom had allergic bronchopulmonary aspergillosis). These patients were subdivided into two groups: (1) patients not on corticosteroids ($n = 7$); (2) patients on corticosteroid treatment ($n = 6$: three were receiving intramuscular triamicinolone acetonide—two at 40 mg/month, one at 60 mg/month; the other three were having oral prednisolone 10 mg/daily. Corticosteroid treatment had no effect on the association of spores of *A fumigatus* with phagocytic cells (>94% cell associated). Similarly, no differences were found between the two groups in the ability of their monocytes and polymorphonuclear leukocytes (PMN) to kill spores of *A fumigatus* (% killed, mean (SEM) not having steroids—monocytes 51·8 (7·4), PMN 50·2 (5·2); steroid treatment—monocytes 51·0 (7·4), PMN 51·0 (3·2)). Thus maintenance dose corticosteroid treatment did not interfere with the ability of these patients to handle spores of *A fumigatus*.

Does impairment of host defences predispose patients to community acquired pneumonia?

BMS RIYAMI, RD STEVENSON, CG GEMMELL *Departments of Respiratory Medicine and Bacteriology, Royal Infirmary, Glasgow* The role of alveolar macrophages (AM) in protection against pulmonary infections is well recognised. To assess the integrity of this aspect of host defence we have measured AM chemotaxis (CX) in 17 patients with community acquired pneumonia (CAP) and 17 control subjects (CS).

In 11 patients bilateral lavages were performed; three patients were lavaged from the area of consolidation only and another three from a radiologically clear area only. Alveolar cells were obtained from one side only in the CS. The macrophage content of lavage fluid from the control group and from the unaffected side in CAP patients was similar, with means of 95·8% and 92·1%. Likewise, no differences in cell type were detected when several macrophage markers were used in these two groups. Heterogeneity of cell types (increased numbers of polymorphonuclear leucocytes) from the affected side rendered measurement of macrophage CX unreliable. Compared with controls, AM from the unaffected side in CAP patients showed impairment of CX towards C5a (zymosan activated serum) ($p < 0·001$), F-Met-Leu-Phe ($p < 0·001$), and casein ($p < 0·01$). Random migration was also depressed ($p < 0·001$). These results demonstrate an impairment of movement of macrophages obtained from an area of lung remote from a pneumonic process and may therefore indicate some predisposition of the host to pulmonary infection.

Alveolar macrophage chemotaxis in burns and smoke inhalation injury

BMS RIYAMI, J KINSELLA, AJ POLLOK, CJ CLARK, RD STEVENSON, CG GEMMELL *Departments of Respiratory Medicine, Anaesthesia, and Bacteriology, Royal Infirmary, Glasgow* A previous study suggested that alveolar macrophage (AM) chemotaxis (CX) is impaired in patients with burns and smoke inhalation injury, rendering them more prone to pulmonary sepsis. We have investigated this aspect of host defence in a group of 24 patients with smoke inhalation, with and without burns and with burns only, as defined by recently established criteria (CT Clark *et al, Br Med J* 1986;**292**:1303) and in 17 control subjects (CS). There is increased CX of AM towards C5a (zymosan activated serum) ($p < 0·05$) and casein ($p < 0·01$) compared with CS. The subgroup of patients with both smoke inhalation and burns ($n = 10$) showed an even greater increase in CX towards C5a ($p < 0·001$), casein ($p < 0·01$), and F-met-leu-phe ($p < 0·05$). In this subgroup random migration was also increased ($p < 0·05$). AM from patients with burns only ($n = 5$) or smoke inhalation only ($n = 9$) showed a trend of increased CX and random migration but this did not reach significance. Furthermore, there appeared to be no correlation between CX and the severity of smoke inhalation (carboxyhaemoglobin levels) or burn injury (percentage burns). Contrary to previous evidence, these results demonstrate a heightened state of activity of AM and thus may be part of the complex pathophysiological mechanisms that play a part in the development of frequent pulmonary complications such as ARDS in inhalation injury.

Dose-response study of metered dose inhaler (MDI) salbutamol in chronic stable asthma

JFJ MORRISON, SB PEARSON *Pulmonary Function Laboratory, Killingbeck Hospital, Leeds* The treatment of chronic asthma is difficult. Despite large doses of inhaled steroids patients may benefit from large doses of inhaled β agonists (for example, by nebuliser). We have performed in an open investigation a dose-response study of supervised metered dose salbutamol in 31 patients with stable, chronic asthma, all taking inhaled or oral steroids. Inhaled β agonists and anticholinergic agents were omitted for 12 hours prior to the study. The subjects had three baseline FEV_1 and FVC measurements at 20 minute intervals. The best FEV_1 and FVC of the nine baseline measurements were used for subsequent analysis. Subjects were given 200 μg of salbutamol via an MDI under supervision and the spirometry was repeated 15 minutes later. The procedure was repeated until a cumulative dose of 1200 μg of salbutamol had been given. Pulse and side effects were recorded. The dose-response relation was analysed by using % predicted values for each patient. Polynomial regression analysis revealed that 100% response was achieved with 1200 μg for FEV_1 and 1000 mg for FVC (table). Three patients experienced tremor. No change in pulse rate was seen.

Percentage of total response to salbutamol

	Dose of salbutamol (μg)					
	200	*400*	*600*	*800*	*1000*	*1200*
FEV_1	53·6	78·3	88·4	92·8	97·1	100
FVC	63·1	81·9	87·2	93·3	100	100

In conclusion, a dose of 1000–1200 μg of MDI salbutamol produces maximal bronchodilation in chronic stable asthma. Most of the benefit is achieved with lower doses of 600–800 μg and this might be more appropriate in clinical practice.

Should nebulised ipratropium be added to salbutamol in acute severe asthma?

RM HIGGINS, JR STRADLING, DJ LANE *Osler Chest Unit, Churchill Hospital, Oxford* A double blind randomised trial was performed to determine whether any benefit might be gained from administering nebulised ipratropium bromide as well as salbutamol to patients admitted to hospital with acute severe asthma. Forty patients (mean age 47·8 (SEM 3·4) years) were given nebulised salbutamol 5 mg (S) or salbutamol 5 mg mixed with ipratropium bromide 500 μg (S + I) on admission to hospital with acute severe asthma. The same treatment was given two hours later. Mean peak expiratory flow rates (PEF, litres/min) for the S and S + I groups respectively were: before treatment, 114·4 (SEM 9·2) and 120·5 (SEM 7·7), two hours later 148·9 (12·8) and 167·0 (12·1), and four hours later 164·6 (17·4) and 178·0 (16·6). There was no significant difference between the S and S + I groups in the overall mean PEF, or in the mean percentage change in PEF at any time. However, there were significantly fewer individual patients in the S + I than in the S group who failed to improve by 10% after two hours, the same being true for a 20% improvement at four hours ($p < 0·05$ and $p < 0·02$ respectively). This study suggests that adding ipratropium to salbutamol in the therapy of acute asthma may not greatly increase the overall speed of recovery but may produce a greater duration of bronchodilator effect than salbutamol alone.

Nebulised salbutamol, ipratropium bromide and their combination: a double blind comparison

BRC O'DRISCOLL, R TAYLOR, A BERNSTEIN *Department of Thoracic Medicine, Hope Hospital, Salford* Seven patients with stable severe asthma (mean FEV_1 1·29 (SD 0·18 l) and 13 smokers with chronic bronchitis and severe chronic obstructive lung disease (mean FEV_1 0·69 (0·37 l) took part in a double blind study of nebulised bronchodilator treatment. Peak flow rate (PFR), FEV_1, and FVC were measured before and 15, 30, 60, 120, 180, and 240 minutes after the following nebulised medications: (1) 4 ml saline; (2) 5 mg salbutamol (S); (3) 0·5 mg ipratropium bromide (IB); (4) 5 mg S and 0·5 mg IB mixed. The patients also rated each treatment for relief of breathlessness on a numeric scale. The subjective and objective response to all active medications was significantly better than the response to saline for both asthmatic and bronchitic patients. However, the subjective response to each of the three active medications was almost identical in the two groups. Although the mean PFR and FVC responses of the asthmatic patients were slightly higher at all times on the day when the S + IB mixture was given, there was no statistically significant difference (paired *t* test) at any time from the response to S or IB alone. In the bronchitic group the response to IB was greater at all times than the response to S, but this difference also failed to reach significance at any time. We conclude that there is no clinically important difference between the response to nebulised salbutamol (5 mg) and ipratropium bromide (0·5 mg) in patients with severe but stable asthma or chronic airflow obstruction. Mixing these medications produced no useful additional benefit.

Effect of franol on breathlessness and exercise tolerance in severe chronic airflow obstruction

S OWEN, P STONE, S WEBSTER, AA WOODCOCK *Manchester Royal Infirmary, Manchester* Since the introduction of Franol (theophylline 120 mg, ephedrine HCl 11 mg, phenobarbitone 8 mg) in 1943, many patients with breathlessness due to chronic airflow obstruction (CAO) have claimed symptomatic benefit from its use. We have investigated the effect of Franol (three tablets) on lung function, exercise tolerance, and dyspnoea in 12 patients (eight male, four female, mean age 64 y) with severe CAO (mean FEV_1 0·74 l) and MRC dyspnoea grade ≥ 3 in a placebo controlled double blind study. Franol produced significant bronchodilatation over the six hours of the study (peak bronchodilatation 180 min; FEV_1 change from baseline, Franol +19 % placebo −2·2%). Franol significantly increased distance walked in six minutes (baseline Franol 437 m, placebo 435 m; walk repeated at one hour Franol 455 m, placebo 439 m) while simultaneously reducing breathlessness (visual analogue scale—Franol 71 mm, placebo 81 mm). At two hours, in a constant speed treadmill test to exhaustion nine out of 11 patients walked longer after Franol ($p = 0·065$). At three hours, in a steady state test on a bicycle ergometer, Franol increased resting and exercise ventilation and pulse rate but had no effect on oxygen saturation or exercise oxygen consumption or carbon dioxide production. Median peak serum theophylline levels (12·9 μg/ml) were achieved at three hours and remained above 9 μg/ml from two to six hours after medication. Individual serum phenobarbitone levels were all less than 1 μg/ml. In breathless patients with severe CAO, three tablets of Franol are an effective bronchodilator and improve exercise tolerance and breathlessness with minimal side effects.

Use of nedocromil in moderate to severe asthma

MF BONE, NP KEANEY, GD SUMMERS, CK CONNOLLY, PS BURGE, RG DENT, GW ALLAN, MM KUBIK *Department of Medicine, Russells Hall Hospital, Dudley, West Midlands* Although generally well tolerated, inhaled steroids are occasionally associated with side effects such as oral thrush or even vocal cord myopathy. Higher doses of inhaled steroids used in the control of moderate to severe asthma may even induce adrenocortical suppression. We therefore investigated whether the regular use of inhaled nedocromil sodium through a novel spacer (Auty Altounyan Device) would be effective in allowing control of moderately severe asthma with a reduction in inhaled steroids. Eighty nine patients who depended on regular inhaled steroids for control of their asthma were studied (43 nedocromil sodium and 46 placebo). Following a two week baseline, patients halved their own inhaled corticosteroid therapy until there was a slight but significant increase in their symptoms, using diary card and peak flow scores for assessment. They then entered a four week period of treatment with regular inhaled nedocromil sodium (4 × 4 mg) or placebo administered in a double blind manner. Symptoms and lung function deteriorated in all patients during the run in prior to trial treatment after they had reduced the inhaled corticosteroids ($p < 0·001$). There was statistically a significant improvement in night time ($-0·29$ *v* $-0·01$; $p < 0·01$) and day time symptoms ($-0·48$ *v* $-0·06$; $p < 0·05$) when active and placebo treatment was compared. The nedocromil sodium treatment group improved and returned to baseline levels whereas placebo treated patients remained with worse symptoms, and the difference between the two groups was statistically significant. Night time bronchodilator usage was also significantly reduced ($-0·51$ *v* $+0·48$; $p < 0·05$) and peak flow recordings were improved throughout the day ($+19·5$ *v* $-3·6$; $p < 0·05$). About half in each group reported unusual symptoms and 10% reported an unpleasant taste from the inhaler. There was no difference between groups. Thus the absolute efficacy of inhaled nedocromil sodium was demonstrated in adults with moderate to severe asthma, and it may allow a reduction in the usage of inhaled corticosteroids.

