Thorax 1984;**39**:687–720

Proceedings of the British Thoracic Society

The 1984 summer meeting of the British Thoracic Society was held on 4–6 July at the Hotel Metropole, Brighton

Undertreatment of asthma in general practice

CR HORN, GM COCHRANE The persistent failure of modern drugs to reduce the excessive death rate from asthma may be the result of undertreatment of patients. We studied 120 patients in two general practices to determine the adequacy of their treatment. Only 50% of the patients had normal spirometric results and in over 20% they were below 50% of predicted values. Worsening spirometric values was associated with a considerable increase in reported morbidity ($r = -0{\cdot}4$: $p < 0{\cdot}001$). The use of therapy was significantly correlated with increasing severity of asthma, subjects with an FEV_1 within normal limits using, on average, 1·2 drugs compared with 2·4 drugs per subject among those with an FEV_1 less than 50% predicted ($p < 0{\cdot}001$). Despite this only 50% of those with an FEV_1 below 50% predicted were having an inhaled steroid and fewer than 50% took β agonist inhalers on a regular basis. Theophylline preparations were taken by 44% of subjects in this group but only one patient (9%) had a therapeutic plasma level. Although there is some encouragement from these results, more treatment being received by patients with the worst airflow obstruction, they still reveal gross undertreatment of many patients with resultant excessive morbidity and possible mortality.

Seasonal variation of asthma deaths in England and Wales

A KHOT, R BURN About 150 deaths in the 5–34 age group in England and Wales are registered every year as being due to asthma. A seasonal variation was noted by Inman and Adelstein *Lancet* 1969;ii:279–85 but this has received little attention The monthly variation in deaths attributed to asthma in the 5–34 age group were examined for England and Wales, over the period 1960–82. Deaths were most frequent in the third quarter (July–Sept) and peaked in August. Analysis of the 1970–82 period shows that this variation is present in the three constituent age groups (5–14, 15–24, 25–34) but is most marked in the 5–14 year olds. Closer scrutiny of the three years 1980–82 suggests that the summer rise is not due to deaths occurring on holidays away from home and there is some evidence that deaths cluster temporally. Since the well documented increase in mortality in the 1960s there has been little alteration in yearly trend, the average monthly death rate remaining at around 6 per 10 million. A minimal increase has occurred in the last few years. The seasonal variation and possible clustering need further evaluation to assess the importance of exogenous triggers and social and medical care factors.

Trends in acute respiratory illnesses in general practice

J AYRES Since 1975 the Royal College of General Practitioners research unit has received weekly returns from 41 general practitioners (population covered about 200 000) throughout the United Kingdom recording weekly attendances for acute respiratory and infectious diseases. There is a wide range of variability in the incidence and prevalence rates from different practices in any one year. However, the data can be used to show trends, as each GP has been shown to be a highly consistent diagnostician. Hayfever attack rates (all ages) peaked at around week 25 (1981–3) (mean peak rate 217/100 000). Asthma attack rates (all ages) showed no regular pattern, although in years 1976, 1979, 1981, and 1983 both summer and autumn peaks were seen. For 1983 asthma attack rates in the diagnostically "clean" 15–44 age group show an increase from 10 to $38/10^5$ in early July. Acute bronchitis attack rates (all ages) show a January peak and August nadir in every year (1976–83). This is partly explained by a summer fall in attendances for all diseases. There were isolated weekly falls in rates during holiday weeks. These data are excellent for assessing trends in acute respiratory illnesses in general practice and can be compared with hospital attendance figures.

I gratefully acknowledge the work and advice of the Birmingham Royal College of General Practitioners Research Unit.

Progesterone in chronic asthma

RW HEATON, M BRINCAT, J STUDD, J MOXHAM Progesterone is a naturally occurring steroid hormone with anti-inflammatory properties. Unlike corticosteroids it is anabolic. Progesterone acts as a membrane stabiliser to relax uterine and vascular smooth muscle. A similar action on bronchial smooth muscle could be of value in the treatment of chronic asthma and anecdotal observations suggest that this is so. We report a double blind, controlled study of the effects of progesterone in a group of male and female patients with chronic asthma. Natural progesterone was administered as an orally absorbed micronised preparation. All subjects had severe chronic asthma and were prednisolone dependent. Progesterone and identical placebo were administered in randomised fashion in two week crossover periods. Patients measured morning and evening peak expiratory flow rates and kept daily diary cards of symptoms. Ten subjects took progesterone 100 mg twice daily; 10 took 200 mg twice daily; and seven took 300 mg twice daily. Although some patients improved the mean

peak expiratory flow rate for the groups did not rise.

Minitracheotomy and jet ventilation: a new method of ventilatory support

HR MATTHEWS, B FISCHER, RB HOPKINSON Conventional methods of artificial ventilation have significant disadvantages, resulting from the presence of a cuff in the trachea, the need for sedation, the complications of tracheostomy, or the discomfort of an endotracheal tube. We have therefore combined the techniques of minitracheotomy (*Br J Surg* 1984;**71**:147–50) and jet ventilation, to provide a system that allows full access to the trachea for suction and ventilation while avoiding the need for a cuff, sedation, or endotracheal tube. Up to March 1983 four patients have been treated for respiratory failure with this technique; two were male and ages ranged from 66 to 77 years; three had acute complications of chronic obstructive airways disease and one had cardiorespiratory failure following abdominal surgery. Ventilation was performed for periods ranging from 12 hours to 8 days, using the Penlon ventilator and a modified minitracheotomy tube, inserted through a stab incision in the cricothyroid membrane and retained for 7–17 days. Two patients made an uneventful recovery and two died from irreversible respiratory disease. Our experience with these patients indicates that the combination of mini-tracheotomy and jet ventilation is technically satisfactory and may offer important advantages over conventional methods of ventilation.

Effect of diaphragmatic plication in unilateral diaphragmatic paralysis

J WILLIAMS, CD WRIGHT, RJ DONNELLY, CM OGILVIE The effect on pulmonary function of diaphragmatic plication is reported in seven patients with non-malignant unilateral diaphragmatic paralysis (four left sided and three right sided). Plication was performed by imbricating the diaphragm in layers. The results tabulated below were obtained immediately before and six weeks after operation.

	Mean (SEM) values	
	Before plication	*After plication*
Total lung capacity (l)	3·99 (0·43)	4·48 (0·48)**
Vital capacity (l)	2·25 (0·26)	2·72 (0·28)**
Expiratory reserve volume (l)	0·46 (0·08)	0·77 (0·07)**
Functional residual capacity (l)	2·20 (0·31)	2·42 (0·38)*
Residual volume (l)	1·73 (0·24)	1·76 (0·29)
Pa O_2 (kPa)	10·00 (0·67)	11·00 (0·54)*
Pa CO_2 (kPa)	5·40 (0·17)	5·20 (0·21)
Diffusion coefficient (KCO)	6·28 (0·41)	5·82 (0·50)

*$p < 0.05$; **$p < 0.01$

After plication there was a significant increase in PaO_2 and all lung volumes except residual volume. A significant decrease was recorded in breathlessness on a visual analogue scale (graded 0–10) after plication (9(0·4) *v* 3 (0·9), $p < 0.01$). There were no postoperative complications and mean hospital stay was 12 days (range 10–15 days). Diaphragmatic plication is a safe and effective procedure for symptomatic adult patients with unilateral diaphragmatic paralysis.

Pulmonary transmission and emission computed tomography in patients becoming breathless after radiotherapy

P GODDARD, JA BULLIMORE, ER DAVIES, II COUTTS, A MITCHELMORE After radiotherapy to the chest some patients develop breathlessness. This breathlessness does not correlate well with the extent of radiation pneumonitis or fibrosis seen on plain chest films. Computed tomography (CT) and/or emission CT of lung perfusion was studied in 16 patients with pulmonary fibrosis due to radiotherapy. Features accompanying the fibrosis were sought. In eight of the patients a considerable decrease in pulmonary vessel size or perfusion was demonstrated throughout the affected lung. This was not confined to the area of fibrosis. The decrease in pulmonary vascularity was greatest when the hila were affected by fibrosis and least when the fibrosis affected only peripheral lung. In addition to compensatory and scar emphysema, obliteration of pulmonary arteries in the field of radiation (progressive vascular sclerosis) results in decreased vascularity of the area being supplied. There was a considerable decrease in lung volume in 10 of the 16 patients. Overall only four patients out of the 16 were devoid of pulmonary abnormalities outside the radiation field. It is postulated that changes outside the direct field of radiation have a profound effect on pulmonary function.

Computed tomography and bronchiectasis

J OSMAN, IM MOOTOOSAMY, RA REZNEK, RSO REES, MALCOLM GREEN Bronchography is the generally accepted technique for defining the extent of bronchiectasis. We have investigated the potential role of computed tomography (CT) of the lung in this condition. Seven patients with clinical bronchiectasis had chest radiographs and bilateral bronchograms assessed for lobar and segmental abnormalities by an independent consultant radiologist. CT was performed on a GE 9800 CT scanner. A second independent consultant radiologist examined the CT scans for the presence of dilated bronchi, bronchial wall thickening (tramline appearances), and cystic changes. Four patients had normal chest radiographs. Bronchographic abnormalities were present in 47 of the individual pulmonary segments studied; abnormalities were detected by CT in 38 of these and in a further eight segments not detected on bronchogram. In all patients CT abnormalities were seen in bronchographically abnormal lobes, although in one lobe this was non-specific consolidation. In a further patient with bronchiectasis CT correlated very closely with the appearances of one lung removed at pneumonectomy and examined in the same planes. CT was preferred to bronchography by all patients. These results suggest that CT of the lungs can play a useful part in the assessment of bronchiectasis.

Effects of long term domiciliary nebuliser treatment

CMB HIGGS, JE HARVEY, P JONES, AR TANSER We studied 20 patients (17 male, 3 female) aged 29–74 years (mean 57·9) with chronic airflow obstruction (14 with chronic asthma) who were being started on domiciliary nebulised bronchodilators. Dose response curves for FEV_1 and FVC using cumulative doses of terbutaline up to 7·5 mg via nebuhaler were recorded before and three and six months after domiciliary nebulisation of terbutaline 5 mg four times a day. At three and six months we assessed symptomatic benefit and took cultures from the equipment. There was no significant difference between (i) baseline FEV_1 or FVC at the start (0·85 (SEM 0·13) l, 2·44 (0·21)l) and at three months (0·82 l, 2·32 l) or six months (0·90 l, 2·42 l) or (ii) between the dose-response curves at the start and at three months or six months. This remained true even for the subgroups with chronic asthma or >20% response in FEV_1 and FVC after terbutaline 7·5 mg. However, 16 patients reported improved effort tolerance after three and six months. Only one patient was less impressed at six months than at three months. Seven patients required less adjuvant therapy. Bacterial cultures were frequently positive, but only for non-pathogenic organisms. We have not demonstrated develoment of β_2-adrenergic resistance. Symptomatic benefit is not supported by improvement in simple lung function tests.

Alpha methyl dopa: its effects on mortality and pulmonary haemodynamics in patients with cor pulmonale

TW EVANS, J WATERHOUSE, AJ SUGGETT, P HOWARD Long term domiciliary oxygen administered for at least 15 hours a day is known to improve survival and reduce the rise of pulmonary artery pressure in patients with cor pulmonale secondary to chronic obstructive airways disease, but is clearly onerous. Alpha methyl dopa has been shown to prevent the anatomical changes and rise of pulmonary artery pressure developing in rats exposed to chronic hypoxia. In this study α methyl dopa was given to patients with cor pulmonale and chronic obstructive airways disease to determine its effects on survival and pulmonary haemodynamics. Twenty five age and sex matched patients were randomly allocated to active therapy or placebo. Long term domiciliary oxygen treatment was equally distributed between the groups. Pulmonary haemodynamics and survival were measured over a period of 14 months. Conventional therapies were continued as needed. There was a significant ($p < 0·005$) improvement in survival in the treated group (11 patients—one death) compared to controls (14 patients—five deaths), although postural hypotension developing in the active group limited the amount of methyl dopa that could be administered. Evidence of the effects of the drug on pulmonary haemodynamics was inconclusive when considered overall but the rise of pulmonary artery pressure with exercise was reversed in over half the active group. No such reversal occurred in the placebo group. In this study improved survival seemed unrelated to abnormalities in pulmonary haemodynamics. Inhibition of circulating catecholamines preventing sudden cardiac arrhythmias may be a plausible explanation for this improved survival.

Primary mediastinal germ cell tumours

H OGUNNAIKE, FC WELLS, JS TOBIAS, MJ PECKHAM, P GOLDSTRAW Non-seminomatous germ cell tumours arising as primaries within the anterior mediastinum are rare, and they are extremely malignant. Historical reports of cure have been anecdotal and death usually results from a failure to control the local disease. Survival has been extended by the use of combination chemotherapy containing cisplatin, with improvement of median survival from four to 14 months. Cure remains elusive. We report our experience with 10 cases treated from 1979 to 1984. Our policy was to stabilise the tumour and obtain normalisation of tumour markers, using chemotherapy followed by surgery to resect residual tumour bulk. In two patients markers failed to normalise and they died six and nine months following diagnosis. In the remaining eight patients chemotherapy caused tumour markers to return to normal. Two of these patients had no residual disease evident on computed tomography scans. Six patients with residual tumour, usually of large bulk, were subjected to surgical excision. There was one postoperative death related to bleomycin lung toxicity. Five patients remain alive and well one to five years (mean 1·8 years) after surgery. We believe that combined modality treatment using chemotherapy followed by radical excisional surgery provides improved survival in this group of tumours.

Twenty years of thymic pathology at a regional cardiothoracic centre

SR LARGE, JM SHNEERSON, PGI STOVIN, J WALLWORK The clinical spectrum and course of thymic disease is not commonly reported. Therefore a retrospective study of thymic pathology at Papworth Hospital over a 20 year period (April 1964 to April 1984) was undertaken. Fifty five patients underwent thymic surgery during this period. Sixty per cent had symptoms. The annual incidence of presentation and frequency of symptoms remained unchanged with time. Of these 55 patients, 44 had tumours (28 thymomas, five with myasthenia gravis and two with red cell aplasia; 9 Hodgkin's disease; four germ cell tumours; and three secondary tumours from bronchogenic primaries). Eleven had cystic lesions (four simple, one foregut, one lymphangiectatic, three dermoid, and two thymomas). The remaining five had follicular hyperplasia (all with myasthenia gravis). Diseases tended to be separated by age: those with hyperplasia had a mean age of 28 years, germ cell tumour 30, Hodgkin's disease 34, cystic lesions 44, thymomas 50, and secondary cancer 60 years. Thirty five of 1580 postmortem examinations during this period showed incidental thymic pathology. Twenty two had previously described involutional changes (Smith SM, Ossa-Gomez LJ. *Am J Clin Pathol* 1981;**76**:657–65). Two patients with hyperplasia died of respiratory infection complicating emphysema, and two of 11 cases with glandular changes were associated with muscular dystrophy. Thymic disease is uncommon, but complete excision carries a good prognosis except for

those with Hodgkin's disease (five year survival 33%).

Bronchoplastic operations

K MOGHISSI During a 13 year period 1119 patients had pulmonary resection for neoplasia. Of these, 133 (11·8%) underwent bronchoplastic operations. They fall into three groups. *Group 1:* 8 patients had bronchoplasty and no pulmonary resection; four had excision of both main bronchi and carina followed by reconstruction. *Group 2:* 73 patients had bronchoplasty following right sided pulmonary resection, of whom 41 had a lobectomy and sleeve resection and the remaining 32 had other types of bronchoplasty; in 18 patients a patch graft of Marlex mesh/pericardium was used, as described by Moghissi (*J Thorac Cardiovasc Surg* 1975;**69**:409–506). *Group 3:* 52 patients had bronchoplasty following left sided pulmonary resection and 26 had upper lobectomy and sleeve resection and 26 others had a vareity of bronchoplasty; 15 patients in this group also had pulmonary artery reconstruction. Hospital mortality was 8·2%. There were four cases of bronchial stenosis without and six with recurrence at the site of anastomosis. Ten-and-a-half per cent of patients had benign and 89·5% malignant tumours; 71% were squamous cell carcinoma. Bronchoplasty achieves economic lung resection. It is, however, difficult to show that in fit patients with good pulmonary function suffering from malignancy it has advantages over more radical surgery.

Surgery for intrathoracic metastatic disease

NTL YEOH, FC WELLS, P GOLDSTRAW Resection of pulmonary metastases to prolong life is now an accepted procedure. We present our experience on the surgical management of intrathoracic metastatic disease in 41 patients, 28 of whom had metastases from testicular teratoma. Two patients had a solitary pulmonary nodule, four had unilateral pulmonary involvement with multiple nodules, and seven patients had multiple nodules in both lungs. Twenty five patients had more than one organ affected by metastases. Patients were initially treated with chemotherapy, and surgery was then used to ablate residual disease. In locating and defining the extent of disease, computed tomography (CT) and chest radiographic findings agreed in 45% of cases. CT underestimated the extent of disease in 37% of patients undergoing thoracotomy. Unilateral thoracotomy was performed in 21 patients. Four patients had bilateral thoracotomies. Eighteen thoracolaparotomies were performed for patients with intrathoracic and intra-abdominal disease, a left, right, or midline approach being used. Twenty seven patients had wedge excisions for their pulmonary nodules while five patients required lobectomies. There was one postoperative death. At the time of writing 22 patients are alive and well with no evidence of any further recurrence at one to 45 months after surgery (mean 22 months).

Incidence and aetiology of a raised left hemidiaphragm after cardiopulmonary bypass

SR LARGE, LJ HEYWOOD, CD FLOWER, R CORY-PEARCE, J WALLWORK, TA ENGLISH A raised left hemidiaphragm has been reported as an uncommon complication of cardiopulmonary bypass. Although a definite cause has not been established it has been suggested by Scannel that it may be due to cold injury of the phrenic nerve. Our method of protection relies in part on profound topical hypothermia. We noted a high incidence of elevation of the left hemidiaphragm after open heart operations. Retrospective review of the chest radiographs of 100 consecutive patients undergoing cardiopulmonary bypass was made. Thirty one had a raised left hemidiaphragm in the early postoperative period. This incidence was related only to aortic cross clamp time (equivalent to the duration of pericardial cold exposure) ($p < 0·03$). A prospective study of 36 consecutive patients undergoing cardiopulmonary bypass was then undertaken with diaphragmatic screening in addition to chest radiography. Preoperative diaphragmatic movement was normal in all. Soon after operation 16 (44%) had developed left hemidiaphragmatic paresis or paralysis, two (5·5%) right paresis, and two (5·5%) bilateral paresis. Six months later repeat screening of these 20 patients showed resolution in all but four. This work has implications with regard to the optimum temperature of the irrigant fluid for myocardial protection during cardiopulmonary bypass procedures.

The risk of malignancy in achalasia

CW PATTISON, HR MATTHEWS To determine the behaviour and characteristics of rare conditions it is necessary to collect information from many clinical sources. We have therefore reviewed 281 cases of oesophageal carcinoma associated with achalasia from 81 reports in the non-communist world literature. The available data on each individual case have been extracted, tabulated, and analysed with reference to many features, particularly age, sex, race, pathology (site, histology, and spread), presenting symptoms, interval between the onset of symptoms of achalasia and the development of a tumour, the effect of treatment for achalasia on tumour development, and the survival after treatment for tumour. Several important conclusions have emerged: (1) there is strong evidence for an aetiological association between achalasia and squamous tumours; (2) there is no evidence of an aetiological association with non-squamous tumours; (3) there is an average interval of 19 (range 0–50) years between the onset of achalasia and the appearance of tumour; (4) this interval is unaffected by treatment for the achalasia, whether by dilatation or operation; (5) screening programmes to detect tumours at an early stage are likely to be time consuming and unproductive and at present cannot be recommended.

Respiratory health of shipyard workers

JE COTES, EL FEINMANN, VJ MALE, F RENNIE During shipbuilding welding in confined spaces may damage the lungs but the evidence is equivocal. Accordingly we sampled the population of one yard and studied 598 men. A respiratory questionnaire, clinical examination, anthropometry, and spirometry were performed; a subsample of 233 men were submitted to more detailed investigation. Radiographs taken two years previously were available for 333 men. Results were submitted to multivariate analysis. Smoking was associated with significant respiratory symptoms and impairment. Independently of smoking, welding was associated with siderosis; there were no demonstrable ill effects. In smokers welding was associated with chronic bronchitis (MRC questionnaire) and airflow obstruction (Cotes JE. *Proc R Soc Med* 1971;**64**:1232); these effects were less than those due respectively to smoking alone and to age. The smoking welders experienced more wheeze, breathlessness, and defective gas transfer than other tradesmen. These features were apparently secondary to chronic bronchitis and were of small magnitude. Caulker burners who smoked experienced similar symptoms. Previous pleurisy, pneumonia, limpet spraying, and metal fume fever were independently associated with abnormality. Overall the occupational factors were not the principal identified causes of respiratory symptoms and impairment in these men.

Pleural effusion and pleural malignancy in former Wittenoom crocidolite millers and miners

WOC COOKSON, AW MUSK, JJ GLANCY, NH de KLERK, BK ARMSTRONG, MST HOBBS Serial chest radiographs of 313 former workers at the Wittenoom crocidolite mine and mill in Western Australia who had applied for compensation for asbestosis or malignant mesothelioma were examined for evidence of pleural effusion or diffuse pleural thickening. Fifty seven pleural effusions were found in 55 men. Twenty seven of these were attributed to benign asbestos pleurisy, 20 to malignant mesothelioma, and 9 to other causes. In one further case follow up was only one year after the effusion and no definite diagnosis had been made. The mean time between the beginning of exposure and onset of effusion was 12·4 years for benign asbestos pleural effusion and 23·3 years for malignant mesothelioma. Diffuse pleural thickening eventually followed benign asbestos pleural effusion in 80% of subjects, but uncommonly preceded either benign asbestos pleural effusion or malignant mesothelioma. The latent period between the start of exposure and onset of disease was strongly negatively correlated with (log) total exposure to asbestos for cases with benign asbestos pleural effusion ($r = -0{\cdot}60$, $p = 0{\cdot}001$) but not for cases with malignant mesothelioma. Most patients with malignant mesothelioma had worked in the mill in contrast to men with benign effusion, who had mostly worked in the mine. There may be a differential effect of fibre dimensions in the pathogenesis of benign and malignant pleural reactions to asbestos.

Development of precipitating antibodies in workers exposed to humidifier fever antigen

MJ FINNEGAN, CAC PICKERING, PS DAVIES, PKC AUSTWICK Factors which determine the development of precipitating antibodies in workers exposed to highly contaminated humidifiers have not previously been studied in detail. Two large work forces (site 1: $n = 206$; site 2: $n = 120$) exposed to such humidifiers have been studied. In most clinical cases of humidifier fever precipitins were present, but this was also true of over 60% of the workers at site 1 and over 40% of the workers at site 2. At both sites we found a strong inverse relationship with smoking ($p < 0{\cdot}0001$) and a strong relationship with duration of exposure ($p < 0{\cdot}0001$ at site 1 and $p = 0{\cdot}0053$ at site 2), despite the fact that there were no significant differences in exposure between current, ex-smokers, and non-smokers at either site. At site 1 there was a linear dose related effect of both amount of cigarettes currently smoked and duration of exposure on precipitin reaction. At both sites the effect of smoking was shown to be rapidly reversible, ex-smokers of less than three years' duration having significantly greater precipitin reactions than current smokers and being not significantly different from non-smokers.

