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Proceedings of the British Thoracic Society

The Summer Meeting of the British Thoracic Society (the first day of which contained the joint and separate meetings of the British Thoracic Association and Thoracic Society) was held from 30 June to 3 July 1982 at the University of York

BTA smoking withdrawal study

IA CAMPBELL for the BTA Research Committee Four methods of achieving smoking cessation were compared in 1618 new patients attending hospital in a multi-centre study and patients were allocated in random order to either: (1) Verbal advice, or (2) Verbal advice plus booklet, or (3) Verbal advice plus booklet and nicotine chewing gum, or (4) Verbal advice plus booklet and placebo chewing gum. Outpatient, heavy-smoking, middle-aged men with lung disease and from social classes IV and V predominated. Abstinence was checked by CoHb and thiocyanate estimations. Eight per cent of patients successfully gave up smoking. Thirty-one per cent were untruthful about their smoking habit at six months. Side effects from the gum were uncommon and minor. Follow-up to 12 months continues.

Combination chemotherapy and radiotherapy in small-cell carcinoma of the bronchus

SG SPIRO, RL SOUHAMI, JS TOBIAS, DM GEDDES, PG HARPER The value of mediastinal irradiation (RT) in small-cell carcinoma of the bronchus (SCCB) treated by combination chemotherapy (CT) is being assessed in a randomised prospective trial. Three hundred and two consecutive untreated patients have been treated with either CT alone (alternating cycles of doxorubicin 50 mg/m^2 plus vincristine 1·4 mg/m^2 and cyclophosphamide 1 g/m^2 plus methotrexate 50 mg/m^2 given every three weeks) or CT plus RT. After four courses of CT, 12 weeks, RT (4000r/4 w, daily fractions) is given to the primary site in those patients randomised to this arm who do not have progressive metastatic disease. CT is continued for 12 courses. One hundred and eight patients had limited disease (LD) and 194 extensive (ED). Of the 238 patients who have died or been reassessed at 12 weeks (64 have not yet reached reassessment), fibreoptic-bronchoscopy-confirmed complete response (CR) was seen in 23 (10%) and partial response (PR) in 85 (33%). For CR median survival is not yet reached. For PR median survival is 43 weeks for LD in the CT group and 57 weeks in the CT plus RT group. For patients with PR median survival in the ED categories are 41 and 37 weeks for CT and CT plus RT respectively. Non-responder survival is 34 weeks for LD and 11 weeks for ED with no difference between treatment arms. With the possible exception of the PR group with LD, there is as yet no survival advantage for the CT plus RT group.

MRC lung cancer working party study of cytotoxic chemotherapy and radiotherapy in the treatment of small-cell carcinoma: third small-cell study

DJ GIRLING The object of the study is to determine in patients with small-cell carcinoma of "limited" extent, all of whom are treated with the same combination of radiotherapy to the primary site and chemotherapy, whether starting treatment with two pulses of chemotherapy, before the radiotherapy, followed by further pulses of chemotherapy (Ct Rt Ct series) is more effective than starting treatment with the radiotherapy followed by the chemotherapy (Rt Ct series). A total of 186 patients were admitted and allocated at random to the two series. The chemotherapy consisted of cyclophosphamide 500 mg/m^2 and methotrexate 50 mg/m^2 by intravenous injection every three weeks for a planned minimum of 10 pulses, together with CCNU 50 mg/m^2 by mouth with the first pulse and alternate pulses therafter. The radiotherapy consisted of megavoltage x-ray therapy of ^{60}Co gamma-ray teletherapy as opposed portals to the primary site and mediastinal nodes, the field extending from the suprasternal notch to 2 cm below the carina and encompassing the full width of the mediastinum and lung hila. The midline dose was 30 Gy given in 15 fractions over 18–20 days, or biological equivalent. The patients have all completed 12 months in the study. On a log-rank test, survival was slightly prolonged in the Ct Rt Ct series, but the difference was not statistically significant ($p = 0·3$), and by 12 months 38 (40%) of the Ct Rt Ct and 33 (36%) of the Rt Ct series were alive. There was no difference between the regimens with respect to the incidence and sites of distant metastases or adverse reactions to treatment during the 12 months.

Compliance with therapy in patients with chronic airflow obstruction

P JAMES, J HENRY, GM COCHRANE Combination drug therapy has been advocated in the treatment of airflow obstruction. However, in patients with hypertension, the more complex the drug regimen the less was compliance with this therapy, although side effects were fewer. A questionnaire completed by the attending physician was given to 185 patients attending hospital clinics. Three main questions were asked: what maintenance therapy was prescribed; what if any of this therapy was taken regularly by the patients; and how did they adjust their therapy during an exacerbation of symptoms? Although individual drug regimens varied considerably, all but two patients were prescribed inhaled β_2-stimulants. Ninety-four patients (50·8%) claimed to take their maintenance therapy regularly. Of these, 66 (33·5%) increased their dose of inhaled bronchodilator therapy during an exacerbation of symptoms. However, four of these patients also increased prophylactic agents as well. Twenty-four patients were on oral methylxanthines and six of these increased this therapy up to six times their normal dose when ill. Eighty-one patients (43·8%) took less and 8 (4·3%) none of their

prescribed maintenance therapy. Again, virtually all increased their inhaled bronchodilator therapy when ill. Female patients were more compliant than males, and patients with predominant asthma more compliant than patients with chronic obstructive bronchitis and emphysema (corrected for sex distribution). Compliance surprisingly increased with the number of drugs taken and is therefore probably related to the severity of the asthma (37·5% one drug; 47·3% two drugs; 59·6% three drugs; 60% four drugs).

Bronchocentric granulomatosis: review of 14 patients

JH LEE, T JOIHOVSKY, K YAN The term bronchocentric granulomatosis was introduced by Liebow in 1972 to describe necrosis of bronchial walls and adjacent lung parenchyma not ascribable to occlusion of blood vessels. The presence of inspissated material containing clusters of eosinophils within the bronchi was noted and the discovery of aspergilli in some specimens led to recognition of similarities between this disorder and allergic bronchopulmonary aspergillosis. Examination of the clinical features and pathological findings in 14 patients gave the following findings: (1) The typical presentation was a prolonged history of generally mild symptoms such as cough and dyspnoea, associated with radiological abnormality and leading to surgical resection. (2) Bronchocentric granulomatosis was always associated with mucoid impaction in this group, either in situ or in the form of previously expectorated mucous plugs. (3) Aspergilli could be found in the lungs of all patients by staining methods, although the results of culture were frequently negative. (4) The development of peripheral bronchiectasis in patients with mucoid impaction strongly suggests the formation of bronchocentric granulomatosis. (5) A history of asthma could be obtained in only eight patients and no evidence of bronchial hyperreactivity could be demonstrated in the non-asthmatic group. Furthermore, the usual markers of allergic bronchopulmonary aspergillosis—increased total IgE level, positive responses to skin tests, and serum precipitin reactions against aspergillus antigen—are absent in the non-asthmatic patients. (6) Microscopic examination of the plugs reveals tightly compacted, laminated clusters of eosinophils and fungal elements in all cases. This appearance is thought to be diagnostic of bronchopulmonary aspergillosis and it can be readily distinguished from the sputum plugs normally seen in asthma, where layers of eosinophils appear as whirls and eddies. (7) Peripheral eosinophilia was present in most patients, including the non-asthmatics. The beneficial effect of corticosteroid drugs in mucoid impaction is well known and unnecessary surgery might be avoided by awareness of the development of this form of aspergillus-related bronchopulmonary disease in non-atopic individuals. Further investigation of the response to injury in this group of diseases is necessary.

Comparison of the effects of histamine H_1- and H_2-receptors on large and small airways in man

JANINE WHITE, NOEMI M EISER Results from a single, in vitro, experiment (Dunlop and Smith. *Br J Pharmacol* 1977;**59**:475P) suggested that bronchodilating H_2-receptors exist on human bronchial muscle. Subsequently, several studies using histamine antagonists in vivo produced conflicting data, but concluded that, if present, H_2-receptors were of minor importance in human airways. The present study re-examines the role of histamine receptors by comparing the bronchial response to a specific H_1-receptor agonist, beta-histine, and a specific H_2-receptor agonist, impromidine, with histamine. On separate days, 10 atopic non-asthmatic subjects each performed bronchial challenges, in duplicate and in a single-blind fashion, with increasing concentrations of histamine (0·2–12·8%) beta-histine (0·5–16%), and impromidine (0·8–25·6%). Each dose consisted of five breaths of aerosol inhaled from a Hudson nebuliser attached to a breath-actuated dosimeter. Before and two minutes after each dose, four measurements of specific airways conductance (sGaw), each followed by a partial expiratory flow-volume curve (PEFV), were made in a whole-body plethysmograph. Dose-response curves were constructed for each challenge. Both histamine and beta-histine induced dose-dependent bronchoconstriction in all subjects, with similar changes in sGaw and in the measurements taken from PEFV curves, while impromidine had no effect on airways function. These responses were reproducible. Our results confirm the presence of bronchoconstricting H_1-receptors and the absence of significant numbers of H_2-receptors on human bronchial smooth muscle.

Is asthma due to partial beta-blockade of airways?