Effect of controlling inspired air temperature on exercise induced asthma

M NISAR, MJ WALSHAW, JE EARIS, PMA CALVERLEY, MG PEARSON *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* A new mask incorporating a heat-moisture exchange element appeared to offer potential for preventing exercise induced asthma (EIA). The heat exchange module is reusable, washable, and capable of prolonged use without saturation and has minimal flow resistance (0·6 mm Hg at 10 l/s) and a dead space of 190 ml. Eight patients with EIA (four male, mean age 27; mean FEV_1 2·7 (0·9), FVC 3·8 (1·0) l) performed

identical bicycle ergometer exercise challenges on three days in the same week. On day one a simple spirometer tube mouthpiece was used and on days two and three in varied order either the black anaesthetic (control) mask "closed" with a single layer of filter paper or the "active" heat exchange mask was used. Fast response thermocouples recorded the temperature difference across the mouthpiece and masks. The mean (SD) initial FEV_1 were similar on the three test days (2·7 (0·7), 2·7 (1·0), 2·8 (0·9) l respectively). Pulse rates achieved and end tidal CO_2 changes were not significantly different between studies. The active mask resulted in significant ($p < 0·01$) warming of inspired air; the mean gain (SD) in temperature with the active mask was 6·32 (1·0)°C compared with 0·71 (0·64)°C with the spirometer tube and 2·41 (1·87)°C with the control mask. The mean fall in FEV_1 of 41·8% (1·22%) l on day one was reduced to 17·4% (0·52%) l with the active heat exchange mask ($p < 0·01$). The control mask produced intermediate falls in FEV_1 (32% (0·85%) l). This new mask effectively exchanges heat and warms inspired air, hence ameliorating EIA. It is thus a useful tool for further study of the role of temperature and humidity in EIA. In modified form it may be of practical value in preventing EIA in non-contact sports.

Modification of exercise induced asthma by felodipine

KR PATEL, E PEERS *Western Infirmary, Glasgow, and Astra Pharmaceutical Ltd, Kings Langley* Felodipine is a new calcium antagonist of the dihydropyridine group. Its vasodilator activity at therapeutic concentrations is probably due to interaction with intracellular calcium binding proteins rather than the inhibition of calcium influx across the potential operated channels. We have examined the effect of 10 mg felodipine in oral solution on the resting bronchomotor tone and exercise induced fall in FEV_1 and FVC in a placebo controlled, double blind, randomised, crossover study in 10 normotensive asthmatic subjects. The exercise challenge consisted of steady state running on a treadmill at submaximal work loads. Heart rate, blood pressure (BP) (measured by an electronic BP monitor), FEV_1 and FVC (Vitalograph) were measured before and up to 30 minutes after treatments and at regular intervals after exercise. Felodipine did not affect the baseline FEV_1 or FVC. However, the exercise induced fall in FEV_1 and FVC was reduced significantly by felodipine ($p < 0·01$, Wilcoxon test). After felodipine seven subjects complained of headache and two of these patients also felt lightheaded and dizzy after exercise. These side effects were transient. The post-treatment BP tended to be lower and heart rate higher with felodipine. Although felodipine is unlikely to be a suitable drug for management of asthma, it can be used safely to treat hypertensive patients with coexisting obstructive airways disease. The mean (SEM) FEV_1 and FVC in litres before and after treatments and the mean maximum fall in FEV_1 were:

		Before	*After*	*% fall*
Placebo	FEV_1	3·1 (0·25)	3·1 (0·25)	24 (4·7)
	FVC	4·2 (0·31)	4·3 (0·35)	17 (5·4)
Felodipine	FEV_1	3·2 (0·25)	3·3 (0·28)	9 (4·1)
	FVC	4·4 (0·38)	4·4 (0·38)	6 (3·5)

Comparison of the onset of exercise induced rhinorrhoea (athletes' nose) in normal and asthmatic subjects

CF STANFORD, K SINCLAIR, MG SCOTT, B MARTIN Exercise induced asthma (EIA) is probably due to drying of the respiratory mucosa (Anderson, *J Allerg Clin Immunol* 1984;**73**:660). Since EIA can be avoided by prior short sprints (RP Schnall and LI Landau, *Thorax* 1980;**35**:828–32) the fault possibly lies in a delayed onset of the normal mechanisms required to humidify the increased minute volume. We have recently demonstrated exercise induced rhinorrhoea (EIR) in normal subjects and we have tested the hypothesis that EIA is caused by a delayed onset in humidification by comparing EIR in normal and asthmatic subjects. Ten patients with asthma (AS) and 10 control (C) subjects were selected. None complained of nasal symptoms or was receiving antihistamine therapy. No antiasthmatic drugs were used during the preceding 18 hours. The standardised exercise was performed on a treadmill for 12 minutes by the two groups and set so that the FEV_1 volumes did not fall sufficiently to interfere with expulsion of nasal secretion (NS). Nasal resistance (NR, mm H_2O l^{-1} s) was measured by posterior rhinometry. The results were expressed as means (SEM). Before exercise there was no significant difference ($p > 0·05$) for NR (C = 2·08 (0·29), AS 2·43 (0·55)). The NR decreased with exercise in both groups and the difference between them was insignificant ($p > 0·05$). Nasal secretion showed no significant difference ($p > 0·05$) before exercise (C = 25·5 (6·4), AS 26·0 (8·1)). The time to maximum secretion after the onset of exercise was 10·8 (1·69) minutes for the controls and 16·2 (2·34) minutes for the asthmatics. This difference was significant ($p < 0·05$). This is consistent with the hypothesis that EIA is due to a delay in the onset of humidification in asthmatic subjects.

Absorption of nedocromil sodium from the lungs: effect of exercise challenge

MG NEALE, M ALBAZZAZ, KR PATEL *Fisons PLC, Loughborough, and Western Infirmary, Glasgow* Nedocromil sodium has recently been approved for the treatment of reversible obstructive airways disease. Absorption of the marketed aerosol formulation (Tilade) has been reported (Neale *et al, Br J Clin Pharmacol* 1987;**24**:493). In the present study we have measured plasma concentrations of nedocromil sodium up to four hours after administration by nebuliser (Henley Fan jet and Wright) of a range of different concentrations (0·05%, 0·25%, 0·5%, 1%, 2%, and 4%—5 ml nebulised for five minutes) in healthy volunteers (n = 6) and in asthmatic patients (n = 11) subjected to exercise challenge. The exercise challenge in patients consisted of steady state running at submaximal workloads for six to eight minutes, 15 minutes after the end of nebulisation. In addition, the absorption of nedocromil sodium (1 ml of 0·5% solution) administered through a fibreoptic bronchoscope (n = 6) and buccally (n = 5) was assessed in non-asthmatic patients and healthy volunteers. Plasma concentrations of nedocromil sodium were measured by radioimmunoassay for up to four hours after dosing. Plasma concentrations of nedocromil sodium in volunteers were proportional to dose with mean (SD) maximum concentrations (ng/ml) of: 0·25%

1·3 (0·7), 0·5% 2·4 (1·0), 1% 7·0 (3·9), 2% 10·6 (5·1), and 4% 28·3 (20·0). Concentrations rose rapidly to maximum then plateaued for about an hour. In patients plasma concentrations began rising as in volunteers but a most interesting finding emerged subsequent to the exercise challenge. Concentration increased after the challenge to approximately double the prechallenge levels. The observation was consistent across subjects and concentrations of nebulised solution. The effect could be due to a change in permeability of the lungs. Further studies are under way to investigate the reasons for this possible effect of exercise on the absorption of nedocromil sodium. No nedocromil sodium was detected in the plasma of subjects dosed buccally. After bronchoscopic administration the mean maximum plasma concentration of nedocromil sodium was 52·8 ng/ml. These findings help in the understanding of the absorption of nedocromil sodium from the respiratory tract.

Dose-response relationships of nebulised nedocromil sodium in exercise challenge

M ALBAZZAZ, MG NEALE, KR PATEL *Western Infirmary, Glasgow, and Fisons PLC, Loughborough* Nedocromil sodium has recently been approved for the treatment of reversible obstructive airways disease and is marketed as a pressurised aerosol (Tilade). It is active in several bronchial challenge systems but its dose-response characteristics have been studied only to a limited extent. We chose to investigate the dose response of nedocromil sodium in exercise challenge in asthmatic patients (n = 11, mean age 36 years, mean predicted FEV_1 91%) using a nebulised solution, as this allows a greater flexibility in dosing. Four concentrations (0·05%, 0·5%, 1%, and 2%) together with placebo were administered in a double blind random order to the subjects by Wright nebuliser (5 ml) nebulised for five minutes) 15 minutes before exercise on a treadmill for six to eight minutes. All subjects had shown clear evidence of a protective effect (>40%) from Tilade. Plasma concentrations of nedocromil sodium were measured by radioimmunoassay. Mean predrug baseline FEV_1 values were similar and were not altered significantly by any treatment. Mean (SD) maximum % falls in FEV_1 were: baseline (no treatment) 31·3 (5·8), aerosol (2 × 2 mg) 13·8 (8·1), placebo 29·8 (13·2), 0·05% 15·2 (10·7), 0·5% 13·9 (9·5), 1% 13·1 (6·6), and 2% 17·8 (11·9). Falls for all active treatments were significantly different from placebo but not significantly different from each other. Individual patients showed some variability in dose-response curves with the occasional unusual result. This was not due, however, to variable absorption since the plasma concentrations were consistent and proportional to dose. The mean (SD) concentrations (ng/ml) immediately prior to challenge were: 0·05%—not detectable, 0·5%—2·7 (1·0), 1%—5·3 (2·7), 2%—15·4 (5·7), and aerosol—2·5 (1·4). The results show that nebulised nedocromil sodium in concentrations from 0·05% to 2% gave a similar degree of protection (about 50%) which seems to be a maximal response. Protection with the aerosol was similar. Plasma data indicate that the 0·5% nebulised solution gave a similar absorption to the pressurised aerosol. We are now studying the duration of action of this range of concentration.

Cost-benefit analysis of a nurse visiting the homes of asthmatic children

F CARSWELL, F ROBINSON, G HEK *Respiratory Research Group, Department of Child Health, University of Bristol* The domiciliary care of asthmatic children is often unsatisfactory. Accordingly, we examined the cost and benefit of sending a trained "asthma nurse" into the homes of families with an asthmatic child. All the school children in two family practices were sent a diagnostic questionnaire: 11·8% of the children had asthma. Eighty six of these asthmatic children were given standard community care and half randomly allocated to visits from the "asthma nurse" for six months. All subjects were assessed by an independent observer (GH). Each of the four assessments included a week's record of twice daily peak expiratory flow rates (PEF) and asthma symptoms and objective measurements of the family's knowledge of asthma. The mean PEFs were 99, 92, 97, 100 (% predicted) in the control, and 99, 106, 108, 109 in the nurse treated group. The three assessments after the nurse started visiting were all significantly better ($p < 0·05$, Mann-Whitney). There was an association between increase in knowledge and PEF improvement. The cost of the asthma nurse was the same per patient (£14) as that of two emergency medical visits. The practitioners and families valued the nurse service. Thus "asthma nurses" are cheap and effective.