Occupational asthma in grain terminal workers: the role of storage mites

AD BLAINEY, S OLLIER, W SMART, RJ DAVIES Storage mites are recognised as a cause of allergic respiratory disease in farm workers but their importance in the development of the respiratory symptoms common among grain workers remains unclear. We have previously reported a survey of grain workers in which occupational asthma (significant bronchial hyperreactivity associated with work related respiratory symptoms) affected 10% of the work force (Blainey *et al. Thorax* 1983;**38**:220). Skinprick tests were performed as part of the survey with extracts of *Dermatophagoides pteronyssinus,* storage mites and grain. Ninety five per cent of the work force of 133 were tested. Atopy was not a predisposing factor for occupational asthma. Sixty two per cent of those with work related asthma had positive skinprick test response to more than one storage mite species. There was a significant correlation between work related respiratory symptoms and positive skin test responses to storage mites, but not between occupational history and *D pteronyssinus* or grain extracts. Skin weal areas correlated strongly within storage mite species and there were significant but weaker correlations between weal areas for *D pteronyssinus* and storage mites. These results suggest that sensitisation to storage mites was responsible for occupational asthma in most of those affected. Some shared allergens are present in *D pteronyssinus* and storage mite extracts but important differences in allergenic determinants must also exist. Results of RAST inhibition studies support these findings.

Smoking, atopy, and specific IgE

KM VENABLES, MD TOPPING, W HOWE, AJ NEWMAN TAYLOR Allergic asthma is associated with specific IgE antibody and surveys of specific IgE distribution can detect risk factors in antibody formation which may be important in the associated asthma. Seven patients with asthma caused by tetrachlorophthalic anhydride (TCPA) were all smokers (Howe *et al. J Allergy Clin Immunol* 1983;**71**:5–11), so in this survey we examined smoking and antibody in the healthy population at the factory where these patients had worked. Blood samples were provided by 300 (90·9%) of 330 exposed workers and in a radioallergosorbent test 24 had specific IgE against a TCPA conjugate. Of the 24, 20 (83·3%) were current smokers, compared with 133 (48·2%) of 276 without antibody ($p < 0·01$); and there was a weaker association with atopy, defined by skin tests. Smoking and atopy interacted, the antibody prevalence being 16·1% in smoking atopics, 11·7% in smoking non-atopics, 8·3% in non-smoking atopics, and nil in non-smoking non-atopics ($p < 0·01$; trend, $p < 0·001$). Smoking has been associated with specific IgE against organic antigens (Zetterström *et al. Br Med J* 1981;**283**:1215–7) but not previously with hapten specific IgE. We believe that this is the first report of an interaction between smoking, atopy, and specific IgE.

Effects of dust on respiratory function in ballet dancers

FS GILL, RB DOUGLAS, JE COE This study was undertaken as a result of complaints by ballet dancers of respiratory symptoms during and after performances. Its purpose was to determine whether respirable dust on the stage could be a source of pulmonary irritation. Airborne dust levels were measured on stage during ballet performances at the Royal Opera House, Covent Garden, and at a temporary theatre in Plymouth. Spirometric tests were done before and after 10 performances on 40 dancers. It was found that this athletic population had above average lung function and a below average (less than half of predicted) rate of decline in FEV_1 with age. The level of respirable dust was higher at Covent Garden than Plymouth, and some dancers showed bronchoconstriction after performances there. The bronchoactive dust was found to be related to tissue "snow" shaken down from overhead during certain scenes in the ballet. After the performance this material was swept up (along with dust from the surface of the stage) and reused, thus providing for repeated exposures. The symptomatic bronchoconstriction at the dustier site contrasts with the postexercise bronchodilation that had been expected (Douglas *et al. Clin Sci* 1980;**59**:4).

Malignant fibrous histiocytoma presenting in thoracic surgical practice

GE VENN, J GELLISTER, PE DaCOSTA, P GOLDSTRAW Malignant fibrous histiocytoma is a rare though increasingly recognised deep seated pleomorphic sarcoma. It is a primitive tumour arising from tissue histiocytes, typically occurring in the extremities. As a primary intrathoracic tumour it has been reported rarely. The presentation of malignant fibrous histiocytoma in our series of seven patients has been varied—two presenting as solitary primary intrapulmonary tumours, two as primary chest wall tumours, one as an anterior mediastinal mass, one as a retroperitoneal tumour extending cephalad through the diaphragm, and one as a late metastasis from a primary pelvic site. Malignant fibrous histiocytoma is aggressive with a propensity for early local and distant spread. The histological nature of the tumour makes diagnosis on small biopsy specimens difficult and frequently inaccurate. We would suggest a policy of open biopsy to obtain adequate and representative material for histological examination and preoperative computed tomography to augment the clinical search for metastatic disease and to facilitate planning of subsequent radical excisional surgery. The aggressive nature of the tumour confers a high relapse rate; three patients have died within 15 months of presentation. The preoperative use of deep *x* ray treatment or the newer chemotherapeutic agents may allow reduction of tumour bulk, thus facilitating radical surgery, which at present appears the most appropriate primary treatment in malignant fibrous histiocytoma.

Effect of rifampicin administration on theophylline pharmacokinetics in man

PR POWELL-JACKSON, AP JAMIESON, B GRAY, J MOXHAM, R WILLIAMS Enzyme inducers and inhibitors are known to affect theophylline metabolism by the cytochrome P-450 dependent mono-oxygenase system and complicate its use in the treatment of asthma and chronic airways obstruction. In the present study the possibility of an interaction between rifampicin, a potent enzyme inducer, and theophylline was investigated. Theophylline pharmacokinetics were studied before and after rifampicin administration (600 mg daily for one week). Rifampicin reduced the area under the concentration time curve by 18% following the oral administration of sustained release aminophylline (450 mg) to seven normal subjects ($p < 0·05$) and increased the metabolic clearance and volume of distribution by 45% ($p < 0·05$) and 17% ($p < 0·05$) respectively following the intravenous administration of aminophylline (5 mg/kg over 30 minutes) to eight normal subjects. These findings are consistent with an inducing and choleretic effect of rifampicin on theophylline disposition. Thus subtherapeutic blood levels of theophylline could follow the initiation of rifampicin therapy and, despite careful monitoring of levels during therapy with both drugs, toxicity from high theophylline levels could follow the discontinuation of rifampicin. In patients receiving theophylline blood levels should be monitored closely and dosage adjusted if rifampicin therapy is introduced or withdrawn.

Self administered home intravenous antibiotic treatment in bronchiectasis and adult cystic fibrosis

RJD WINTER, RJD GEORGE, SM DEACOCK, CD SHEE, DM GEDDES Ten patients (mean age 23·1, range 17·1–40·5

years), eight with cystic fibrosis and two with advanced bronchiectasis without cystic fibrosis, have been taught to administer their own intravenous antibiotics at home to treat infective exacerbations due to *Pseudomonas aeruginosa*. Patients were instructed during hospital admission for infective exacerbations requiring antibiotic therapy. After satisfactory antibiotic levels had been achieved 22 courses in all were given at home totalling 116 patient days. In 14 of these the majority of the antibiotic course was given at home (mean duration 6·6, range 5–10 days), in two of them without admission to hospital. Clinical assessment was by temperature, lung function, body weight, and well being. All these episodes improved with home based treatment. Eight patients had two or more infective exacerbations during the 12 month period treated both conventionally in hospital and partly or wholly at home. There was no difference between hospital and home treatments in the improvement in lung function seen or in mean relapse time, defined as the interval between completion of treatment and subsequent antibiotic therapy. Self administered home intravenous antibiotic therapy for selected patients with adult cystic fibrosis and severe bronchiectasis leads to shorter hospital admission and does not appear to be associated with an increased rate of recurrent infection.

Danazol does not significantly augment alpha$_1$ antitrypsin concentrations in patients with a deficiency

SJ WINNER, DI SMITH, HM CHAPEL, DJ LANE Danazol, an androgen derivative, has been reported to produce significant increases in serum α_1 antitrypsin in deficient patients. Mean α_1 antitrypsin levels were reported to rise by 37% in six homozygotes (PiZ), and by 87% in a heterozygote (PiSZ) after 30 days oral therapy (Gadek *et al. J Clin Invest* 1980;**66**:82–7). We have studied seven homozygotes (PiZ) with airways obstruction (mean age 53 years (range 39–73) years, mean FEV_1 0·7 l) and one heterozygote (PiSZ) with normal lung function. After two baseline serum samples had been taken, oral danazol 600 mg daily was given for 30 days. In the homozygotes α_1 antitrypsin levels (assayed by rate nephelometry) were not significantly changed by treatment: mean pretreatment level 18·5 (SEM 2·0) mg/dl, end of treatment level 21·5 (1·9) ($p > 0·1$, paired t test). The heterozygote showed a 12% rise (from 69·3 to 77·6 mg/dl). By contrast, serum C1 esterase inhibitor levels showed a mean rise of 78% ($p < 0·001$). Antithrombin III and α_2 macroglobulin levels showed small changes, significant statistically but not biologically. Thus danazol failed to alter serum α_1 antitrypsin levels significantly, despite producing changes in another serum antiprotease, and its role in restoring the protease-antiprotease balance in α_1 antitrypsin deficient patients remains unsubstantiated.

Carcinoembryonic antigen: a marker of lung epithelial damage?

RA STOCKLEY, J SHAW The serum concentration of carcinoembryonic antigen in normal smokers is higher than non-smokers or ex-smokers (Clarke C, *et al. J R Coll Phys* 1980;**14**:227), which is thought to represent epithelial damage due to smoke and leakage of protein from the lung into serum. To investigate this further we measured serum carcinoembryonic antigen levels by specific radioimmunoassay in 47 control subjects, 21 patients with obstructive bronchitis, 21 with pneumonia, 12 with active fibrosing alveolitis, nine with bronchiectasis before and after antibiotic therapy, and nine bronchitic subjects before and during steroid therapy. Values are expressed in ng/ml. The range in normal subjects was wide (6·5–41·5, mean (SD) 15·4 (6·5) but the average value in non-smokers (12·16 (3·5)) was lower ($p < 0·005$) than that in smokers (17·83 (7·04)). Patients with obstructive bronchitis also had raised levels ($p < 0·005$) when compared with normal subjects (mean 21·2 (6·2)). Patients with pneumonia (mean 18·6 (7·42)), fibrosing alveolitis (16·5 (6·07)) and bronchiectasis (12·1 (4·1)) had values similar to those of the normal subjects. Antibiotic treatment had no effect on the value in patients with bronchiectasis (11·45 (3·40)) but steroids lowered the carcinoembryonic antigen concentration in nine patients with bronchitis ($p < 0·05$) from 52·3 (62·1) to 20·7 (13·0). The results suggest that serum carcinoembryonic antigen does not reflect pulmonary inflammation or epithelial damage but is associated with exposure to cigarette smoke and may be a useful predictor of the susceptibility to progressive smoke related lung disease.

Tuberculosis among Rastafarians in Birmingham

GE PACKE, PA PATCHETT, JA INNES In 1981 and 1982 there was a considerable increase in tuberculosis notifications for West Indians living in Birmingham. This was due to an outbreak of tuberculosis among Rastafarians, centred on the Handsworth district of Birmingham. The Rastafarian cult began in Jamaica and gained popularity in the 1970s among young unemployed blacks who felt rejected by white society. From 1981 to 1983 44 Rastafarians, including children, have been treated (mean age 16·5 years, range 4 months to 41 years). Eight were immigrants and the remainder UK born. Fifteen had received BCG vaccination, including a patient who died of tuberculous meningitis. An additional seven patients were given chemoprophylaxis. A clinical impression was gained that many of the Rastafarians were presenting with advanced disease. The chest radiographs of those with pulmonary disease were graded according to the extent of disease (Simon. *Br Med J* 1966;ii:491–4). Larger pulmonary lesions were proportionately more common in the Rastafarians than in the national survey of tuberculosis notifications in England and Wales (*Br Med J* 1980;**281**:895–8) ($p < 0·05$). Compliance as assessed by failed clinic attendances and clinical evaluation was significantly worse among the Rastafarians than in a matched control group ($p < 0·01$).

1983 survey of notifications of tuberculosis in England and Wales

JH DARBYSHIRE, SP BYFIELD, KM CITRON, W FOX, MJ HUMPHRIES, AJ NUNN An analysis of all notifications of tuberculosis for the first six months of 1983 has been undertaken

and compared with the results of the six month survey of 1978–9 (Medical Research Council. National survey of tuberculosis notifications in England and Wales 1978–9. *Br Med J* 1980;**281**:895). The number of newly notified previously untreated patients has dropped by 19%, from 3732 to 3029. Of the latter, 68% had respiratory disease only, 25% non-respiratory disease only, and 7% both; 55% of the patients were of white and 36% of Indian subcontinent (Indian, Pakistani, or Bangladeshi) ethnic origin, findings similar to those for 1978–9. The age distribution of the patients in each of the two main ethnic groups showed little change between the two surveys. However, the proportion of Indian subcontinent patients under the age of 15 who were born in the United Kingdom increased from 58% in 1978–9 to 78% in 1983. Of the patients with pulmonary disease, 64% had a positive culture and 45% also had a positive smear. As in 1978–9, both proportions were higher in the white group. There were differences between the ethnic groups in the types of non-respiratory lesions but, as in 1978–9, the commonest non-respiratory lesion in both main ethnic groups was lymph node disease—37% of non-respiratory lesions in the white and 54% in the Indian subcontinent patients. Genitourinary lesions were the next most common for the white patients (29%), and bone and joint for the Indian subcontinent patients (20%).

Lung cancer, smoking, and what the patients think and wish to know

JA HUGHES, J ROSE Five hundred patients attending a chest clinic were asked to fill in a short questionnaire on their attitudes to lung cancer and whether they thought that smoking contributed to "smoking related disease." Fifty seven per cent were male (mean age 58) (SD 14), 42% female (mean age 52 (15)); 21% were current smokers and 52% ex-smokers and 27% had never smoked. When asked, "If you developed lung cancer would you wish to be told?" 83% of men answered "Yes" and 9%, "No" compared with 74% women saying "Yes" and 16% "No"; the remainder were unsure ($p < 0.05$, χ^2 test). There were no differences between the smoking groups. Forty five per cent thought that lung cancer could be cured and 24% that it could not, while 31% were unsure. The following answers were given to the question "Would the following phrases used by a doctor possibly mean that you had lung cancer?": "A growth on the lung"—79% said "Yes" and 5% "No"; "A shadow on the lung"—29% said "Yes" and 47% "No." "An area of inflammation on the lung"—17% said "Yes" and 52% "No." Significantly more current smokers than ex-smokers and non-smokers though that smoking did not help to cause chronic bronchitis, emphysema, heart disease, or lung cancer.

Incidence of pulmonary nodules detected by computed tomography in patients with lung cancer

DM MITCHELL, S SHAH, D EDWARDS, SG SPIRO, DM GEDDES, RL SOUHAMI, JS TOBIAS, PG HARPER The incidence of pulmonary nodules detectable on computed tomography (CT) scans but not visible on chest radiographs in patients who do not have malignant disease is low (Edwards SE, Fry IK. *Br J Radiol* 1982;**55**:715–6). We analysed CT scans of the thorax from 158 patients with small cell carcinoma of the bronchus. Forty two (27%) had one or more nodules seen on CT scans distinct from the primary tumour. In 17 of these patients CT was repeated following chemotherapy and in eight (47%) of these the nodules had cleared or decreased in size, suggesting that they were malignant. In a further 78 patients with non-small cell lung cancer, 22 (28%) had nodules visible on a CT scan. Follow up information was available on 16 of these patients, with a total of 22 nodules on CT scans at diagnosis. Four of these were subsequently shown to be malignant histologically and a further eight were thought to be malignant, although this remained unproved. The other 10 were found to be benign. Thus of 22 nodules seen on CT scan in non-small cell lung cancer, four (18%) were definitely malignant and a further eight (36%) probably were. Although not all nodules seen only on CT scans in patients with lung cancer are malignant, a considerable proportion are, and these findings may have implications in particular for the surgical staging of patients with lung cancer.

Amenorrhoea in cystic fibrosis

RJ STEAD, ME HODSON, JC BATTEN, J ADAMS, HS JACOBS Primary and secondary amenorrhoea are common complications of cystic fibrosis. We assessed menstrual history, nutritional state, and respiratory function in 42 cystic fibrosis patients (age range 15·5–40·0 years). Nutrition was estimated by the body mass index (weight/height^2) and skinfold measurements, and respiratory function by percentage of predicted forced vital capacity. Pelvic ultrasonography was performed in 22 patients to estimate ovarian volume and morphology. Uterine cross sectional area was calculated as a biological assay of endogenous oestrogenic activity. Twenty seven patients had regular menstruation, 10 had primary or secondary amenorrhoea, two were premenarchal, two were assessed at menarche, and five had irregular cycles. Four patients were included in two categories. Nutrition was better in those with regular cycles than in those with primary or secondary amenorrhoea ($p < 0.001$), as was respiratory function ($0.01 > p > 0.001$). In amenorrhoeic patients there was a positive correlation between uterine size and sum of the skinfold thicknesses ($r = 0.611$, $p < 0.05$) but not with respiratory function. Seven patients had "megalocystic" ovaries containing multiple cysts 6–10 mm in diameter. This study demonstrates a relationship between poor nutrition, poor lung function, and amenorrhoea in cystic fibrosis, and suggests a critical effect of body fat on oestrogen production. Megalocystic ovaries have been associated with amenorrhoea in "normal" women.

Bronchoconstriction induced by ipratropium bromide in asthma: relationship with hypotonicity

PH HOWARTH, JS MANN, ST HOLGATE Ipratropium bromide administered by nebuliser to patients with asthma has on

occasions been associated with bronchoconstriction rather than bronchodilatation. As commercially available ipratropium bromide nebuliser solution (0·25%) is hypotonic, and nebulisation of hypotonic solutions can cause bronchoconstriction in asthma, we investigated the effect of vehicle tonicity on this paradoxical airway response. Eight atopic asthmatic subjects with considerable non-specific airway reactivity (geometric mean methacholine PC_{20} (provocative concentration required to produce a 20% fall in FEV_1) 0·22 mg/ml) participated in a double blind, randomised, placebo controlled study. On four separate days each subject received one of four nebulised solutions: ipratropium bromide in hypotonic vehicle, the hypotonic vehicle alone, ipratropium bromide in isotonic vehicle, and isotonic saline. There were no significant differences in mean baseline FEV_1 values (litres) on any of the four days, with respective values of 3·01, 2·96, 2·95 and 3·13. Both hypotonic solutions caused appreciable falls in FEV_1 (ipratropium bromide 48·0% (SEM 2·0%) vehicle 55·5% (5·6%), which were significantly greater than with the isotonic solutions (ipratropium bromide 12·5% (6·1%), saline 8·4% (3·4%), $p < 0·01$). Thus paradoxical bronchoconstriction reported in asthma following nebulised ipratropium bromide is likely to be due to the hypotonicity of the inhaled solution. An isotonic solution would overcome this problem.

Smoking, allergy, and rate of decline in FEV_1

RG TAYLOR, E GROSS, H JOYCE, F HOLLAND, NB PRIDE We examined the Dutch hypothesis that an allergic tendency contributes to the development of chronic airflow obstruction in smokers by relating allergic markers to annual height corrected decline in FEV_1 ($\Delta FEV_1/ht^3$) over 7·5 years in 117 non-asthmatic male smokers, 71 ex-smokers, and 39 non-smokers. The three groups were similar in personal and family histories of allergy. Positive skinprick test responses were commoner in ex-smokers (59%) than in smokers (33%; $p < 0·001$) or non-smokers (34%; $p < 0·02$). In skin test negative men total serum immunoglobulin E was higher in smokers (log_{10} mean 1·53 (SEM 0·06), $p = 0·06$) and ex-smokers (log_{10} mean 1·68 (0·07), $p < 0·001$) than in non-smokers (log_{10} mean 1·31 (0·09). Even after five years' abstention IgE was higher (log_{10} 1·64 (0·09)) than in current smokers or non-smokers. There was an increase in the peripheral blood absolute eosinophil count in smokers that was disproportionate to that in the total white cell count. In smokers, despite these increases in allergic markers (which were smaller than those seen in asthmatics), only a personal history of allergy (usually rhinitis) was associated with accelerated $\Delta FEV_1/ht^3$; $\Delta FEV_1/ht^3$ was not related to family history of allergy, IgE level, skinprick test score, or eosinophil or total white cell count. These results show that increases in allergic markers are related to smoking rather than to rate of loss of FEV_1, and provide little support for the Dutch hypothesis. They suggest that skin test positive smokers tend to give up smoking, and raise the possibility that skin test negative smokers develop antibodies to cigarette smoke.

Bronchial hyperreactivity in corticosteroid responsive patients with chronic airflow obstruction

RI GOVE, JANIS SHEPHERD, PS BURGE Thirty eight patients with chronic airflow obstruction (mean (SD) FEV_1 in litres 1·1 (0·44)) underwent a double blind, placebo controlled, crossover trial of prednisolone 40 mg daily for two weeks. The provocative concentration of histamine required to cause a 20% fall in FEV_1 (PC_{20}) was measured in all patients, as were the reversibility caused by 200 μg of inhaled salbutamol and the diurnal variation in peak flow. These measurements were made before the corticosteroids were administered. There was a significant correlation between PC_{20} and FEV_1 in all patients ($r = 0·65$, $p < 0·001$). Fourteen patients (38%) satisfied the criteria of a response to corticosteroids (20% improvement in FEV_1, FVC, or mean daily peak flow). These patients had a significantly lower mean FEV_1 (litres) than the non-responders (responders 0·8 (0·26); non-responders 1·2 (0·44): $p < 0·05$). Despite the correlation between PC_{20} and FEV_1, the mean PC_{20} values (mg/ml histamine) were similar in the two groups (responders 0·3 (0·5), non-responders 2·7 (7·0); NS). The other features of asthma were also similar in the two groups (mean percentage diurnal variation in peak flow: responders 22·2 (7·2), non-responders 18·9 (9·8); NS); and mean percentage reversibility in response to salbutamol (FEV_1): responders 14·2 (16·3), non-responders 9·4 (7·6); NS). In conclusion, bronchial hyperreactivity, in association with the other two features usually associated with asthma, does not differentiate between corticosteroid responsive and non-responsive patients with chronic airflow obstruction.

The acid test for gastro-oesophageal reflux in children with asthma

N WILSON, L CHARETTE, A THOMSON M SILVERMAN As gastro-oesophageal reflux can be demonstrated in both normal and asthmatic subjects (Hughes DM *et al. J Pediatrics* 1983;**102**:666) its relevance to asthma is controversial and depends on airway changes being produced by acid in the oesophagus in asthmatic subjects. This study was designed to investigate whether in children with asthma (1) acid in the oesophagus could be detected by overnight oesophageal monitoring with a pH probe and (2) a drink of dilute hydrochloric acid could induce changes in bronchial responsiveness (histamine PC_{20}) when given double blind—the "acid test." Nineteen children (aged 5–14 years) with moderately severe asthma completed both parts of the study. In nine gastro-oesophageal reflux (pH < 4 for more than two minutes) was detected during continuous overnight monitoring. There was no significant change in baseline peak expiratory flow rate after the drink of either placebo or 0·001 N hydrochloric acid (pH 3·1) but the latter induced a significant fall in histamine PC_{20} in 9 of the 19 children (outside the 95% confidence limits of PC_{20} set by placebo). A further three children showed increased responsiveness after 0·01 N hydrochloric acid (pH 1·9). Gastro-oesophageal reflux with a positive acid test response occurred in 6 of the 19 of the subjects and in these we feel that the reflux is likely to be clinically relev-

ant. The critical investigation is the detection of increased bronchial responsiveness after an acid drink.