AE TATTERSFIELD, ST HOLGATE, JE HARVEY, HR GRIBBIN If asthma is due to partial beta-blockade (BB) of airways, the airway dose-response curve (DRC) to a beta-adrenoceptor agonist should be displaced to the right in asthmatic patients compared with normal subjects. We therefore reviewed our airway DRCs to salbutamol in normal and asthmatic patients. To demonstrate that our methodology was sensitive to the measurement of airway BB six normal subjects inhaled increasing doses of salbutamol from 10 to 400 μg to produce a 27–78% increase in resting sGaw (mean baseline sGaw $1{\cdot}7 s^{-1}\ kPa^{-1}$). They then repeated the salbutamol DR study two hours after 80 mg oral propranolol using appropriate doses of salbutamol to cause bronchodilatation. There was a parallel displacement of the airway DRC after propranolol, the geometric mean dose of salbutamol causing a 50% response (Dmax 50) being 18 μg before and 500 μg after propanolol. We then compared the airway DRCs to salbutamol in these normal subjects to those in eight patients with mild but unequivocal asthma (mean FEV_1 91% predicted, resting sGaw $1{\cdot}35 s^{-1}\ kPa^{-1}$). Mean Dmax 50 for asthmatic patients (29 μg) did not differ significantly from normal subjects (18 μg). Finally, we compared IV salbutamol DRCs in five asthmatic and six different normal subjects (resting sGaw 1·7 and $1{\cdot}8 s^{-1}\ kPa^{-1}$; % increase in sGaw 53 and 60%). Mean Dmax 50 was 89 μg in normal subjects and 67 μg in asthmatic patients. Thus we have demonstrated with propranolol, firstly, that our methodology is sensitive to the measurement of BB in airways, and, secondly, that there is no evidence of partial BB in

airways of patients with mild asthma. If partial BB is an important basic abnormality in asthma it should be present in patients with mild asthma.

Opiate sensitivity in chronic airflow limitation

AA WOODCOCK, M JOHNSON, DM GEDDES Evidence has accumulated that the clinical spectrum of chronic airflow limitation is related to differences in respiratory centre output and respiratory timing. Since there are high concentrations of opiate receptors and enkephalins in respiratory control centres, it is possible that differences in respiratory control are secondary to changes in opiate receptor sensitivity or endogenous opiate activity. This study investigates respiratory, pupillary, and hormonal responses to an exogenous opiate dihydrocodeine in 26 patients with severe chronic airflow obstruction. Patients were divided into two groups: A—normocapnic $PaCO_2 < 41$ mm Hg; PaO_2 mean 69·5 mm Hg; n = 15. B—hypercapnic $PaCO_2 > 45$ mm Hg; PaO_2 mean 57·3 mm Hg; n = 11. The hypercapnic group were all able to restore PaO_2 and $PaCO_2$ towards normal by hyperventilation (PaO_2 57·3 → 74·6; $PaCO_2$ 49·4 → 41·7 mm Hg). The two groups were closely matched for spirometry (FEV_1 587 *v* 622 ml; A:B). Hypercapnic patients had a lower minute ventilation at rest (123 *v* 150 ml/kg/min; $p < 0·001$) owing to a lower tidal volume. Pupil size was significantly lower (4·27 *v* 5·49 mm; $p < 0·02$) and growth hormone higher ($p < 0·05$) in hypercapnic patients. Dihydrocodeine had different effects in the two groups, normocapnic patients having significantly greater sensitivity in terms of reduction of ventilation, oxygen consumption, and pupil size. Dihydrocodeine significantly increased growth hormone levels in the normocapnic group, but decreased hormones in the hypercapnic group. Naloxone reversed the effects of dihydrocodeine on ventilation, oxygen consumption, and pupil size in the normocapnic group but not in hypercapnic patients. These findings suggest that variations in opiate sensitivity might play a part in the differences in respiratory and non-respiratory parameters seen within the clinical spectrum of chronic lung disease.

Coded peak flow measurement and the perception of asthma

CMB HIGGS, G LASZLO To investigate the relationship between subjective and objective assessment of asthma we have developed a portable coded peak flow meter. This incorporates a turbo-flow transducer with peak detect electronics. It is linear when calibrated against a pneumotachograph for steady-state and artificial peak flows, whereas the Wright's peak flow meter is alinear, and its comparison with the Wright's meter was validated in 100 outpatients. Twelve subjects with variable asthma were asked to record subjective assessment of their asthma on a visual analogue scale (VAS) followed by three consecutive PEFR measurements, at least three times a day for four weeks. They used a coded and an uncoded peak flow meter for two two-week periods, in randomised order. Analysis of variance of the relationship between VAS and PEFR showed significant differences ($p < 0·01$) in the subjective assessment of asthma between the coded and uncoded periods in six subjects—five being more acutely aware of the variability of their asthma during the uncoded period. In eight subjects the linear correlation between VAS and PEFR was greater when an uncoded meter was used, and in four subjects there was no difference. We suggest that knowledge of recent PEFR measurement can alter the subjective assessment of asthma.

Are medical staff any better at using inhalers than patients?

AJ FREW, JTM MACFARLANE Although pressurised aerosol inhalers are widely used, some patients do not gain full benefit because of incorrect technique. It is generally agreed that inhaler technique should be checked regularly, but do medical staff themselves know the correct technique? Inhaler technique was assessed prospectively using a placebo pressurised inhaler in 79 consecutive patients attending for lung function testing and also in 101 doctors (52 general practitioners, 49 hospital doctors), 59 trained nurses from medical wards, and 18 hospital pharmacists. Technique was scored using a simple five-point assessment. Seventy-five per cent of the patients had correct technique; the commonest problem was failure to co-ordinate inhaler activation and inspiration in 19% of patients. Thirty per cent of the patients had not been shown initially how to use an inhaler and 57% (30 of 53 asked) had not had their technique subsequently checked. The majority of patients with poor technique were successfully reinstructed. Correct technique was found in only 28% of doctors, 22% of nurses, and 17% of pharmacists. The commonest problems were failure to shake the canister and to hold their breath after inhalation; other comparisons will be discussed. Inhaler technique should be checked in patients, but also in medical staff who teach them.

A follow-up study of pneumoconiosis in miners and ex-miners

CA SOUTAR, W MACLAREN A follow-up study of British coalminers has been completed in order to compare the effects of exposure to dust in men who continue to work in the coal industry and in those who leave, and to examine changes in the appearances of the chest radiograph occurring after men have left the industry. A sample of men working in the coal industry in the 1950s has been traced and examined 22 years later. Prevalences of simple pneumoconiosis among 7073 men at follow-up were generally higher among men who left the industry than those who stayed. These differences were partly accounted for by the higher cumulative dust exposures experienced by those who had left the industry, and the quantitative relationship between dust exposure and simple pneumoconiosis was similar in men who left and men who stayed. Progressive massive fibrosis (PMF) was more likely to develop in older men and in men with simple pneumoconiosis at the start of the period, though it could rarely occur in men without simple pneumoconiosis. PMF frequently occurred after

men had left the industry and were no longer exposed to dust, and was much more common among men who had left the industry than among men who stayed in it.

Interstitial lung disease in hard-metal workers: bronchoalveolar lavage, ultrastructural and analytical findings

AG DAVISON, PL HASLAM, B CORRIN, II COUTTS, A DEWAR, WD RIDING, AJ NEWMAN TAYLOR We have investigated three hard-metal workers with interstitial lung disease. The duration of exposure before the onset of symptoms varied between 17 months and 15 years. One man at work mixed the raw materials (cobalt and tungsten carbide); the other two ground the sintered hard metal. Two patients had a restrictive ventilatory defect. The third patient had nodular shadowing on the chest radiograph, but had an obstructive ventilatory defect and an asthmatic reaction provoked by cobalt. Bronchoalveolar lavage cell counts demonstrated a high percentage of macrophages with refractile particles in two patients, and bizarre multinucleate giant cells in one patient. Open lung biopsy in the two patients who had restrictive ventilatory defects showed interstitial pneumonia with giant-cell features. Electron microscopy of the lung demonstrated that the multinucleate giant cells comprised both type II pneumocytes and multinucleate macrophages, whereas in the lavage only multinucleate macrophages were identified. Tungsten, titanium, and tantalum, but not cobalt, were demonstrated in both lung tissue and bronchoalveolar lavage cells.

Radiographic effects in workers engaged in man-made vitreous fibre production

HANS WEILL, JANET HUGHES, YEHIA Y HAMMAD, HENRY W GLINDMEYER, GIL SHARON, ROBERT N JONES A study of respiratory health of workers engaged in man-made vitreous fibre (MMVF) production included 1028 men employed in seven fibrous glass and mineral wool plants, which were categorised by fibre diameter (> 3 μm, 1–3 μm, < 1 μm). Health assessment was by respiratory questionnaire, ILO (1980) classification chest x-ray readings, and complete pulmonary function testing. The study population was found to be generally healthy with respiratory symptoms not convincingly related to the man-made vitreous fibre exposure, and no detected adverse lung function consequences of that exposure. X-ray readings revealed low-category profusion of small opacities: 94 (10%) with profusion $\geq$ 0/1, six with profusion 1/1, none higher than 1/1. Correlated with the presence of small opacities were some of the function measurements, which showed a decreasing trend with increasing profusion level. No film had large opacities; less than 2% had pleural abnormalities. Probability of small opacities was significantly related to age and smoking. After accounting for non-exposure-related influences, probability of small opacities was found to be related to certain fibre exposure indices, notably fine-diameter exposure, and among current smokers duration of employment, average concentration, and cumulative dose. It is uncertain, however, whether this is the result of dust deposition alone (for example, dust macule) or in conjunction with an early adverse tissue reaction (for example, fibrosis). In the absence of intermediate and higher-level profusion of small opacities in a population with a considerable range of exposure duration, a diffuse tissue reaction in association with MMVF dust inhalation seems unlikely but cannot yet be excluded.

A standardised method for assessing carbon monoxide transfer on exercise

E NEVILLE, AH KENDRICK, GJ GIBSON Ingram *et al* (*Thorax* 1982;**37**:129–32) found the relationship between CO transfer coefficient (K_{CO}) and heart rate on progressive exercise more sensitive than resting measurements in assessing patients with sarcoidosis. We have measured K_{CO} in normal subjects exercising on a bicycle ergometer to assess variability and to standardise a technique for use in patients. Preliminary studies showed that if K_{CO} was measured immediately after pedalling ceased it was appreciably lower than if the subject continued exercising. Reducing the breath-holding time to six seconds made measurements during heavy exercise more comfortable without affecting the K_{CO}. Studies were performed in 50 normal subjects at rest and at three different work loads maintained for three minutes with a pause of five minutes between each. Ventilation, heart rate, and expired gas concentrations were recorded continuously. The relationships between K_{CO} and heart rate, oxygen uptake, work load, and minute ventilation were linear. The slope of the relationship between K_{CO} and oxygen consumption (or work load) was steeper in women than in men (0·620 and 0·349 mmol min^{-1} $kPa^{-1}l^{-1}$ per 1 min^{-1} respectively). The heart rate also rose more steeply in relationship to $\dot{V}O_2$ in women so that the relationships of K_{CO} to heart rate were similar (0·0103 ± 0·0022 mmol min^{-1} $kPa^{-1}l^{-1}$ per beat). Repeated studies on a small group of subjects gave coefficients of variation for these slopes between 5% and 10%.