Can the morbidity of asthma be reduced by high dose inhaled therapy? A prospective trial

CR HORN, TJH CLARK, GM COCHRANE *Department of Respiratory Medicine, Guy's Hospital, London* Asthma continues to be a cause of appreciable morbidity but there is little evidence that it is possible to affect such morbidity with therapy. We have prospectively treated 162 adults with airflow obstruction with up to 2000 μg qds of salbutamol and up to 1000 μg bd of beclomethasone (BDP) for nine months. Sixty five patients (30 female; mean age 41·7 years) were fully compliant with the prescribed regimen throughout and their results are presented. At the start of the study only 1·7% were completely symptom free by day and 19% at night; 58% had an FEV_1 below 80% predicted. After nine months 39% were completely free of symptoms in the daytime and 50% at night but 40% still had abnormal spirometric values. The mean FEV_1 rose from 72% to 80% predicted. The average frequency of acute attacks of asthma was reduced from 0·13 to 0·02 per week. Two thirds of the patients received inhaled steroids (double blind) and these patients were more likely to be symptom free in the day (42% *v* 24%) and to have normal spirometric values (21% *n* 6%) than those patients who did not have BDP. The mean increase in FEV_1 in the two groups was +11·8% *v* −0·4%. Among patients on salbutamol alone 12% continued to suffer acute attacks of asthma compared with only 4% of patients having combined therapy. Our results suggest that the earlier introduction of inhaled steroids leads to a clinically significant reduction in the morbidity of asthma.

Survey of general practice asthma management

CE BUCKNALL (on behalf of the Glasgow Asthma Study Group) *Department of Respiratory Medicine, Royal Infirmary, Glasgow* General practitioners of five health centres serving a population of 120 000 (17% of Glasgow's population) completed a simple encounter form for 782 attendances due to asthma during a two month period. This sample was estimated to represent 56% of all such consultations over this period. Eighty one consultations were recorded by a single practitioner with a special interest in asthma, 701 by others. The practitioner with a special interest in asthma saw cases more frequently ($p < 0.005$) and judged more to be adequately controlled ($p < 0.05$) than others. More of his cases were receiving inhaled corticosteroids ($p < 0.005$) and fewer long term oral corticosteroids ($p < 0.05$). If a change in therapy was made, this practitioner increased inhaled therapy most often (68%), with a course of oral corticosteroids his second option (18%). Other practitioners were most likely to use antibiotics (56%) and least likely to use oral corticosteroids (15%, NS) in these circumstances. This sample of general practice asthma consultations shows the same discrepanciese in asthma management as were observed in a hospital survey (CE Bucknall *et al, Thorax* 1987;**42**:720), where differences in management between physicians with an interest in asthma and others were shown to be associated with considerable differences in short and long term morbidity.

Assessment of an asthma management programme for general practice

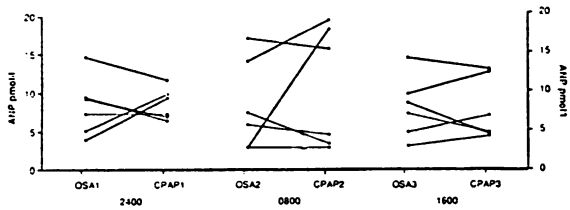
CE BUCKNALL (on behalf of the Glasgow Asthma Study Group) *Department of Respiratory Medicine, Royal Infirmary, Glasgow* A survey of current general practice asthma management was performed before and after implementation of an asthma management programme. The survey was carried out by recording details of asthma visits to practitioners in five Glasgow health centres for the same two month period in two consecutive years. Repeat prescriptions for steroid inhalers and sodium cromoglycate were also monitored. In the intervening period practitioners in two of the five health centres (the active group) had access to a prepared programme of information on asthma management, health education material for their patients, and peak flow meters presented at an open meeting with two local chest physicians. There was an increase in the use of inhaled steroids in the active group only, as judged by practitioners' opinions as to how, if at all, their practice had changed, and confirmed independently by monitoring repeat prescriptions. This group's use of antibiotics in the management of asthma decreased and there was an upward trend in the use of oral corticosteroids. No such changes were seen in the control group. This locally evolved programme of practitioner information and patient education material is therefore judged to be a moderate success and further use of it worthwhile.

Use of protriptyline in chronic airflow limitation

N CARROLL, RA PARKER, MA BRANTHWAITE *Brompton Hospital, London* Protriptyline reduces nocturnal hypoventilation in patients with restrictive chest wall disease by decreasing the duration of rapid eye movement (REM) sleep. A double blind crossover trial was undertaken to assess the efficacy of protriptyline as a means of controlling nocturnal hypoventilation in patients with chronic obstructive airways disease accompanied by hypoxaemia and hypercapnia. Eighteen patients (13 male, five female) with severe airflow limitation (mean % predicted FEV_1 24·6, range 13–42·7) used protriptyline 10 mg or placebo in six week phases. Assessment included polysomnography, diurnal arterial blood gas analysis, spirometry, six minute walking distance, and mouth pressures. One patient died during the trial. In the remaining 17 the use of protriptyline was associated with an increase in the mean daytime Pao_2 from 7·07 kPa (range 4·84–10·11) to 7·73 kPa (range 4·96–10·11), with a corresponding fall in mean $Paco_2$ from 6·65 kPa (range 5·2–8·47) to 5·99 kPa (range 5·04–8·07; $p \leq 0.01$). REM time as a % of total sleep time fell from 15·7% (range 0–25) to 8·6% (range 1·5–16·4; $p \leq 0.01$). Mean Pemax improved from 94 (range 50–140) to 120 cm H_2O (range 80–200; $p \leq 0.05$). Mean Pimax increased from -40 (range -15 to -70) to -51 cm H_2O (range -25 to -80; $p \leq 0.01$). The six minute walking distance increased from 271 metres (range 58·5–450) to 307 metres (range 170–598), but these changes did not reach statistical significance. Only nine patients out of 17 reported symptomatic improvement, and all noted anticholinergic side effects.

Plasma levels of atrial natriuretic peptide (ANP) in obstructive sleep apnoea (OSA)

ARH WARLEY, A MORICE, JR STRADLING *Chest Unit, Churchill Hospital, Oxford, and Clinical Pharmacology Unit, Addenbrooke's Hospital, Cambridge* Because ANP is released into the circulation following atrial distension, large swings in pleural pressure (for example, in obstructive lung diseases) and right sided intravascular pressures (for example, during hypoxaemia) may be an important stimulus for its release. OSA is characterised by repetitive upper airway occlusion and arterial desaturation during sleep. When the upper airway is occluded, large negative intrathoracic pressures (for example, -40 cm H_2O) are generated by continued respiratory effort, and the right atrium is therefore subjected to powerful dilating pressures. Furthermore, the apnoea episodes are associated with hypoxaemia, which is sometimes profound (for example, $Sao_2 < 70\%$). OSA is known to increase sodium and water excretion. This can be reversed by treatment, and would be consistent with the known effects of circulating ANP. We made paired measurements of ANP in six patients with severe, symptomatic OSA (> 300 apnoea episodes per night), during and after a night in which they experienced severe OSA, and during and after a night in which the apnoea was successfully abolished with continuous positive airway pressure (CPAP) applied via the nose. Sample 1 (2400) was taken after 1–2 hours' sleep, sample 2 (0800) just prior to rising, and sample 3 (1600) in mid-afternoon.



All levels were in the normal range. Time of day and nasal CPAP did not have any consistent effect on ANP levels. We conclude that the diuretic and natriuretic effect of OSA is not mediated through release of ANP.

Clinical features of the sleep apnoea syndrome in Scotland

GA GOULD, KF WHYTE, MB ALLEN, CM SHAPIRO, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* It has been estimated that the sleep apnoea syndrome occurs in 1% of adults (P Lavie, *Sleep* 1983;6:312) but in Britain the condition has been claimed to be rare (CM Shapiro *et al, Lancet* 1981;ii:523). Since February 1984 we have offered a diagnostic service for sleep disorders in Scotland (population about five million) and have identified 70 patients with the sleep apnoea syndrome. All patients had abnormal breathing during sleep ($\geq$15 apnoea + hypopnoea episodes per hour slept), 62/70 an increased frequency of arousals ($\geq$10 per hour slept) and 69/70 an increased frequency of episodes of arterial desaturation ($\geq$ one 4% desaturation per hour slept), the phenomena that produce the clinical sequelae. The patients were predominantly male (59/70) and most, but by no means all, were obese (45/70 $\geq$ 130% ideal body weight), eight being within 10% of their ideal body weight. Sixty six of the 70 patients reported that they snored, and 61 reported excess daytime sleepiness, which was severe (frequently falling asleep when actively trying to achieve a task) in 22 and moderate to mild (falling asleep daily in front of the television) in 39. The other most common clinical features were unsatisfying nocturnal sleep (39/70), disturbed sleep (30/70), ankle swelling (18/70), morning headache (10/70), and unexplained polycythaemia (7/70). All patients had at least two (mean 3·5) of the above symptoms. All patients are told to avoid sedation (for example, alcohol) and obesity is treated by diet, but in addition 11 patients have been treated successfully with nasal continuous positive airways pressure (CPAP) with substantial improvement in both sleep study abnormalities and symptoms. We conclude that sleep apnoea is not uncommon in Britain but is probably underdiagnosed.

Effect of additional weight on exercise performance in patients with chronic obstructive airways disease (COAD)

CR SWINBURN, H MOULD, BG COOPER, PA CORRIS, GJ GIBSON *Department of Respiratory Medicine, Freeman Hospital, Newcastle* Obesity increases ventilation and oxygen consumption during exercise but its effects on the exercise tolerance of patients with COAD have not been quantified. We have investigated the effects of an acute increase in weight in 12 male patients (mean (SD) age 60·1 (8·2) y) with COAD of varying severity (FEV_1 1·34 (0·5) 1, range 25–79% predicted). Exercise capacity was assessed by both the distance walked on the level in six minutes (6 MWD) and a simple timed step test at a constant rate of 15 steps/min (up to a maximum of 10 minutes). During stepping, ventilation ($\dot{V}E$) and oxygen consumption ($\dot{V}O_2$) were measured each 20 seconds. The subjects who were of normal body weight (body mass index 23·3 (2·9)) performed both forms of exercise with and without a 10 kg leaded apron which represented an additional 15% (2%) of their body weight. Spirometry was unaltered by the additional weight. In two patients able to complete 10 minutes of stepping both with and without the additional weight, the tests were terminated by the observer. Overall the number of steps climbed fell considerably (median unweighted 76·5 and weighted 45·5 steps, $p < 0.01$). Both ventilation and oxygen consumption were increased throughout exercise by the additional weight. After the longest period of stepping which was common to both unweighted and weighted tests, ventilation was 33·7 (6·6) and 38·6 (8·5) 1 min^{-1} ($p < 0.001$) and oxygen consumption 1·33 (0·16) and 1·46 (0·22) 1 min^{-1} ($p < 0.01$) respectively. The maximum ventilation achieved was similar during unweighted and weighted tests (38·4 (7·2) and 39·2 (8·7) 1 min^{-1} respectively). By contrast, walking distance on the level was not significantly altered by the additional weight (6 MWD unweighted 567 (55) m; weighted 554 (55) m). We conclude that a modest acute increase in body weight had little impact on level walking in patients with COAD in this study. Their ability to perform "uphill" exercise was, however, substantially reduced as a result of the ventilatory cost of increased work against gravity. Even a modest reduction of body weight might be of considerable benefit to patients with symptomatic COAD.