Can once daily inhaled steroids control chronic asthma?

DV McGIVERN, M WARD, WH RODERICK-SMITH, J MACFARLANE It is known that twice daily inhalations of corticosteroids can effectively control chronic asthma. To see if once daily inhalation is sufficient we compared standard dose beclomethasone (50 μg/puff) given three or four times daily with the same daily dose given once each morning from a high dose beclomethasone inhaler (250 μg/puff). Twelve patients (aged 22–71 years) who had stable chronic asthma normally controlled with standard dose inhaled beclomethasone and bronchodilators were studied. After a two week run in period on their usual medication they entered a double blind crossover study using (1) their usual dose of beclomethasone three or four times a day plus a placebo once each morning for four weeks and (2) an equivalent dose from a high dose beclomethasone inhaler once each morning plus a placebo three or four times a day for four weeks. Patients recorded peak expiratory flow rate (PEFR) morning and evening and symptom scores for nocturnal asthma, daytime wheeze, and shortness of breath. Two patients withdrew because of increasing shortness of breath seven and 10 days after starting the once daily regimen. In the remaining 10 patients there was no difference between the run in and the divided daily dose regimen. However, on once daily inhalations morning PEFR fell by 17% ($p < 0.05$) and evening PEFR by 15% ($p < 0.05$). Symptom scores for shortness of breath, nocturnal asthma, and daytime wheeze increased by 98% ($p < 0.05$), 62% (NS), and 110% (NS) respectively. The results show that chronic asthma cannot be adequately controlled with the total daily dose of inhaled steroids taken once each morning.

Theophylline specifically antagonises adenosine induced bronchoconstriction

JS MANN, ST HOLGATE Adenosine, a purine nucleoside, is released following antigen challenge in asthma and causes bronchoconstriction in asthmatic subjects. Adenosine has therefore been proposed as an inflammatory mediator of asthma. Adenosine induced bronchoconstriction is selectively antagonised by inhaled theophylline suggesting an effect mediated through adenosine receptors. To determine whether therapeutic plasma levels of theophylline exert a similar effect we have observed the comparative effect of oral theophylline on adenosine and histamine induced bronchoconstriction in nine allergic asthmatic subjects. On each of four study days subjects inhaled increasing concentrations of nebulised adenosine or histamine 90 minutes after receiving 375–500 mg micronised theophylline or placebo. Airway calibre was measured as sGaw and dose response curves constructed adenosine and histamine after each treatment. Following placebo, adenosine and histamine caused bronchoconstriction (PC_{35} 0·61 and 0·1 mg/ml respectively). Theophylline (plasma levels >10 μg/ml) caused bronchodilatation, sGaw increasing by 41% (SEM 11%) and 53% (10%) on the adenosine and histamine challenge days respectively. Following theophylline both adenosine and histamine produced falls in sGaw (PC_{35} adenosine 7·8, PC_{35} histamine 0·51) but when compared with placebo the dose-response curves were displaced to the right ($p < 0.01$). However, theophylline provided greater protection from the bronchoconstrictor effect of adenosine (dose ratio 12·8) than histamine (dose ratio 5·34 $p < 0.02$). Thus in addition to being both a bronchodilator and a functional antagonist, theophylline at therapeutic concentrations preferentially antagonises the bronchoconstrictor effect of adenosine.

Prostacyclin: a functional antagonist of prostaglandin D_2 induced bronchoconstriction

C HARDY, C ROBINSON, P BRADDING, ST HOLGATE Prostacyclin (prostaglandin I_2, PGI_2) and prostaglandin D_2 (PGD_2) are released in large amounts with IgE-dependent challenge of human lung tissue. In contrast to PGI_2, which has no overall effect on airway calibre in man, inhaled PGD_2 is a bronchoconstrictor agent, four times more potent than $PGF_{2\alpha}$. We have investigated the effect of inhaled PGI_2 on both PGD_2 and methacholine induced bronchoconstriction in eight mild allergic asthmatic males (age 26 (SEM 1) years, baseline sGaw 1·67 (0·28 s^{-1} kPa^{-1})). On five study days subjects received doubling concentrations of nebulised PGI_2, PGD_2 (3·9–500 μg/ml) and methacholine alone (4·9–1250 μg/ml) or PGI_2 followed immediately by similar concentrations of (1) PGD_2, (2) methacholine. Aerosols were generated by an Inspiron nebuliser driven by air at 8 l/min from a starting volume of 1 ml, subjects breathing tidally for one minute. Airway calibre was followed as specific airway conductance (sGaw), and concentration-sGaw response curves were constructed. Geometric mean PC_{35} sGaw for PGD_2 and methacholine were 11·8 and 229 μg/ml respectively. Prostacyclin alone had no effect on airway calibre, yet protected against PGD_2 and methacholine induced bronchoconstriction, reflected by an increase in PC_{35} sGaw to >500 μg/ml and >1250 mg/ml respectively. This suggests that PGI_2 may be a functional antagonist of PGD_2 and methacholine induced bronchoconstriction, lending further support to the idea that PGI_2 protects against other non-specific bronchoconstrictor stimuli such as exercise.

Bronchoconstrictor interactions: a rational approach

P BRADDING, C HARDY, ST HOLGATE, AE TATTERSFIELD The limited number of airways interactive studies may reflect difficulties in methodological design. Current investigation involves the construction of a concentration-bronchoconstrictor response curve after prior inhalation of a single concentration of a second constrictor substance. To overcome the inherent difficulties and flaws of this approach we have designed a time course study for investigating bronchoconstrictor interactions. Eight allergic asthmatic males (mean age 24 (SEM 2) years, baseline sGaw 1·79 (0·16) s^{-1} kPa^{-1}, geometric mean PC_{35} sGaw methacholine 158 μg/ml) received on two study days doubling concentrations of nebulised adenosine and methacholine (4·9–5000 μg/ml), airway calibre being fol-

lowed as specific airway conductance (sGaw). Individual PC_{25} and PC_{50} values for adenosine (a, b μg/ml) and methacholine (x, y μg/ml) were calculated. On three time course study days subjects received either (1) adenosine a μg/ml, followed at three minutes by (b-a) μg/ml calculated to produce 25 and 50% falls in sGaw respectively; (2) methacholine x μg/ml followed at 3 minutes by (y-x) μg/ml to achieve similar falls in sGaw; (3) methacholine x μg/ml followed by adenosine (b-a) μg/ml, and sGaw was followed for 30 minutes after the second nebulisation. Maximum bronchoconstriction, three minutes after nebulisation, was not significantly different on the three study days at 49% (7%), 51% (6%), and 47% (5%) respectively, with similar rates of recovery towards baseline. This suggests an additive effect only of adenosine and methacholine as constrictor agents.

Effect of preinhalation of leukotriene D_4 on sensitivity to inhaled prostaglandin $F_{2\alpha}$

N BARNES, A WATSON, N KOULOURIS, PJ PIPER, J COSTELLO It has been suggested that leukotrienes (LTs) may cause hypersensitivity to other allergic mediators (Griffin *et al. N Engl J Med* 1983;**308**:436–9). To test this hypothesis we have investigated whether preinhalation of LTD_4 causes hypersensitivity to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Six normal, non-atopic subjects (three male, three female), mean age 26 years, were studied in whom dose-response curves for LTD_4 had been established. Baseline sGaw was measured and then subjects inhaled saline or a non-bronchoconstricting dose of LTD_4 generated from a Wright nebuliser driven by compressed air at 7 l/min for two minutes. sGaw was measured to ensure that there had been no change from baseline. The subjects then inhaled $PGF_{2\alpha}$ in doses varying from 10^{-6} to 10^{-3} mol/l, and sGaw was measured every two minutes; on further days different concentrations of $PGF_{2\alpha}$ were used so that, with single doses of $PGF_{2\alpha}$ at a time, dose-response curves for $PGF_{2\alpha}$ were constructed after inhalation of saline and after inhaling a subthreshold dose of LTD_4. The geometric mean concentration of $PGF_{2\alpha}$ needed to cause a 20% drop in sGaw (PD_{20}) was $3{\cdot}4 \times 10^{-5}$ mol/l after inhalation of saline and $4{\cdot}9 \times 10^{-6}$ mol/l after inhalation of LTD_4 ($p < 0{\cdot}005$). This result supports the hypothesis that the hypersensitivity to inhaled $PGF_{2\alpha}$ observed in asthmatics may be due to leukotrienes.

Effect of inhaled leukotrienes C_4 and D_4 in mild asthma

N BARNES, PJ PIPER, J COSTELLO We have previously shown that inhaled leukotriene C_4 (LTC_4) and LTD_4 are potent longlasting bronchoconstrictors in normal subjects, causing a fall in sGaw and $\dot{V}max_{30}$ (Barnes *et al. Thorax*). Eight mild asthmatics (three male, five female), mean age 27 years, controlled only with inhaled β_2 agonists, were studied. On separate mornings subjects inhaled normal saline followed by increasing concentrations of histamine, LTC_4, or LTD_4, generated by a Wright nebuliser containing 2 ml of test solution driven by compressed air at 7 l/min. sGaw was then measured at two minute intervals with a whole body plethysmograph. All baseline FEV_1 measurements were within the predicted normal range. LTC_4, LTD_4, and histamine reduced sGaw. Histamine caused cough and throat irritation, whereas inhalation of leukotrienes caused wheezing but no cough. The geometric mean concentration needed to cause a 35% drop in sGaw (PD_{35}) for histamine was $4{\cdot}9 \times 10^{-3}$ mol/l, for LTC_4 $1{\cdot}7 \times 10^{-5}$ mol/l, and for LTD_4 $1{\cdot}8 \times 10^{-5}$ mol/l. The onset of leukotriene induced bronchoconstriction was slower and their action was approximately twice as long as that of histamine. Compared with a group of six normal subjects, the asthmatics were 11 times more sensitive to histamine ($p < 0{\cdot}001$), 4·3 times as sensitive to LTC_4 ($p < 0{\cdot}01$), and 4·9 times as sensitive to LTD_4 ($p < 0{\cdot}001$). These results show that inhaled LTC_4 and LTD_4 are potent long acting bronchoconstrictors in those with mild asthma.

Role of physiological concentrations of catecholamines in the control of airway calibre in asthmatic patients

KE BERKIN, GC INGLIS, SG BALL, NC THOMSON Physiological concentrations of adrenaline, but not noradrenaline, influence airway calibre in normal subjects (Berkin KE *et al. J Physiol* 1983;**345**:35P); but the role of the catecholamines in the control of airway calibre in asthmatic patients is less clearly established. Beta and α receptor responsiveness may be altered in asthma. Five asthmatic patients (FEV_1 65–117% predicted) abstained from β adrenergic agonists for 10 days prior to the study. Airway responses (specific conductance (sGaw), flow rates from flow-volume curves ($\dot{V}_{50}C$, $\dot{V}_{25}C$, $\dot{V}_{25}P$)) were measured during separate infusions of adrenaline, noradrenaline, and saline. Adrenaline and noradrenaline were infused at four incremental rates (4, 10, 25, 62·5 ng/kg/min), achieving mean maximal concentrations of 3·29 (SEM 0·45) and 7·76 (0·96) nmol/l respectively. sGaw, $\dot{V}_{50}C$, $\dot{V}_{25}C$, $\dot{V}_{25}P$ increased sequentially during adrenaline infusion, reaching mean maximal increases of 114%, 36%, 56%, and 69% respectively during the highest infusion rate, when plasma adrenaline concentration was 0·98 (0·25) (baseline 0·19 (0·06)) nmol/l. No changes in flow rates occurred during noradrenaline or saline infusion. Physiological concentrations of adrenaline influence airway calibre in asthmatic patients. The magnitude of response compared with normal subjects suggests no reduction in β receptor responsiveness. The lack of response to noradrenaline indicates that α receptors are unlikely to be important in the control of airway calibre.

Comparison of cumulative and non-cumulative techniques for measuring dose response curves to beta agonists in patients with asthma

JR BRITTON, AE TATTERSFIELD Dose response curves for inhaled β agonists can be constructed on the basis of cumulative or non-cumulative doses. Williams and Kane (*Am Rev Respir Dis* 1975;**111**:321–4) reported a plateau in the peak expiratory flow rate (PEFR) response curve after 20 μg isoprenaline with a non-cumulative technique, and proposed that further increases in PEFR after successive cumulative doses are the result of increased penetra-

tion of the drug following bronchodilatation from preceding doses. Since the two techniques have not been compared directly we have compared cumulative and non-cumulative dose response curves for inhaled isoprenaline in 10 subjects with stable asthma, measuring FEV_1, FVC, and PEFR. With both techniques there was an increasing response with increasing doses of isoprenaline for all the dose-response curves except the non-cumulative PEFR response, which reached a plateau with the 20 μg dose. The area under the dose-response curve for FEV_1 was significantly higher ($p < 0.05$, paired t test) after cumulative administration of isoprenaline than with the non-cumulative technique. The increases in FVC and PEFR tended to be greater with the cumulative technique but the differences were not significant. This study confirms that the airway response to an inhaled β agonist may be greater when a cumulative inhalation technique is used.

Histamine challenge testing: a method comparison study

JR BRITTON, A MORTAGY, AE TATTERSFIELD The method of histamine challenge testing described by Cockcroft *et al.* (*Clin Allergy* 1977;**7**:235–43) and based on the Wright nebuliser has been well standardised. However, it takes up to 45 minutes to perform and depends on a supply of pressurised air. Methods based on the hand held DeVilbiss No 40 (Yan *et al.* *Thorax* 1983;**38**:760–5) or the Pulmasonic ultrasonic nebuliser (Mortagy, PhD thesis) do not have these disadvantages. We have compared these methods with the Wright technique for repeatability, sensitivity, and convenience in 24 subjects with asthma by measuring the provocative concentration (PC_{20}) or dose (PD_{20}) causing a 20% fall in specific airways conductance by each method in a balanced design on two occasions one to seven days apart. The Wright method was the least repeatable, with a 95% confidence limit for the difference between replicates of 4·43 doubling concentrations, compared with 4·00 and 3·67 for the DeVilbiss and Pulmasonic methods. The Wright technique was also least sensitive, recording a repeatable PC_{20} of up to 8 mg/ml in only 16 subjects, as opposed to 24 for the other methods. The DeVilbiss method was the least complicated to perform and, like the Pulmasonic method, took 15 minutes to complete. In this study the DeVilbiss and Pulmasonic methods offered faster, more convenient, and more repeatable alternatives to the Wright method, and have clear advantages for clinical and epidemiological use.

Leucocyte activation during allergen induced late phase reactions

SR DURHAM, MARY CARROLL, GM WALSH, AB KAY We previously demonstrated activation of peripheral blood neutrophils after exercise induced (Papageorgiou *et al.* *Lancet* 1983;ii:1220–3) and allergen induced (Durham *et al.* *Thorax* 1984;**39**:231) early asthmatic reactions. In the present study we measured neutrophil and monocyte rosette formation (as a marker of activation) during allergen induced late phase reactions. In 11 asthmatic subjects with dual reactions there was a significant increase in neutrophil (NCR) and monocyte complement rosettes (MCR) accompanying both the early and the late falls in FEV_1 and elevations in neutrophil chemotactic activity (NCA). These increases in NCR, MCR, and NCA were not observed when the same individuals had a control (methacholine induced bronchoconstriction) day. Furthermore, when six subjects with isolated early asthmatic reactions were studied for 24 hours there was only a single early peak in NCR, MCR, and NCA. Peripheral leucocyte counts in the dual responders revealed significant elevations in lymphocytes at 6 hours ($p < 0.01$), in neutrophils at 9 hours ($p < 0.05$), and in eosinophils at 24 hour ($p < 0.01$). These observations suggest that allergen induced dual asthmatic reactions are associated with biphasic mast cell degranulation and activation of neutrophils and monocytes, which may contribute to peribronchial inflammatory events associated with late phase responses and possibly ongoing asthma.

Effect of passive sensitisation of human bronchial smooth muscle on in vitro sensitivity to histamine

JA ROBERTS, MA GIEMBYCZ, D RAEBURN, IW RODGER, NC THOMSON Atopy is closely associated with asthma. In sensitised subjects, antigen exposure may precipitate acute bronchospasm and may increase non-specific airway responsiveness. The mechanism of this is unknown. Serum from atopic subjects can sensitise bronchial tissue so that addition of specific antigen will produce mediator release and hence smooth muscle contraction. We passively sensitised human bronchial strips to house dust mite (HDM), using serum obtained from an atopic asthmatic, and then examined the effect of this on in vitro smooth muscle sensitivity to histamine. Four bronchial strips were obtained from each of six patients and thoracotomy. Two were incubated overnight in the presence of anti-HDM IgE serum and two in the presence of non-reaginic serum. Bronchial strips were hung under a resting tension of 1·5–2·0 *g*. HDM antigen solution (E Merck Ltd) was added to one sensitised and one control bronchial strip. In all cases this produced contraction of the sensitised strip, which was then washed and allowed to relax to baseline. A dose-response curve for histamine was then performed and the sensitivity of each strip assessed by the concentration producing a contraction 50% of maximum (EC_{50}). Neither sensitisation per se nor the addition of antigen to sensitised tissue altered in vitro sensitivity to histamine of airway smooth muscle. This suggests that increased non-specific airway responsiveness following allergen challenge in sensitised subjects may not be related to the acute effects of mediator release on airway smooth muscle.

Mediator release associated with clinical models of asthma

PH HOWARTH, TH LEE, T NAGAKURA, SR DURHAM, AB KAY, ST HOLGATE To clarify controversy concerning increases in mast cell associated mediators following bronchoprovocation in asthma, nine atopic asthmatic subjects (geometric mean methacholine PC_{20} 0·08 mg/ml) underwent both treadmill exercise and isocapnic hyperventilation chal-

lenge, matched for respiratory heat exchange. Seven of these subjects were also subjected to antigen and methacholine inhalation challenge. Airway calibre was measured as specific airways conductance (sGaw) and mast cell mediator release monitored by serial measurements of plasma histamine (single isotopic, microenzymatic radiotransfer assay) and serum neutrophil chemotactic activity (modified Boyden chamber technique). Baseline sGaw values were not significantly different on the challenge days. All challenges produced comparable maximal percentage falls in sGaw—exercise (59·5 (SEM 4·3)), isocapnic hyperventilation (57·9 (5·2)), antigen (61·2 (5·6)), and methacholine (55·7 (3·7)). Serum neutrophil chemotactic activity increased significantly with exercise (87·0% (21·6%)) and antigen (69·6% (15·9%)) but not isocapnic hyperventilation (36·8% (24·2%)) or methacholine (18·4% (10·9%)) induced bronchoconstriction. In these subjects with hyperreactive airways, in contrast to previous findings in asthmatics with less reactive airways, no significant increases in plasma histamine were identified with any challenge. Thus both immunological and non-immunological mechanisms can initiate mediator release in asthma, the profile of which may be dictated by patients' non-specific airway reactivity.

Monocyte activation and corticosteroids in asthma

W GIN, AB KAY It is generally assumed that chronic asthma is associated with bronchial inflammation and that agents such as corticosteroids act by suppressing the activity of infiltrating leucocytes (such as cells of the monocyte/macrophage series). However, there is no direct evidence for this theory and the precise mode of action of corticosteroids remains uncertain. In the present study we have examined the effect of corticosteroids in asthma by measuring membrane receptors (using the rosette technique) for IgG-(Fc) and complement (C) (indices of cell activation). Peripheral blood monocytes from 29 asthmatics receiving inhalant therapy alone had an increase in the expression of IgG-(Fc) and complement receptors by comparison with 14 healthy controls ($p < 0.001$). Furthermore, in 14 asthmatics receiving corticosteroid therapy monocyte receptor expression was lower than those asthmatics who were not receiving prednisolone ($p < 0.001$). In a further four subjects serial measurements were undertaken before and after the administration of 30 mg/day of prednisolone for 10 days. In all subjects there was a significant reduction in receptor expression that paralleled the improvement in airflow obstruction. These results support the view that corticosteroids act by "dampening" the inflammatory response in asthma and that cells of the monocyte macrophage series might play a central part in tissue damage.

Allergic rhinitis, asthma, and leukotrienes

RJ SHAW, P FITZHARRIS, SR DURHAM, O CROMWELL, AB KAY The leukotrienes (LT) are lipid mediators with potent pharmacological properties. These include bronchial smooth muscle contraction (LTC_4, LTD_4, and LTE_4), mucus secretion (LTC_4, LTD_4), altered vascular permeability and tone (LTC_4, LTD_4), and recruitment and activation of inflammatory cells (LTB_4). We have measured concentrations of leukotrienes in nasal secretions after nasal provocation in patients with allergic rhinitis. Similar studies were undertaken in the plasma of asthmatics during allergen induced early and late phase responses. Leukotrienes were measured by specific radioimmunoassay and high pressure liquid chromatography (HPLC) with authenticated synthetic markers. Six patients with rhinitis had up to a 35 fold increase in LTC_4 and D_4 and an eight fold increase in LTB_4 concentrations in secretions after nasal challenge. These responses were both concentration and time dependent, maximal increases being observed seven to 22 minutes after challenge. Elevated levels were also detected in the plasma of asthmatics after antigen provocation, although the increases were considerably less (approximately 20% above baseline during early and late phase reactions). These findings support the view that leukotrienes are generated in allergic rhinitis and asthma after specific allergen challenge, and that these potent lipid mediators might play an important part in the pathogenesis of these diseases.

Effect of high dose inhaled nifedipine on bronchial reactivity to histamine

FM CUSS, PJ BARNES While calcium channel blockers protect against histamine induced bronchoconstriction in asthmatic patients the effect is modest. Nifedipine is more potent than verapamil for airway smooth muscle but when given orally or sublingually the dose is limited for cardiovascular side effects. We have now given nifedipine by aerosol to see whether a high local concentration has any greater effect on the airways. In six subjects with mild asthma (age 20–38 years) a histamine challenge was performed and the concentration of histamine causing a 35% fall PC_{35} in specific airways conductance (sGaw) was determined. Subjects then received either nifedipine, 10 mg in 10 ml of 40% ethanol in saline, or diluent alone in a double blind, randomised fashion from a light free nebuliser system. sGaw, blood pressure, and heart rate were recorded before and after nebulisation and did not change significantly after either treatment. PC_{35} increased from a geometric mean of 5·0 (SEM 1·4) mg/ml to 10·9 (1·5) mg/ml after nifedipine ($p < 0.05$), with no significant change after placebo. There was no correlation between the ratio of PC_{35} before and after nifedipine and the initial PC_{35} ($r = -0.11$). Inhaled nifedipine has a protective effect against histamine induced bronchoconstriction; but this is no greater than when it is given sublingually, and there is no significant change in bronchomotor tone despite a high local concentration. It is likely that this marks the limit of efficacy of acute blockade of voltage dependent calcium channels in the airways.