Blood lactate and respiratory muscle fatigue in patients with chronic airways obstruction

NT COOKE, SH WILSON, S FREEDMAN In normal subjects sustained maximum ventilation (SMVV) raises blood lactate levels by 1–2 mmol/l (Cobley *et al. J Physiol* 1981;**315**:35P) and we expected a comparable increase in patients with chronic airways obstruction. We studied five such patients with FEV_1 ranging from 0·72 to 1·34 litres. Each performed a standard 12-minute walk and 10-minute SMVV with end-tidal P_{CO_2} kept constant. Standard force frequency curves of the sternomastoid muscle (Carswell *et al. Thorax* 1981;**36**:717) were carried out before and after each experiment to assess respiratory muscle fatigue. We also measured ventilation during a walk on a treadmill at the same speed and heart rate as the 12-minute walk. Ventilation on SMVV and the treadmill walk both averaged about 70% of predicted maximum breathing capacity. Four patients developed low-frequency fatigue of the ster-

nomastoid after the 12-minute walk and three of them had an increase in blood lactate. After SMVV all patients had low-frequency fatigue but none of them had an increased lactate. Ventilation in these patients is limited by airways obstruction to a level at which the aerobic working capacity of the respiratory muscles is not exceeded.

Pulmonary emphysema: a comparison of alpha-1-antitrypsin-deficient patients (Pi phenotypes Z and SZ) with patients of normal phenotype

JA HUGHES, MJ TOBIN, BJ GRAY, PJL COOK, DCS HUTCHISON Homozygotes for the Z α_1-antitrypsin (AT) phenotype have 10–20% of normal serum AT concentration and heterozygotes of type SZ 30–40% of normal. In a multicentre survey, we identified 166 type Z subjects (126 "index" cases and 40 "non-index") and 25 type SZ subjects (14 index and 11 non-index); they have been compared with 140 emphysematous patients of normal phenotype. In type Z subjects radiological emphysema was found in 66% of non-index cases and in 65% of subjects who had never smoked; in type SZ subjects and in those of normal phenotype emphysema was virtually confined to smokers. Type Z index cases were younger by six years ($p < 0.001$) than non-deficient cases, but lung function was significantly worse. Type SZ index cases were older than non-deficient cases by six years ($p < 0.01$) but there was no difference in lung function. The ratio of Z to SZ index cases was 9:1 in the survey; the UK population ratio is 1:7. SZ cases are therefore similar to non-deficient cases of emphysema and the SZ phenotype appears to carry little or no extra risk.

Inhibition of exercise-induced asthma by an orally absorbed mast-cell stabiliser (M&B 22,948)

ROBIN RUDD, ANDREW GELLERT, PETER STUDDY, DUNCAN GEDDES M&B 22,948 (2-*o*-propoxyphenyl-8-azapurin-6-one) is 30 times as potent as disodium cromoglycate (DSCG) in inhibiting allergen-induced mediator release from sensitised human lung tissue in vitro. In a double-blind placebo-controlled crossover trial we examined the effect of a single oral dose of 10 mg of M&B 22,948 on asthma induced by exercise and by histamine, each in 12 patients with asthma. Compared with placebo the drug significantly inhibited the fall in FEV_1 induced by exercise on a treadmill ($p < 0.005$). The maximum fall in FEV_1 was less following M&B 22,948 than placebo in all patients and the fall was inhibited by more than 50% in five (42%) of the 12 patients. The degree of inhibition was significantly correlated with the plasma concentration of M&B 22,948 ($r = 0.65$, $p < 0.025$). Compared with placebo M&B 22,948 had no significant effect on the dose of inhaled histamine required to produce a 20% fall in FEV_1 (PC_{20}). There was no relationship between the plasma drug concentration and the difference in PC_{20} after active drug and placebo. M&B 22,948, like DSCG, inhibits asthma induced by exercise but not by histamine in a dose that has no bronchodilator effect. M&B 22,948 merits evaluation in the therapy of asthma.

Recognition of a characteristic laryngeal abnormality as a cause of dysphonia in patients receiving inhaled corticosteroids for asthma

AJ WILLIAMS, MS BAHGAT, PM SHENOI, RM CAYTON, DE STABLEFORTH, C SKINNER Inhaled corticosteroids have a well-established role in the treatment of asthma. Side effects include candidiasis and dysphonia. A causal relationship between candidiasis and dysphonia has been suggested. In previous studies ENT examination of the patients has been incomplete. We have examined by indirect and direct laryngoscopy and voice recordings nine patients (six male) aged 61 ±8 years, who presented with severe and persistent dysphonia. Eight patients were receiving aerosol corticosteroid:beclomethasone dipropionate (five patients); budesonide (two patients), and betamethasone valerate (one patient). One patient was receiving beclomethasone dipropionate inhaled as a dry powder. A characteristic bilateral adductor vocal cord abnormality ("bowing" on phonation) was observed in all patients. Only three patients were judged to have candidiasis, with laryngeal involvement in two of these. Discontinuation of the inhaled corticosteroid led to return of normal phonation and vocal cord mobility over a period of weeks or months. Resumption of inhaled corticosteroid in one patient led to a recurrence of the vocal cord abnormality and dysphonia in four weeks. In conclusion, dysphonia in patients receiving inhaled corticosteroids usually occurs without candidiasis and is due to a distinctive laryngeal abnormality, which is probably the result of a local steroid myopathy.

Steroid resistance and bronchial asthma

TW EVANS, P HOWARD A number of patients with severe bronchial asthma require high maintenance doses of prednisolone (more than 10 mg daily) for the control of breathlessness. It is questioned whether these high doses are required because of deficient absorption through the gut, increased metabolism of steroid necessitating increased amounts for their further effect, or end-organ insensitivity. After a test dose of 20 mg oral prednisolone serum prednisolone concentration was measured on seven occasions in the ensuing 12-hour period in normal subjects, non-steroid-taking asthmatics, and prednisolone-dependent asthmatics. Peak serum concentration and peak-time measurements did not differ significantly between the three groups, giving no evidence for deficient steroid absorption. A number of patients on high maintenance doses of prednisolone had significantly smaller areas under their serum concentration-time curve, suggesting increased metabolism of ingested steroid. It is possible that this is a factor in clinical insensitivity to ingested steroids displayed by some patients with bronchial asthma.

Hyposensitisation to Dermatophagoides pteronyssinus in perennial rhinitis

AD BLAINEY, MJ PHILLIPS, S OLLIER, RJ DAVIES Although hyposensitisation with extracts of *Dermatophagoides*

pteronyssinus is widely used in the treatment of asthma and rhinitis, conflicting reports of its effectiveness make its role uncertain. A randomised, double-blind, placebo-controlled trial of a tyrosine-adsorbed extract of *D pteronyssinus* has been carried out in patients with perennial rhinitis in whom allergy to *D pteronyssinus* was confirmed by nasal provocation testing, and who had responded poorly to topical corticosteroids. Patients received six weekly injections, followed by monthly injections for one year. Symptoms were recorded daily using diary cards, and response was assessed objectively by measuring changes in nasal airway resistance after provocation with *D pteronyssinus* allergen. Forty-four patients entered the study; nine were withdrawn before completing the first six injections. Of the remainder, 17 received active injections and 18 received placebo. At three months, symptoms had improved in both groups but peak NAR after challenge had fallen significantly only in the group receiving active treatment. After one year, symptom scores in both groups remained similar, but nine patients had withdrawn from the control group before completing one year of therapy, compared with only three from the active group. This difference was statistically significant.

Comparison of oxitropium bromide and ipratropium bromide in asthma

E'G ANDERSON, ET PEEL, B CHEONG, N BRODERICK Parasympathetic blockade is one method of treating asthma. Oxitropium bromide is a scoline derivative which protects against acetylcholine-induced bronchospasm. In this study its effects in asthma were compared with those of ipratropium bromide and placebo. Twenty-four atopic asthmatics received on three consecutive days, in randomised double-blind fashion, inhalations of placebo, oxitropium bromide 200 μg and ipratropium bromide 80 μg. Peak expiratory flow rate (PEFR) measurements were made before the inhalers were taken and at intervals up to 10 hours afterwards. Twenty patients had data suitable for analysis. For both active drugs PEFR levels were significantly higher than baseline between 10 minutes and 10 hours. There were no significant differences between PEFR values for the active drugs. Side effects were minimal with both active drugs. Oxitropium bromide is an effective bronchodilator with a prolonged duration of action.

Irradiated autologous tumour cells with percutaneous BCG in resectable lung cancer

BHR STACK, N McSWAN, JM STIRLING, DJ HOLE, WGS SPILG, CR GILLIS, I McHATTIE, JA ELLIOTT, RG WHITE, MA TURNER Immunological tests were performed before and after operation on 83 patients with lung cancer, all of whom received a single treatment with percutaneous BCG (Glaxo) one week before operation. After randomisation at the time of operation, autograft patients received serial injections of irradiated autologous tumour cells and BCG over a three-week period. From actuarial life tables, the projected three-year survival for patients with stage I tumours was 67% (autograft group) and 44% (controls) ($p = 0.09$); for DNCB-positive patients it was 69% (autograft group) and 25% (controls) ($p = 0.02$). The median survival times of stage I patients calculated for the first 36 months were >36 months (autograft group) and 17 months (controls) ($p = 0.07$). Similar figures were obtained for freedom from tumour recurrence after operation. Although the graphs for survival and freedom from tumour recurrence of all the autograft patients were better than those of the controls, the difference was not significant. The main immunological effect was a significant increase in tuberculin reactivity between seven weeks and 11 months after operation ($p < 0.05$). The results suggest that adjuvant specific immunotherapy may delay or prevent tumour recurrence in patients with stage I tumours and in DNCB-positive patients.