Effect of massive weight reduction after gastroplasty on respiratory function in the morbidly obese

PS THOMAS, ERTC OWEN, G HULANDS, JS MILLEDGE *Departments of Respiratory Medicine, Surgery, and Anaesthesia, Northwick Park Hospital and Clinical Research Centre, Harrow* Twenty nine morbidly obese patients (mean 126·4 kg, range 92–174 kg) were studied before and after weight loss, having undergone vertical banded gastroplasty, a relatively conservative form of bariatric surgery and currently the most widely performed operation of this type. The effects of this operation on pulmonary function have not previously been reported. All patients lost weight (mean 34·2 kg, range 2–64 kg) and were followed up for a mean of 26 months (range 2–66 months). Their lung function showed a predominantly restrictive pattern on initial testing, which was reversed by weight loss with a significant improvement in functional residual capacity (FRC), residual volume, and total lung volume ($p < 0.002$ in each case). Spirometry also improved (non-significant) and gas transfer showed a non-significant fall in 10 subjects assessed. These improvements probably reflect a greater excursion of the diaphragm and possibly improved chest wall movement after weight loss. Airway closure may occur within the tidal volume of the obese (Santesson J, Nordenstrom J, *Acta Chir Scand* 1978;suppl 482:36–40) and the increase in FRC after weight loss reverses this trend. Our data suggest that patients' weight should always be taken into account when assessing the results of pulmonary function tests and demonstrate one of the benefits of weight loss in the morbidly obese.

Comparison of balloon and perfusion systems in the measurement of transdiaphragmatic pressure

W KINNEAR, K KNOWLES, G ROCKER *City Hospital, Nottingham* Gastric and oesophageal pressures were measured in

10 seated normal subjects with 10 cm air filled balloons (B) and a triple lumen catheter (C). The catheter was positioned with the distal lumen 5 cm beyond and the proximal lumen 5 cm above the cardia and perfused with water at a constant rate. The gastric and oesophageal balloons were positioned with their tips 65 and 45 cm from the nares. Maximum transdiaphragmatic pressure (Pdi max) was recorded between the two balloons and between the distal and proximal lumens of the catheter during 10 sniffs in each subject. For Pdi max and the maximum relaxation rate of transdiaphragmatic pressure (R): Pdi max (C) = 1·25 × Pdi max (B) −2 cm H_2O, r = 0·879 R (C) = 1·02 × R (B) + 1·13 cmH_2O/s, r = 0·803 R/Pdi max (C) = 0·86 × R/Pdi max (C) + 0·008/s, r = 0·764. The cardia was located with the balloon advanced 10·2 (1·9) cm further from the nares than when located by the catheter lumen, suggesting that pressure is recorded from the top of the balloon. In the oesophagus the top of the balloon was 12·3 (1·4) cm proximal to the cardia. With the lumens of the catheter positioned 5, 10, and 15 cm proximal to the cardia, the lowest oesophageal pressure during sniffs was recorded at 10 cm. The response times to a square pressure edge of 100 cm H_2O were 0·01 s and 0·02 s for catheter and balloon respectively. We conclude that Pdi max (C) is greater than Pdi max (B), and that this difference is not explained by the site of oesophageal pressure recording.

The repeatability of a measure of cough

C WITHEY, C PRICE, A SWAN, A PAPACOSTA, W HOLLAND *Department of Community Medicine, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London* In studies to compare individuals with respect to the severity of their respiratory symptoms, the precision and in particular the reliability of the measures used are important in order that clearcut results can be obtained with practical samples sizes. This is a report of a study on a group of smokers to assess the repeatability of a number of symptoms, focusing on cough in particular. In the first part of the study 30 participants were interviewed on two occasions by different observers and in the second part 60 participants were interviewed on two occasions by the same observer. Data were collected on respiratory symptoms with standard questions taken from the Medical Research Council Respiratory Symptoms Questionnaire and a technique described by Field for obtaining a quantitative estimate of cough frequency (*Int J Epidemiol* 1974;3:135). The results showed that Field's system is highly repeatable and relatively unaffected by observer variation. The repeatability was assessed by obtaining the within subject component of variance estimated from all the pairs reinterviewed and was 0·788. The between subject variance was 16·8% of the total variation. Thus 83·2% of the variation was not due to within subject variation and this is a measure of repeatability. In the individuals interviewed by different observers the within subject variance estimate was 0·431. This is smaller than the estimated error above so there is no evidence of variation due to observer differences. Using data from all the 90 pairs in both groups gave an estimate of repeatability for Field's system of 84·9%. Thus we conclude that Field's system is highly repeatable and not effected by the observer. Consequently it compares very favourably with the MRC questions as a measure for detecting differences in severity of symptoms in situations where small effects are expected or large sample sizes are impractical.

Tachyphylaxis and the cough reflex

A MORICE, R LOWRY, M SMOLIRA, M BROWN, T HIGENBOTTAM *Clinical Pharmacology Unit and Department of Respiratory Physiology, Addenbrooke's Hospital, Cambridge* Electrophysiological studies in animal models of the cough reflex have demonstrated responses which show a rapid adaptation to diverse stimuli such as a change in pH and mechanical stimulation of the airways. These responses are thought to be mediated through the rapidly adapting receptors (RARs). We have investigated in 14 healthy volunteers the degree of adaptation which occurs during a standardised cough challenge in man. Challenge was performed on two separate days by inhalation of a nebulised solution of distilled water, citric acid (0·67%), and incremental doses of capsaicin (0·5–20 μmol/l). Cough frequency during one minute was recorded using a pneumotachograph and pen recorder. Marked tachyphylaxis occurred during inhalation of both distilled water and citric acid, mean cough per 10 seconds decreasing to 19% and 9% of initial values during challenge. This response was much less evident with capsaicin challenge (80% at 1 μmol/l). A significant ($p < 0·005$) learning effect was demonstrated between sequential citric acid challenges. The rapid occurrence of tachyphylaxis to distilled water and citric acid challenge observed in this study supports the view that RARs may be important in the mediation of the cough reflex in man.

Patients with a non-productive cough have an increased cough reflex

RW FULLER, NB CHOUDRY *Departments of Clinical Pharmacology and Medicine, Royal Postgraduate Medical School, London* Cough is a common respiratory symptom which is usually related to the clearance of secretions from the respiratory tract. However, some patients complain of persistent dry cough following respiratory infection or as a symptom of interstitial or other lung disease. It is not known what causes the cough in these patients, although it is likely that it is due to an increased sensitivity of the cough reflex. In order to determine the sensitivity of the cough reflex in patients we have examined the cough reflex in 54 (23 females) normal subjects (mean age 35 (SD 18) years) and compared this in eight patients with productive cough (P), 19 patients with non-productive (NP) cough, and eight patients with stable asthma (A). None of the patients had evidence of acute respiratory infection. Capsaicin dose-cough responses were determined by recording the number of coughs after inhaling single breaths of saline or capsaicin (0·4–50 nmol) given in a random order. The geometric mean (95% CI) dose causing two or more and five or more coughs (D_2, D_5) was 2·4 (1·9–3·0) nmol and 8·0 (6·2–10·4) nmol respectively in the normal subjects. These values were similar in the patient group (P) (D_2 was 2·3 (1·0–5·4) nmol and D_5 was 11·5 (6·2–21·1) nmol) and in group A (1·9 (1·3–3·0) nmol and 5·8 (3·4–10·0) nmol

respectively); in contrast in group NP the values were 1·0 (0·6–1·5) nmol and 2·6 (1·5–4·6) nmol respectively, both of which were significantly different ($p < 0.01$) from the normal values. This result is compatible with the hypothesis that an altered cough reflex is responsible for the persistent dry cough. This technique may prove useful in the assessment of patients with cough. (The Medical Research Council and the Chest, Heart and Stroke Association supported this work.)

Antitussive effect of nedocromil sodium on chemically induced cough

RH LOWRY, TW HIGENBOTTAM *Department of Respiratory Physiology, Addenbrooke's Hospital, Cambridge* Inhaled ultrasonically nebulised distilled water (UNDW) and citric acid aerosols appear to stimulate airway rapidly adapting receptors (RARs) (Lowry *et al, Thorax* 1987;**42**:240) while capsaicin stimulates "c" fibres (Coleridge *et al, J Physiol* 1965;**79**:248). We have previously described reduced cough response to UNDW following inhaled β agonists and anticholinergics (Lowry *et al, Br J Clin Pharmacol,* in press). We have studied the antitussive effect of inhaled nedocromil sodium on cough induced by UNDW, 0·68% citric acid in 0·79% saline, and capsaicin aerosol generated by a jet nebuliser (System 22). Pretreatment with nedocromil (NED) was compared with placebo (PLAC) and inhaled fenoterol hydrobromide (FEN) in a single blind randomised study in 12 normal volunteers. Baseline challenges were performed to determine a dose of capsaicin to cause more than 10 coughs in a one minute inhalation. Treatments were administered on separate days and cough frequency was recorded during one minute inhalations.

	Mean cough frequency (95% confidence limits)		
	UNDW	*Citric acid*	*Capsaicin*
PLAC	20·2 (15·0–26·0)	9·3 (6·3–12·8)	19·1 (13·1–26·0)
NED	10·5 (6·8–14·9)	8·9 (6·0–12·3)	8·9 (4·9–14·0)
FEN	4·7 (2·2– 7·9)	5·5 (3·2– 8·2)	13·6 (8·6–19·6)

Fenoterol inhibited cough induced by UNDW ($p < 0.001$) but not by capsaicin ($p > 0.05$), consistent with our previous observation. Nedocromil inhibited both capsaicin ($p < 0.025$) and UNDW ($p < 0.01$) induced cough, but neither drug significantly affected citric acid induced cough ($p > 0.05$). This suggests that the challenges and drugs have different mechanisms of action. Also nedocromil may reduce both RAR and "c" fibre responsiveness.

Effect of sodium thiophene carboxylate on the properties of pig tracheal mucus

C MARRIOTT, GP MARTIN *Pharmaceutical Sciences Research Group, Department of Pharmacy, Brighton Polytechnic, Brighton* Sodium thiophene carboxylate (TCS) is a compound which is claimed to be mucolytic but is not available in the United Kingdom (Cheminat and Aiache, *Sem Hop Paris* 1981;**57**:307). The purpose of the present study was to evaluate this claim using a mini-pig model (*Suis scrofa domestica*, Gottingen strain) equipped with a tracheal pouch. TCS was administered orally to each of three animals at a dose of 125 mg/kg twice daily for seven days following a seven day control period. Mucus was aspirated from the pouch each day and for a further seven days after treatment. The wet and dry weights of the samples were determined, the viscoelastic properties measured by a creep compliance technique and the fucose and protein concentrations estimated (Marriott *et al, Eur J Respir Dis* 1983;**64**(suppl 128):441). Neither the wet nor the dry weight of the mucus altered during treatment, which indicates that TCS has no activity as an expectorant. The mean viscosity fell from $1{\cdot}42 \times 10^6$ poise in the control period to $5{\cdot}55 \times 10^{-5}$ poise in the treatment period; the compliance (the reciprocal of elasticity) rose from $1{\cdot}7 \times 10^{-3}$ to $2{\cdot}5 \times 10^{-3}$ cm^2/dyn concomitantly. These changes are indicative of mucolytic activity, which is supported by the qualitative observation that the mucus was easier to aspirate from the pouch. After treatment these values became $8{\cdot}24 \times 10^{-5}$ and $2{\cdot}3 \times 10^{-3}$ respectively, which would suggest that this reversion to normal takes longer than seven days. A significant increase in protein concentration ($p < 0.05$) occurred during the treatment period and since the level of fucose remained constant the fucose to protein ratio decreased from 1·09 to 1·02. This indicates that the glycoprotein which is secreted under the influence of TCS is less glycosylated than the normal and may be released before synthesis is complete. The secretion of this immature biopolymer may explain the mucolytic activity that has been demonstrated with TCS.