Inhaled prostaglandin D_2 potentiates histamine induced bronchoconstriction

RW FULLER, CMS DIXON, CT DOLLERY, PJ BARNES Prostaglandin D_2(PGD_2) and histamine are potent bronchocon-

strictor mediators produced by human lung mast cells. As neither antihistamines nor aspirin like drugs inhibit antigen induced asthma, it is unlikely that either mediator alone is responsible for antigen induced asthma. As synergism occurs between mediators in the skin (Williams *et al. Nature* 1973;**246**:215) we have examined the possible interaction between histamine and PGD_2 in human airways. Five asthmatic subjects (age 24–34 years) in whom the geometric mean of the dose of mediator which would cause a 35% fall (PC_{35}) in specific airways conductance (sGaw) was 0·86 mg/ml for histamine and 0·035 mg/ml for PGD_2. On each day following a histamine dose response study and a recovery period a second histamine dose response study was performed; on this occasion each dose was preceded by inhalation of one breath of either histamine or PGD_2. The concentration of histamine and PGD_2 used was that causing a greater than 35% fall in sGaw when given as five breaths. There was no significant difference between the starting sGaw and initial PC_{35} histamine on the two days. Both histamine and PGD_2 given as one breath caused a small fall in sGaw (−0·078 and −0·142 kPa^{-1} s^{-1} respectively). Histamine pretreatment did not significantly change PC_{35} histamine (0·86 before and 0·82 mg/ml after). However, PGD_2 pretreatment significantly decreased the PC_{35} histamine (1·55 before and 0·59 mg/ml after; $p < 0·01$). Neither bradykinin nor methacholine given by the same protocol potentiated the effect of histamine. This study demonstrates that PGD_2, but not bradykinin or methacholine, potentiates the response to a given dose of inhaled histamine.

Effect of S-carboxymethylcysteine on tracheal mucus secretion in "bronchitic" rats

NC TURNER, DF ROGERS, C MARRIOTT Chronic exposure of rats to tobacco smoke elicits epithelial secretory cell hyperplasia and submucosal gland hypertrophy (Jeffery and Reid *J Pathol* 1981;**133**:341–59), which is associated with an increase in secretion into the tracheas of anaesthetised animals (Jeffery *et al J Physiol,* in press). The present study investigates whether this hypersecretion is inhibited by *S*-carboxymethylcysteine (SCMC, Mucodyne), an agent which is used in the treatment of bronchitis. Two groups of male specific pathogen free rats were rendered "bronchitic" by exposure to the smoke of 25 cigarettes per day for 14 days, one group being given 1% SCMC ad lib in their drinking water over the same period. A third group of rats not exposed to tobacco smoke served as controls. At the end of the exposure period the rats were anaesthetised and secretion into tracheal segments, isolated in situ, was assessed. Following equilibration, the mean basal concentrations μg/sample) of fucose, hexose, and protein were higher in bronchitic rats than in controls. The values are: controls—fucose 3·0 (1·12); hexose 51·36 (10·55); protein 1279·6 (412·3) and bronchitics—35·15 (18·59) (SD); 117·1 (33·07); 2090·4 (546·1) μg/30 min respectively. The elevation in secretory rate associated with the cellular "bronchitic" changes was prevented by concurrent administration of SCMC, the values being: fucose 4·91 (0·80) ($p < 0·01$); hexose 33·24 (11·46) ($p < 0·05$); protein 1510·98 (167·66) (NS).

Isolation of spheroplasts of Haemophilus influenzae in primary culture on supplemented selective medium from the sputum in persistent bronchial infection: a reservoir for reinfection

D ROBERTS, A RUTMAN, E HIGGS, P COLE Supplementing selective medium for *Haemophilus influenzae* (Roberts DE, Cole PJ. *Lancet* 1980;i:796) with the cell wall constituent *N*-acetyl-D-glucosamine (NAG) promoted primary culture of large spheroplasts, from the sputum of patients with persistent bronchial sepsis, similar to those inducible with amoxycillin in vitro (Roberts DE *et al. J Clin Pathol* 1974;**27**:560). Electron microscopy showed these to possess intact cell walls and to revert to normal forms on subculture. In vitro titration of the minimum inhibitory concentration (MIC) and mean bactericidal concentration (MBC) of amoxycillin for *H influenzae* induced spheroplasts at concentrations (< 1·5 μg/ml) most commonly achieved in sputum by conventional oral dosage. These abnormal forms (which are a reservoir for reinfection in vivo) should be vulnerable to cell wall attacking antibiotics; but the intrabronchial (sputum) concentration (MBC) of amoxycillin required to kill *H influenzae* was found to be 3 μg/ml. Appropriate oral dosage of antibiotic is required to achieve such a sputum level, particularly in view of the fact that MIC and MBC laboratory titrations are performed under ideal conditions, which are not present in patients with chronic bronchial infection.

Histones: a role as opsonins

C KELSEY, P COLE "Classical" opsonisation of particles with immunoglobulin and complement enhances phagocytosis and related cellular events, such as respiratory burst activity. Basic proteins have also been shown to influence phagocyte particle interaction. Histones are the most abundant basic protein in tissues, being found (for example, in sputum) during inflammation. We have investigated the effect of nuclear histones (types 1, 2, 3) and other basic proteins (protamine, lysozyme, polyarginine, polylysine) on luminol enhanced chemiluminescence induced in human polymorphs by unopsonised zymosan, unopsonised bacteria (*Staphylococcus, Streptococcus pneumoniae, Haemophilus influenzae, Escherichia, Pseudomonas, Klebsiella,* and *Listeria*), and zymosan opsonised with pooled human serum. Arginine rich histones, types 2 and 3 enhanced chemiluminescence elicited from polymorphs by unopsonised zymosan 10 fold in a dose dependent manner maximal at 250 μg/ml. This value was similar to that induced by zymosan opsonised by 50% pooled human serum. Polyarginine produced similar enhancement but other basic proteins with similar PI values (9·5–10·7) produced less than three fold enhancement. Histone type 2 also enhanced chemiluminescence elicited by all unopsonised bacteria tested except hydrophobic *Listeria;* 10–25 μg/ml caused 40% inhibition of chemiluminescence in polymorphs by opsonised zymosan.

Defective opsonisation of Haemophilus influenzae by hypogammaglobulinaemic sera: in vitro effects of modified immunoglobulin preparations

CS MUNRO, PJ STANLEY, PJ COLE Hypogammaglobulinaemic (HG) patients, who commonly present with respiratory sepsis, are usually treated with intramuscular (IM) immunoglobulin, but intravenous (IV) treatment is sometimes necessary. To be safe, intravenous preparations must be chemically or enzymatically treated, which by modifying the Fc portion of the molecule may affect immunoglobulin function (Romer *et al. Vox Sang* 1982;**42**:74). One function can be tested with bacteria opsonised in vitro to stimulate luminol enhanced chemiluminescence of normal human neutrophils (Williams *et al Immunology* 1980;**41**:903). Using this technique we studied the ability of normal and hypogammaglobulinaemic sera to opsonise *Haemophilus influenzae,* a common respiratory pathogen of hypogammaglobulinaemic patients (Roberts and Cole. *Lancet* 1980;i:796). With eight normal sera mean chemiluminescence, expressed as percentage of a pooled serum standard, was 97% (SD 8%). Sera from five hypogammaglobulinaemic patients (three on intramuscular treatment) resulted in chemiluminescence of 55% (18%) ($p < 0.001$ compared with normal). In vitro addition of various immunoglobulin preparations at 10 mg/ml to the hypogammaglobulinaemic sera resulted in opsonic activity reflected by chemiluminescence as follows: Cohn fraction II (IM) 111% (18%) ($p < 0.001$ compared with hypogammaglobulinaemic sera alone); β propionolactone treated (IV) 78% (10%) ($p < 0.05$); pH4 treated (IV) 97% (10%) ($p < 0.01$); pepsin cleaved (IV) 52% (13%) (NS). We conclude that pH4 and β propionolactone treated immunoglobulins retain opsonic activity for *H influenzae.*

Measurement of growth factor production by alveolar macrophages with a rapid assay for fibroblast numbers grown in microwell cultures

MH OLIVER, GA CURRIE, GJ LAURENT, PJ COLE Alveolar macrophages, when activated in insterstitial lung disease or by manipulation in vitro, secrete growth factors stimulating fibroblast replication. Bitterman *et al (J Clin Invest* 1982;**70**:806–22) have described a serial dilution technique for quantifying growth factor concentration in macrophage conditioned culture medium. We have adapted this technique for use with fibroblasts grown in 96 well plates, which allows economies of scale and ease of handling. It required an assay for the small number of fibroblasts in a microwell culture. We describe this new assay and illustrate its use in measuring growth factor concentration. The assay involves (1) fixing the fibroblast monolayer with 10% formol saline, (2) staining with 1% methylene blue, (3) washing away unbound dye, (4) eluting bound dye into 0·1 mol/l HCl/C_2H_5OH (1:1), and (5) measuring absorbance at 650 nm of the dye solution with a microwell plate spectrophotometer. Absorbance is proportional to cell numbers for a range of epithelial and fibroblast cell lines. The coefficients of variation are: within plate 4·36%; between plates component 2·03%. The assay is rapid and easy to perform. It is particularly suited to the measurement of growth factor concentration, as the serial dilution cultures required can be set up in replicate in a single 96 well plate.

Increased capacity for solubilisation of immune complexes in patients with cryptogenic fibrosing alveolitis

PM EVANS, PL HASLAM, M TURNER-WARWICK Sera from patients with cryptogenic fibrosing alveolitis (n = 38) showed an increased ability to solubilise radiolabelled immune complexes compared with normal controls (n = 30) ($p < 0.001$). Of these, 10/15 (66%) untreated and 12/23 (52%) prednisolone or cyclophosphamide treated patients had elevated solubilisation. Solubilisation is mediated by the complement system, but the increase in solubilisation capacity was not a simple acute phase response to inflammation and did not correlate with levels of C3, C4, factor B, C reactive protein, or the erythrocyte sedimentation rate. Longitudinal studies have been conducted and changes in solubilisation assessed in relation to changes in lung function. A total of 200 serum samples (mean five per patient) were studied over a period of from two to 21 months (mean 14). Patients who showed progressive deterioration either in the FVC, the transfer factor or both (>10% change) all showed a parallel fall in solubilisation capacity (>10%). By contrast, solubilisation levels either increased (>10%) or remained constant (within 10%) in patients who improved or who showed stabilisation. These findings provide evidence that complement dependent events are related to clinical progression in cryptogenic fibrosing alveolitis; whether this reflects a normal host response in regulating the formation and clearance of immune complexes, which if exceeded leads to clinical deterioration, or implies a more direct role for complement in pathogenesis is not known.

Transepithelial potential difference in cystic fibrosis

JG HAY, DM GEDDES Membrane transport of ions and solutes may have a major role in bronchoalveolar clearance and airway humidification. The electrical potential generated by an epithelium is one facet of membrane transport that can be measured. Knowles *et al (N Engl J Med* 1981;**305**:1489–95) have demonstrated an increased negative potential across respiratory epithelia and Quinton (*Nature* 1983;**301**:421–2) across sweat duct epithelia of cystic fibrosis patients. The explanation proffered is either a decreased permeability to chloride or increased transport of sodium by cystic fibrosis epithelia—the former explanation being most acceptable on the basis of ionic substitution experiments. We have measured the potential difference between the interstitial fluid of the forearm, several skin sites, and two nasal sites in a group of normal individuals (22) and patients with cystic fibrosis (19) (table). We have confirmed the observations of increased potential across the ciliated nasal epithelium (the tip of the turbinate is squamous) and have also found increased potential across several skin sites. Because of the overlap of normal and cystic fibrosis values these measurements have limited

Mean transepithelial potential differences (SE) (in mV)

Site	*Normal*	*Cystic fibrosis*	*Significance (p) (Mann-Whitney)*
Arm	−13 (1·2)	−21 (2·1)	< 0·01
Cheek	−14 (1·4)	−14 (1·4)	NS
Lip	−19 (1·1)	−26 (2·7)	< 0·05
Nose	−19 (1·3)	−17 (1·7)	NS
Tip inferior turbinate	−10 (0·8)	−10 (1·3)	NS
1 cm distal inferior turbinate	−13 (1·3)	−25 (3·4)	< 0·02

diagnostic application, but the finding of a diffuse abnormality in cystic fibrosis may point to an important pathogenetic mechanism.

Tar of tobacco smoke interacts with pulmonary surfactant

R DAVIS, T HIGENBOTTAM, N CRACKNELL, C HILL, C MORLEY We suspected that "tar" of tobacco smoke can physically intereact with a monolayer of pulmonary surfactant. To test this we have studied the effect (see table) of tobacco smoke on surface tension of surfactant and water on a Longmuir-Wilhemy balance. Tobacco smoke was generated by a single port smoking machine providing eight puffs of 35 ml, which delivered over the trough surface. Both whole smoke and gas phase from a middle tar cigarette was used. Surfactant was obtained by lavaging isolated rabbits lung, spinning out cells at 1200 rev/min (5 min) and supernatant freeze dried. Studies were performed at least in triplicate.

"Tar" but not gas phase of tobacco smoke physically interacts with surfactant. This interaction may explain retention of tar within the peripheral airspaces and could account for the bronchiolitis and macrophage alveolitis in symptomless cigarette smokers (Niewoekner DE *et al. N Engl J Med* 1974;**291**:755–8).

Ciliary function in Young's syndrome

M GREENSTONE, A RUTMAN, W HENDRY, P COLE Like males with primary ciliary dyskinesia, patients with Young's syndrome are infertile and have decreased tracheobronchial clearance and a tendency to recurrent sinopulmonary infection. The finding of normal ciliary ultrastructure in some patients does not exclude ciliary dyskinesia (Greenstone, *et al. Thorax* 1983;**38**:875). Ciliary function in this condition has not been reported. Thirteen azoospermic men (mean age 38·8 (SD 7·8) years) were studied. Twelve had bronchiectasis, of whom six had had lobar resections. Eleven had radiological evidence of sinusitis. Nasal mucociliary clearance (Stanley *et al. Br M Dis Chest* 1984;**78**:62) was prolonged beyond 30 minutes in five and grossly prolonged (> 1 hour) in six. Nasal cilia were obtained from the inferior turbinate by a brushing technique and ciliary beat frequency measured photometrically. The mean ciliary beat frequency of 11 subjects was 13·0 (SEM 0·87) Hz in 11 subjects and was not significantly different from that of 15 healthy controls—13·8 (1·2) Hz. Transmission electron microscopy of nasal cilia (mean 200 cross sections) revealed only occasional microtubular abnormalities (<6%) and a normal complement of dynein arms. Intrinsic ciliary function is normal in Young's syndrome, suggesting that the observed mucus impaction in respiratory and genital tracts is due to an abnormality of epithelial secretions.

Oral high frequency oscillation increases mucociliary clearance in normal man

RJD GEORGE, MA JOHNSON, D PAVIA, JE AGNEW, SW CLARKE, DM GEDDES Data on the effect on the mucociliary clearance of oscillating air within the lungs is conflicting. By means of a technique to superimpose oral high frequency oscillation (OHFO) on tidal breathing (*Thorax* 1984;**39**:234) changes in mucociliary clearance during oral high frequency oscillation were studied in seven normal non-smokers by monitoring the clearance of inhaled radio labelled aerosol from the lungs. Following inhalation of 5 μm ^{99m}Tc labelled particles under controlled conditions, whole lung clearance was monitored by scintillation counter half hourly for six hours with a final count at 24 hours, from which tracheobronchial deposition and clearance could be calculated. Control and oral high frequency oscillation runs were performed on separate days in random order. Oral high frequency oscillation was applied by a bass loudspeaker through a mouthpiece to superimpose sine wave oscillations (RMS input pressure 1·2 cm H_2O, mean pressure zero) on normal breaths. During OHFO days 30 minutes of oscillation alternated with 30 minutes

Effect of tobacco smoke on surfactant (mean values with standard deviations in parentheses)

	Minimum surface tension (dyn/cm)	*Maximum surface tension (dyn/cm)*	*Hysteresis area (cm²)*	*Hysteresis energy (MJ)*
Rabbit lung surfactant	3·1 (0·9)	34·0 (±2·0)	32·4 (±2·0)	0·170
Whole smoke	18·2 (1·6)	36·5 (±0)	18·1 (±0·9)	0·095
Whole smoke plus surfactant	21·0 (0·5)	31·6 (±2·2)	11·4 (±2·3)	0·060
Gas phase plus surfactant	3·8 (0·3)	34·3 (±0·6)	28·1 (± 1·2)	0·147

Gas phase had no effect on surface properties of water.

of rest. Between 3 and 4·5 hours mucociliary clearance with OHFO exceeded control by approximately 10% ($p < 0·05$). The time taken to eliminate 90% of deposited radioaerosol from the tracheobronchial tree fell from 4 hours 50 minutes (range 1 hour 52 minutes to 6 hours 50 minutes) during control to 3 hours 43 minutes (range 2 hours 28 minutes to 5 hours 54 minutes) during the OHFO run ($p < 0·05$). This comfortable, simple technique may be of therapeutic benefit to those with chronic sputum retention and merits further investigation.

Lack of effect of sputum sols from cystic fibrosis patients on ciliary beat frequency of human nasal and rabbit tracheal epithelium

W GRIFFIN, J RUTLAND, P COLE Ciliary dyskinetic factor or factors has been demonstrated in cystic fibrosis serum for rabbit tracheal but not human nasal and tracheal cilia (Rutland J *et al. Am Rev Respir Dis* 1983;**128**:1030). We report the effect of sputum sols from 10 cystic fibrosis patients on normal human nasal and rabbit tracheal cilia after centrifugation of sputum at 30 000 *g* for 90 minutes at 4°C and storage of the supernatant fluid in liquid nitrogen. Ciliary beat frequency was measured at 37°C by a photometric technique (Rutland J, Cole PJ. *Lancet* 1980;ii:564). Ciliary beat frequency was unimpaired in human and rabbit cilia exposed to neat sol and sol diluted 25%, 50%, and 75% with tissue culture medium 199. However, addition of cystic fibrosis serum to cystic fibrosis sputum sol in ratios of 1:1 and 1:3 (serum:sol) reduced and abolished (respectively) the inhibition of rabbit tracheal cilia seen with exposure to neat serum. Cystic fibrosis diluted to 25% concentration in medium 199 was still ciliostatic; so the phenomenon is unlikely to be a dilutional effect but may be due to substances (eg enzymes) in the cystic fibrosis sputum sol inactivating ciliary dyskinetic factors present in cystic fibrosis serum.

Products released from bacteria are toxic for human ciliary function in vitro

R WILSON, D ROBERTS, P COLE An in vitro ciliostatic effect of bacteria has been reported in trachea of chick, rodent and human fetus (Denny F. *J Infect Dis* 1974;**129**:93), *Haemophilus influenzae* being used as the bacterium. We have studied the effect of bacteria (*H influenzae, Staphylococcus aureus, Pseudomonas aeruginosa*) on human nasal cilia, measuring their in vitro ciliary beat frequency by a photometric technique (Rutland J, Cole PJ. *Lancet* 1980;ii:564). Some supernatants were obtained from centrifuged 18 hour broth cultures. Other supernatants were filtered (0·2 μm) and thirdly, some cultures were exposed to antibiotic (ciprofloxacin 100 μg/ml for one hour) and then ultrasonicated (or, with staphylococci, lysostaphin added). Test material was mixed 50:50 with medium 199 containing nasal ciliated epithelium. Unfiltered *Ps aeruginosa* supernatants (n = 5) slowed cilia to 55% of control ciliary beat frequency, to 80% after filtration, and to 62% after ultrasonication. With *H influenzae* (n = 4) cilia were slowed to 80%, 84%, and 74% respectively of control values. Slowed cilia were dyskinetic. The effects were abolished by heating to 56°C for 30 minutes. Staphylococcal products (n = 4) were not ciliotoxic. We conclude that *Ps aeruginosa* and *H influenzae* release a factor or factors ciliotoxic for human cilia in vitro.

Ciliotoxic agents in nose drops: Discrepancy between in vitro and in vivo results

PJ STANLEY, WM GRIFFIN, MA GREENSTONE, PJ COLE Patients with allergic and infective respiratory disease often require chronic topical nasal therapy. Because preservatives in nasal drops are toxic to animal cilia in vitro (van de Donk *et al. Rhinology* 1980;**18**:119) we studied the effect of Betnesol drops (betamethasone 0·1%) and Betnesol-N drops (betamethasone 0·1%, neomycin 0·5%) on human nasal ciliary beat frequency in vitro (Rutland and Cole. *Lancet* 1980;ii:564) and nasal mucociliary clearance (Stanley *et al. Br J Dis Chest* 1984;**78**:62) after acute and longer term use. Both preparations caused immediate ciliostasis at 3 drops/ml. Bethamethasone 0·1% was not ciliotoxic, but neomycin 0·5% reduced ciliary beat frequency to 82% of control after six hours (Tissue culture medium alone). The preservatives benzalkonium chloride (in Betnesol) and thiomersal (in Betnesol-N) were ciliotoxic at concentrations equivalent to a dilution of 1:25 of the drops. The mean nasal mucociliary clearance did not significantly change 15 minutes after three drops of Betnesol in six healthy controls, after treatment for one month with Betnesol in 36 patients with perennial rhinitis, or with Betnesol-N in 40 patients with chronic sinusitis. Despite in vitro ciliotoxicity, these preparations did not impair nasal mucociliary clearance after topical administration.

Effects of iodopropylidene glycerol on tracheobronchial mucociliary clearance in patients with stable chronic bronchitis

SW CLARKE, JE AGNEW, JM GLASSMAN, PP SUTTON, MT LOPEZ-VIDRIERO, JP SOYKA, D PAVIA Iodides have been prescribed for more than a century for their expectorant action. However, there is little objective evidence of their efficacy. We carried out a double blind, crossover study in 14 patients with stable chronic bronchitis (13 M, 1 F; mean (SD) age 66 (10) years, % predicted FEV_1 57 (35)) to ascertain the effect on tracheobronchial clearance of one week's treatment with iodopropylidene glycerol (IPG Organidin), two tablets (each containing 15 mg organically bound iodine) four times daily, compared with matched placebo. Tracheobronchial clearance was measured by an objective, non-invasive radioaerosol technique. The drug did not significantly alter it in the group as a whole but did significantly enhance it in six patients who expectorated during both placebo and IPG six hour observation periods. In four patients who did not expectorate in either period no change in tracheobronchial clearance occurred. In 10 patients who expectorated in either one or both observation periods a significant positive correlation ($p < 0·01$) was found between an index of the patients' sputum pro-

duction and improvement in tracheobronchial clearance following IPG treatment. These findings indicate that IPG can be an effective expectorant in patients with mucus hypersecretion and particularly so in patients with copious sputum production.

What is the commonest pulmonary function abnormality in sarcoidosis?