Single-agent high-dose cyclophosphamide with autologous bone marrow transfusion (ABMT) as initial treatment for small-cell carcinoma of the bronchus (SCCB)

RL SOUHAMI, PG HARPER, DC LINCH, AH GOLDSTONE, JDM RICHARDS, C TRASK, JS TOBIAS, SG SPIRO, DM GEDDES Twenty-one previously untreated patients with SCCB have been treated with very high doses of cyclophosphamide with ABMT. Eighteen patients had limited disease and three extensive, age range 39–69 years (mean 52 years). Bone marrow was harvested and cryopreserved prior to chemotherapy with cyclophosphamide (total dose 160–200 mg/kg) in divided doses on four consecutive days. Urothelial toxicity was prevented by MESNA (2-mercapto-ethane sodium sulphonate). Two weeks after bone marrow recovery the response was assessed by chest x-ray examination and bronchoscopy. Radiotherapy was given (40 Gy) to the primary site in 20 daily fractions. No further chemotherapy was given until relapse. Response assessed prior to radiotherapy gave a complete response in 12 patients (normal chest x-ray film and bronchoscopy in seven and a normal chest x-ray film, bronchial narrowing, but negative biopsy in five), a partial response in five, and no response in four. Follow-up is now 12 months (range 2–20 months), and median duration of response is 39 weeks. Median survival has not been reached. Haematological toxicity is predictable but easily manageable, with profound neutropenia lasting 8–18 days (median 11·8 days), and platelet count below $50{\cdot}0 \times 10^9$/l. High doses of cyclophosphamide can be given safely and a single cycle is associated with a high response rate. The disease-free interval is comparable with cyclical chemotherapy. Results may be improved by combination with other agents and repeated treatments.

Miliary tuberculosis in south and west Wales (1976–8)

RDH MONIE, AM HUNTER, KAREN ROCCHICCIOLI, JANINE WHITE, IA CAMPBELL, GS KILPATRICK In a retrospective survey of 1000 cases of tuberculosis 28 patients (2·8%) had miliary spread. Seventeen patients (61%) had miliary shadows on the chest radiograph, seven (25%) had radiographic changes suggestive of pulmonary tuberculosis, and

four (14%) had a normal radiograph. Twenty-one (75%) were male and 50% were 60 years or over. Ten patients (36%) were alcoholics or receiving steroids or immunosuppressives at the time of diagnosis. Positive cultures were obtained in 22 patients (79%). In four of the remaining six patients no specimens were sent for culture. Nine patients (32%) died, three of whom were diagnosed at necropsy. The chest radiographs of three patients who died showed miliary shadowing but consideration of alternative diagnoses resulted in delay in diagnosis. The only haematological abnormalities related to the tuberculosis infection seemed to be a normochromic normocytic anaemia (25%) and neutrophil leucocytosis (14%), fewer abnormalities than noted by Proudfoot *et al* (*Br Med J* 1969;ii:273–6). A low plasma sodium was seen in one-third of patients, 44% were hypoalbuminaemic and a third had raised liver transaminases. Of 12 patients who completed chemotherapy, only four received it for 18 months. There have been no relapses within the area surveyed.

Comparison of the Mantoux, Tine and Imotest tuberculin tests

ROBIN RUDD, ANDREW GELLERT, MICHAEL VENNING We compared the Tine and Imotest multiple-puncture tuberculin tests with the Mantoux test in 200 subjects. All received a standard Mantoux test (10 IU Weybridge PPD intradermally) and either a Tine (OT) or Imotest (PPD) simultaneously to the other forearm. Tests were read after 72 hours by two independent observers. The false-negative rate for the Mantoux test was estimated by immediate repetition of the Mantoux in subjects with an initially negative Mantoux but a positive multiple-puncture test. The sizes of reactions to the Tine and Imotest were correlated with that of the simultaneous Mantoux ($r = 0{\cdot}70$, $p < 0{\cdot}001$ in each case). Regression relationships indicated that 2 mm of induration to either Tine or Imotest is equivalent to 5 mm of induration to the Mantoux test. Taking 2 mm as positive did not result in any false-positive multiple puncture tests. The false-negative rate for the Imotest was 27%, significantly higher than the 4% for the Tine and 5% for the Mantoux ($p < 0{\cdot}001$). There was concordance between readers in interpretation of 98% of all tests and there were no significant differences between testers in frequency of false-negative results for any test. The Research Committee of the British Thoracic Association reported a high frequency of false-negative reactions and poor reproducibility with the Tine test. These disappointing results are attributable to poor technique in applying the tests and interpretation of reactions of 2–4 mm as "doubtful". The Tine test, when carefully applied and correctly interpreted, is a reliable tuberculin test. The Imotest has a higher false-negative rate than the Tine test and is more difficult to use.

Retrospective study of Mycobacterium kansasii infection in Wales (1970–9)

JOHN BANKS, AM HUNTER, IA CAMPBELL, PA JENKINS, AP SMITH Thirty-five patients with pulmonary infection caused by *Mycobacterium kansasii* have been reviewed, of whom 88·5% were male. In 66% there was evidence of pre-existing lung disease, chronic bronchitis/emphysema accounting for half of these disorders. In only 17% was there any evidence of occupational exposure to dust or fumes, and only three patients were coalminers. Unilateral lesions were present in 69% of patients whose chest *x*-ray films were reviewed and 90% had cavitating disease. The development of unilateral or bilateral disease appeared to be independent of any delay in starting treatment and bore no relationship to the presence, or absence, of pre-existing lung pathology. Five patients died while receiving treatment, but none of these deaths were due to *M kansasii* infection. The remaining 30 patients were successfully treated with drug regimens which included rifampicin. There was 100% sputum conversion with no relapses after a mean follow-up period of five and a half years. Rifampicin plus ethambutol, given for a mean period of 15 months, appeared to be a non-toxic, effective combination.

Notification of tuberculosis: a code of practice for England and Wales

KM CITRON, JANET DARBYSHIRE A number of ambiguities and inaccuracies in the notification procedures for tuberculosis in England and Wales were revealed by a recent national survey of notifications (Medical Research Council. *Br Med J* 1980;**281**:895–8). In consequence the Joint Tuberculosis Committee has prepared a recommended code of practice. This takes into account the revised system for the submission of statistical returns by medical officers for environmental health (MOsEH) to the Office of Population Censuses and Surveys (OPCS) introduced in January 1982. The recommendations, summarised here, will be discussed. *The clinician*—(1) Every effort should be made to ensure that notifications are made for all patients suffering from tuberculosis. (2) All sites involved in tuberculosis should be recorded on the notification form. (3) Cases of chemoprophylaxis should not be notified on the standard form. (4) If the diagnosis is changed from tuberculosis to a non-tuberculous disease, the MOEH should be informed. (5) If a patient who has had tuberculosis develops a new episode of disease a new notification should be made. *The MOEH*—A system for recording all notifications received should be kept and each notification checked against it in order to identify duplicates. If there is doubt whether a second notification is a duplicate or a new notification of a new episode of disease, the MOEH should contact the clinician to clarify the position.

Emphysema in coalworkers and non-coalworkers

A COCKCROFT, RME SEAL, JC WAGNER, JP LYONS, R RYDER, N ANDERSSON A postmortem survey of emphysema in coalworkers and non-coalworkers was carried out. It was determined that in men between 50 and 70 years dying of ischaemic heart disease (IHD) selection to necropsy was similar in coalworkers and non-coalworkers and such men were included in the study. All lungs were examined in a standard way and the amount of emphysema was scored on

a numerical scale. This incidental emphysema in men dying of IHD was of greater frequency in the coalworkers than the non-coalworkers. The difference was significant at the 0·01% level and remained after age and smoking habits were taken into account by stratification. In the coalworkers the amount of emphysema was related to the amount of dust in simple dust foci in the lungs. Because both groups were selected similarly from their parent populations the relative frequency of emphysema in this study reflects that in the whole populations of coalworkers and non-coalworkers in the study area. The excess of emphysema found in the coalworkers supports previous findings (Ryder R *et al. Br Med J* 1970;iii:481–7) and seems likely to be due to occupational factors.

Evaluation of a new pocket-sized device for measurement of FEV_1 and FVC

PJ CHOWIENCZYK, CP LAWSON, PNE JAMES, GM COCHRANE Monitoring of peak expiratory flow rate at home using a Wright mini-peak flow meter has proved useful in assessing response to treatment in patients with asthma (Webb J, Chilvers C. *Thorax* 1981;**36**:18–21). In chronic bronchitis and emphysema, however, peak flow measurements may underestimate the response to treatment (Bellamy D, Hutchinson DCS. *Br J Dis Chest* 1981;**75**:90–96). In these patients FEV_1 and FVC are more important measurements. We have developed a pocket-sized instrument for measuring FEV_1 and FVC designed for use by patients at home. The instrument, which is based on a commercially available turbine flow transducer (PK Morgan Ltd, Rainham, Kent), is battery powered and provides a digital display of the measurements. Accuracy of this "turbine spirometer" has been assessed by placing it in series with an Ohio spirometer (Ohio Inc, Texas). Three measurements were made on each of 29 subjects having a wide range of FEV_1 and FVC values (FEV_1 range 0·4–4·8 l; FVC range 0·9–6·2 l). The mean percentage difference between the FEV_1 readings was 1·1% and the standard deviation of the difference 3·7%; for FVC these values were 0·7% and 4·3% respectively. The greatest differences observed were 10% for FEV_1 and 12% for FVC. The clinical applications of this new accurate pocket-sized spirometer will be demonstrated.