Patterns of chronic bronchitis in Bombay and Edinburgh

AA JEFFREY, MF SUDLOW, DC FLENLEY, SV SHAH, AA MAHASHUR, RV RUPAWATE, AP MEHTA, J GREGRAT, PR VALDYA, SR KAMAT *City Hospital, Edinburgh, and KEM Hospital, Bombay* We have compared a group of patients presenting to a respiratory outpatients clinic with symptoms of chronic bronchitis in Bombay with a group with similar symptoms in Edinburgh. Patients with clinical or radiological bronchiectasis, pulmonary tuberculosis, pneumonia, or asthma were excluded. In Bombay (B) 127 patients were recruited and in Edinburgh (E) 53. Bombay patients were significantly younger (B: 53·0 (SD 11·3), E: 60·9 (7·0) y; $p < 0.001$), had a higher FEV_1 as % predicted (B: 62·5 (24·1), E: 41·9 (25·6); $p < 0.001$), and were less hypoxic (B: 80·00 (12·3), E: 68·6 (11·6) mm Hg) at time of presentation, these differences perhaps reflecting the patterns of medical care provision in the two centres. Patients were matched in pairs from the two groups on the basis of FEV_1% predicted (less than 4% difference for each pair). Thirty three matches were possible. In these matched groups there were no significant differences in Pao_2 (B: 77·4 (SD 12·6), E: 70·2 (SD 10·8) mm Hg, NS) or $PaCo_2$ (B: 36·7 (5·4), E: 38·1 (3·1) mm Hg, NS) or in MRC dyspnoea grade. Bombay patients were still younger than those in Edinburgh (B: 55·9 (9·8), E: 62·1 (5·6) y; $p < 0.01$). The pattern of cigarette smoking in the groups was significantly different with more non-smokers in Bombay (B: 33%, E: 3%) and more heavy smokers in Edinburgh (B: 6%, E: 54%). Thus, while chronic bronchitis exists in both centres, in Bombay it appears to affect a younger age group, who are less likely to be smokers than their Scottish counterparts.

Is there a dichotomy in acinar unit size and number within the population?

A MCLEAN, O LAMB The density of non-respiratory bronchioles was measured in 30 lobectomies (23 male, seven female, aged 51–71 y). Lobes were fixed at inflation with formal saline and cut into 1 cm parasagittal slices. Six $(\frac{3}{4}'')^2$ random blocks of tissue were taken from each of the first two lateral subpleural slices, embedded in GMA, cut at 3 μm and stained with haematoxylin and eosin. All non-respiratory bronchioles were located and counted and bronchiolar density expressed per cm (0·37–1·22 cm^{-2}). This figure is proportional to the density of terminal bronchioles/acinar units. Regression analysis of bronchiolar density against height clearly revealed a separate subgroup of five outliers. The regression line for this subgroup ran higher and parallel to that for the larger group (v = 2·79–1·09 hgt), p = 0·018 (n = 5) as against v = 2·39–1·06 hgt, p < 0·001 (n = 25). Calculating airway density from these equations indicates that the smaller subgroup had twice the expected number of bronchioles for a given height. This is equivalent to an extra generation of bronchioles. Importantly, the subgroup of five cases span a similar range in height to that of the larger group. These regressions are independent of both microscopic alveolar wall loss (AWUV) and the presence and amount of macroscopic emphysema.

Reversible hypercapnic respiratory failure related to exacerbation of chronic obstructive pulmonary disease (COPD)

WT MCNICHOLAS, E MCNALLY, S BOURKE *Department of Respiratory Medicine, St Vincent's Hospital, Dublin* To determine the course of respiratory failure in exacerbations of COPD, we prospectively studied clinical and physiological parameters in 61 such patients admitted over a two year period. Fourteen (23%) patients were hypoxic but normocapnic on admission (group 1) and 46 (77%) were hypoxic and hypercapnic. Of these hypercapnic patients, 20 (43%) reverted to normocapnia on discharge (group 2) and 26 (57%) remained hypercapnic (group 3). Admission P_{CO_2} in group 2 (7·7 (0·3)) kPa (mean (SEM)) was similar to group 3 (7·9 (0·25)), whereas discharge P_{CO_2} in group 2 (5·5 (0·12)) was similar to group 1 (5·0 (0·14)). Admission P_{O_2} in group 3 (5·8 (0·27)) was significantly lower than group 1 (7·4 (0·37)) and group 2 (6·8 (0·31)) (p < 0·002, ANOVA). All groups had similar increases in P_{O_2} between admission and discharge (mean 1·8 kPa). Admission pH in group 2 (7·32 (0·02)) was significantly lower than group 1 (7·41 (0·02)) and group 3 (7·37 (0·01); p < 0·005)) and rose most between admission and discharge (0·13 (0·2); p < 0·001)). Group 3 had the most severe airflow obstruction, FEV_1 26 (3·1)% of predicted, compared with groups 1 (33 (4))% and 2 (39 (4·3))% (p < 0·05). Fourteen patients in group 3 had cor pulmonale, compared with only five in group 2 and three in group 1. We conclude that a large proportion of COPD patients admitted with hypercapnic respiratory failure will revert to normocapnia during recovery. Clues to recognition of such patients include low pH and absence of cor pulmonale.

Acute bronchitis and bronchial hyperreactivity to histamine: a descriptive study in the community

DAR BOLDY, JG AYRES *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* Acute bronchitis (AB) is common, usually viral in origin, and underlying asthma is often missed. In a community study to investigate this diagnosis during the winter 1986–7, 67 patients with AB were seen (excluding childhood bronchiolitis and exacerbations of known chronic lung disease), of whom 57 agreed to further studies at two and six weeks (mean age 35·5 years (range seven months to 73 years), 37 (65%) female). The main symptoms were acute cough (100%), upper respiratory tract symptoms (87%), sweating (58%), and wheeze (55%). On examination, wheeze was present in 18 (32%); 26/51 (51%) aged 16 or over were current smokers. Thirty three (61%) patients gave a personal/family history of atopic disease. Positive skinprick test responses (≥3 mm diameter) were observed in 37% of patients, more commonly in younger patients (χ^2 = 20·19, p < 0·001). A microbiological diagnosis (by serology or culture) was made in only 16 out of 48 (33%) cases: 10 viruses (four rhinoviruses, three influenza A, one each of adenovirus, influenza B, and RSV), five *M pneumoniae* and three bacteria (one each of *B catarrhalis, H influenzae* and *S pneumoniae*). A small reduction was seen in both the FEV_1 and FVC at presentation compared with two weeks (p < 0·02 and p < 0·05 respectively). A histamine challenge test (HCT) was performed at six weeks: in 11 out of 35 (31%) cases, the PD_{20} for histamine was <7·8 μmol. A bronchodilator response to inhaled terbutaline at the initial visit was associated with a positive HCT at six weeks (p = 0·036), but there was no correlation between a positive HCT and smoking history, positive skin test responses or proved infection. The high incidence of bronchial hyperreactivity (BHR) at six weeks may be secondary to infection but, more likely, suggests that patients with BHR are either more prone to develop AB or more liable to be symptomatic enough to consult their doctor with an infection.

Effects of aspirin, ipratropium and salbutamol on bronchial hyperresponsiveness in middle aged smokers

TK LIM, A WATSON, H JOYCE, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* The origins and significance of bronchial hyperresponsiveness (BHR) in smokers remain uncertain, though BHR is known to be closely related to baseline airway dimensions and a popular hypothesis is that it is related to airway inflammation. We have studied BHR before and one hour after an oral anti-inflammatory drug (1·2 g aspirin) and after inhaled bronchodilator drugs (salbutamol 5 mg, ipratropium 0·5 mg, and a mixture of the same doses of both drugs). BHR was assessed as the provocation concentration (mg/ml) of histamine required to reduce FEV_1 by 20% (PC_{20}). In 15 male smokers (mean age 58 y) the repeatability of PC_{20} one hour after placebo was good (r = 0·97) without attenuation of the bronchoconstrictor response to inhaled histamine. 1·2 g of aspirin did not significantly alter PC_{20} (placebo day, mean (SEM) pre 1·81 (1·29), post 1·81 (1·32); aspirin day, pre 1·88 (1·32), post 1·89 (1·42)) or FEV_1 (placebo day, pre 2·20 (0·16), post 2·12 (0·15); aspirin day, pre 2·16 (0·16), post 2·10 (0·16)). In eight men (mean age 60 y, basal mean FEV_1 2·24 l) a full comparison of salbutamol and ipratropium has been made. The combination of 5 mg salbutamol and 0·5 mg ipratropium produced a mean 5·40

fold increase in PC_{20} and 15·9% increase in FEV_1; 5 mg salbutamol a mean 4·04 fold increase in PC_{20} and 10·9% increase in FEV_1; and 0·5 mg ipratropium a 2·15 fold increase in PC_{20} and a 12% increase in FEV_1. There were between individual differences in the relative efficacy of the drugs as bronchodilators, and three individuals who showed no bronchodilator response to either drug still showed an increase in PC_{20}. Further bronchodilator studies are under way. We conclude that (1) the short term repeatability of PC_{20} at one hour was good and the attenuation of BHR to histamine reported in asthma was not found in these smokers; (2) aspirin had no effect on BHR or baseline FEV_1; (3) there was a dissociation between bronchodilator efficacy and attenuation of BHR.

Airway responsiveness to histamine and airway dysfunction in low birthweight children at school age

KN CHAN, C NOBLE-JAMIESON, M SILVERMAN *Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London*
Respiratory symptoms are common following preterm birth. Previous small studies have demonstrated evidence of persistent airway dysfunction and increased airway responsiveness in prematurely born children (Noble-Jamieson *et al, Semin Perinatol* 1982;**6**:266; Bertrand *et al, N Engl J Med* 1985;**312**:742). Their prevalence in low birthweight children is not known. We used a heated pneumotachograph and a microcomputer to record forced expiratory flow time and flow-volume curves in a cohort of 140 low birthweight children (under 2000 g at birth) at seven years. The rapid method of (Yan *Thorax* 1983;**30**:760) was used to measure the airway response to histamine, which was expressed as the PD_{20}. We also studied a reference population of 120 local school children of equivalent age. Airway responsiveness to histamine was increased in low birthweight children; a PD_{20} of < 6 μmol (cumulative dose) was found in 71% of the LBW cohort and in 41% of the reference group. The frequency distribution curves of both the cohort and the reference population were continuous and unimodal; but that of the cohort was shifted to the left compared with the reference population. A significant proportion of LBW children had evidence of airflow obstruction in both large and small airways. Increased airway responsiveness and airflow obstruction occurs at school age following preterm birth. This may have long term implications for lung disease in adult life.

Prevalence of asthma, related symptoms, and school absence in children aged 5–11 years

R HILL, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Estimates of the prevalence of current asthma in schoolchildren in the UK vary widely, although the prevalence of episodic wheezing has been relatively constant at around 10% (DA Lee *et al, Br Med J* 1983;**286**:1256). We describe the results of a questionnaire survey of parents of 4750 primary schoolchildren in Nottingham aged 5–11 years, asking about their child's history of respiratory symptoms, school absence because of episodic wheezing, the diagnosis given, and treatment prescribed. An 80% response rate was achieved. Wheeze in the previous year was reported by 11·5% of respondents, 4·4% having had five or more episodes. One third of all children were reported to have had night cough, although only 8% had had five or more attacks. Both symptoms were reported for 9·6% of children. A diagnosis of asthma had been given to 5·9% of respondents (51% of the children reporting wheeze) and a further 1·3% were having bronchodilator therapy. Overall 57% of children who had wheezed in the previous year had been prescribed asthma medication. Seven per cent of all children reported school absence due to wheezing, of whom two thirds had been given a diagnosis of asthma or were taking asthma medication. Average school loss was two weeks per year, although a quarter of these children were away for longer and 24 reported more than four weeks' absence. Of the children losing more than two weeks from school, 70% were taking occasional β agonists only or no medication at all. This study demonstrates that, despite an increased prevalence of diagnosed asthma, wheeze is still an important cause of school absence in primary schoolchildren and many of the children losing school are receiving little or no treatment.