JM SHAYLOR, TC STOKES, BDW HARRISON A prospective study of lung function in a consecutive, unselected series of 47 newly diagnosed patients (24 men) with sarcoidosis (aged from 21 to 69 years) revealed: Seventeen stage 1 patients: no restrictive defects (VC < 80%; TLC < 80% predicted normal), 1 low transfer factor (TLCO < 70% predicted normal), 2 obstructive defects (maximum expiratory flow at 50% VC < 50% predicted normal, FEV_1/FVC < 70%). Twelve stage 2 patients: 1 restrictive defect, 1 low TLCO, 8 obstructive defects. Eleven stage 3 patients: 4 restrictive defects, 6 low TLCO, 6 obstructive defects. Six patients with non-thoracic sarcoid: no restrictive defect, 1 low TLCO, 2 obstructive defects. Eighteen of 47 patients had airways obstruction, 10 had severe airways obstruction (MEF_{50} < 40% normal). Eleven of 18 had never smoked, 3 were ex-smokers, none had asthma. Also referred during this period were 4 men with chronic sarcoidosis (aged 28–32 years, 2 non-smokers, 1 ex-smoker) who had severe airways obstruction (MEF_{50} 9–34% normal). Another non-smoking man aged 67 died of cor pulmonale secondary to chronic sarcoid airways obstruction. Airways obstruction is the commonest and most clinically important functional abnormality in sarcoidosis.

Sarcoidosis in London: differences between caucasians, blacks and Asians

WM EDMONDSTONE, AG WILSON The incidence and clinical features of sarcoidosis were studied in a retrospective survey of 68 caucasians, 59 black immigrants, and 29 Asian immigrants attending two South London hospitals since 1969. The annual incidence in the local community in 1977–8 was 19·8 per 10^5 for blacks and 16·8 per 10^5 for Asians compared with 1·5 per 10^5 for caucasians. Caucasians presented with erythema nodosum more commonly than blacks ($p < 0.001$) or Asians ($p < 0.05$). Compared with caucasians, blacks presented at a later age ($p < 0.05$), had more widespread extrathoracic disease ($p < 0.001$), and were more commonly treated with corticosteroids ($p < 0.001$). Asians also had more extrathoracic sarcoidosis than caucasians ($p < 0.001$) and more of them were treated with corticosteroids ($p < 0.05$). A stage 2 chest radiograph at presentation ($p < 0.05$) and skin sarcoidosis ($p < 0.05$) were less common in Asians than blacks, but otherwise there were no significant differences between the two groups. In this study the incidence of sarcoidosis in Asians approached that in blacks, while the clinical features were intermediate in severity between those of blacks and caucasians. In both blacks and Asians the disease was more common, more severe, and more extensive than in caucasians.

Sarcoidosis in a racially mixed population: experience at Willesden Chest Clinic

PJ LUCE, MW McNICOL From 1960 to 1983 497 patients with sarcoidosis were seen. One hundred and fifty one were British (30%), 105 Irish (21%), 165 (33%) West Indian, and 35 Asian (7%). The estimated annual incidence/100 000 population was: British 4 Asian 14, Irish 21, and West Indian 58. There was a female preponderance in the Irish (65%) and West Indians (57%). The female mean age was 35 years, the male mean age 32 years. Asian and West Indian patients were older (mean 37 and 38 years), and Irish younger (mean 29 years). Skin and eye disease was rare in the Irish. In the West Indians multiple site disease and non-pulmonary disease were common, and erythema nodosum rare. Of the 374 patients followed up for five years or more, 261 had recovered (mean duration 2·5 years). In 54 patients duration was greater than 15 years; the longest recorded duration was 28 years. Fewer West Indians recovered. Two hundred and thirty nine patients had pulmonary disease. One hundred and nineteen recovered (mean duration 4 years); 88 had persistent disease (mean duration 16 years). Erythema nodosum had an excellent prognosis. Sarcoidosis affecting the eyes, ear, nose, and throat, central nervous system or liver had a high morbidity. Two hundred and twenty five patients received steroids, West Indian and Asian patients more often than others. The commonest indication was lung disease, but in West Indian and Asian patients extrapulmonary disease was important. Steroids did not affect interracial differences in the disease. The outcome was worse in patients treated with steroids.

Clinical, radiographic, and pathological features of amiodarone pulmonary toxicity

PA CORRIS, PC ADAMS, AJ WRIGHT, AR MORLEY, RWF CAMPBELL, GJ GIBSON Six patients (five male; ages 40–75 years) with amiodarone pulmonary toxicity have been seen in a regional cardiothoracic centre over three years. Duration of treatment was 6–26 months with daily maintenance doses of 200 mg (1), 400 mg (3), and 600 mg (2). All developed dyspnoea, and three had cough and two pleuritic pain. All had diffuse crackles and one had a pleural rub. In two patients the chest radiograph showed bilateral apical shadowing resembling that of tuberculosis; the other four showed diffuse alveolar or interstitial shadowing. In three patients left ventricular failure could be excluded only after measurement of wedge pressure. Lung function (five patients) showed a restrictive defect (VC 56–79% predicted) with a low transfer factor (28–69% predicted). Bronchoalveolar lavage (three patients) gave normal total and differential cell counts and ^{67}Ga scanning in one patient showed no increased lung uptake. Histology (five patients) showed varying degrees of inflammation with interstitial and intra-alveolar fibrosis: alveoli contained numerous foamy and granular macrophages. One patient who required artificial ventilation died after one week. Drug withdrawal and corticosteroids led to clinical and radiographic improvement in the other five, but two relapsed on reduction of steroids and one of these subse-

quently died. Lung function abnormalities persist in the survivors, suggesting that pulmonary damage is only partly reversible.

Does bronchography have a role in the assessment and management of patients with haemoptysis?

DK JONES, P CAVANAGH, JM SHNEERSON, CDR FLOWER After a full history clinical examination, chest radiograph, and bronchoscopy no cause for a patient's haemoptysis will be found in 15% of cases (Pursel SE, Lindskog GE. *Am Rev Respir Dis* 1961;**84**:329–36). Bronchography may be readily performed via the fibreoptic bronchoscope at the same time as bronchoscopy (Flower CDR, Shneerson JM. *Thorax* 1984;**39**:260–3). To assess the value of bronchography we have retrospectively studied 99 patients whose presenting complaint was haemoptysis, who gave no clinical history of bronchiectasis, and in whom no cause was found at bronchoscopy. The patients were divided into three groups on the basis of their chest radiograph: 12 had radiographic abnormalities compatible with previous tuberculosis; 10 had radiographic abnormalities suggestive but not diagnostic of bronchiectasis; and 77 had radiographs which were either normal or had incidental abnormalities not suggestive of bronchiectasis. Of these 77 patients, 14 (17%) were shown to have bronchiectasis by bilateral bronchography. Of the remaining 63 patients with normal bronchograms, 23% were diagnosed as having asthma, 27% had other recognised causes of haemoptysis—for example acute bronchitis—but in 50% no diagnosis was reached.

The diagnosis and spectrum of disease caused by Mycoplasma pneumoniae during an epidemic period

NJ ALI, M SILLIS, BE ANDREWS, PF JENKINS, BDW HARRISON We reviewed the clinical, radiographic, and microbiological data in 47 patients with *Mycoplasma pneumoniae* infection admitted to three Norfolk Hospitals during a 20 month period in 1982–3. Thirty nine of the 47 presented with pneumonia and eight with non-pulmonary infection. Among those with pneumonia, pleuritic pain (28%) and haemoptysis (15%) were more common than previously reported. Physical signs of consolidation were detected in 89% of patients with pneumonia. No specific radiographic pattern emerged. The *M pneumoniae* specific IgM test was positive in 42 of 45 patients (89%), in 39 the levels were diagnostic on admission. Sputum culture was positive in 19% and cold agglutinins in 57%, and the complement fixation test showed a fourfold rise in 29%. Non-pulmonary manifestations were: haemolytic anaemia in 17%, Stevens-Johnson syndrome (4·2%), neurological syndromes (4·2%), arthritis (2·1%), hepatitis (2·1%), and pericardial effusion (2·1%). One patient died. Seven patients presented with a history of illness longer than a month; in three the clinical picture suggested chronic disease (pulmonary tuberculosis, lymphoma, or unresolving pneumonia). There were no distinctive clinical or radiographic features of *pneumoniae* infection. The most useful diagnostic test is the rapid specific IgM test, positive in 86% of the admission sera.

Diffuse pulmonary shadowing in ventilated patients with acute renal failure: a diagnostic pitfall

MS HENDY, JD EDWARDS, P ACKRILL Diffuse pulmonary shadowing in acute renal failure is often due to pulmonary oedema secondary to fluid overload. Less common causes are infection, immune complex disease, and shock lung. We describe five patients admitted over 12 months with diffuse pulmonary shadowing and acute renal failure who required ventilation with $F_1O_2 \geq 0{\cdot}8$ and PEEP $\geq$ 5 cm H_2O. Initial assessment pointed to fluid overload and pulmonary oedema and suggested that weight loss during haemodialysis was desirable. Subsequent evidence revealed this to be inappropriate. Following dialysis one patient developed ischaemic hepatitis and in four others Swan-Ganz measurements indicated fluid depletion with low pulmonary wedge pressures (mean $\leq$ 2 mm Hg); however, elevated pulmonary artery pressures (mean $\geq$ 30 mm Hg) suggested primary lung pathology. Final diagnoses were immune complex disease with pulmonary and renal vasculitis in two and acute tubular necrosis and shock lung in three. Confusion with fluid overload occurred because of leg and sacral oedema (due to high central venous pressure and hypoalbuminaemia); facial and conjunctival oedema (due to PEEP); a raised central venous pressure; and diffuse pulmonary shadowing interpreted as pulmonary oedema. We recommend that in ventilated patients with diffuse pulmonary shadowing and acute renal failure invasive manometry is mandatory to allow differentiation between primary pulmonary disease and fluid overload.

Nebulised lignocaine as anaesthesia for fibreoptic bronchoscopy

JG PRIOR, JB ANDERSON, AJ WARDLAW, A SINCLAIR, JR WEBB The efficacy of nebulised lignocaine as anaesthesia for fibreoptic bronchoscopy was assessed. After premedication with intramuscular atropine 0·6 mg, 59 patients undergoing diagnostic fibreoptic bronchoscopy were randomly allocated to receive either 4 ml 4% lignocaine or 4 ml saline by jet nebulisation (Acorn, flow rate 5 l/min) prior to fibreoptic bronchoscopy. The study was double blind. All patients received 5 ml 1% lignocaine gel in each nostril and 4 ml 4% lignocaine on the vocal cords. Fibreoptic bronchoscopy was performed. Additional lignocaine or intravenous diazepam was administered if thought necessary by the bronchoscopist, who assessed patient tolerance and cough using a visual analogue scale (VAS). Blood lignocaine concentrations were measured at 10, 20, 30, 40, and 60 minutes after cessation of nebulisation. Less diazepam (2·2 (SD) 3·1) *v* 6·5 (5·5) mg ($p < 0{\cdot}01$) and additional lignocaine (3·6 (2·4)) *v* 5·9 (3·3) ml ($p < 0{\cdot}01$) were required in the 28 patients receiving nebulised lignocaine. Patient tolerance was better (VAS: 39 (21·6) *v* 56 (23·5) ($p < 0{\cdot}01$) and cough less (VAS: 41·8 (23·6) *v* 59·3 (22·5) ($p < 0{\cdot}01$) than in the saline group. Blood lignocaine concentrations were below the toxic range. Thus nebulised lignocaine has potential as anaesthesia for fibreoptic bronchoscopy.

Effect of budesonide on bronchial hyperreactivity

JPR HARTLEY Although clinical experience suggests that corticosteroids reduce bronchial hyperreactivity in asthma, evidence for this is surprisingly scarce. The effect of inhaled budesonide on histamine reactivity has been studied in 12 subjects with mild asthma (mean FEV_1 97% predicted). Their mean age was 32 years; eight were male and nine atopic. Ten subjects inhaled bronchodilators and four took regular sodium cromoglycate. After initial histamine challenge, subjects were randomly given budesonide 200 μg twice daily and matching placebo aerosol for four weeks each in a double blind crossover study. At the end of each period histamine challenge was carried out by the method of Cockcroft *et al* (Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. *Clin Allergy* 1977;7:235–43). The concentration causing a 20% fall in FEV_1 (PC_{20}) was obtained by linear interpolation from the log dose response curve. Main baseline FEV_1 following placebo was 3·37 l and following budesonide 3·56 l ($p = 0·001$). Mean PC_{20} values for histamine were 2·53 mg/ml for placebo and 3·71 mg/ml for budesonide ($p = 0·04$; paired t test). This study confirms that inhaled corticosteroids can reduce bronchial hyperreactivity, even in those with mild asthma who do not clinically require them.

Effect of regular treatment with sodium cromoglycate on non-specific bronchial hyperreactivity

K ROCCHICCIOLI, CAC PICKERING, M COLE, N HORSFIELD A randomised double blind crossover study was performed to compare the effect of regular treatment with sodium cromoglycate (20 mg four times daily for six weeks) and placebo on baseline bronchial hyperreactivity in 12 adult asthmatic patients (age range 16–55 years) whose airways were hypersensitive to inhaled histamine. The dose of histamine (provocation concentration) causing a 20% fall in the one second forced expiratory volume (PC_{20} histamine) was determined in each patient from dose-response curves. The PC_{20} histamine was measured on two separate occasions prior to entry into the study to establish baseline values, and thereafter at intervals of two weeks throughout the 12 weeks of the study. On analysis there was no significant difference between the mean PC_{20} histamine at the point of entry into the study and the mean PC_{20} histamine during treatment with placebo. In contrast, there was a significant increase in the mean PC_{20} histamine in the period of treatment with sodium cromoglycate compared with placebo ($p < 0·01$). We conclude that regular treatment with sodium cromoglycate is effective in reducing baseline bronchial hyperreactivity in adult patients with symptoms of asthma.

A mechanism for airway hyperresponsiveness?

EH WALTERS, PM O'BYRNE, LM FABBRI, JA NADEL Tracheal smooth muscle strips taken from dogs with induced airway hyperresponsiveness were compared with strips from control animals. Ten dogs were studied. On day 1 airway responsiveness (RL) to acetylcholine aerosol was assessed in vivo, as the log concentration causing a rise in RL of 5 cm H_2O l^{-1} s^{-1}. On day 3 five dogs were exposed to ozone (3·0 ppm for two hours) and five to filtered air. One hour later airway responsiveness to acetylcholine in vivo was reassessed. Ozone only caused a marked increase in responsiveness ($p < 0·001$). Each trachea was then rapidly removed and strips of smooth muscle were prepared. These were tested in vitro after two or six hours of washing. For each strip dose-response curves both for electrical field stimulation to postganglionic parasympathetic fibres and for acetylcholine were constructed. The mean frequency-response curve for electrical stimulation after two hours for strips taken from ozone exposed dogs was displaced to the left of the others ($p < 0·05$). All concentration-response curves for acetylcholine were similar. There was a significant correlation between the responsiveness of the airways in vivo immediately before sacrifice and the mean log EF_{50} for electrical stimulation in vitro for each dog obtained two hours later ($r = 0·701$, $p < 0·05$). The results suggest a prejunctional change in parasympathetic nerve endings in hyperresponsive airways, lasting for only a short time after removal from the inflammatory milieu.

Influence of non-specific airway reactivity on the immediate airway response to inhaled allergen in asthma

JS MANN, ST HOLGATE, PH HOWARTH The influence of non-specific responsiveness on the immediate airway response to inhaled allergen was investigated in 38 atopic asthmatic subjects (26 M, 12 F). Concentration-response studies were performed to define the inhaled allergen (Ag) and methacholine (M) concentrations required to produce 20% falls in FEV_1 (PC_{20}). To define mast cell sensitivity the allergen skinprick concentration producing an 8 mm weal (SW_8) was determined. FEV_1 values (% predicted) were not significantly different on the Ag (93·2 (SEM 3·1)) or M (94·0 (3·3)) concentration-response days. A weak correlation existed between the PC_{20} Ag and the PC_{20} M values ($r = 0·34$, $p < 0·05$) and the PC_{20} Ag and the SW_8 values ($r = 0·33$, $p < 0·05$). Correcting the specific airway responsiveness for the non-specific responsiveness (PC_{20} Ag/PC_{20} M) considerably improved the relationship between the airway and skin (SW_8) response to allergen ($r = 0·54$, $p < 0·001$). This relationship persisted if the patients were subdivided on the basis of allergen sensitivity (mixed grass pollen $p < 0·05$, *Dermatophagoides* sp $p < 0·01$) or into perennial (PC_{20} M 0·018–0·68 mg/ml; $p < 0·05$) and seasonal (PC_{20} M 0·94–53·0 mg/ml; $p < 0·02$) asthma. These results confirm that both mast cell sensitivity and non-specific bronchial responsiveness are important determinants of the immediate airway response to inhaled allergen in asthma.

Platelet activation during exercise induced asthma

CE JOHNSON, S DAVIS, PW BELFIELD, NJ COOKE, JA DAVIES Platelet activation occurs in antigen induced bronchoconstriction and has been taken to indicate mast cell involvement in asthma. We have investigated platelet activation in

exercise induced asthma, in which it is disputed whether mast cells play a part. Peak expiratory flow rate (PEFR) and plasma concentrations of the platelet release protein, platelet factor 4 (PF4), determined by radioimmunoassay were measured in 12 non-asthmatic healthy volunteers (controls) and in nine patients with stable asthma before and after six minutes' submaximal exercise on a treadmill. Ten minutes before exercise drug or placebo was administered from a pressurised inhaler. Controls received placebo only. Patients exercised on three separate occasions; placebo, sodium cromoglycate, and salbutamol were randomly allocated to the three tests for each patient. There were no significant changes after exercise in the controls in either mean PEFR (483 (SEM 27)) *v* 475 (29) l/min or PF4 (8·1 (2·4)) *v* 9·0 (2·1) μg/ml) at 10 minutes. In contrast, in patients there was a 27% fall in PEFR (423 (38) to 309 (39) l/min and a 92% rise in plasma PF4 (6·9 (1·0) to 12·7 (2·6) μg/ml) following placebo. The exercise induced changes in patients were abolished by pretreatment with cromoglycate or salbutamol. These results support the view that exercise induced asthma and antigen induced asthma share a common mechanism.

Platelet function in exercise and allergen induced asthma

SR DURHAM, JOAN DAWES, DS PEPPER, TH LEE, AB KAY In a previous study elevated plasma concentrations of platelet factor 4 (PF4) were reported in asthmatic subjects after allergen inhalation challenge when compared with methacholine induced bronchoconstriction (Knauer *et al. N Engl J Med* 1981;**304**:1404–6). The aim of the present study was to evaluate further the role of platelets in both exercise and allergen induced asthma. We measured β thromboglobulin (a further specific marker of platelet activation) and PF4 after allergen induced asthma (13 subjects), methacholine induced bronchoconstriction (9), and exercise induced asthma (EIA positive) (10), and in 10 documented asthmatics who did not wheeze after a comparable treadmill exercise task (EIA negative). Venous blood samples were collected into Thrombotect anticoagulant (Abbot Laboratories Ltd) according to a standard protocol, and plasma was separated and stored at -20°C prior to measurement of β thromboglobulin and PF4 by specific radioimmunoassay. There were no significant elevations in either β thromboglobulin or PF4 in any of the groups studied. Moreover, there were no significant changes in these variables when the allergen group was compared with the methacholine group, or when the EIA positive and negative subjects were compared. These results do not support a role for platelet activation in asthma.

Pulmonary platelet transit in allergic asthma

PW IND, AM PETERS, F MALIK, JP LAVENDER, CT DOLLERY Platelets produce a variety of bronchoconstrictor mediators. Measurements of plasma factors have implicated platelet activation in allergic asthma and sensitised guineapigs challenged with ovalbumin show pulmonary platelet aggregation accompanying bronchoconstriction. To investigate this further we injected ^{111}In labelled autologous platelets and ^{99m}Tc labelled red cells into three young asthmatic and three non-asthmatic volunteers and continuously monitored lung indium and technetium activities. Comparison with the corresponding activities in blood samples allowed calculation of pulmonary platelet (t_P) and red cell transit time (t_R). The asthmatics were then challenged with Dermatophagoides pteronyssinus, in a dose which one week earlier had induced a 20% fall in FEV_1, and monitoring continued. After equilibration, t_P/t_R for the non-asthmatics was 0·9, 1·02, and 0·98 compared with 1·04, 0·97, and 1·17 in the asthmatics. Following antigen induced falls in FEV_1 of 20–50% there was no change in ^{111}In or ^{99m}Tc signal and t_P/t_R was unaltered at 0·89, 0·89, and 1·05. Platelet survival time was normal at 10·2 days in both groups of subjects. Antigen induced bronchoconstriction was not accompanied by intrapulmonary platelet accumulation, though this does not exclude platelet activation.

Use of vasoactive intestinal peptide in severe acute asthma

A MORICE, PS SEVER The neurotransmitter vasoactive intestinal peptide (VIP) relaxes smooth muscle in vitro and is a bronchodilator in both man and animals. We have compared the bronchodilating properties of intravenous salbutamol and VIP in severe asthma. Eight inpatient volunteers recovering from status asthmaticus were given sequentially the following infusions in a single blind study: (1) vehicle for 15 minutes; (2) VIP (6 pmol/kg/min) for 30 minutes; (3) vehicle for 15 minutes; and (4) salbutamol (5 μg/min) for 30 minutes. Peak expiratory flow rate (PEF—the best of two readings) was recorded at five minute intervals with a Wright peak flow meter and the pulse rate was recorded at the radial artery. Results were compared with the preinfusion baseline. All bronchodilating agents were withheld for at least eight hours and all studies were performed in the afternoon. Where marked "morning dipping" was present, baseline observations were continued for one hour. VIP caused bronchodilation in all subjects after 30 minutes' infusion (mean improvement in PEFR 26 (SEM 9) l/min; $p < 0.01$). Salbutamol infusion caused a mean bronchodilation of 39 (19) l/min. Both infusions were associated with tachycardia, mean pulse increasing by 14 beats/min with VIP compared with 16 beats/min with salbutamol. These preliminary results provide further evidence that intravenous VIP may have a place in the treatment of severe bronchospasm.

Alpha$_1$ protease inhibitor function in broncho-alveolar lavage fluids and its relationship to cell profile

HM MORRISON, RA STOCKLEY Bronchoalveolar lavage fluids are thought to reflect the interaction between proteases and antiproteases at alveolar level more accurately than expectorated sputum. We have studied sequential aliquots of bronchoalveolar lavage fluids from 10 patients with chronic obstructive bronchitis and assessed the porcine pancreatic elastase (PPE) inhibitory capacity using the substrate Succ $(Ala)_3$ pNA to discover any differences in

inhibitory function between aliquots and determine whether this is related to the cellular profile of bronchoalveolar lavage. A total of 120 ml of normal saline was instilled through a fibreoptic bronchoscope in six aliquots and gently aspirated into two containers for separate analysis. All but one sample inhibited less PPE than predicted from the amount of α_1 proteinase inhibitor (α_1PI) present. There was no difference in the PPE inhibitory capacity between the first aliquot (mean 0·46 mol (SD 0·33) PPE inhibited/mol α_1 PI) and the second aliquot (mean 0·44 (0·27) mol PPE inhibited/mol α_1 PI), suggesting that α_1 PI is uniform throughout the lavage procedure. The absolute PPE inhibitory capacity (in μg PPE/μl bronchoalveolar lavage fluid) was not related to either the number of cells/μl bronchoalveolar lavage fluid for macrophages ($r = -0·2335$), neutrophils ($r = -0·0776$), or total white cell count ($r = +0·0884$). This suggests that α_1 PI function at bronchoalveolar level is independent of the number of cells present (and hence potential elastase burden).