Treatment of acute severe asthma with intravenous aminophylline and nebulised ipratropium bromide after salbutamol

MJ WARD, JT MACFARLANE, D DAVIES In acute severe asthma an earlier study (Ward *et al. Br Med J* 1981;**282**:598) showed that nebulised ipratropium bromide given two hours after salbutamol produced considerable additional bronchodilatation, the mean PEFR rising by 96% within four hours. Whether this was due to combining drugs which act in different ways or to the effect of sequential inhalations has now been investigated. Twenty-four asthmatics (PEFR < 25% predicted, Pao_2 < 9·3 kPa) were allocated at random to double-blind treatment. Thirteen had 10 mg of nebulised salbutamol on admission and again two hours later. The PEFR rose from 92 to 128 l/min after the first treatment and to 139 l/min after the second. The response to the second treatment was not significant. Eleven patients had 10 mg salbutamol on admission and 500 μg ipratropium bromide two hours later. The PEFR rose from 93 to 145 l/min after salbutamol and to 179 l/min after ipratropium. The response to ipratropium was significant ($p < 0·001$). A second study investigated the value of giving aminophylline as well as nebulised bronchodilators. Twenty-seven patients were allocated at random to receive either (*a*) intravenous aminophylline (6 mg/kg followed by an infusion 0·5 mg/kg/h) and nebulised salbutamol on admission followed two hours later by ipratropium or (*b*) intravenous saline and nebulised salbutamol on admission and ipratropium two hours later. The addition of aminophylline did not improve the response.

Use of nebulisers to administer beta-agonists in hospital: a questionnaire study

JN STAINFORTH, RA LEWIS, AE TATTERSFIELD The use of a nebuliser to administer beta-agonist drugs has increased recently in hospital. A questionnaire was sent to 94 chest physicians to establish how frequently nebulisers are used in hospital and to determine how they are used. All of the 66 physicians replying (70%) used nebulisers to administer beta-agonists in hospital and 80% used a nebuliser more than 10 times per month. The drugs used were salbutamol (71%), terbutaline (18%), or both and the dose most commonly prescribed was 5 mg for salbutamol (range 2·5–12·5 mg) and 5 mg for terbutaline (range 2·5–10 mg). The beta-agonists were usually diluted with saline, administered via a facemask, and run to dryness. The Inspiron "Mini-neb" was used most commonly (62%). Flow rates varied from 1 to 10 l/min and diluent volumes from 0 to 10 ml. Our own studies with the Mini-neb have shown a residual volume of 0·6 ml after nebulisation to dryness. The diluent volume therefore becomes important; for example, when 2·5 mg salbutamol is diluted in 0·5 ml diluent only 1 mg will leave the nebuliser; in contrast, when 10 mg salbutamol is diluted in 5 ml diluent 9 mg will leave the nebuliser. Thus there is probably a nine-fold variation in the amount of drug leaving the nebuliser in clinical practice. Further variations in administered dose may be attributed to the wide range of flow rates since this is known to affect particle size leaving the nebuliser. Variations in the way nebulisers are used have considerable implications for the amount of drug delivered to the patient.

Steroid-responsive relapsing cryptogenic organising pneumonitis

AG DAVISON, BE HEARD, WAC McALLISTER, M TURNER-WARWICK In organising pneumonia small buds of connective tissue ("bourgeons conjunctifs") occur in the alveoli; they indicate organisation of a persistent exudate by fibroblasts and capillaries from the alveolar walls. Organising pneumonia was characteristically seen in the preantibiotic era following non-resolution of an infective pneumonia.

We report five patients with such histology in whom no evidence of an infective or other aetiological agent could be found. They characteristically presented with severe dyspnoea, cough, malaise, and weight loss. The mean age was 57. Symptoms had been present for two months or less in four patients. Radiologically bilateral homogeneous shadowing was present in four and bilateral poorly defined opacities in the other. Four had pleural shadowing. The mean erythrocyte sedimentation rate in one hour was 77. Prednisolone produced rapid relief of symptoms and substantial clearing of the radiological shadowing. However, as the dose of prednisolone was reduced or stopped relapse occurred and the radiological shadowing increased. Control was re-established with increased prednisolone, again with remarkable clearing of the radiological shadowing. As no aetiological factor could be identified for the intra-alveolar organisation, and in order to avoid confusion with classical post-infective organising pneumonia, the term cryptogenic organising pneumonitis is suggested. The relapse and subsequent response to steroids is difficult to explain on an infective basis.

Asthma and cigarette smoking

ROGER LOWRY Many asthmatics are exquisitely sensitive to the effects of inhaled tobacco smoke. A less well-known phenomenon is the onset of asthma for the first time in people who have recently stopped smoking. Farmers and bird fanciers who smoke may have a lower incidence of allergic alveolitis than non-smokers. Experimental work in animals and humans has shown that cigarette smokers have altered immune function. Pulmonary alveolar macrophages from smokers do not respond to migration-inhibitory factors. Nine patients have been collected who give a history of asthma commencing shortly after giving up cigarettes. Data will be presented to show the effects of a trial period of smoking on two of these patients. Peak expiratory flow rates were measured for a period before, during, and after smoking cigarettes. During the smoking period symptoms and signs of asthma resolved and there was a statistically significant improvement in peak expiratory flow rates. When smoking was stopped, symptoms and signs returned and there was a deterioration in peak expiratory flow rates. All other therapy was withheld during the trial period.

Catamenial pneumothorax

BA ROSS Three patients with catamenial pneumothorax are presented (a postal survey of many thoracic surgical centres in the United Kingdom having been carried out). One patient will be described in detail, together with operative photographs and photomicrographs of biopsy material. The theoretical causes of this rare condition and the association of pneumothorax with endometriosis are discussed. Treatment is by surgical pleurodesis.

Improved technique for excision of giant lung bullae

HR MATTHEWS, K HASHEMI Excision of giant lung bullae commonly results in a persistent air leak, which delays recovery and requires prolonged intercostal drainage. To minimise this we have used Teflon felt to buttress the suture line and secure pneumostasis in five male patients, aged 54–65, one having an infected bulla at the time of operation. This is performed through a standard thoracotomy with a double-lumen endotracheal tube. When the chest is opened the affected lung is deflated so that the bulla becomes an empty sac. The line of excision across its base is selected and a strip of ⅛-inch felt placed on either side of it. Horizontal mattress sutures are then inserted through both layers of felt and both walls of the bulla and tied securely. The bulla is excised and suturing completed by a continuous over-and-over suture, again through all four layers. All patients made an uneventful recovery with an average drainage period of only three and a half days. Follow-up extends from six months to four years, with no evidence of any adverse reaction to the felt. The technique appears to reduce postoperative air leak and is also useful in other procedures where the lung substance has to be incised.

Preoperative staging of carcinoma of the bronchus using computed tomography (CT) scanning and mediastinoscopy.

PG GOLDSTRAW, M KURZER, D EDWARDS Forty-four patients with a known or presumed diagnosis of bronchogenic carcinoma underwent preoperative CT scanning and cervical mediastinoscopy with or without left anterior mediastinotomy prior to thoracotomy. The ability of CT scanning to predict mediastinal node involvement or mediastinal invasion was compared with the assessment given by mediastinoscopy and these figures were studied overall and in upper and lower lobe subsets. When mediastinal node involvement was assessed the sensitivity and specificity of CT scanning was seen to be inferior to that of mediastinoscopy overall (57% and 86% versus 71% and 100%) and for upper and lower lobe subsets (56% and 79% versus 78% and 100%, 60% and 93% versus 60% and 100%). The sensitivity with which CT scanning predicted mediastinal invasion (77%) was superior to that for mediastinoscopy (46%) and this was especially marked for lower lobe tumours (67% versus 17%). However, mediastinoscopy retained the considerable advantage of 100% specificity. In those subgroups where CT scans showed a normal mediastinum or demonstrated enlargement of the hilar glands only, mediastinoscopy conferred no additional information and could be omitted in this subgroup. A CT scan showing mediastinal abnormalities is an indication for mediastinoscopy and not a contraindication to surgery.

Prediction of lung function after pneumonectomy for bronchial carcinoma

DA ELLIS, T HAWKINS, GJ GIBSON, S NARIMAN It has been suggested that lung function after pneumonectomy can be estimated from the preoperative perfusion lung scan. We have assessed the accuracy of prediction using both perfusion and ventilation scans in 13 patients undergoing pneumonectomy for bronchial carcinoma. Lung volumes

and carbon monoxide diffusing capacity (TLCO) were measured before and six months after surgery. Perfusion scans using ^{99m}Tc labelled microspheres and ventilation scans using both ^{81m}Kr and ^{133}Xe were obtained. Following pneumonectomy the mean fall in FEV_1 was 0·68 l, VC 1·22 l, and TLCO 1·63 mmol min^{-1} kPa^{-1}. Postoperative function was estimated from each scan using the number of radioactive counts over each lung as follows: Postoperative function = preoperative function × contribution of non-affected lung ÷ total counts. FEV_1 and VC were estimated with reasonable accuracy (r for relationship of estimated to measured value 0·85 and 0·83 respectively). Prediction of TLCO was less accurate (r = 0·76); the postoperative value was underestimated in patients with substantial function in the lung removed, presumably because of diversion of blood to the remaining lung. Estimates of postoperative function from perfusion or ventilation scans were similar, but prediction using ^{133}Xe was least accurate. Lung scanning can predict postoperative function with sufficient accuracy to be useful in the assessment of patients who may require pneumonectomy but who are at risk of postoperative disability because of poor lung function.

Does platelet-activating factor mimic the dual response to allergen?