Asthma in children: a comparison of community surveys in the UK

R HILL, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* The prevalence of wheeze in recent community surveys of children[1–4] has been consistently around 10%. The prevalence of diagnosed asthma (D asthma) however has been more variable (table). Three GP surveys in 1983[5–7] showed a relatively high prevalence of D asthma, presumably reflecting the particular interests of the authors and/or a discrepancy between doctors' diagnosis and parental knowledge or reporting of the diagnosis. In four

Asthma in children: a comparison of community surveys in the UK

	First author	*Date of survey*	*Age (y)*	*No*	*Response rate (%)*	*Wheeze (%)*	*Asthma diag (%)*
1	Anderson	1979	9	5100	87	11·1	3
2	Lee	1979	7	2700	99	9·3	1·2
3	Colver	1981	3–11	2978	90	12·4	3·8
4	Hill	1985	5–11	4750	80	11·5	5·9
5	Levy	1983	1–11	470	—	—	11
6	H-Den Bak	1983	< 16	655	—	—	7·8
7	Toop	1983	7	214	—	—	8
8	Mitchell	1964	10–15	2511	92	—	4·8
9	Graham	1967	9–11	3300	—	—	2·3
10	Peckham	1969	11	13509	—	4·9	3·5
11	Morrison-Smith	1968–9	5–18	20958	—	5·4	4·2

community based studies in the 1960s using parent interviews[8-11] D asthma ranged from 2% to 5%, higher figures than were obtained in the questionnaire studies in Newcastle[2] and Croydon[1] (1·2% and 3%). However, in a recent questionnaire survey to parents of 4750 children in Nottingham primary schools[4] 5·9% of respondents (4·7% of all children) had D asthma and a further 1·3% received asthma medication—bronchodilators or sodium cromoglycate. The increase in D asthma in Nottingham compared with similar studies in Newcastle upon Tyne and Croydon may be due to local factors or may reflect increased awareness of asthma or increased willingness to use the diagnostic label of asthma following increased publicity about asthma.

Airway responsiveness to hypertonic saline and methacholine after hypertonic saline challenge

SP O'HICKEY, JP ARM, PJ REES, TH LEE *Department of Respiratory Medicine, Guy's Hospital, London* In order to assess whether the changes in airway methacholine responsiveness induced by an initial hypertonic challenge determines the response to a subsequent hypertonic provocation, 11 asthmatic subjects underwent bronchial challenges with 3·6% hypertonic saline and methacholine. These were performed in a dose dependent manner and in random order, consisting of (1) a hypertonic saline challenge (HS1) followed one hour later by a second HS challenge (HS2), (2) a methacholine challenge alone (Meth 1), and (3) an HS challenge followed one hour later by a methacholine challenge (Meth 2). The dose of HS which produced a 35% fall in sGaw (PD_{35}) in HS1 was 87 (15) litres (mean (SEM)) and the PD_{35} in HS2 was 167 (40) litres ($p = 0·03$). The refractory index ($PD_{35}HS2/PD_{35}HS1$) ranged from 0·7 to 5·0. There was a correlation between PD_{35}/HS1 and PD_{35} Meth 1 ($r = 0·7$, $p = 0·017$) and between PD_{35}/HS2 and PD_{35} Meth 2 ($r = 0·73$, $p = 0·01$). For the same responsiveness to HS challenge three fold less methacholine was required to produce a 35% fall in sGaw when methacholine was given after HS1 than when methacholine was given at baseline, and for the same methacholine responsiveness 4·5 fold more HS was needed to elicit the same bronchoconstriction. There was a linear correlation between the refractory index and change in methacholine sensitivity (PD_{35} Meth 2/PD_{35} Meth 1) ($r = 0·69$, $p = 0·017$). These results suggest that an initial HS challenge may induce both protective mechanisms toward a subsequent HS challenge and methacholine hyperresponsiveness. The extent of "refractoriness" may be determined by an interaction between these two events.

Relationship between salt intake and bronchial reactivity in asthma

A JAVAID, K BRIDGE, MJ CUSHLEY, MF BONE *Russells Hall Hospital, Dudley, and Wordesley Hospital, Stourbridge, West Midlands* A recent community survey suggested that increased dietary salt intake is associated with increased bronchial reactivity (*Br Med J* 1986;**292**:1483–6). We therefore examined the relationship between salt intake and bronchial reactivity in asthma. We studied 10 asthmatic subjects (18–63 years) and five non-asthmatic controls (23–50 years). Daily salt intake was estimated by a dietitian, and also assessed by measurement of 24 hour urinary salt excretion. Bronchial reactivity to histamine was measured in all subjects. Results were expressed as the concentration of histamine which caused a fall in FEV_1 of 20% or more (PC_{20}); a PC_{20} greater than 8 mg/ml was considered normal. Salt intake was then doubled in all subjects for one month, after which measurement of histamine reactivity and urinary salt excretion was repeated. Patients' treatment was not changed over the study period. In the asthmatics the initial PC_{20} was 2·3 (2·0) mg/ml (mean (SD)). After salt intake was increased PC_{20} fell to 1·6 (2·0) (paired *t* test; $p < 0·05$). Twenty four hour urinary salt excretion increased from 156 (50) mmol to 216 (39) mmol ($p < 0·005$). In the controls bronchial reactivity was normal before and after salt loading; urinary salt excretion increased from 104 (22) mmol to 183 (48) mmol ($p < 0·05$). Increased salt intake may increase bronchial reactivity and contribute to the severity of asthma.

Effect of changing dietary sodium on the bronchial response to histamine

PGJ BURNEY, J NEILD, C TWORT, S CHINN, TD JONES, D MITCHELL, C BATEMAN, IR CAMERON *Departments of Community Medicine, Medicine, and Clinical Chemistry, United Medical and Dental Schools, (St Thomas's), London* The bronchial response to histamine is related to the 24 hour excretion of sodium in men (*Br Med J* 1986;**292**:1483–6). To assess whether this relationship is likely to represent a direct causal association we performed a randomised double blind, cross-over trial of slow sodium (80 mmol/day) against placebo in subjects on a low sodium diet. Urinary sodium output/24 hours was a mean (SEM) of 47 (17) mmol higher on slow sodium than on placebo among the males and 44 (11) mmol among the females. The dose of histamine causing a 10% fall in one second forced expiratory volume (FEV_1) (PD_{10}) fell by 66% (95% CI: 23–85%) among men but rose 53% among the women (95% CI: fall of 28% to 223% increase) when they were taking slow sodium compared with placebo. The results indicate a significant relation ($p < 0·01$) between the PD_{10} (histamine) and urinary sodium excretion in a within subject analysis for the men. No corresponding relation was found in women. This finding is compatible with the differences in the regional mortality data for England and Wales, which show higher asthma mortality rates among men and children, though not among women, in areas with higher consumption of table salt ($p < 0·05$) (*Chest* 1987;**91**:143S).

Effect of inhaled amiloride on bronchial reactivity

AJ KNOX, AE TATTERSFIELD, JR BRITTON *Respiratory Medicine Unit, City Hospital, Nottingham* Epidemiological evidence suggests a link between dietary salt consumption and both bronchial reactivity and asthma mortality (Burney, *et al, Br Med J* 1986;**292**:1483; Burney, *Chest* 1987;suppl) but the mechanism underlying these associations is unknown. An increased contribution of the electrogenic sodium pump has been demonstrated in sensitised guinea pig airway smooth

muscle and amiloride, an inhibitor of Na/H exchange, prevents the contractile response to antigen (Souhrada *et al, Am Rev Respir Dis* 1985;**131**:A356). To assess whether alterations in amiloride sensitive sodium flux in human airway smooth muscle are important in determining bronchial reactivity in man, we have studied the effect of inhaled amiloride on bronchial reactivity to histamine in six normal and 24 asthmatic men in a double blind, placebo controlled, crossover study. Following baseline measurement of specific airways conductance (sGaw), subjects inhaled 10 ml of 10 mmol amiloride or placebo via a nebuliser on two separate days. Immediately after inhalation repeat measurement of sGaw was made and a histamine challenge was performed by the method of Yan *et al* to estimate the provocative dose of histamine causing a 35% reduction in sGaw (PD_{35}). There was no significant difference in sGaw after amiloride and placebo. Geometric mean (95% CI) PD_{35} did not differ significantly after amiloride and placebo, being 3·0 (1·6–5·7) and 4·3 (2·3–7·9) μmol respectively in normal and 0·33 (0·17–0·64) and 0·29 (0·17–0·50) μmol respectively in asthmatic subjects. We have been unable to show that alterations in amiloride sensitive sodium flux are important in determining bronchial reactivity to histamine in man.

Morning dipping: really an exaggeration of normal rhythm?

CK CONNOLLY *Friarage Hospital, Northallerton, North Yorkshire*

Bronchoconstriction induced by nebulised lignocaine in asthmatic patients

LG MCALPINE, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow* Topical lignocaine, used to produce anaesthesia of the lower respiratory tract, may cause bronchoconstriction in some asthmatic patients. We have investigated whether the degree of histamine airway responsiveness can be used to predict which asthmatic patients will develop lignocaine induced bronchoconstriction. Twenty asthmatic patients (16 atopic, four non-topic) were studied, mean age 42·5 years (range 23–71). On one day, a histamine inhalation challenge was performed to determine the provocation concentration of histamine causing a 20% fall in FEV_1 (PC_{20}). On a separate day patients inhaled 6 ml lignocaine (Xylocaine 4% topical) from a DeVilbiss 646 nebuliser; FEV_1 was recorded over a 30 minute period following lignocaine challenge. In the group as a whole there was no correlation between the response to lignocaine and either the histamine PC_{20} ($r = -0·048$) or atopic state. Five patients (25%) showed a fall in FEV_1 of greater than 15% (max 42·1%). In those reacting to lignocaine there was no correlation between the fall in FEV_1 and the histamine PC_{20}. As the response to lignocaine appears idiosyncratic, we examined whether the preservative, methylparaben, in the Xylocaine preparation may be responsible for the bronchoconstriction. Three of the five responders agreed to double blind rechallenge with Xylocaine 4% topical and with a preservative free 4% lignocaine solution of identical pH. There was no difference in the response of these two solutions. In conclusion, topical lignocaine induces bronchonconstriction in an appreciable proportion of asthmatic patients. The response cannot be predicted by the degree of histamine airway responsiveness and does not relate to the preservative in the Xylocaine 4% topical preparation.

In vivo effect of β agonists on human lung membrane β_2 adrenoceptor number and affinity

SJ TITINCHI, KR PATEL *Departments of Biochemistry and Respiratory Medicine, Western Infirmary, Glasgow* We have previously shown that there is no significant difference in lymphocyte β_2 adrenoceptor number (Bmax) and affinity (Kd) between normal subjects and asthmatic patients in remission (Titinchi *et al, Clin Sci* 1984;**66**:323). However, oral salbutamol down regulated β_2 receptor number in both groups. In this study we have measured β_2 receptor Bmax and Kd in freshly prepared lung membrane in seven patients (six female) (mean age (SEM) 58·8 (3·5) y), who underwent lung surgery with ^{125}I-CYP as the radioligand. Specific binding represented 82% (3%) of the total binding. Six patients (smokers) had bronchial carcinoma and one patient (non-smoker) had bronchopulmonary aspergillosis with a lung abscess. Two of the patients, including one with the lung abscess, had partially reversible airflow obstruction and were having inhaled salbutamol. The third patient was given intravenous dopamine during and after surgery. Our Bmax and Kd values were similar to those in previous reports (Engel, *Triangle* 1980;**19**:69). $Beta_2$ numbers in three patients receiving β agonists were significantly down regulated compared with the four patients who did not receive β agonists before surgery. The reduced receptor numbers were associated with decrease in Kd (increase in sensitivity). Whether this change in β_2 receptor Bmax and Kd has any functional relevance needs to be investigated.