Significance of mast cells in bronchoalveolar lavage fluid

RM AGIUS, RK KNIGHT, RC GODFREY, PJ COLE, ST HOLGATE Mast cells have been implicated in other inflammatory reactions besides immediate hypersensitivity. Their numbers and histamine content may vary in different circumstances. Mast cell contribution to bronchoalveolar lavage was studied in 91 consenting patients undergoing clinical fibreoptic bronchoscopy. They included 24 with bronchogenic carcinoma, 18 with sarcoidosis, and eight with cryptogenic fibrosing alveolitis. The bronchoalveolar lavage cells were stained with May-Grunwald-Giemsa and toluidine blue. In 26 of the bronchoalveolar lavage fluids supernatant and cells were separated and their histamine assayed. Comparison of differential mast cell counts when May-Grunwald-Giemsa stain was used with those obtained with toluidine blue showed a bias of $-0·074\%$ and a precision of $0·15\%$ ($y = 0·87x - 0·05$). Cell lysate histamine correlated better with counts of mast cells stained with toluidine blue ($r = 0·68$, $p < 0·001$, slope = 3·5 pg histamine/mast cells). Supernatant histamine correlated less well with mast cell count ($r = 0·57$, $p < 0·01$). The mean (SEM) mast cell differential counts were higher in cryptogenic fibrosing alveolitis (0·64% (0·15%) than in sarcoidosis (0·12% (0·02%); $p < 0·01$) and the latter counts were higher than in carcinoma (0·08% (0·01%); $p < 0·05$). Three asthmatics had a mean mast cell differential count of 0·085%. These data support the concept that mast cells may participate in diverse pulmonary inflammatory responses.

Altered T lymphocyte subsets in cells obtained by bronchoalveolar lavage from lobes containing peripheral squamous cell carcinomas

CWG TURTON, K CHIPPENDALE, J LINEHAN In an investigation of the immunological interactions between lung tumours and the host, 12 patients with peripheral squamous cell carcinomas of the lung and 10 bronchitic controls underwent bilateral bronchalveolar lavage at diagnostic fibreoptic bronchoscopy. All subjects were either present smokers or ex-smokers. The pathological diagnosis of squamous cell carcinoma was established by histological examination of bronchial biopsy in four patients and by cytological examination of bronchial brushings in six and specimens of percutaneous aspirations in two. The proportions of macrophages, lymphocytes, and granulocytes on May Grunwald and Giemsa stained cytocentrifuge preparations did not differ between the two sides of patients with tumours, or between patients and controls. Lymphocyte subsets were determined by a standard monoclonal antibody immunofluorescent technique. In cells from the neighbourhood of the tumour proportions of inducer and helper T4 lymphocytes were reduced and suppressor and cytotoxic T8 cells increased, resulting in a T4:T8 ratio (mean 0·5) less than that on the healthy contralateral side (mean 2·7) or in bronchitic controls (mean 1·8) ($p < 0·001$). Nothing suggested that these results were caused by either sampling factors or infection distal to the tumour. This major change of the proportions of tumour related immunoregulatory lymphocytes has implications both for the use of cytotoxic drugs and for the possible development of adjuvant specific immunotherapy.

Bronchoalveolar lavage fluid in cryptogenic pulmonary eosinophilia

CWG TURTON, J LINEHAN, K CHIPPENDALE Blood eosinophilia and chest radiographic shadowing in cryptogenic pulmonary eosinophilia may be transient, which can delay diagnosis. Three women aged 51, 67, and 74 years with cough, dyspnoea, intermittent blood eosinophilia, chest radiographic shadowing, steroid responsiveness, and no evidence of aspergillosis, drug hypersensitivity, parasitic infestation, or vasculitis were investigated. In one patient the predominant bronchoalveolar lavage cell was the neutrophil (88%), with 7% eosinophils, though there was no evidence of infection. In another 67% eosinophils were found. The third patient was lavaged one month after the apparent spontaneous recovery, yet 85% eosinophils were found in the recently affected middle lobe and 24% for the lingula, which had cleared radiographically. The results of studies of immunoregulatory lymphocytes and macrophage FC and C3b receptors were unremarkable. We conclude that (1) Eosinophilic alveolitis, as defined by the findings in the BAL fluid, exists. (2) Eosinophilia of BAL fluid may occur in the absence of blood eosinophilia suggesting underdiagnosis may happen. (3) Bronchoalveolar lavage may lack sensitivity in that marked eosinophilia was absent in one patient. (4) Examining bronchoalveolar lavage fluid has the advantage of being an assessment of the target organ rather than the transport vehicle (blood). (5) Bronchoalveolar lavage may occasionally avoid the need for open lung biopsy.

Blood and bronchoalveolar lavage T subsets in sarcoidosis and extrinsic allergic alveolitis

DA HUGHES, PL HASLAM, PJ TOWNSEND, M TURNER-WARWICK Patients with chronic pulmonary sarcoidosis (n

= 20) had reduced total circulatory T lymphocytes (OKT3+) ($p < 0.01$) and both helper-inducer (OKT4+) ($p < 0.001$) and cytotoxic-suppressor (OKT8+) ($p < 0.01$) T subsets compared with normal individuals ($n = 20$). By contrast, in extrinsic allergic alveolitis ($n = 9$) there was a significant increase in OKT8+ cells ($p < 0.05$) and trends of increase in OKT3+ and OKT4+ numbers ($p < 0.1$). The OKT4:OKT8 ratio was significantly reduced in the sarcoid group ($p < 0.025$) but not in extrinsic allergic alveolitis. However, in comparisons of similar numbers of separated lymphocytes both patient groups showed a similar impairment of in vitro T suppressor function against the proliferative response of allogeneic T cells to phytohaemaglutinin ($p < 0.025$), although suppression of the immunoglobulin secreting response of B cells to pokeweed mitogen stimulation was normal. In bronchoalveolar lavage fluid lymphocytes were increased (>11%) in 18 of the sarcoid patients (range 2–73%) and in the nine with extrinsic allergic alveolitis (62% (17%), range 33–77%). In sarcoidosis the majority had higher OKT4:OKT8 ratios than in their blood, often associated with T cells bearing either both or neither subset markers. In contrast, most extrinsic allergic alveolitis patients had reduced OKT4:OKT8 ratios in their bronchoalveolar lavage fluid and only one had anomalously marked T cells.

Bronchoalveolar lavage and clearance of ^{99m}Tc-DTPA in asbestosis

AR GELLERT, RJD WINTER, S UTHAYAKUMAR, A LANGFORD, RM RUDD The half time clearance of an inhaled aerosol of technetium 99m labelled diethylene triamine pentacetate from lung to blood (T½LB) was measured with a gamma camera in 24 patients (mean age 58, range 45–74 years) with clinical and radiological features of asbestosis and a mean time since first asbestos exposure of 34 (25–47) years. Bronchoalveolar lavage was performed in 20 patients and lung function tests in all. Mean T½LB was 21·6 (9·5–57·0) minutes in 10 smokers, significantly less than the 32·8 (10·0–59·5) minutes in 14 current non-smokers ($p < 0.05$). In non-smokers T½LB correlated negatively with time since first asbestos exposure ($r = -0.52$, $p < 0.05$) and duration of asbestos exposure ($r = -0.63$, $p < 0.025$). The mean results for the bronchoalveolar lavage fluid were: total cells per ml 485×10^3 (264–660), asbestos bodies per ml 142 (15–642), % macrophages 65 (18–93), % lymphocytes 12 (1–47), % neutrophils 19 (2–68), % eosinophils 4 (0–21). Smokers had a lower percentage of lymphocytes than non-smokers ($p < 0.02$). Asbestos bodies correlated positively with % macrophages ($r = 0.82$, $p < 0.001$) and PaO_2 on exercise ($r = 0.54$, $p < 0.025$) but negatively with % lymphocytes ($r = -0.49$, $p < 0.05$) and time since first exposure to asbestos ($r = -0.61$, $p < 0.01$). In non-smokers T½LB correlated positively with % macrophages ($r = 0.76$, $p < 0.005$) and asbestos bodies ($r = 0.67$, $p < 0.025$). In asbestosis increased inflammatory cells other than macrophages in the bronchoalveolar lavage fluid are associated with longer time since first exposure to asbestos, more disturbed T½LB and greater physiological impairment.

Lung permeability in patients with interstitial lung disease

CFA PANTIN, A BRITTEN, R LAWRENCE, M SWEATMAN, M TURNER-WARWICK The clearance of technetium-99m labelled diethylene triamine penta-acetate (^{99m}Tc-DTPA) has been considered as a measure of lung permeability (Jones JG *et al. Br J Anaesth* 1982;**54**:705–21). A mono-exponential curve describes the clearance with time in the lungs of normal subjects and patients with airways obstruction and asthma, whether smokers or non-smokers. We measured the clearance of ^{99}Tc DTPA from the lungs of nine patients with cryptogenic fibrosing alveolitis and two with sarcoidosis, all proved by lung biopsy. All had a multiexponential clearance with time, which could be described as two components: one fast, with a range of half time clearance from lung to blood (T½) of 2·2–8·2 minutes, and the other slow (T½ 23–105 minutes). The proportion amount of Tc^{99} DPTA cleared in the fast component ranged from 7% to 58%. Only in patients with adult respiratory distress syndrome has a similar multiexponential clearance been reported (by Jones *et al*—see above). The disease process in interstitial lung disease is known to have a patchy distribution, with areas of normal lung parenchyma interspersed with diseased parenchyma. This may explain the multiexponential clearance found. We do not yet know whether the observed increase in permeability differentiates between early changes associated with oedematous but intact pulmonary epithelium and late changes associated with destroyed epithelium and bare basement membrane.

Clearance of ^{99m}Tc Labelled DTPA in asbestos exposed subjects

AR GELLERT, JA LANGFORD, RJD WINTER, RM RUDD The half time clearance of an inhaled aerosol of technetium 99m labelled diethylene triamine pentacetate fom lung to blood (T½LB) was measured with a gamma camera in 20 non-smoking subjects (mean age 53·9, range 40–69 years) with previous occupational asbestos exposure but no clinical or radiological evidence of asbestosis, and 20 non-smoking normal subjects (mean age 54, range 40–62). Exposed subjects underwent lung function tests. Mean T½LB was 44·7 (12–102) minutes in exposed subjects, significantly less than 57·2 (30·5–109) minutes in normal subjects ($p < 0.05$). There was no correlation between age and T½LB in either group. In exposed subjects T½LB showed a weak rank correlation with the membrane component of TLCO (Dm) ($r = 0.40$, $p < 0.05$) but no significant correlation with FVC, TLC, TLCO, KCO, resting PaO_2, or change in PaO_2, with exercise. In six exposed subjects T½LB was shorter than in any of the normal subjects. These six did not differ from the other 14 exposed subjects in any physiological variables. In a separate study of 14 non-smoking patients with clinical and radiological evidence of asbestosis, we found a mean T½LB of 32·8 (10·0–59·5) minutes. T½LB is abnormal in some asbestos exposed subjects without clinical, radiological, or physiological evidence of asbestosis. Follow up will show whether it is an early indicator of development of interstitial lung disease.

Bronchoconstriction stimulated by hyperventilation of cold dry air: magnitude and duration of inhibitory effect of three doses of sodium cromoglycate

EF JUNIPER, KM LATIMER, RS ROBERTS, FE HARGREAVE The magnitude and duration of the inhibitory effect of sodium cromoglycate on the bronchial response to heat and water loss was examined in a double blind and randomised controlled trial. Eight well controlled asthmatics were studied. On four separate days doses of either 2 mg, 10 mg, 20 mg, or placebo were given by metered dose inhaler. Twenty minutes, two hours, and four hours after each medication bronchial responsiveness to isocapnic hyperventilation of cold dry air was measured by a standardised dose response method (*Am Rev Respir Dis* 1980;**121**:621–8). At 20 minutes all three doses inhibited bronchoconstriction ($p < 0.01$) and there was no difference in the magnitude of the inhibition between the doses. All three doses progressively gave less protection with time but at four hours all were still different from placebo. The rate of decrease in protection was greatest with 2 mg and least with 20 mg. The difference in protection between these doses was significant at both two and four hours ($p < 0.05$). The results demonstrate that, although the initial magnitude of inhibition is not different between 2 mg and 20 mg, the rate of decrease in protection is dose related.

Airflow obstruction induced by ultrasonically nebulised water: the underlying mechanism

KM ROCCHICCIOLI, CAC PICKERING The mechanism by which an inhalation of ultrasonically nebulised water, "fog," causes airflow obstruction in asthmatics has not been established. Using a pair of "fog" challenges with a 40 minute interval, we looked for the presence of a refractory period in 18 asthmatic patients (aged 16–67 years). The subjects fell into two groups. Eight in the "non-refractory" group showed less than 25% reduction in response to the second challenge, but the 10 in the "refractory" group showed at least a 30% reduction ($p < 0.001$). Ten subjects also performed "fog" challenges after premedication with inhaled atropine methonitrate and, separately, sodium cromoglycate. In five subjects in whom no refractoriness after "fog" challenge was seen there was significant protection from atropine methonitrate ($p < 0.001$). The remaining five subjects, in whom a refractory period was demonstrated, gained no protection from atropine. All subjects developed significant protection following sodium cromoglycate ($p < 0.001$). We suggest that more than one mechanism is responsible for the airflow obstruction induced by "fog" challenge.

Is intravenous aminophylline usage in accident and emergency departments haphazard?

C MUNRO, K PROWSE Intravenous aminophylline is often given in accident and emergency departments to patients with acute asthma or bronchitis, although many are already receiving treatment with oral theophylline. We examined the influence of drug history on emergency aminophylline dosage and measured serum theophylline before and 1–2 hours after the bolus in 33 adult patients. We found that 250 mg aminophylline was given in 32/33 cases, including 16/17 who gave a clear history of previous theophylline treatment. Five of the 16 patients thought not to be taking oral theophylline had detectable serum levels. In three the history was unsatisfactory, but two patients were taking a compound preparation whose theophylline content was not appreciated by casualty doctors. In 11/22 patients, already having treatment, serum theophylline was above 10·0 mg/l (including two > 20 mg/l). The mean concentration rose from 10·4 mg/l (range < 2·5–40·0 mg/l) to 16·2 mg/l (range 6·0– > 50·0 mg/l), with 18 in the range 10·0–20·0 mg/l but still only 2 > 20 mg/l). In the group without previous treatment, the mean serum theophylline after the injection was only 7·5 mg/l (range 5·8–9·7 mg/l). We conclude that more discrimination is required in the emergency use of aminophylline, both in the selection of patients and in the choice of dose. At present the main determinant of dose is the size of the ampoule.

Theophylline in chronic asthma: its role and the value of monitoring drug concentration

JPR HARTLEY, TJG BARLOW, P GRAHAM, JM HARRIS, CWG TURTON We studied 30 non-smoking chronic asthmatics (20 male), mean age 52 (range 21–71). All used bronchodilator inhalers, 26 inhaled steroids, and nine oral steroids. The individual dose of sustained release theophylline producing desired blood levels was found (peak 12–20, trough 8–12 μg/ml, EMIT), then subjects were allocated to receive placebo, theophylline 300 mg twice daily (standard), or individual dosage theophylline (titrated). The three treatments were given double blind in random order for four weeks. Assessment was made four weekly, and by diary card and PEFR recordings at home. In the whole group FEV_1, FVC, and PEFR were significantly better following both treatment periods than after placebo. Titrated dose was also significantly better than standard dose with respect to morning PEFR. One third of subjects had mild side effects, as did 20% on placebo. Fourteen subjects achieved adequate drug levels on the standard dose (mean 13·5 μg/ml). Sixteen subjects did not (mean 8·0 μg/ml) and required a dosage increase to reach the therapeutic range. All measurements of lung function were further improved by the increase, though only in clinic PEFR was this significant (means 379 and 335 l/min for titrated and standard doses; $p = 0.02$). Thus 53% of patients benefited directly from monitoring of drug concentrations.

Interaction of inhaled corticosteroids and beta$_2$ agonists in asthmatic subjects

AR HARRISON, R RICHARDS, P HOWARTH, AE TATTERSFIELD It has been suggested that part of the beneficial effect of corticosteroids in asthma is due to a permissive action on β_2 adrenoceptors. Previous studies have demonstrated potentiation between corticosteroids and β_2 agonists in vitro but clinical studies have been contradictory. We studied eight non-smoking patients with mild asthma aged 21–37 years (FEV_1 52–106% predicted). None had used

regular corticosteroid therapy in the past. Each was given, single blind, a two week course of placebo aerosol followed by a two week course of inhaled beclomethasone diproprionate, 250 μg twice daily. Dose response studies, using low concentrations of nebulised salbutamol (1, 2, 5, 10, 100, 400 μg), and as a control ipratropium bromide (2, 5, 10, 30, 100, 200 μg) were carried out, the airway response being measured as specific conductance (sGaw) and FEV_1. The two studies were carried out on adjacent days (1) before the start of treatment; (2) after two weeks of placebo; (3) after two weeks of beclomethasone; and two weeks after the cessation of all treatment. There was a dose related increase in sGaw and FEV_1 for both ipratropium and salbutamol on all four occasions. The response to both salbutamol and ipratropium after two weeks' beclomethasone was identical to the response on the other three occasions. This study found no evidence to support the suggestion that inhaled corticosteroids enhance β adrenoceptor responsiveness in patients with mild asthma.

Dose-response effect of sodium cromoglycate pressurised aerosol in exercise induced asthma

WM TULLETT, KM TAN, RT WALL, KR PATEL We have previously shown that the preventive effect of nebulised sodium cromoglycate in exercise induced asthma is dose related. The effect of different doses of sodium cromoglycate given by aerosol in exercise induced asthma is unknown. Using two pressurised aerosol formulations of sodium cromoglycate delivering 1 and 5 mg per actuation, we have compared the effect of 2, 10, and 20 mg aerosol sodium cromoglycate with that of a placebo in a double blind study in 11 patients (aged 19–51 years) with exercise asthma. The effect of sodium cromoglycate nebuliser solution was also studied (10 g/l—estimated dose 12 mg). The patients were exercised on a treadmill for up to eight minutes at submaximal work loads. The responses were assessed by change in FEV_1. The mean baseline FEV_1 before and after treatment was comparable on five days of testing. After exercise the mean (SEM) maximum percentage falls in FEV_1 after placebo; SCG nebuliser solution; and 2, 10, and 20 mg sodium cromoglycate aerosol were 31·3 (3·8), 9·4 (4·6), 19·4 (4·6), 13·7 (3·5), and 9·4 (1·9) respectively. Sodium cromoglycate inhibited exercise induced asthma at all the doses used and the protective effect increased from 2 to 20 mg. The protective effect of 20 mg sodium cromoglycate was comparable to that of 12 mg nebulised sodium cromoglycate.

Assessment and management of asthma in an accident and emergency department

S DIGGLE, S REED, MJ CUSHLEY, RA SLEET, AE TATTERSFIELD There is little information about how patients with asthma are assessed and managed in an accident and emergency (A and E) department. We carried out a retrospective study at Southampton General Hospital, in which the A and E records of all patients presenting with chest complaints other than pain over a 12 month period were reviewed to identify those presenting with asthma. One hundred and fifty two patients made 193 visits (0·48% of the total work load), in addition to 35 requests for repeat prescriptions. Patients were more likely to attend in the autumn, at the weekend, and in the evenings. The frequency with which relevant information was recorded was very variable—for example, dyspnoea in 35%, ability to speak in 13%. Heart rate and blood pressure were common (84% and 63%) in the records but pulsus paradoxus (13%) and peak flow rate (11%) uncommon. Blood pressure was five times more likely to be recorded than peak flow rate. The drugs used most frequently to treat asthma were β adrenoceptor agonists (120 patients), usually by nebulisation, intravenous aminophylline (39), and intravenous steroids (30). Sixty per cent of patients were discharged home after treatment. Factors associated with admission were cyanosis, pulsus paradoxus, and parenteral treatment, but not heart rate (112 beats/min admitted *v* 107 beats/min discharged). A follow up questionnaire showed that patients discharged home from A and E departments returned to normal activity more quickly and required further treatment less often than patients discharged from a medical ward. Although there was no evidence of inappropriate management, the poor documentation of important signs and lack of any measure of airflow obstruction is cause for concern and highlights an area where management could be improved.

Effect of verapamil on bronchodilator response to beta receptor agonists in asthma

JA ROBERTS, NC THOMSON Recent in vitro experiments in animals have suggested that calcium antagonists may potentiate the relaxant effects of β receptor agonists (Peck MJ, Towart R. *Br J Pharmacol* 1984;**81**:183P). If a similar interaction occurred in man this would have important therapeutic implications. We therefore examined the effect of inhaled verapamil on the bronchodilator response to the β receptor agonists terbutaline and isoprenaline in a group of eight adult asthmatic patients (age range 21–60 years). In six asthmatics, after baseline measurements of FEV_1 the following treatments were administered via a Wright nebuliser in a randomised double blind fashion: terbutaline 0·5%, verapamil 0·25%, verapamil 0·25% plus terbutaline 0·5%, and buffered saline as control. Spirometry was repeated at regular intervals up to 480 minutes after each inhalation. In a further three patients isoprenaline 0·1% was administered for one minute on two days and preceded by verapamil 0·25% for five minutes on a third day. Terbutaline and isoprenaline produced significant increases in FEV_1, but these bronchodilator responses were not significantly different after pretreatment with verapamil. We conclude that the calcium antagonist verapamil, at a dose previously shown to inhibit exercised induced asthma, does not prolong the bronchodilator response to inhaled β receptor agonists in asthma.

Effect of cigarette withdrawal in smoking asthmatics

AG FENNERTY, J BANKS, P EBDEN, C BEVAN, BH DAVIES Asthmatics who stop smoking frequently complain of deterioration in their symptoms. Fourteen asthmatics were asked to

stop smoking for one week. Diary cards recording symptom scores, treatment, and twice daily peak flow readings were kept for one week prior to and during the week of abstention. At the end of the assessment period a histamine bronchial challenge established the dose required to give a 20% fall in sGaw (PD_{20}). The subjects then stopped smoking and the challenge was repeated at 24 hours and, if appropriate, at seven days. All 14 subjects stopped for 24 hours but only seven managed for seven days. There were no significant changes in any measurements after 24 hours' abstention for the whole group, and the seven patients who resumed smoking did so because of craving for tobacco. After seven days' abstention there was a significant increase in mean log PD_{20} ($p < 0.02$), with an increase in mean peak flow and sGaw ($p < 0.05$). Two patients complained of deteriorating asthma but there was no objective evidence for this. Thus we have shown a significant improvement in objective lung function measurements after seven days' cigarette abstention and were unable to find any evidence for the common claim of asthmatics of deterioration following cessation of smoking.

The site of airway obstruction in asthma induced by cold air

BK ASSOUFI, S LOZEWICZ, DM DENISON The effect of breathing helium on maximum expiratory flow at 50% of vital capacity ($\dot{V}max_{50}$) was studied in 16 patients with asthma before and after cold air induced bronchoconstriction. Patients breathed subfreezing dry air at $-15°C$ for three minutes at a ventilatory rate which had been shown on a separate occasion to produce a 15–20% fall in FEV_1. Patients were classified as responders when the increase in $\dot{V}max_{50}$ while breathing 20% helium and 80% oxygen was greater than 20%. Those with values of less than 20% were classified as non-responders. In general, patients who were responders before breathing cold air remained responders after cold air induced bronchoconstriction. Thirteen patients were responders before breathing cold air; of these, 10 remained responders and three became non-responders. Three patients were non-responders before breathing cold air; two became responders and one remained a non-responder, but in each case the increase in $\dot{V}max_{50}$ during the breathing of helium was greater after cold air. There was no significant correlation between the severity of airway obstruction as measured by $\dot{V}max_{50}$ and the response to helium either before or after cold air induced bronchoconstriction. The results of this study suggest that in most patients with asthma the predominant location of cold air induced airways obstruction is in large airways.