GS BASRAN, CP PAGE, W PAUL, L WOOD, J MORLEY, M TURNER-WARWICK Certain allergic asthmatics exhibit dual responses in skin or lung following intradermal or bronchial challenge respectively with the appropriate allergen, but the mechanisms underlying this phenomenon are not clearly established. Platelet-activating factor (PAF-acether) is a phospholipid which has been characterised and recently synthesised. In addition to being a platelet-activating agent it is also a powerful bronchoconstrictor and is released by IgE-dependent mechanisms from basophils and alveolar macrophages and from activated neutrophils and platelets. It has recently been reported that platelet activation takes place in asthmatics during antigen challenge (KA Knauer *et al. N Engl J Med* 1981;**304**:1404) and that products from activated platelets produce delayed responses in human skin (RP Day *et al. J Allergy Clin Immunol* 1975;**55**:87). We have studied the inflammatory actions of PAF-acether in skin of man (using a method described by GS Basran *et al* (*Lancet* 1982, in press) and skin and lung of experimental animals (using radioisotopic techniques). In man, intradermal PAF-acether induced biphasic cutaneous responses which mimicked in time the dual response to allergen. In experimental animals, PAF-acether produced inflammatory oedema and cell infiltration in lung and in skin. In addition to platelet-dependent bronchoconstrictor effects, our results indicate that PAF-acether also has powerful inflammatory actions in man and animals. We suggest that PAF-acether exhibits properties appropriate to a mediator of both acute and persistent inflammation and asthma.

Neutrophil chemotactic factor (NCF) in exercise- and hyperventilation-induced asthma

T NAGAKURA, TH LEE, B ASSOUFI, DM DENISON, AJ NEWMAN TAYLOR, AB KAY A circulating NCF, with the same physicochemical properties as antigen-induced NCF, has been identified in atopic asthmatic subjects following treadmill exercise. NCF release was inhibited by prior administration of disodium cromoglycate, suggesting that this activity might be mast-cell-associated. The initiating stimulus for exercise-induced asthma (EIA) appears to be respiratory heat exchange (RHE) and a similar degree of bronchoconstriction can be produced by isocapnic hyperventilation (ISH) with cold air. We have therefore compared the appearance of NCF after exercise and ISH in five atopic asthmatics, to assess whether the RHE was the stimulus for NCF release. There was a rise in the concentration of circulating NCF in all asthmatics following exercise, but in ISH under conditions which produced a comparable fall in FEV_1 NCF was not detected. This rise in NCF following treadmill tasks was accompaned by a post-exercise basophilia, a feature that was not observed following ISH. Nevertheless, when the release of NCF in asthmatics with EIA {EIA(+)} was compared with that of asthmatics without EIA {EIA(−)}, after an identical exercise task, the rise in NCF was three times greater in EIA(+) subjects despite a similar postexercise basophilia. These observations, together with those of others, indicate that EIA and ISH differ in several respects: EIA is associated with a lag phase, a refractory period, a basophilia, and a basophil-independent elaboration of circulating NCF, whereas these do not occur with ISH-induced asthma.

Effects of nifedipine on antigen-induced bronchoconstriction

AF HENDERSON, RW HEATON, LS DUNLOP, JF COSTELLO Contraction of smooth muscle and degranulation of mast cells are calcium-dependent processes. We have investigated the effects of the calcium antagonist nifedipine on antigen-induced bronchoconstriction in vivo and in vitro. Eight grass-pollen-sensitive asthmatics aged 19–31 years were given either nifedipine (20 mg sublingually) or placebo 30 minutes before antigen challenge. The fall in FEV_1 after pretreatment with placebo was 42·8 ± 10·1%. After nifedipine this fall was significantly reduced to 26·5 ± 11·7% ($p < 0·005$). Two in vitro models of allergic asthma have been studied—actively sensitised guinea-pig tracheal strips (GPT) and passively sensitised human bronchial muscle (HBM). Tissues were suspended in organ baths and contractions recorded via isotonic transducers. Contraction of GPT by acetylcholine, histamine, and antigen challenge was unaffected by nifedipine 0·1 mmol/l. Contraction of HBM by acetylcholine, histamine, and grass-pollen-antigen challenge was significantly reduced by nifedipine 0·1 mmol/l and 1μmol/l. The magnitude of the reduction in contraction to antigen challenge was comparable to the inhibition of acetylcholine and histamine responses. It would appear most likely that nifedipine exerts its effect mainly on bronchial muscle contractility rather than by stabilising mast cells.

Bronchial response to cold air: evidence for a different mechanism in normal and asthmatic subjects

RW HEATON, AF HENDERSON, BJ GRAY, JF COSTELLO We have studied the effect of isocapnic hyperventilation with

subfreezing air in a group of 12 asthmatic and 10 normal subjects. Bronchial responses to the challenge were determined by measuring the change in forced expired volume in the first second (FEV_1) and specific airways conductance (sGaw). To investigate the refractory period to cold air the procedure was repeated 40 minutes after the initial challenge. The effects of predosing the subjects with disodium cromoglycate (DSCG) 40 mg and ipratropium bromide (IPTB) 36 μg were also studied. The asthmatic subjects were more sensitive than the normals, requiring a lower level of ventilation and showing more profound falls in FEV_1 and sGaw and slower recovery. Neither group showed a refractory period to cold air challenge. In the normal subjects the fall in FEV_1 and sGaw following cold air was completely abolished by IPTB, whereas DSCG had no effect. In the asthmatics both drugs provided significant protection, but neither completely abolished the response. We conclude that in normal subjects the bronchial response to cold air is purely a neural reflex. Asthmatics show an additional, cromoglycate-sensitive response, and thus differ in the mechanism of their response to cold air, as well as being more sensitive to the stimulus.

The mast cell and basophil in exercise-induced bronchoconstriction

PH HOWARTH, GJ-K PAO, MK CHURCH, ST HOLGATE As controversy exists over the role of mediator release from mast cells in exercise-induced bronchoconstriction we investigated this further. Seven normal and seven atopic asthmatic subjects were exercised on a treadmill and specific airway conductance (sGaw) and plasma and total blood histamine (H) levels and white blood cell counts (WBC) were followed for two hours afterwards. On a separate day the asthmatic subjects underwent matched isocapnic hyperventilation (IH). After exercise sGaw fell, in both normal and asthmatic subjects, by 8·0 ± 3% (1 SEM) and 61 ± 5% of baseline respectively, with a comparable fall after IH. Both resting plasma and total blood H levels, measured by a sensitive enzymatic radiotransfer assay, were higher in asthmatic than normal subjects—5·23 ± 0·58 *v* 3·15 ± 0·63 nmol and 847·0 ± 143 cf 643·0 ± 74·3 nmol/l respectively; basophils from asthmatic subjects also had a higher spontaneous histamine release, 13·40 ± 2·0% *v* 6·46 ± 0·71% ($p < 0·001$). The higher total blood H levels and increased spontaneous basophil release could account for the increased plasma H levels observed in asthma, since plasma and total blood H were shown to correlate ($p < 0·01$) and total blood H is basophil derived. Following exercise and IH there were no significant changes in plasma H levels, but exercise caused an immediate increase in the total blood H and WBC not seen with IH. We suggest that plasma histamine is mainly derived from basophils and therefore is not a good marker of pulmonary mast cell degranulation.

Histamine and circulating basophil levels in exercise-induced asthma

DJR MORGAN, MJ PHILLIPS, I MOODLEY, RJ DAVIES Ten atopic asthmatics were subjected to a standard exercise test. The mean fall in FEV_1 from the pre-exercise value was 26%. Ten non-atopic, non-asthmatic control subjects were similarly exercised: their mean fall in FEV_1 was less than 2%. Arterial plasma histamine (PH), whole blood histamine (WBH), neutrophil chemotactic factor (NCF), and circulating basophil levels were measured. Histamine was assayed by a single isotopic radioenzymatic assay. Pre-exercise PH levels were significantly higher in asthmatic subjects. Following exercise a significant elevation of PH, WBH, and NCF occurred within the first hour in asthmatic subjects, but similar changes for PH and WBH were also found in the control group. Basophil counts rose significantly following exercise and were significantly correlated with WBH ($p < 0·0001$). Barnes *et al* (*Clin Sci* 1981;**61**:159) reported a significant difference in PH levels between asthmatics and controls following exercise, attributed to a more sensitive double isotopic radioenzymatic assay. We studied changes in PH following exercise in five asthmatic and five control subjects using their assay, but were unable to show any significant differences. We conclude that there is no evidence to support the suggestion that mast-cell mediator release is involved in the pathogenesis of exercise-induced asthma, and that observed changes in mediator levels following exercise are likely to relate to changes in levels of circulating basophils.

Efficiency of jet nebulisers in the production of therapeutic aerosols

MICHELLE CLAY, D PAVIA, SP NEWMAN, SW CLARKE Although jet nebulisers are widely used to deliver therapeutic aerosols in pulmonary disease, there are few data available to indicate their output characteristics or optimum operating conditions. Four commonly used types of nebuliser were studied: Acorn, Upmist, Turret, and Inspiron. Both size distribution and aerosol output varied with air flow rate through the device. At 8 l/min the mass median diameter of the aerosol was smaller and the output was larger than at 4 l/min. Output in all nebulisers fell from the initial level during the first few minutes of neublisation. This was accompanied by a 10°C drop in the reservoir solution temperature, which increased the surface tension and viscosity. Thereafter output remained constant until the solution volume had fallen to about 2 ml. Below this level output was further reduced and the final 1–2 ml, comprising droplets entrained on the internal structures of the nebulisers, could not be released as aerosol. This "dead volume" was directly related to the initial volume admitted but independent of flow rate. It could be reduced by intermittent nebulisation. These results suggest that the volume of respirator solution admitted should not be less than about 4 ml to achieve a satisfactory aerosol volume; instructions with several respirator solutions suggest using only 2 ml. Furthermore, the flow rate of compressed air through the nebuliser should be about 8 l/min to obtain an aerosol of appropriate therapeutic size.