	Bmax and Kd of β_2 receptors in lung membranes	
	Bmax (f mol/mg protein)	*Kd (p mol/l)*
Not on β agonists (n = 4)	140·3 (9·1)	58·7 (7·7)
	$p < 0·01$	$p < 0·02$
On β agonists (n = 3)	42·0 (7·6)	23·1 (4·7)

Factors predicting early asthmatic responsiveness and late asthmatic response

WOCM COOKSON, SR DURHAM, JA FAUX, CF CRADDOCK, MK BENSON *Osler Chest Unit, Churchill Hospital, Oxford* In order to investigate factors predicting the early and late asthmatic responses to inhaled allergen (EAR and LAR), 11 asthmatic subjects with documented house dust mite (HDM) allergy were challenged with HDM. The subjects mean age was 27 years (range 20–36) and their mean FEV_1 102% of predicted (range 87%–119%). The eosinophil count (EOS), specific IgE to HDM (RAST), airway responsiveness to histamine (HPC_{20}), skin responsiveness to HDM ($AgPD_4$), and skin responsiveness to histamine (HPC_4) were estimated prior to challenge. The challenge was carried out with half log increments of antigen concentration until there was a 20%

fall in FEV_1. Following challenge the range of EAR was from 24% to 44% of initial FEV_1 values, and the range of LAR was from 5% to 55%. There was no relationship between EAR and LAR. Multiple stepwise regression with $AgPC_{20}$ as the dependent variable found log HPC_{20} (R^2 = 42%, p = 0·0001), log RAST (additional R^2 = 44%, p = 0·003), and EOS (additional R^2 = 9%, p = 0·011) to be entered in the equation. Thus 95% of the variability in $AgPC_{20}$ could be predicted by these parameters. With LAR as the dependent variable only the log HPC_4 correlated with LAR (R^2 = 59%, p = 0·006). The results indicate that HPC_{20}, RAST, and EOS can predict almost entirely the $AgPC_{20}$.

Nocturnal asthma: effect of vagal activity and plasma adrenaline

JFJ MORRISON, P MARSHALL, NM DWYER, SC JONES, SB PEARSON, HG DEAN *Pulmonary Function Laboratory, Killingbeck Hospital, Leeds, and Department of Pharmacology, University of Leeds* Previous work has demonstrated that alterations in vagal activity and plasma adrenaline levels both influence the nocturnal fall in PEF in asthmatics. We have shown previously that when vagal blockade is administered at 4 am the maximum bronchodilation achieved reaches the baseline values seen at 4 pm but fails to achieve the levels seen after daytime vagal blockade. This study was designed to see whether this is altered by adjusting nocturnal plasma adrenaline levels to day time values. In a placebo controlled, double blind study seven asthmatics with a diurnal variation in PEF of >20% were admitted to hospital for one day's acclimatisation followed by measurements at 4 am and 4 pm on two successive days. At 4 am they were awoken, PEF was measured and plasma adrenaline sampled. They then received either placebo injections and infusions or intravenous atropine 30 μg/kg followed by infusions of adrenaline in doses of 1, 2, 4, 8, 16, and 32 nm/kg/min each for 20 minutes. PEF measurements were made five minutes after atropine and after each adrenaline infusion when plasma adrenaline was also sampled. At 4 pm, after subjects had rested supine for one hour, PEF was measured and either placebo or 30 μg/kg atropine given intravenously followed five minutes later by PEF measurements and sampling for plasma adrenaline. Placebo days and active days were allocated in random order. Vagal blockade reversed the nocturnal fall in PEFR to the levels seen at 4 pm after placebo as shown previously. Plasma adrenaline showed a significant diurnal variation and the infusion rate required to reverse the nocturnal fall in plasma adrenaline was 2 ng/kg/min. The increase in PEF produced by this dose of adrenaline was 17 l/min, which was not significantly different from the nocturnal post-atropine value, and fails to account for the difference between the post-atropine PEF at 4 am and 4 pm.

Pathology and radiology correlations in Welsh slate workers

K MCCONNOCHIE, A GIBBS, MJ CAMPBELL, R SADLER, JP LYONS, JC WAGNER *Thoracic Department, Llandough Hospital, Penarth, and Medical Statistics and Computing, University of Southampton* Until recently, North Wales was the largest producer of slate in the world. Analysis has shown the quartz content of this slate is 30–40%. A recent review suggests that silicosis occurs in about 10% of the workforce (Glover JR *et al, Br J Ind Med* 1980;37:152). The aim of this study is to correlate pathology of the postmortem lung with the chest radiograph taken closest to time of death, to explore the relationship between pulmonary nodules and round opacities and interstitial fibrosis and irregular opacities. All deaths of slate workers should be reported to HM Coroner and a post-mortem examination performed. From 1972 to 1983 333 deaths were identified, from which 301 suitable post-mortem lungs were obtained. These lungs were examined macroscopically and representative tissue blocks taken for histological examination. The following features were graded semiquantitatively on an 0–4 scale: profusion of nodules, amount of fibrosis within nodules, degree of interstitial pigmentation, and fibrosis. Most workers had regular chest radiographs and suitable films were found for 245 of the original 333 cases. These films were read to the ILO classification by three experienced readers. Median readings were used for this analysis. We found a good correlation between the pathological profusion of nodules and the radiological profusion of opacities (r = 0·49, p < 0·01). The relationship between pathological interstitial fibrosis and radiological profusion of opacities was less powerful (r = 0·39). Increasing fibrosis within the silicotic nodule correlates well with round radiological opacities (r = 0·92). The discreet silicotic nodule is relatively well identified on the radiograph, making it possible to explore further the significance of irregular opacities.

Relative contribution of macrophages and neutrophils to proteolytic damage in an experimental model of lung inflammation

GM BROWN, K DONALDSON, A SEATON *Institute of Occupational Medicine, Edinburgh* Numbers of leucocytes in the alveolar region may be dramatically increased in inflammatory lung disease and neutrophils, rare in normal alveoli, are often present in large numbers. To assess the relative contributions of macrophages and neutrophils to the overall protease burden in the lung during pulmonary inflammation, we utilised the inflammatory reaction present five days after intratracheal instillation of silica in rats. Silica treatment caused a seven fold increase in total leucocytes in the bronchoalveolar lavage fluid (mean 14·1 (SEM 1·7) × 10^6) compared with untreated control animals (1·9 (0·5) × 10^6; p < 0·0025); the silica elicited population also showed a three fold increase in neutral protease activity, as measured by proteolysis of a radiolabelled fibronectin matrix, compared with controls. Macrophages and neutrophils in the silica population were separated by means of a Sepracell density gradient (macrophages 94% (3%); neutrophils 81% (6%)). These were tested for proteolytic activity compared with macrophages (96% (1%)) from control animals. Fibronectin degradation by the neutrophil enriched population (5872 (1360) cpm) was significantly greater than by control macrophages (1983 (718)) or the quartz macrophage enriched population (2740 (572); p < 0·05). There were no significant differences in proteolytic activity between silica elicited and control macrophages. In this model of silica induced lung inflammation neutrophils are the predominant

source of neutral protease activity. However, the seven fold increase in inflammatory macrophages suggests that, although their levels of protease per cell are similar to those of control macrophages, total protease secretion by the inflammatory macrophage population must make a significant contribution to the total protease burden in the lung. (This study was funded in part by the Colt Foundation.)

Prevalence of respiratory symptoms in an engineering factory with exposure to oil mists

MDL MORGAN, D GLASS, AS ROBERTSON, A BORAN, SH JONES, F MURRAY, PS BURGE *East Birmingham Hospital, Birmingham* Oil mist exposure is the commonest recognised cause of occupational asthma in Birmingham. We report a cross sectional study designed to detect upper and lower respiratory symptoms, completed by 90% of 134 workers exposed to oil mists. The factory made gearboxes and the survey followed complaints of upper respiratory symptoms. The exposed population was divided into three groups with increasing exposure to soluble oil mists, and one group exposed to mineral oils. Each worker had measurements of lung function and completed a doctor administered questionnaire followed by a clinical opinion on symptoms related to work. Independently, the workers' oil mist exposure was assessed by an occupational hygienist. The exposure groups were matched in age and duration of employment. Work related dry throat and sore throat increased from 19% to 45% with increasing exposure. Other symptoms were prevalent in the workforce but were not significantly increased in those with higher exposure. The prevalence of work related symptoms was: wheeze 15%, chest tightness 14%, breathlessness 7%, rhinitis 15%, and eye irritation 11%. No workers with unequivocal occupational asthma were seen. Lung function was not significantly related to oil mist exposure group. The results can be interpreted in two ways: either very low levels of oil mist exposure ($<0{\cdot}15$ mg/m^3) cause symptoms which do not increase with higher (2·09 mg/m^3) exposure or the work related symptoms were unrelated to oil mist.

Inflammatory effects in the rat lung caused by dust collected from the air of British wool factories

K DONALDSON, RG LOVE, RT CULLEN, GM BROWN, DM BROWN, CA SOUTAR *Institute of Occupational Medicine, Edinburgh* We have previously reported a relationship between respiratory symptoms and exposure to wool dust in factories and mills in Yorkshire. As part of this study we have also examined the ability of wool dust samples to cause pulmonary inflammation. Dusts collected from the air of three different factories, chosen to represent the start (S), middle (M), and end (E) of the industrial processing of wool, were injected into the lungs of groups of three syngeneic PVG rats and the course of the bronchoalveolar leucocyte response was followed by lavage. Titanium dioxide (TiO_2), an inert particulate, was used as a control. The wool dusts caused considerable inflammation compared with the TiO_2: neutrophils $\times 10^6$ at three days (mean (SEM))—TiO_2 0·29 (0·15), wool dust S 4·30 (1·31), wool dust M 3·04 (0·43), wool dust E 0·78 (0·40); there were significant differences between TiO_2 and all three wool dusts and between wool dusts SvE and MvE ($p < 0{\cdot}\ 0{\cdot}05$). By day 14 the neutrophil numbers had waned but the alveolar macrophages from the wool dust treated rats were found to have formed aggregates of cells, often in association with particles of wool dust. Soluble components derived from the wool dusts were capable of causing inflammation when injected: cells $\times 10^6$—saline 2·6 (0·4) macrophages, 0·1 (0·0) neutrophils; saline extract of wool dust 7·2 (0·4) macrophages, 1·3 (0·4) neutrophils ($p < 0{\cdot}05$). The saline extracts did not possess chemotactic activity for bronchoalveolar leucocytes but wool dust caused activation of chemotaxin (presumed to be complement) in serum: migrated cells/high power field—control serum 23·9 (3·2), wool dust treated serum 61·4 (8·0), zymosan treated serum 86·3 (11·8); there was a significant difference between control and wool dust treated serum ($p < 0{\cdot}01$). The ability of dust collected from the air of wool factories to cause pulmonary inflammation may be related to the prevalence of respiratory symptoms in wool factory workers. (This research was supported by the Health and Safety Executive.)

Bronchoalveolar leucocyte response in experimental silicosis and its modulation by a soluble aluminium compound

GM BROWN, K DONALDSON, DM BROWN, A SEATON *Institute of Occupational Medicine, Edinburgh* A protective effect of aluminium compounds in silica induced lung damage has been well documented and may be important in determining the pathogenic potential of silica containing mixed dusts, such as coalmine dust. To investigate the mechanism of this protection, we have assessed the ability of soluble aluminium lactate to alter the biological activity of silica (quartz) in vivo. Rats were exposed by intratracheal instillation to no quartz (controls), DQ_{12} quartz (Q), or DQ_{12} quartz pretreated with aluminium lactate (QA). The degree of inflammation in the lungs four or 12 weeks later was assessed by measuring the number and types of cells present at bronchoalveolar lavage and by measuring the functional status of these cells. At four weeks there were significantly more leucocytes in the Q population (mean 52·6 (SEM (22·2) $\times 10^6$) than in the controls (3·0 (0·15)) or the QA cells (3·4 (1·1)); $p < 0{\cdot}01$. The Q cells comprised 46% (5·5%) neutrophils, significantly more than the controls (0·3% (0·6%)) or the QA cells (8·3% (4·5%)); $p < 0{\cdot}001$. Neutral protease production, assessed by degradation of iondinated fibronectin, was also significantly greater in the Q cells (4443 (191) cpm) than the controls (1598 (46) cpm; $p < 0{\cdot}001$). However, Q cells produced significantly less superoxide (9·4 (0·7) μmol) than controls (49·4 (5·2)) or QA cells (41·3 (1·7); $p < 0{\cdot}001$). Similar differences between the treatment groups were present at 12 weeks. It is frequently suggested that coalmine dusts with high silica content should cause increased prevalence of pneumoconiosis, but this is not always the case. In collieries where the incidence of disease is not consistent with the silica content of the mine dust, the ameliorating action of aluminium from other minerals, such as aluminium silicate clays, on quartz toxicity may offer an explanation.