Ultrasonic and jet nebulisers: differences in their physical properties and fractional deposition and in the airway response to nebulised water and saline solutions

RA LEWIS, CJ ELLIS, JS FLEMING, W BALACHANDRAN Ultrasonically nebulised hypotonic and hypertonic saline solutions are known to cause cough and bronchoconstriction, but the effect of similar jet nebulised solutions has not been systematically studied. We delivered nebulised water and 0·45%, 0·9%, and 5% saline from a DeVilbiss Pulmasonic ultrasonic nebuliser and an Inspiron Mini-Neb jet nebuliser driven with 8 l air/min to eight normal and eight asthmatic subjects. Subjective sensation of irritation was assessed on a visual analogue scale with an objective assessment of cough frequency and changes in specific conductance. Water from jet nebulisers caused significantly less subjective irritation ($p < 0.01$), cough ($p < 0.01$) and bronchoconstriction ($p < 0.05$) than water from ultrasonic nebulisers in both normal and asthmatic subjects; 0·45% and 5% saline from jet nebulisers was significantly less irritant in normals and asthmatics, and 5% saline from jet nebulisers caused less cough in asthmatics than that from ultrasonic nebulisers. There was a correlation between cough and VAS in asthmatics and normal subjects and between cough and bronchoconstriction in asthmatics. Differences between ultrasonic and jet nebulisers are not explained by differences in output (0·25 and 0·31 ml/min), particle size (5·46 and 4·85 μm median mass diameter), or temperature. In separate subjects there was no significant difference in lung deposition of saline labelled with technetium-99m from ultrasonic nebulisers and from JN (17·3% (SD 12·6%) and 11·6% (4·2%) respectively, but oropharyngeal deposition was increased (22·9% (16·0%) and 1·5% (0·8%) respectively—$p < 0.005$). This may explain the increased irritant response from the ultrasonic nebulisers.

Effect of bronchodilators on the cough response to citric acid in normal subjects and asthmatics

JC POUNSFORD, KB SAUNDERS, RN DAVIDSON Eight normal subjects and eight asthmatics inhaled increasing concentrations of an aerosol of citric acid. At each concentration the cough response was measured in terms of the number of coughs, the cough index (number of coughs divided by latency), and the cough threshold. The subjects were then given nebulised salbutamol (5 mg), ipratropium (1 mg), or placebo (× 2) in a double blind crossover design. The cough response to citric acid was then measured again. Each of the four experiments was conducted on a different day. Airways impedance (Ros) was measured during the study with an oscillometer (Siemens Siregnost FD5). Prior to administration of bronchodilator or placebo the cough response in both the normal subjects and the asthmatics was the same. In the asthmatics prior treatment with both bronchodilators produced a significant fall in the cough response and Ros ($p < 0.05$, Wilcoxon's rank sum) compared with treatment with placebo. No effect was seen in the normal subjects. Ros was not altered by citric acid in either group. The cough response to inhaled citric acid was reduced by treatment with salbutamol and ipratropium in the asthmatics. The effect might be related to the change in airways resistance produced in the asthmatic patients.

Occupational asthma due to methyl methacrylate and cyanoacrylates

S LOZEWICZ, AG DAVISON, A HOPKIRK, P SHERWOOD BURGE, DAR BOLDY, JR RIORDAN, DV McGIVERN, BW PLATT, D DAVIES, AJ NEWMAN TAYLOR Acrylates are widely used in the manufacture of adhesives, solvents, acrylic resins, and thermoplastics. Cyanoacrylate based glues give a high bond strength between a variety of materials and are avail-

able for domestic use as Superglue. Methyl methacrylate is widely used in surgery as a bone cement and in dentistry as a ceramic filler or cement. We report five cases of asthma occurring in association with exposure to cyanoacrylate based adhesives, and one case occurring in relation to exposure to methyl methacrylate. In each case there was an initial symptom free period of exposure, and an asthmatic reaction occurred following occupational type inhalation testing with the respective acrylate but not after provocation with a non-acrylate material on a separate control day. Each of the five patients who worked with cyanoacryates had non-immediate asthmatic reactions after provocation with cyanoacrylate, and none of three who underwent inhalation testing with histamine demonstrated increased airway reactivity. These findings suggest that the cyanoacrylates were the primary cause of asthma and not acting as non-specific provocative stimuli. Acrylic systems are widely used and inhalation of the vapours emitted from them by exposed workers may become an important cause of occupational asthma.

Does response to a standard dose of inhaled salbutamol in chronic bronchitis predict response to oral theophylline?

ET PEEL, G ANDERSON, H PAYNE Forty patients with chronic bronchitis and airflow obstruction were divided into those who did not respond to 200 μg of inhaled salbutamol (improvement in FEV_1 < 10%—group A) and those who did (improvement in FEV_1 11–20%—group B). Each group was then given placebo or an incremental dose of theophylline to a maximum of 800 mg for two weeks. Measurements were made of PEFR and spirometry before and after each treatment period and patients assessed their subjective response to each treatment and completed a respiratory questionnaire. During each day of the study patients made recordings of PEFR four times daily. In group A at clinic visits there was significant improvement in FVC but not in FEV_1 or PEFR and in group B there was a significant improvement in FEV_1 but not in FVC or PEFR. Analysis of diary cards showed that in group A and group B there was a large subgroup of patients with an improved PEFR who were not detected from the single PEFR level recorded at the clinic. Improvements recorded on diary cards correlated well with patients' impression of overall benefit. Plasma theophylline levels were similar in patients showing a diary card response in PEFR and those who did not. Improvement in FEV_1 after 200 μg of inhaled salbutamol is a poor indication of response to oral theophylline. Single measurements of PEFR are not an accurate predictor of theophylline response, which is best assessed by the use of a diary card.

Is the combination of ipratropium and fenoterol aerosols useful in chronic steroid unresponsive airflow obstruction?

P LAWFORD There is little evidence of additional bronchodilatation from a combination of ipratropium and β_2 agonist in chronic bronchitis compared with β_2 agonist alone, in contrast to that obtained in bronchial asthma (Leitch AG *et al. Thorax* 1978;**33**:711–3). We describe the effects of a combination of fenoterol and ipratropium compared with fenoterol alone in patients with chronic airflow obstruction with no asthmatic features. Ten patients with chronic sputum production whose increase in FEV_1 15 minutes after 200 μg Salbutamol before and after seven days of 20 mg a day of oral prednisolone was less than 15% took part in a randomised, double blind cross-over study. The mean age was 59 (44–68) years and the mean initial FEV_1 was 43% predicted. After baseline measurements of pulse, blood pressure, and tremor and spirometry they received one puff of aerosol every 30 minutes for two hours from masked canisters. On day one each puff contained 100 μg fenoterol and on day two 100 μg fenoterol and 40 μg ipratropium bromide. Subsequent measurements were made every 30 minutes up to 150 minutes and the results assessed by three way analysis of variance. The mean absolute change in FEV_1 (ml ATPS) after one, two, and four puffs was 80, 130, and 140 for the combination and 120, 140, and 180 for fenoterol alone. No significant difference in bronchodilator response or change in pulse, blood pressure, or tremor score was found between the two treatment days. The combination appears to offer no more bronchodilatation than a β_2 agonist alone.

Interaction of leukotrienes and cyclo-oxygenase products mediate pulmonary and systemic haemodynamic effects of leukotriene D_4

T AHMED, B MARCHETTE, L YERGER, A WANNER We investigated the role of leukotriene (LT) receptor stimulation and cyclo-oxygenase metabolites in the mediation of the haemodynamic effects of LTD_4. In six conscious sheep pulmonary artery pressure, pulmonary arterial wedge pressure, systemic arterial pressure, and cardiac output were measured for the calculation of pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) before and immediately after a rapid injection of LTD_4 into the pulmonary artery. 0·1 μg/kg and 0·5 μg/kg of LTD_4 increased mean PVR to 421% and 400% of baseline ($p < 0·001$), and had a biphasic effect on SVR, which following an initial decrease of 18% ($p < 0·05$) increased to 143% and 155% of baseline respectively ($p < 0·05$). Both PVR and SVR returned to baseline within 10 minutes. The effects of LTD_4 (0·1 μg/kg) on the pulmonary circulation were completely blocked by the SRS-A antagonist FPL-57231 as well as by indomethacin. In the systemic circulation FPL-57231 blocked the biphasic effects of LTD_4 on SVR, while indomethacin prevented the initial decrease without attenuating the subsequent increase in mean SVR (135% of baseline; $p < 0·05$). We conclude that the pulmonary and systemic haemodynamic effects of LTD_4 are mediated by an interaction between the leukotriene receptor stimulation and cyclo-oxygenase matabolites.

Effects of haematocrit reduction on renal haemodynamics in secondary polycythaemia and cor pulmonale

PJW WALLIS, PM DEAN, J CUNNINGHAM, AC NEWLAND, DW EMPEY Renal haemodynamics were assessed before and

three days after haematocrit reduction in 10 patients with secondary polycythaemia and cor pulmonale (mean FEV_1 0·72 1, PaO_2 6·75 kPa, red cell mass 165% predicted) and with normal renal function. Erythrapheresis was used to lower mean haematocrit from 0·62 to 0·50. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured by ^{125}I iodohippuran and $_{51}CR$ EDTA clearances respectively, ERPF was low at 251 (SEM 19) ml/min/1·73 m² (52% predicted), increasing to 297 ml/min/1·73 m² after erythrapheresis ($p < 0·01$). GFR was unaffected by the procedure (84 (10) *v* 88 (11) ml/min/1·73 m²). Filtration fraction (GFR/ERPF), initially high at 0·335 (0·03), decreased to 0·296 (0·03) ($p < 0·05$). Renal blood flow fell by 10% from 660 (38) to 517 (34) ml/min/m² (72% predicted) ($p < 0·05$), with a 25% reduction in renal oxygen delivery ($p < 0·01$). These results suggest that in cor pulmonale polycythaemia maintains renal oxygen delivery at the expense of a reduction in ERPF. Despite this reduction, GFR is maintained by an increase in filtration fraction. The process raises peritubular plasma oncotic pressure and favours increased tubular sodium and water reabsorption. By these mechanisms polycythaemia may exacerbate oedema formation in cor pulmonale. Reversal of these events by haematocrit reduction may usefully diminish fluid retention, although the large fall in renal oxygen delivery may encourage the recurrence of polycythaemia through erythropoietin secretion.

Effect of hypoxia on respiratory and limb muscle endurance

N KOULOURIS, J MOXHAM, N BARNES, B GRAY, R HEATON, M GREEN At altitude exercise capacity is reduced, possibly owing to impairment of muscle function by hypoxia. Hypoxia in patients could impair respiratory and limb muscle contractility. To assess the importance of hypoxia we have studied the endurance of respiratory and limb muscles during the breathing of hypoxic gas mixtures. Five normal subjects breathed through an inspiratory resistance, achieving a target mouth pressure of 80% maximum for as long as possible. The subjects were studied single blind on eight occasions breathing 21% or 13% oxygen. Hypoxia reduced the endurance time from a mean of 11·43 (SD 2·76) minutes to 7·13 (2·29) ($p < 0·001$). The subjects also performed isometric intermittent contractions of the right quadriceps at various levels of work and the endurance time was measured. Quadriceps endurance was then investigated while they were breathing 13%, 12%, and 11% oxygen. At 11% subjects developed minor cerebral symptoms due to hypoxia. The endurance of the quadriceps was not reduced by hypoxia. Hypoxia has been reported as reducing respiratory muscle endurance (Jardim *et al. Am Rev Respir Dis* 1981;**124**:274–9) and our study confirms this. Previous workers have concluded that hypoxia impairs muscle contractility; our study of the quadriceps suggests that this is unlikely unless the respiratory muscles are much more sensitive to the effects of hypoxia. A more probable explanation is that hypoxia increases respiratory drive, which makes breathing through a high resistance more difficult.

Effects of haematocrit reduction on pulmonary haemodynamics and oxygen delivery in patients with secondary polycythaemia and cor pulmonale

PJW WALLIS, JD SKEHAN, AC NEWLAND, JA WEDZICHA, PG MILLS, DW EMPEY Haematocrit was lowered by erythrapheresis from 0·61 to 0·50 (mean values) in 13 patients with secondary polycythaemia and cor pulmonale (FEV_1 0·89 l, Pao 6·74 kPa, red cell mass 148% predicted), reducing blood viscosity from 11·4 and 6·5 mPas to 7·5 and 4·3 mPas at shear rates of 23/s and 230/s respectively ($p < 0·001$). Haemodynamic assessments were made before and 30 minutes after the isovolaemic procedure. Mean pulmonary artery fell from 38 (SEM 3·3) to 35 (3·2) mm Hg ($p < 0·01$), without any change in right atrial or pulmonary wedge pressures. The cardiac index rose from 3·06 (0·26) to 3·41 (0·25) l/min/m² ($p < 0·01$) and total pulmonary vascular resistance fell from 62 (8) to 51 (8) kPa $s^{-1} l^{-1}$ ($p < 0·01$). Right ventricular work rate was unchanged. Arterial oxygen content decreased by 17%, with a fall in systemic oxygen delivery from 1·170 (0·104) to 1·036 (0·084) l/min ($p < 0·01$). Despite this reduction peripheral oxygen consumption increased by 12% (5%) ($p < 0·05$), with a fall in $P\bar{v}O_2$ from 4·95 (0·17) to 4·64 (0·1 q) kPa ($p < 0·01$). The decrease in blood viscosity improved pulmonary haemodynamics by reducing pressure and increasing flow within the pulmonary circulation, producing a fall in right ventricular afterload. The rise in peripheral oxygen consumption following haematocrit reduction may reflect an improvement in tissue oxygenation due to enhanced tissue perfusion. These effects may explain the improvements in wellbeing and work performance which we have reported following erythrapheresis (JA Wedzicha *et al. Br Med J* 1983;**286**:511–4).

Assessment of the informational value of lung function tests

NJ RUSSELL, AD MORGAN, NJ CRICHTON, PA EMERSON Physicians requesting lung function tests for breathless patients were asked to predict the type and severity of any abnormality and to attach probabilities to their predictions. Patients assessed their breathlessness using the MRC questionnaire and an oxygen cost diagram. Results were returned with post-test probabilities of the functional abnormality and its severity. Doctors' pretest predictions and the patient's assessment of the severity of their disability were compared with the test results. Analysis of results from 37 cases showed that requesting physicians correctly identified the type of lung function abnormality in 26 patients (70%). Where an obstructive ventilatory defect was predicted, reversibility was correctly identified in 44% of cases. A test was considered useful where a greater than 50% change occurred between the pre test and post-test probability for any one category. This was the case in 63% of tests. Forty per cent of doctors and 44% of patients accurately predicted the severity of the measured defect. Agreement between patients, doctors, and laboratory occurred in 22% of tests. Thus while doctors can reasonably predict the type of functional abnormality they are less often able to identify reversibility of airflow obstruction than they would by chance, and neither patients nor doctors can accurately predict the severity of a defect.

A simple system for monitoring sleep disordered breathing

SJ CONNELLAN, DN COOPER, K SMITH We have developed a simple bedside system for diagnosis and assessment of patients suspected of having sleep disordered breathing. This consists of measuring transthoracic impedance using two opposing ECG electrodes placed on the lower lateral chest wall at the point of maximum excursion. The signal is processed by an intensive care monitor with respiratory module. Sounds generated in the airways are simultaneously recorded via an electric condenser microphone which is secured over the manubrium sterni. These signals are recorded on an FM recorder with open reel tape giving six hours' recording time. This system enables us to correlate the phases of respiration with pulmonary and cardiac sounds. In asthmatics we have been able to detect the onset of mild inspiratory and expiratory wheeze progressing through the night to severe "morning dipping". Both the classical pattern of obstructive sleep apnoea in a patient with daytime somnolence and central apnoea in a patient with severe airflow obstruction were easily demonstrated. With the facility of fast playback it is possible to analyse these recordings in one hour.

Effect of rapid saline infusion on breathing pattern in normal man

JA FLEETHAM, AL MUIR, DR TAYLOR Pulmonary congestion stimulates intrapulmonary receptors and causes rapid shallow breathing in certain animal models. To examine the effect of pulmonary congestion in humans we have monitored breathing pattern during rapid saline infusion. Six semirecumbent healthy adults (age range 25–45 years) fitted with a respiratory inductive plethysmograph calibrated for volume received an intravenous infusion of normal saline (30 ml/kg) over 20 minutes in a single blind placebo controlled study. Breathing pattern was analysed in terms of respiratory rate (RR), tidal volume (VT), mean inspiratory flow rate (VT/Ti), and fractional inspiratory time (Ti/Ttot). Heart rate (HR) was monitored continuously and spirometric values and central venous pressure (CVP) obtained at regular intervals during the study. Both forced expiratory volume in one second (FEV_1) and vital capacity (VC) decreased with the infusion ($p < 0.01$) and mean (SEM) CVP rose by 7·3 (0·8) cm/H_2O ($p < 0.01$). No significant changes were observed in either breathing pattern or heart rate.

Thus the infusion of a fluid volume known to reduce lung volume, induce premature airway closure, and cause interstitial oedema (*J Appl Physiol* 1975;**38**:786) had no effect on breathing pattern. We conclude that intrapulmonary receptors are relatively insensitive to pulmonary congestion in normal man.

Relative contributions of the rib cage and the abdomen to breathing in normal subjects and tetraplegics

MDL MORGAN, AR GOURLAY, JR SILVER, SJ WILLIAMS, D DENISON Methods which partition ventilation between the rib cage and the abdomen normally require assumptions about the relationship between dimension change and volume. These may be satisfactory in normal subjects but will not be accurate when there are unpredictable distortions of the chest wall—for example, in tetraplegia. We describe a development of optical mapping which divides the volume change of the trunk along the costal margin in supine subjects. We compared six normal subjects with ten tetraplegic patients. The normal subjects behaved in a similar way in both quiet breathing and a vital capacity. The volume displacements of the rib cage and abdomen were orthodox (rib cage 35%) (SD 18%) in quiet breathing and 40% (15%) in vital capacity. Seven tetraplegics showed paradoxical rib cage motion in quiet breathing and three of them also demonstrated it in a vital capacity. The technique allows the volume of paradoxical motion to be described quantitatively. This is an advantage in following recovery and distinguishing otherwise very similar patients. The importance of this is well illustrated by examples, one of which is a patient who could achieve a tidal volume of 500 ml only in the face of 1800 ml of rib cage paradox.

Response characteristics of a transcutaneous oxygen electrode and an ear oximeter compared at rest and during exercise

BJ GRAY, NC BARNES, RW HEATON, J CALLAGHAN Transcutaneous oxygen tension ($tcPo_2$) is an accurate indicator of both the magnitude and the timing of changes in arterial oxygen tension (Pao_2) during exercise, but such changes may not be large. We have investigated the in vivo response characteristics of a radiometer transcutaneous oxygen electrode and a Hewlett-Packard ear oximeter during rapid and large falls in Pao_2 at rest and during exercise. Six normal subjects breathed air and a hypoxic gas mixture (11–12% O_2 in nitrogen) both at rest and during exercise. End tidal oxygen tension (E-T Po_2), $tcPo_2$, and Sao_2 were continuously recorded. The time taken for a 90% fall in these parameters after the subjects were rapidly switched from breathing air to breathing the hypoxic gas was calculated. At rest the 90% response times of both $tcPo_2$ (81 (SEM 11·9) s) and Sao_2 (70·3 (9) s) were significantly greater than E-T Po_2, (50·8 (10) s). During exercise the 90% response times of E-T Po_2 (15·8 (3) s), $tcPo_2$ (33 (5) s), and Sao_2 (28·7 (2·7) s) all fell markedly; but the Sao_2 and $tcPo_2$ response remained significantly slower than that of E-T Po_2. The 90% response times of the ear oximeter and skin electrode were not significantly different during exercise. We conclude that both instruments respond rapidly to large changes in Pao_2 and that the small differences in response characteristics between instruments is probably

Analysis of breathing pattern (mean values with standard errors in parentheses) during rapid saline infusion in six healthy adults

	VC (l)	*FEV_1 (l)*	*RR*	*VT (l)*	*VT/Ti (l/s)*	*Ti/Ttot*	*HR (beats/min)*
Before infusion	4·5 (0·3)	3·4 (0·1)	19 (1)	0·34 (0·01)	0·35 (0·02)	0·32 (0·01)	70 (3)
After infusion	4·0 (0·2)	3·1 (0·1)	18 (1)	0·35 (0·03)	0·31 (0·04)	0·36 (0·02)	75 (4)

unimportant in clinical exercise testing.

Relationships between ventilatory and mouth occlusion pressure responses to carbon dioxide in normal subjects and patients with muscle weakness

JJ GILMARTIN, TJ WALLS, TN STONE, GJ GIBSON The ventilatory response to carbon dioxide ($\Delta\dot{V}E/\Delta PaCO_2$) in both normal subjects and weak patients depends on many factors other than medullary output, including lung size and muscle strength (Serisier DE *et al. Q J Med* 1982;**51**:205). The mouth occlusion pressure ($\Delta P_{0\cdot1}/\Delta PaCO_2$) is theoretically a more specific index of central drive, but its dependence on size and muscle strength is not clear. We have examined relationships between these two indices of ventilatory control in 26 normal subjects, 12 patients with myotonic dystrophy (MD), and seven patients with muscle diseases in which no suspicion of CNS disease exists (non-MD). In the normal subjects $\Delta\dot{V}E/\Delta PCO_2$ (mean (SD): 2·54 (1·07) l min^{-1} $mmHg^{-1}$) showed a weak correlation ($p = 0\cdot05$) with vital capacity (VC), but there was no significant relationship between $\Delta P_{0\cdot1}/\Delta PaCO_2$ (0·45 (0·19) cmH_2O mm Hg^{-1}) and VC. $\Delta\dot{V}E/\Delta PaCO_2$ and $\Delta P_{0\cdot1}/\Delta PaCO_2$ were highly correlated with each other ($r = 0\cdot72$) and the correlation was not improved by correcting $\Delta\dot{V}E/\Delta PaCO_2$ for size by dividing by VC. In the patients both $\Delta\dot{V}E/\Delta PaCO_2$ (MD 0·88 (0·42); non-MD 0·82 (0·45)) and $\Delta P_{0\cdot1}/\Delta PaCO_2$ (MD 0·14 (0·09); non-MD 0·16 (0·07)) were significantly lower than in the normal subjects and not different from each other. Individual values appeared to fit the relationship of $\Delta\dot{V}E/\Delta PaCO_2$ to $\Delta P_{0\cdot1}/\Delta PaCO_2$ found in normal subjects. The mouth occlusion pressure is reduced by muscle weakness and a low $\Delta P_{0\cdot1}/\Delta PaCO_2$ is not a valid index of central output in such patients.