Comparison of response to beta-agonists given by nebuliser, IPPB, and modified pressurised aerosol

JF O'REILLY, DR BUCHANAN, MF SUDLOW The relative efficacy of bronchodilators given by nebuliser, intermittent

positive-pressure breathing (IPPB), and metered aerosol is unclear in patients with chronic stable asthma. A metered aerosol fitted with conical spacer (CS) may improve lung deposition and produce greater bronchodilatation than a nebuliser. We have compared responses to a bronchodilator given by nebuliser, IPPB, and CS in nine patients with chronic stable asthma (mean % predicted FEV_1 53·3%). Patients inhaled cumulative doses of terbutaline (0·5, 1, 2, and 4 mg) by each technique in random order on separate days. Bronchodilator response was assessed by FEV_1, FVC, and maximal expiratory flows at 30% and 40% VC ($\dot{V}_{30}$ and $\dot{V}_{40}$). Mean baseline measurements on the different days did not differ significantly. Dose-response curves for FEV_1 and FVC were similar with all the techniques. Dose-response curves for $\dot{V}_{30}$ and $\dot{V}_{40}$ were similar for IPPB and CS but mean maximal $\dot{V}_{30}$ and $\dot{V}_{40}$ with CS were significantly greater than with nebuliser ($p < 0·05$, Student's paired t test) at cumulative doses of 1·5 and 3·5 mg respectively. These results suggest that bronchodilator doses given by CS are as effective as those from IPPB and may penetrate into peripheral airways more effectively than those from a nebuliser.

Bronchodilator efficacy of nebulised salbutamol and ipratropium bromide in chronic airflow obstruction

PH HOWARTH, JN STAINFORTH, ST HOLGATE The efficacy of nebulised salbutamol (S) and ipratropium bromide (IB), alone and in combination, were investigated in 12 patients with severe chronic airflow obstruction. Their mean age was 65 years and baseline pulmonary function as a percentage of predicted was FEV_1 35 ± 3% (± 1 SEM), FVC 65 ± 7%, PEFR 32 ± 3%, and T_{LCO} 45 ± 6%. While the patients were having no other bronchodilator therapy, increasing doses of S (1·25–10 mg) and IB (0·5–2·0 mg) were administered by inhalation from Inspiron mini-nebulisers (8 l/min), and PEFR was measured 10 minutes after each inhalation. Both S and IB caused a dose-dependent increase in PEFR approaching a plateau with 10 mg S (36·0 ± 7·5% increase ± 1 SEM) and plateauing with 1 mg IB (29 ± 6·0%). In a randomised study, single inhalations of equipotent concentrations of S (5 mg) and IB (1 mg) produced maximal increases in PEFR at 2 hours of 33·0 ± 6·0 and 35·0 ± 6·0% of baseline, with decay to 6·5 ± 5·5% and 14·5 ± 4% respectively at 7 hours. When S (5 mg) and IB (1 mg) were inhaled in combination the peak response was slightly greater at 2 hours (40·0 ± 5·5%), but bronchodilatation persisted so that at 7 hours PEFR was still 25·5 ± 6·0% above baseline. Thus the prolonged course of action of nebulised ipratropium bromide and salbutamol in combination would produce maximum bronchodilatation with a twice-daily dose regimen in patients with chronic airflow obstruction.

Development of polycythaemia after intermittent exposure to hypoxia in rats

JC MOORE-GILLON, IR CAMERON Polycythaemia may develop in chronically hypoxic patients, and is observed in some individuals with sleep apnoea. If polycythaemia in this latter group is attributable to short hypoxic episodes, then it must be assumed that such intermittent stimuli are sufficient to induce erythropoiesis and sustained polycythaemia. We have investigated this assumption in the rat. Rats maintained hypoxic (12% inspired O_2) for 28 days develop increased right ventricular weight, pulmonary artery pressure, and packed cell volume (PCV). We have exposed rats ($n \geq 11$ in each group) to hypoxia for small proportions of each 24-hour cycle. After 28 days PCV was assessed by a microhaematocrit method and red cell mass (RCM) calculated using a ^{51}Cr-labelled erythrocyte dilution technique.

Hours hypoxic/day	*PCV% (mean ± SEM)*	*RCM ml/100 g body wt (mean ± SEM)*
0	42·4 ± 0·3	2·02 ± 0·05
2	44·1 ± 0·3	2·27 ± 0·05
4	46·8 ± 0·2	2·38 ± 0·05
24	51·5 ± 0·3	2·76 ± 0·08

PCV and RCM were significantly greater ($p < 0·005$, Student's t test) in all the hypoxic groups than in the normoxic controls. It is concluded that hypoxia for periods as short as two hours each day may result in significant polycythaemia.

Slow-release metoprolol in chronic bronchitis

ET PEEL, G ANDERSON, G CHAPPELL In a double-blind crossover study 17 patients with chronic bronchitis (MRC criteria) and airways obstruction were given 200 mg slow-release metoprolol per day and placebo in two one-week periods separated by a one-week washout period. Assessments were made at the end of each period and consisted of peak expiratory flow rate (PEFR) and spirometry, with reversibility to 200 μg salbutamol. Despite adequate beta-blockade (as assessed by reduction in resting pulse rate) there was no significant change in PEFR after metoprolol. The mean FEV_1 dropped from 1264 ml to 1218 ml ($p = 0·03$)—that is, a reduction of 3·6%—and the mean FVC from 2384 ml to 2250 ml (5·6%) ($p = 0·01$). There was no change in the response to inhaled salbutamol. Only one patient experienced an increase in wheeze associated with a modest (10%) drop in FEV_1 and PEFR. Subsequent investigation demonstrated that he was in fact asthmatic. It is concluded that metoprolol is safe to use in chronic bronchitis and that it does not affect responsiveness to sympathomimetic bronchodilators.

A new nasal oxygen mask

JE HARVEY, BJ SCHLECHT, LJ GRANT, CR TOTTLE, AR TANSER Continuous domiciliary oxygen therapy is usually administered with nasal prongs, which are said to be well tolerated and to remain in position during use (MRC Working Party, *Lancet* 1981;i:681). Some of our patients find the prongs uncomfortable and experience in hospital shows that they do not always stay in place. We have devised a new nasal mask and have compared this with nasal prongs by measuring end-tidal oxygen concentrations with a mass spectrometer and changes in arterialised capil-

lary oxygen tension. In 15 normal subjects oxygen was administered through each device for 10 minutes at a flow rate of 2 litres per minute. End-tidal oxygen concentration at the mouth increased from 16 ± 0·8 (mean ± SD) to 22·5 ± 2·5% with the mask and from 15·8 ± 1·0 to 24·5 ± 2·9% with the prongs ($p < 0.005$). In 13 patients with chronic airflow obstruction (mean FEV_1 0·9 l) there was no significant difference in the increases in end-tidal oxygen concentration after one hour's oxygen administration (15·1 ± 0·6 to 23·7 ± 1·6% mask; 15·3 ± 0·7 to 25·5 ± 2·5% prongs). There was also no significant difference in the increases in arterialised oxygen tension in these patients (8·0 ± 1·6 to 11·5 ± 2·2 kPa mask; 8·2 ± 1·5 to 12·2 ± 2·6 kPa prongs). The relative comfort of each device was assessed during the study and during prolonged (22 hours') use. Some patients preferred the mask and others the prongs, though neither device proved more popular overall. The new mask is a useful alternative to conventional prongs.

Down with the bad lung

P HELMS, DP HEAF, H TURNER, I GORDON We have observed the effects of posture on the distribution of perfusion, ventilation, and pulmonary gas exchange in 11 infants with unilateral lung disease, either congenital diaphragmatic hernia or unilateral consolidation and collapse. Measurements of transcutaneous oxygen (Tc P_{O_2}) and carbon dioxide (Tc P_{CO_2}) were made (Roche, Kontron) with in vivo calibrations at the beginning and end of each study. Supine, left, and right lateral postures were assumed in random order with 10 minutes in each position; all studies were performed in duplicate. The effects of posture on the distribution of ventilation and perfusion were assessed using ^{81m}Kr and ^{99m}Tc lung scans. Reference values were obtained in the supine posture, when the effects of gravity on each lung are equal. In the lateral position variable changes in Tc P_{O_2} were observed (range 8–105%) with smaller changes in Tc P_{CO_2} (range 3–20%). In all but three subjects Tc P_{O_2} was reduced when the better lung was dependent. Perfusion was distributed towards and ventilation away from the dependent lung. These changes are the reverse of those found in adult subjects. Body posture can be used to improve ventilation-perfusion matching in infants with unilateral lung disease. The distribution of ventilation in response to gravity is quite different in the infant from the adult subject, a consequence of the reduced distending pressure around the lung in infancy. More attention should be given to the effects of posture on pulmonary gas exchange, particularly in the neonatal period when arterial oxygen tension is critical.

Bronchoalveolar lavage in lung transplantation

JR PEPPER, MN WHITELAW, P GIGLI, P HASLAM Bronchoalveolar lavage was performed on normal and transplanted lungs of dogs that had received autografts or allografts without immunosuppression. The lavage fluid was used for a total cell count, differential cell count, and analysis of *N*-acetyl-β-glucosaminidase (NAG). The percentage of neutrophils (N), macrophages (M), lymphocytes (L), and eosinophils (E) from transplanted (left) and unoperated (right) sides are given. Allografts showed a progressive fall in the proportion of macrophages in the left lung compared with the right.

% cell counts in allografts: mean ± SEM (No of dogs = 6)

	Left			
Day:	0	2	4	7
N	4·6 (±0·7)	41·4 (±9·1)	28·9 (±11·9)	42·9 (±12·9)
M	63·4 (±5·4)	40·3 (±8·9)	47·7 (±9·4)*	43·1 (±5·8)*
L	11·1 (±1·3)	4·6 (±1·1)	6·3 (±3·0)	9·9 (±3·1)
E	18·6 (±5·3)	3·7 (±1·7)	7·6 (±6·3)	12·2 (±4·1)

	Right			
Day:	0	2	4	7
N	5·4 (±0·9)	32·6 (±14·9)	19·3 (±2·1)	19·2 (±4·4)
M	66·3 (±5·5)	54·2 (±12·2)	63·0 (±3·1)*	69·4 (±5·1)*
L	14·0 (±3·3)	6·5 (±2·3)	5·7 (±1·9)	9·4 (±2·3)
E	12·5 (±3·9)	4·0 (±2·6)	4·9 (±1·3)	7·2 (±1·9)

* = $p < 0.05$.

In autografts there was no significant difference in differential counts between operated and unoperated sides. NAG was estimated in serum and lavage fluid. It was not a reliable indicator of rejection. Differential cell counts on bronchoalveolar lavage specimens may be useful as an indicator of lung allograft rejection.