Progression of the bronchoalveolar leucocyte response in experimental silicosis after cessation of airborne exposure to silica

K DONALDSON, GM BROWN, MD ROBERTSON, J SLIGHT, A SEATON *Institute of Occupational Medicine, Edinburgh*
Exposure to airborne silica (quartz) causes silicosis, a disease which can be progressive even in the absence of further exposure to silica dust. We report here on the effects of cessation of exposure to airborne silica on the further development of the leucocyte response in rats. Groups of four rats were exposed to 10 or 50 mg/m^3 airborne mass concentration of quartz or the inert particulate titanium dioxide (TiO_2). The total and differential leucocyte counts in the bronchoalveolar lavage were assessed at various times including 75 days. "Recovery" rats were exposed for 75 days, removed from the exposure chamber and maintained in room air for a further 64 days. In the case of TiO_2 at 10 mg/m^3 there was no progression (all subsequent data given as mean (SEM) cells $\times 10^6$): 75 days TiO_2 4·04 (0·58) macrophages, 0·01 (0·00) neutrophils; 75 days TiO_2 + recovery 4·21 (0·42) macrophages, 0·01 (0·01) neutrophils; NSD between treatments. With quartz at 10 mg/m^3, however, there was considerable progression of the leucocyte response during recovery: 75 days quartz 19·79 (2·21) macrophages, 18·78 (7·00) neutrophils; 75 days quartz + recovery 44·23 (10·52) macrophages, 20·88 (5·77) neutrophils; the differences in macrophage numbers between treatments were statistically significant ($p < 0·05$). At the 50 mg/m^3 airborne concentration, TiO_2 caused a low level of inflammation but this was reduced during the recovery period. With quartz at 50 mg/m^3, however, the number of leucocytes approximately doubled during the period when rats were breathing room air: 75 days quartz 105·43 (17·04) macrophages, 119·18 (18·37) neutrophils; 75 day quartz + recovery 262·93 (50·65) macrophages, 213·66 (27·31) neutrophils. Chrysotile asbestos at 10 mg/m^3 did not result in progression of bronchoalveolar leucocyte responses on cessation of exposure. The progression in response found here experimentally may be related to the progression of silicosis seen in the clinical context. (This research was funded by the European Coal and Steel Community.)

Shipyard data revisited

JE COTES, DJ CHINN, FM EL-GAMAL, CAC WICKHAM, V WOOLLEY *Department of Occupational Health, Medical School, Newcastle upon Tyne, and MRC Environmental Epidemiology Unit, Southampton*
Previously communicated results from sample surveys of two shipyards presented conflicting views on the respiratory impairment associated with welding or caulker/burning. For Yard A (607 men aged 17–67 years), on the basis of a multiple regression model which included interaction terms, the fumes appeared to augment only smoking related respiratory symptoms (Cotes JE *et al, Thorax* 1984;**39**:691). With a principal component model and retaining factors which together explained 98% of the variance, the factor identified with fume exposure was significantly associated with reduced forced expiratory volume-time and flow-volume indices (El-Gamal FM, Cotes JE, *Bull Eur Physiopath Respir* 1985;**21**:48k; El-Gamal FM *et al, Thorax* 1985;**40**:702). The analyses have now been repeated with a multiple regression model which rigorously excluded collinearity. After allowance for age and smoking, work as a welder or caulker/burner was associated with relatively low values for peak expiratory flow rate and FEV% of forced vital capacity. Among welders the decline with age in FEV% and among caulker/burners the decline in forced expiratory flow rate ($MEF_{50\%FVC}$), mean transit time and its standard deviation were all related to the fume exposure expressed as the average intensity over the period of employment. For Yard B (513 men aged 18–47 years) the previously reported enhanced decline in forced expiratory volume and peak expiratory flow rate with age in welders was confirmed. Thus fumes from welding and caulker/burning significantly affected the lung function of the present shipyard workers but the estimated magnitude of the response was greatly influenced by the model used for the analysis. Respiratory symptoms were associated with smoking and with age. In Yard A (where the sample included older men) chronic cough, phlegm, and breathlessness of grade 3 or above were associated with fume exposure in the smokers but not the non-smokers or ex-smokers. A significant excess of welders had become ex-smokers. In both yards chronic wheeze was associated with fume exposure in the non-smokers and ex-smokers but not the smokers. Thus fume related wheeze appeared to be relatively unresponsive to abandoning smoking.

Relation between passive cigarette smoke exposure and "building sickness"

AS ROBERTSON, P SHERWOOD BURGE, A HEDGE, S WILSON, J HARRIS-BASS *East Birmingham Hospital, Birmingham*
Four thousand four hundred and four office workers in 46 different office sites completed a self administered questionnaire (average response rate 92%). Smoking status was determined for 99·7% of the 4373 full time workers. Twenty two per cent were current smokers, 16% were ex-smokers, and 62% were non-smokers. Smoking was commoner in women (23% *v* 20%) and was less common in professional employees (professional 17%, managerial 25%, clerical 23%). Questions on passive smoking were added after the first questionnaire had been completed, giving results for 3416 sequential workers. Forty seven per cent of non-smokers were being passively exposed at work. All of the symptoms of building sickness were more common in non-smokers who were passively exposed at work compared with those who were not (work related symptoms, passive *v* non-passive: itchy eyes 31% *v* 22%, runny nose 26% *v* 18%, dry throat 51% *v* 40%, headache 48% *v* 39%, lethargy 60% *v* 52%, $p < 0·001$). Buildings were ranked according to smoking prevalence. Work related symptoms were more common in those buildings with a high smoking prevalence than those with a low smoking prevalence ($p < 0·01$). This difference was more marked in the naturally ventilated buildings as compared with the sealed, air conditioned buildings. We have previously shown that non-smoking can be validated in at least 97% of office workers who say that they do not smoke and that passive smoking is three times as common at work as at home. The present study shows a dose related increase in the symptoms of building sickness associated with passive exposure to cigarette smoke, suggesting that cigarette smoke contributes to building sickness.

Occupational asthma due to a bleach activating agent

SC STENTON, MJ CONNOLLY, IS WINTERTON, EH WALTERS, DJ HENDRICK *Newcastle General Hospital, University of Newcastle upon Tyne, and Procter and Gamble, Newcastle upon Tyne* Research with a low temperature bleach activating agent (sodium iso-nonanoyl oxybenzene sulphonate) for use in a washing powder was complicated after 12–18 months by the occurrence of rashes and rhinitis in three of 60 exposed workers. A fourth worker then developed asthma. He was an atopic 38 year old technician who had suffered asthma previously between the ages of two and 14 years. Following four to six weeks in which he experienced rhinitis, rash, dry cough, and undue breathlessness on exertion, he woke on two successive nights with wheezing, chest tightness, and breathlessness. His symptoms resolved completely within two weeks away from work. A return to work to greatly reduced exposure levels was accompanied by a minimal recurrence of his symptoms, a mild fall in peak expiratory flow, and a significant increase in bronchial responsiveness to methacholine. Laboratory based inhalation challenge tests were undertaken using a locally designed "dosimeter" to nebulise 50 μl doses from sulphonate solutions of increasing concentration (0·2–640 μg/ml). Using daily increments of $10^{0.5}$ (that is, about 3·2 fold), a dose range of 0·01–32 μg was administered over the course of two weeks together with two "blinded" control tests with saline alone. Late asthmatic reactions of increasing strength were observed following the higher doses, and were accompanied by a further increase in bronchial responsiveness. They were reproducible but were not observed following the control tests. The cumulative obstructive effect 2–12 hours following each challenge was expressed by measuring the area above the FEV_1 time plot using the baseline FEV_1 (mean of 15 prechallenge recordings) to define the upper boundary of the area measured. There was a linear relationship between this area and the log challenge dose. It is unclear whether this favours a hypersensitivity or irritant mechanism as an analysis of this type for the evaluation of asthma due to occupational agents has not previously been described.

Increased risk of occupational allergy in smokers working in a platinum refinery

KM VENABLES, J STEVENS, AJ NUNN, RJ STEPHENS, NM FARRER, M STEWART, EG HUGHES, AJ NEWMAN TAYLOR *Cardiothoracic Institute, London, and Johnson Matthey PLC* Platinum salts cause asthma, rhinitis, and urticaria. At a UK platinum refinery, medical examinations are performed when workers join and regularly during employment. Since 1973, skin prick tests have been carried out with common allergens and with platinum salts. Atopy is defined as a weal of diameter 2 mm or more to common allergens. A cohort of 91 workers joined the refinery in 1973–4 and a previous analysis suggested that atopy predisposes to allergy to platinum salts (Dally *et al, ARRD* 1980;**121**:A230). Several recent cross sectional surveys suggest that smoking is a risk factor for occupational allergy, so we have now abstracted additional information on smoking from refinery records. At joining, 29 workers were atopic and 57 were current smokers. The cohort was followed until April 1980, when 81 had left. During follow up the records indicated either lower respiratory tract symptoms or a diagnosis of occupational allergy in 51. In skin tests 26 developed a weal from platinum salts and all had symptoms, though not necessarily developing at the same time as the skin weal. Cox regression analyses were used to identify factors present at the start of exposure which predicted subsequent (*a*) leaving, (*b*) symptoms and (*c*) skin weal from platinum salts. Smoking was a significant predictor of all three outcome variables. Atopy was a secondary significant predictor for skin weal from platinum salts. This is the first prospective study to confirm that smoking increases the risk of occupational allergy. The finding has important implications for preventive strategies.

Dust exposure, symptoms, lung function, and immunological reactivity in UK bakers

KM VENABLES, AW MUSK, B CROOK, A NUNN, R HAWKINS, G CROOK, BJ GRANEEK, RD TEE, NM FARRER, D JOHNSON, DJ GORDON, JH DARBYSHIRE, AJ NEWMAN TAYLOR *Cardiothoracic Institute, London, and Rothamsted Experimental Station, Harpenden, Herts* In 1986, 279 of 318 (88%) bakery workers took part in a cross sectional survey. Jobs were ranked from 0 to 10 by assumed dustiness. This correlated well with total dust measured in 79 personal samples, which ranged from 0 to 37·6 mg/m^3, nine being over 10 mg/m^3. A self completed questionnaire noted chronic bronchitis (phlegm for three months/year), chest symptoms (tightness, wheeze, dyspnoea), and nasal symptoms and if chest or nasal symptoms were work related (improved during holidays or days off). FEV_1 and FVC were measured (Vitalograph) and bronchial reactivity to methacholine. Skin prick tests were done with three common allergens and 11 allergens potentially in bakery dust, including mites and moulds. Atopy was defined as a weal of at least 2 mm diameter from common allergens. Serum was tested in radioallergosorbent tests with bakery allergens. In 234 regularly exposed workers, symptoms, lung function and immunological reactivity were related to either current or past dust exposure. For example, work related chest symptoms were reported by 8% of 60 with current low exposure, 12% of 104 with medium exposure, and 17% of 70 with high exposure; the corresponding figures for work related nasal symptoms were 5%, 20%, and 30%. These relationships with exposure were confirmed by logistic regression analyses, which showed that an exposure variable was the major significant factor for most response variables studied, with some exceptions—for example, skin weals to bakery allergens, where exposure was significant but secondary to atopy. Thus in a modern UK bakery there was high dust exposures, varying with type of job, and measures of respiratory ill health were associated with exposure.