Is pulmonary surfactant abnormal in adult lung disease?

PETER BOFFA, CHARLES HILL, BETTY BROWN, COLIN MORLEY, TIM HIGENBOTTAM Deficiency of surfactant in the lungs of newborn infants leads to respiratory distress syndrome. No comparable deficiency has been established in adult lung disease. For this reason, as a preliminary study, we have surveyed during life pulmonary surfactant in over 50 patients suffering a variety of lung diseases and values were compared with pulmonary surfactant from neonates. Surfactant was obtained by means of bronchial lavage using 30 ml of normal saline instilled into a segmental bronchus at bronchoscopy (performed for clinical indications). Phospholipids were identified from the cell-free lavage fluid by separation into component parts by 2-D thin-layer chromatography and quantified by phosphorus content after acid digestion. This analysis was performed blind. Chest radiographs and lung function were obtained in each patient. Phospholipid composition of pulmonary surfactant in patients with clear radiographs and normal lung function was similar to that found in neonates with normal lungs. Patients with pneumonia and asthma had reduced levels of

phosphatidyl choline by comparison with normal subjects, but patients with fibrosing alveolitis and granulomatous lung disease had normal levels. These observations may have importance for our understanding of alveolar and small-airways stability in different lung diseases and of how different disease processes influence the function of type II pneumocytes.

Effect of nicotine on pulmonary epithelial permeability in man

BD MINTY, D ROYSTON, JG JONES We have developed an index of pulmonary epithelial permeability based on the half-time clearance from lung to blood (T½LB) of the hydrophilic chelate ^{99m}TcDTPA, mol wt 492 daltons (Jones *et al. Lancet* 1980;i:66). Using this index we have demonstrated that cigarette smokers have an increased pulmonary epithelial permeability, which is significantly correlated with the carboxyhaemoglobin concentration (COHb) (Minty *et al. Thorax* 1981;**36**:709). This does not necessarily imply that carbon monoxide is the cause of this increase in permeability, nor is there evidence to indicate which of the toxic components of the smoke may induce this change. The aim of the present study was to show whether nicotine by itself had any adverse effect on epithelial permeability. Five healthy non-smoking volunteers chewed one piece of chewing gum containing 2 mg nicotine (Nicorette, Lundbeck Ltd) every hour for 12 hours for seven days. The method of chewing was that recommended on the product data sheet. This dose regimen should achieve plasma nicotine levels similar to those of a moderate cigarette smoker. Baseline measurements of pulmonary epithelial permeability were made on all subjects prior to the start of the study and then after one, three, and seven days of nicotine administration. Blood was taken for measurement of nicotine concentration immediately after the ninth piece of chewing gum on days 1, 3, and 7. There was no change in pulmonary epithelial permeability for the seven-day study period. The mean baseline T½LB was 56 ± 2·7 min (SEM) compared with 55 ± 3·1 min (SEM) following seven days of nicotine administration. This lack of effect of nicotine is in striking contrast to the increase in epithelial permeability observed in two non-smoking subjects who took up cigarette smoking. After three days one subject showed a change in T½LB from 65 min to 44 min (peak COHb 1·8%) and the other from 68 min to 32 min (peak COHb 4%). Within two days of stopping smoking both subjects' T½LB had returned to their baseline values.

Respiratory disturbances during sleep in kyphoscoliosis

EH SAWICKA, MA BRANTHWAITE, GT SPENCER Disturbances of respiration during sleep have been reported in patients with severe kyphoscoliosis and may contribute to or cause cardiorespiratory failure. Ten patients with kyphoscoliosis of varying aetiology and moderate-to-severe deformity (Cobb angle 66–131°) were studied during sleep. Their vital capacity ranged from 15% to 56% of predicted; one patient had had an episode of cor pulmonale and one was in respiratory failure at the time of study. Recordings of the following were made on each patient: expired CO_2 at the nose, gas flow at the mouth, oxygen saturation, chest wall movement, EEG, EOG, and ECG. Disturbances of respiration during sleep were similar regardless of the aetiology of the kyphoscoliosis. The major abnormality was hypoventilation with a rise in the end-tidal P_{CO_2} and reduction in frequency and amplitude of chest wall movement. In all patients this occurred in REM sleep, while in three patients there was a progressive rise in end-tidal P_{CO_2} through NREM sleep also. Nine patients showed falls in oxygen saturation in REM sleep, and two showed falls in NREM sleep as well. Episodes of apnoea were uncommon, and could not account for all the hypoxaemic episodes. The major abnormality of respiration during sleep in kyphoscoliosis is hypoventilation and is of sufficient magnitude to be an important contributory factor to the development of cor pulmonale.

Overnight sleep deprivation decreases ventilatory drive

NJ DOUGLAS, DP WHITE, JV WEIL, CK PICKETT, CW ZWILLICH Patients with asthma or chronic bronchitis and emphysema are often kept awake all night during exacerbations of their disease. The effect of such sleep deprivation on ventilatory drive is unknown. We have therefore studied the effect of 24 hours of sleep deprivation on the isocapnic hypoxic and rebreathing hypercapnic ventilatory responses in nine healthy men. As both the hypoxic and hypercapnic drives decrease during sleep, measurements were made during electroencephalographically confirmed wakefulness. Sleep deprivation significantly decreased both the hypoxic (control 1·42 ± 0·32 (SEM), sleep deprived 0·96 ± 0·20 l/min/% Sa_{O_2}; $p = 0·05$) and the hypercapnic ventilatory responses (control 17·6 ± 1·9, sleep deprived 12·0 ± 1·5 l/min/kPa CO_2; $p < 0·001$). Thus overnight sleep deprivation resulted in a one-third decrease in ventilatory drive. This might contribute to the clinical deterioration of patients who are unable to sleep because of exacerbation of their airways obstruction.

A controlled trial of six months' chemotherapy in pulmonary tuberculosis—second report: results up to 24 months following the end of chemotherapy

AR SOMNER, JH ANGEL, KM CITRON (for the BTA Research Committee) Two six-month regimens of isoniazid and rifampicin, supplemented for the first two months by streptomycin and pyrazinamide or by ethambutol and pyrazinamide, were compared with a nine-month regimen of isoniazid and rifampicin supplemented for the first two months by ethambutol. All 444 patients who completed chemotherapy had negative sputum cultures by the end of treatment. Adverse reactions were not a problem. Hepatitis occurred in 4% of patients who received pyrazinamide (SHRZ6 and EHRZ6) and 4% of patients in the regimen without pyrazinamide (EHR9). Three hundred and ninety-three patients have been followed up for 24 months after the end of chemotherapy. Relapse has

occurred in one of 125 SHRZ6 patients, three of 132 EHRZ6, and two of 136 EHR9 patients. These observations suggest that six months' chemotherapy with these regimens is as effective as the currently recommended nine months' regimen and has the advantages of being shorter and cheaper while being equally well tolerated.

Treatment of tuberculous pyopneumothorax

AG NORMAN Pyopneumothorax is an uncommon complication of pulmonary tuberculosis. A computer printout of references to this condition obtained from the Sheffield University library gave only two titles over the last 10 years, both in Russian. Five cases of this condition have been encountered recently. All the patients were quite ill when first seen and were initially treated medically by antituberculous drugs and tube drainage. After this treatment thoracotomy and decortication were performed. No lung resections were carried out. Initial lung expansion was not ideal and a bronchopleural fistula has persisted in some cases at first. However, long-term results have proved acceptable in these cases.

Adverse effects of rifampicin on prednisolone disposition

WAC McALLISTER, PJ THOMPSON, S AL-HABET, HJ ROGERS Rifampicin is a well-known inducer of hepatic microsomal enzymes, which may cause a serious reduction in plasma concentration of concomitantly administered drugs metabolised in the liver. Prednisolone, which undergoes hepatic metabolism, and rifampicin are often used in combination in respiratory patients when tuberculosis is suspected in addition to a steroid-sensitive disease or where the diagnosis is unclear. We have therefore studied the pharmacokinetics of prednisolone in eight patients to establish and quantify the effect of rifampicin on prednisolone metabolism. At 08.00 fasted subjects were given 20 mg of prednisolone *BP* and plasma samples were taken over the ensuing eight hours for measurement of plasma prednisolone concentration by thin-layer chromatography. Studies were performed once when subjects had been taking rifampicin regularly for at least a month and on a second occasion either before rifampicin was started or at least a month after therapy was discontinued. Plasma prednisolone concentrations were used to calculate pharmacokinetic data, which revealed a 50% ($p = 0{\cdot}001$) increase in prednisolone clearance and a 50% ($p = 0{\cdot}001$) reduction of prednisolone available to the tissues (area under plasma concentration time curve) in all patients while on rifampicin. These very significant changes may render prednisolone ineffective and indicate that the prednisolone dose should be at least doubled in the presence of rifampicin.

Adult community-acquired pneumonia: a hospital study of its causes and outcome

JT MACFARLANE, RG FINCH, MJ WARD, D DAVIES The few studies of pneumonia in Britain over the last 25 years have consistently found a large proportion of patients in whom no aetiological agent can be identified. We studied 127 consecutive adult patients (< 80 years) admitted to the City Hospital, Nottingham, with primary pneumonia over 13 months. Particular emphasis was placed on specimen collection using invasive techniques as appropriate, complete serological follow-up, postmortem examination, and the use of countercurrent immunoelectrophoresis (CIE) for the detection of pneumococcal antigen in specimens. An aetiological diagnosis was made in 97% of the 127 patients studied. Pneumococcal pneumonia was diagnosed in 76% of patients. Legionnaires' disease was the second commonest infection identified (15% patients), and included three atypical legionella infections. Other bacterial infections were uncommon but usually severe. Eleven patients had "atypical" pneumonia, including seven with psittacosis. There were several mixed infections and the majority of the 11 patients with viral infections also had bacterial pneumonia. Nineteen patients died (15%) and mortality varied widely with the cause of the pneumonia. The recognition of the causes of severe pneumonia allows a logical initial antibiotic therapy for such patients admitted to hospital.