The mechanism whereby changes in PCo alter airways resistance

CHC TWORT, JE NEILD, IR CAMERON Tracheal spirals from 18 rats were suspended in Ringer's solution, pH 7·49, bubbled with 5% CO_2. Tension, developed after the addition of acetylcholine, was measured. Extracellular pH was varied by alteration of PCO_2. At pH 7·84 tension increased to a mean of 104% (SEM 0·3%) µmol of control ($p < 0\cdot0005$); at pH 6·74 tension decreased to 68·3% (1·7%) ($p < 0\cdot005$). Varying extracellular Ca^{++} concentration and adding verapamil (10 µmol/l) indicated that extracellular pH regulated Ca^{++} uptake into tracheal smooth muscle. Ca^{++} uptake was measured directly in 12 rats with labelled $^{45}Ca^{++}$. At pH 7·49 uptake was 5·3 (0·4) mmol Ca^{++}/kg trachea. At pH 7·85 this increased to 6·6 (0·5) mmol/kg trachea ($p < 0\cdot05$), and at pH 6·88 it decreased to 4·3 (0·3) mmol/kg trachea ($p < 0\cdot025$). In man the rise in airways resistance known to occur during hypocapnia should therefore be reduced by prior administration to verapamil. In eight normal subjects airways resistance was measured as specific conductance (sGaw) and respiratory impedance (Ros). Hyperventilation for 90 seconds (end tidal PCO_2 3·3 kPa) produced a fall in sGaw of 0·69 (0·21) kPa^{-1} s^{-1} ($p < 0\cdot02$), and a rise in Ros of 0·92 (0·21) mbar s l^{-1} ($p < 0\cdot0025$). Pretreatment with oral verapamil reduced the fall in sGaw to 0·19 (0·25) ($p < 0\cdot02$) and the rise in Ros to 0·63 (0·2) mbar s l^{-1} ($p < 0\cdot005$). We conclude that changes in airways resistance with PCO_2 are mediated by H^+ dependent alteration in Ca^{++} uptake by the smooth muscle.

Mouth occlusion pressure: a new test for inspiratory muscle fatigue

PMA CALVERLEY, D La PORTA, B FLEURY, A COMPTOIS, A GRASSINO The pressure developed 100 ms after inspiration against an occluded airway at FRC ($P_{0\cdot1}$) reflects both the drive to breathing and the mechanical properties of the inspiratory muscles. To investigate the influence of inspiratory muscle fatigue on $P_{0\cdot1}$ we studied six healthy men while they were breathing against a range of inspiratory loads at a constant inspiratory flow (VT/Ti) both with and without a knowledge of their target transdiaphragmatic pressure (Pdi) and respiratory frequency. We measured diaphragmatic EMG, Pdi, VT/Ti, and duty cycle (Ti/Ttot) and, knowing their Pdi_{max}, calculated the diaphragmatic tension time index (TTdi). We measured $P_{0\cdot1}$ after maximum voluntary inspiration before study and at 10–15 breath intervals during spontaneous breathing against an inspiratory resistance. In eight studies where only VT/Ti was fixed (TTdi 0·1 (SEM 0·02) VT/Ti 276 (58) ml/s) and no signs of EMG fatigue was seen, $P_{0\cdot1}$ as a percentage of initial value was 101·5% and $P_{0\cdot1}/P_{0\cdot1\ max}$ was 0·075% (0·03%): In eight similar studies with EMG evidence of fatigue (TTdi 0·16 (0·04)) and with $P_{0\cdot1}/P_{0\cdot1\ max}$ 0·18%, $P_{0\cdot1}$ fell to 44% (9·4%) of the initial value despite an unchanged VT/Ti. Even when all variables were controlled $P_{0\cdot1}$ fell by 51% when fatigue developed while TT/Ti was again constant. In both types of study $P_{0\cdot1}/P_{0\cdot1\ max}$ was closely related to TTdi ($R = 0\cdot8$, $p < 0\cdot001$). Thus $P_{0\cdot1}$ falls during the development of inspiratory muscle fatigue and changes in this index and in $P_{0\cdot1}/P_{0\cdot1\ max}$ may provide a useful non-invasive method for detecting early inspiratory muscle failure.

Regional deposition of particles in the lung during cigarette smoking

MG PEARSON, S VINITSKI, MJ CHAMBERLAIN, WKC MORGAN Ventilation scans with a nebuliser generated aerosol of submicron, technetium-labelled, sulphur colloid particles are well established. The method was adapted for use during smoking by means of a cigarette "holder" designed to permit inhalation of equal volumes of smoke and aerosol in a manner similar to smoking a filter tipped cigarette. Eleven volunteers, with normal spirometric values, smoked two cigarettes using the special holder and had the resulting images recorded on a computerised gamma camera acquisition system. On a separate day a resting ventilation aerosol scan was performed followed by the smoking of their normal cigarette. Breathing patterns throughout were monitored with an inductance plethysmograph (Respitrace). All subjects had increased central deposition during smoking (mean central/peripheral ratio 3·1 (SEM 0·5) *v* 2·5 (0·3)) and also a shift of deposition

towards the lung apices (mean apex: base ratio 0·89 (0·15) *v* 0·66 (0·10) ($p < 0·001$). Both lateral views indicated that the major shift was a lobar one towards the upper lobes, which in three subjects was such that upper lobe exceeded lower lobe deposition. Respitrace analysis confirmed that the "holder" did not affect smoking patterns but that, although each subject inhaled the bolus a little faster and more deeply than tidal breaths, no one parameter correlated with the deposition pattern. These new observations offer a possible explanation for the apical localisation of centilobular emphysema.

Effect of hypoxia and hypercapnia on subsequent ventilatory response to hypercapnia in normal subjects

AR GELLERT, RM RUDD We measured the ventilatory response to progressive hyperoxic hypercapnia 20 minutes before and 20 minutes after a four minute period of isocapnic hypoxia (breathing 8% O_2, 7% CO_2, 85% N_2) on one occasion and a four minute period of hyperoxic hypercapnia (rebreathing with end tidal P_{CO_2} held at 7·6 kPa) on another. Minute ventilation was integrated from a pneumotachograph in a rebreathing circuit and breathlessness was assessed with 10 cm visual analogue scales. We studied 14 subjects (seven men, seven women), mean age 28 (range 19–39) years. The ventilatory response (l min^{-1} kPa^{-1}) to carbon dioxide increased by 33% 15·7 (8·0–27·0) to 20·3 (7·2–45·8) after hypoxia ($p < 0·05$) and by 35% from 13·9 (6·2–28·4) to 17·7 (8·3–34·5) ($p < 0·01$) after hypercapnia. The percentage increases in ventilatory responses correlated with percentage increases in breathlessness measured at the end of progressive hypercapnia at end tidal P_{CO_2} 8 kPa. The correlation was 0·51 ($p < 0·05$) after hypoxia and 0·80 ($p < 0·001$) after hypercapnia. Breathlessness and ventilation was similar during the four minute periods of hypoxia and hypercapnia. Transient hypoxia has been reported to potentiate subsequent ventilatory response to carbon dioxide and it has been suggested that this effect is analogous to the potentiation of respiratory efferent activity following carotid body stimulation in cats (Davidson and Cameron. *Clin Sci* 1982;**63**:18P). Our findings show that the potentiation in humans is not a specific effect of hypoxia but also occurs after hypercapnia.

Respiratory muscle training compared with physiotherapy in chronic obstructive airways disease

CB COOPER, CM SMITH, IR CAMERON We have compared methods of training respiratory muscles in patients with chronic obstructive airways disease. They were divided into two groups matched for age, FEV_1, and six minute walking distance. Each group trained for half an hour daily for eight weeks. We excluded those with improvement in FEV_1 greater than 15% after inhaled salbutamol. The conventional physiotherapy group (n = 7, age 60 (SEM 3) years, FEV_1 0·84 (0·1) l, % predicted FEV_1 35% (6%), six minute walking distance 462 (22) m trained by supervised walking and stair climbing. The other group (n = 9, age 60 (3) years, FEV_1 0·83 (0·1) l, % predicted FEV_1 29% (4%), six minute walking distance 477 (29) m) specifically trained their respiratory muscles. They breathed through inspiratory resistances which were adjusted to achieve approximately 20% of Pi_{max} with each breath. The physiotherapy group improved their mean six minute walking distance by 32 m (7%; $p < 0·05$) and felt less breathlessness as quantitated by visual analogue scales. The inspiratory muscle training group showed improvement in their walking distance of 23 m (5%; $p < 0·05$) but there was no change in breathlessness. Neither group showed an increase in maximal inspiratory or expiratory mouth pressures and during a progressive exercise test on a bicycle ergometer there was no improvement in maximal ventilation or maximal uptake. Neither physiotherapy nor respiratory muscle training produced improvement in six minute walking distance which is likely to be of practical benefit. We were unable to demonstrate any improvement in respiratory muscle strength or endurance.

Oral high frequency oscillation improves exercise tolerance and recovery from breathlessness

RJD GEORGE, RS HOWARD, DM GEDDES Oral high frequency oscillation reduces resting minute ventilation in chronic airflow obstruction (*Thorax* 1984;**39**:235). To seek a practical benefit from this technique we asked 11 subjects with chronic respiratory disease to perform six minute walks (chronic airflow obstruction 7, fibrosing alveolitis 4) with and without oral high frequency oscillation. Two devices were used: a fixed frequency portable oscillator (DeVilbiss) and a bedside oscillator with the frequency selected by the patient (range 12 Hz–26 Hz). Oral high frequency oscillation was delivered through a mouthpiece open to the atmosphere. During each walk the subject carried the oscillator. Breathlessness was scored each minute throughout the study by a visual analogue scale. Recovery was taken as the time to return to baseline breathlessness. All studies were randomised, comparing exercise with and without portable oral high frequency oscillation and control recovery with the portable device or oscillation at preferred frequency. Exercise tolerance was increased by 10% (range 99–129%; $p < 0·01$). There was a slight reduction in breathlessness during exercise. Median recovery time fell from 190 seconds (range 70–660 s) to 115 seconds (range 30–210 s) with the portable device ($p < 0·01$) and to 80 seconds (range 30–165 s) at the preferred frequency ($p < 0·01$). Oral high frequency oscillation increased tolerance to and recovery from exercise and has potential as a practical, portable treatment for breathlessness.

"Invalidity" due to chronic bronchitis and emphysema: how real is it?

SJ PEARCE, V POSNER, AJ ROBINSON, JR BARTON, JE COTES Hospital discharges and deaths due to chronic bronchitis and emphysema have fallen in recent years while the numbers of those receiving invalidity benefit (the "long term sick") for these conditions have remained constant. One hundred and fifty seven such persons were invited to take part in this study, in which the diagnosis,

degree of respiratory impairment, and other factors contributing to invalidity were reviewed. The scope for rehabilitation was considered. One hundred subjects agreed to take part; 96 were men and 70 were over 60 years. They were more overweight than the general population. In only 67 was the main diagnosis chronic bronchitis and emphysema. There was a bimodal distribution of functional impairment, most being severely disabled, but in 20 the FEV was within the normal range. Among these asthma was more common and psychological factors were important. Economic factors contributed to "invalidity," especially among those with a normal FEV. Among 32 non-participants for whom information was available the findings were similar. There was little scope for rehabilitation in the group as motivation seemed poor. In many treatment could have been improved. Not much more than half had ever seen a chest physician. Specialist assessment before invalidity benefit is claimed is probably desirable.

Nebuhaler versus nebuliser: a comparison of the effects of terbutaline on lung function and exercise tolerance in patients with severe airflow obstruction

SJ CONNELLAN, D HONEYBOURNE We have studied nine patients (age range 55–74 years) with severe airflow obstruction (mean FEV_1/VC 28% and mean KCO 71% of predicted) in a double blind placebo controlled manner on four separate days. Lung function and at least two practice 12 minute treadmill walks were performed at a preliminary visit. On subsequent visits, in a randomised fashion, they received: 5 mg (0·5 ml) of terbutaline in 1·5 ml of normal saline via a Turret (NL) Nebuliser (output 1·58 ml) or 2 ml of normal saline or two puffs (500 μg/puff) × 5 via Nebuhaler (NH) or placebo via NH. FEV_1 and slow VC (best of three) and 12 minute walking distance (12 MWD) were measured before and 15 minutes after therapy. Mean baseline measurements on the separate days did not differ significantly. The mean % ΔFEV_1 after 100 μg of isoprenaline prior to the study was 14%. There was no statistically significant difference in the response achieved by either form of therapy (table). These findings suggest that a similar therapeutic response may be obtained in such patients when the same dose of terbutaline is added to either of these delivery systems.

Technetium glucoheptonate lung scanning in the diagnosis of bronchial carcinoma

MCP APPS, N GARVIE, PJW WALLIS, DW EMPEY Lung tumours concentrate technetium glucoheptonate (Tc-GH). Passamonte *et al (J Nucl Med* 1983;**24**:997–1000) showed uptake of Tc-GH in 91% of lung tumours and less intense uptake in 90% of patients with metastatic or inflammatory lung disease. We have performed Tc-GH lung imaging in patients with pulmonary shadowing referred for bronchoscopy, to investigate its sensitivity and specificity in the diagnosis of carcinoma of the bronchus. Forty patients (25 carcinoma, 15 non-carcinoma) were given 15 mCi Tc-GH intravenously and anterior and posterior lung images were obtained five hours later. Tc-GH scans were reported without knowledge of radiographic appearance or diagnosis. Tc-GH uptake was described as focal or diffuse, and graded for intensity 0–3. There was localised uptake of Tc-GH in 19/25 patients with bronchial carcinoma, but in none of the patients without carcinoma (sensitivity 76%, specificity 100%). In 5/15 patients without carcinoma there was diffuse uptake only (four consolidation, one sarcoid). In two patients with bronchial carcinoma and mediastinal enlargement on the radiograph there was additional focal uptake, suggesting mediastinal metastases. When Tc-GH is taken up by bronchial carcinoma it produces a focal abnormality on scanning in contrast to a diffuse uptake in inflammatory disease. This may be helpful in the investigation of patients with suspected bronchial carcinoma.

Prognostic significance of laboratory parameters and performance status at diagnosis for survival in small cell lung cancer

SG SPIRO, I BRADBURY, RL SOUHAMI, JS TOBIAS, DM GEDDES, PG HARPER, H QUINN Previous studies have shown that performance status and disease extent (limited or extensive disease) are the most useful prognostic parameters in small cell lung cancer (SCLC). We have assessed the prognostic impact of these and other measurements made at diagnosis in 370 patients with SCLC entered into a randomised trial assessing the effect of radiotherapy to the primary tumour and mediastinum in addition to 12 courses of cyclical chemotherapy. The effect of the addition of radiotherapy to survival was negligible. The following parameters were individually significantly related to survival at $p < 0{\cdot}01$: disease extent, performance status, albumin (Alb: ≤ 39 *v* ≥ 40 g/l), sodium (Na: ≤ 135 *v* ≥ 135 μmol/l), alkaline phosphatase (AP: $\leq 1{\cdot}5$ × upper normal limit $\geq$), γ glutamyl transferase ($\leq$ 0–28 *v* ≥ 29 IU/l). Two stepwise multiple regression analyses both showed that only performance status, Alb, Na, AP, and disease extent each added significantly to prognosis. The best prognostic group (63 patients) with Alb ≥ 40 g/l, Na ≥ 136 μmol/l, AP $\leq 1{\cdot}5$ × upper normal limit, and performance status ≥ 7 (Karnofsky) comprised 35 patients with limited disease and 25 with extensive disease; they had a median survival in excess of that of the 127 limited disease patients in the entire study. It appears possible to select different prognostic groups at diagnosis on the basis of simple laboratory

Comparison of Nebuhaler (NH) and Turret Nebuliser (NL): mean (SD) percentage differences in the variables between the treatments

	%ΔFEV$_1$	*%ΔVC*	*%Δ12 min walking distance*
NH (active)	22·2 (24·6)	25·1 (13·4)	13·4 (16·6)
NH (placebo)	0·8 (22·7)	−2·7 (6·3)	−8·9 (18·8)
NL (active)	19·3 (17·8)	25·0 (15·1)	14·0 (19·3)
NL (placebo)	−5·8 (8·9)	−6·9 (9·6)	−2·9 (12·1)

parameters (Alb, Na, AP) and performance status. These variables offer as good a stratification of disease prognosis as disease extent, which usually includes more numerous and invasive tests.

Prospective study of the neuromuscular disorders associated with carcinoma of the lung

SA GOMM, WJK CUMMING, N THATCHER, PV BARBER Among neoplasms lung cancer has the highest incidence of non-metastatic neuromuscular complications (Wilkinson, Croft *Proc R Soc Med* 1967;**67**:683). The aetiology and pathogenesis of these remain unknown but they have previously been classified into four groups: polymyopathies, "cachectic" (type I fibre atrophy), and "proximal" (type II fibre atrophy); disorders of neuromuscular transmission; myositis (muscle necrosis); and endocrine metabolic myopathies (Henson, Urich. *Cancer and the nervous system.* 1982:406). The incidence of neuromuscular disorder was estimated prospectively in 55 patients, and the muscle biopsy features correlated with clinical and biochemical findings and with tumour types. Needle biopsies were performed under local anaethesia in the rectus femoris, the tissue being placed in liquid nitrogen. Histology and enzyme histochemistry were carried out on transverse frozen sections. Twenty six patients had small cell (SC) and 29 non-small cell (NSC) tumours. Twenty three patients (42%) were myopathic; 12 of these were "cachectic", with a significant increase in the NSC group ($p < 0.05$), and 11 "proximal" with no significant difference in tumour type. Fifty four abnormal muscle biopsy specimens were reported, of which 31 were not myopathic clinically. The histochemical abnormalities present were at variance with previous clinicopathological classifications and indicate that further clinical and histochemical studies are required to classify and assess the true incidence of these disorders.

Effects of chemotherapy on quality of life in patients with lung cancer

S AHMEDZAI, J REID, A MORTON, A STOREY, RD STEVENSON We have prospectively assessed physical, emotional, and social parameters of quality of life in 162 patients with small cell (SCLC) and non-small cell lung cancer (NSCLC). A nurse and social worker interviewed the patients monthly. Questionnaires covered symptoms, mood, disease awareness, and satisfaction with treatment. Seventy per cent of patients were aware of the diagnosis at the outset. Psychological disturbance was initially recorded, however, only in the 13% who regarded themselves as terminal. Symptoms and mood were significantly improved after five drug chemotherapy in 44 SCLC subjects; physical toxicity was usually well tolerated. The majority thought treatment was worthwhile at three months. Forty NSCLC patients received vindesine and cisplatin. Respiratory symptoms improved but pain was unchanged at three months. Gastrointestinal toxicity was common with DDP but was tolerable when nabilone, a cannabinoid antiemetic, was used. Thirty per cent of NSCLC patients did not find chemotherapy worthwhile. Overall, the most troublesome symptoms were anorexia (66%), alopecia (66%), pain (61%), and constipation (48%). Thirty four per cent of patients had been in active employment but only 4% returned to work. Social support was usually adequate except in the terminal stages. In conclusion, chemotherapy improved quality of life in SCLC patients in the short term, but did not subjectively benefit NSCLC patients.

Ceftazidime compared with a combination of gentamicin and carbenicillin in cystic fibrosis patients with persistent pulmonary pseudomonas infection and an acute exacerbation of respiratory symptoms

(IBTS RESEARCH COMMITTEE BHR STACK, DM GEDDES, KJ WILLIAMS, R DINWIDDIE, JB SELKON, RC GODFREY) Ceftazidime (CAZ) is a recently developed cephalosporin with excellent in vitro activity against *Pseudomonas*. In a multicentre open randomised trial this antibiotic was given to 50 cystic fibrosis patients over five years of age with previous persisting pseudomonas infection and acute exacerbations of respiratory symptoms and 32 similar patientis received gentamicin and carbenicillin (G/C). Eradiction of *Pseudomonas* from the immediate aftertreatment sputum occurred in 26% G/C and 18% CAZ treated patients ($p < 0.05$) but the organism was present in the sputum of all except one patient in each group three months after treatment. Coexisting *Straphylococcus aureus* and *Haemophilus influenzae* were eliminated in only 3/7 G/C treated patients but in all 10 CAZ patients. Clinical improvement occurred in 96% CAZ and 81% treated patients ($p < 0.05$). Readmission to hospital or intravenous antibiotic therapy or both was necessary during the three months after treatment in 12/50 (24%) of the CAZ group and 16/32 (50%) of the G/C treated group ($p < 0.05$). In the G/C group 4/32 patients developed thrombophlebitis at the site of intravenous infusion and two patients in each group suffered mild allergic reactions. Eight of the nine participating clinicians considered CAZ to be more acceptable to the patients. Ceftazidime is an effective and better tolerated alternative to gentamicin and carbenicillin in these patients.

Treatment of pseudomonas infestation in bronchiectasis with the quinolone ciprofloxacin

DE ROBERTS, DP DHILLON, E PORTEOUS, PJ COLE Ciprofloxacin (BAY 09867) is a newly synthesised compound of the nalidixic acid family quinolonecarboxylic acids, which has an added piperazinyl radical and fluorine atom. Its potential clinical value lies in its oral absorption, novel antibacterial activity (affecting DNA topoisomerases), and lack of plasmid borne acquisition of resistance. In chronic respiratory sepsis its particular value may be in its activity against *Pseudomonas*—up to 500 times the activity of carbenicillin (Wise R, Andrews JM, Edwards JLV. *Antimicrob Agents Chemother* 1983;**23**:559–64). To date we have treated nine patients with severe bronchiectasis chronically carrying *Pseudomonas aeruginosa* in the sputum and have assessed clinical response, sputum bacteria, and drug levels in the serum and sputum. Eight of nine patients showed significant

clinical improvement. Reduction in pseudomonas load occurred in three and clearance in four. Drug levels in the sputum exceeded the MIC for the organism in all patients. It is concluded that this drug may be of considerable use in management of chronic bronchial sepsis where pseudomonas carriage is a problem.

Singapore Tuberculosis Service and British Medical Research Council trial of three six month regimens for pulmonary tuberculosis given three times weekly in the continuation phase: results up to 30 months

DJ GIRLING A previous study in Singapore had shown that a six month daily regimen of streptomycin (S), isoniazid (H), rifampicin (R), and pyrazinamide (Z) for two months, followed by isoniazid and rifampicin (2SHRZ/4HR) was highly effective and had a low incidence of adverse reactions. Every dose was given under full supervision because in Singapore treatment is organised through 26 community health clinics, making even daily supervision practicable. However, in an attempt to simplify chemotherapy further it was decided to study three six month regimens, all given three times weekly in the continuation phase, and the feasibility of reducing the duration of the initial daily phase from two months ($2SHRZ/4H_3R_3$). to one month ($1SHRZ/5H_3R_3$) and of omitting the streptomycin injections ($2HRZ/4H_3R_3$). In patients with sensitive strains pretreatment, 101 (99%) of 102 $2SHRZ/4H_3R_3$ patients had negative cultures at two months, compared with 88 (85%) of 103 $1SHRZ/5H_3R_3$ ($p < 0{\cdot}001$) and 102 (90%) of 113 $2HRZ/4H_3R_3$ ($p < 0{\cdot}02$) patients. Only one patient ($2SHRZ/4H_3R_3$ had an unfavourable response during chemotherapy, and there was only one subsequent relapse up to 30 months in each regimen, giving an overall therapeutic failure rate of only four (1%) of 319 patients. Among the 32 patients with strains initially resistant to isoniazid or streptomycin or both there were three (10%) relapses. The incidence of adverse reactions was low.

Screening contacts of patients with tuberculosis in the Edinburgh area

S CAPEWELL, AG LEITCH Nine hundred and forty seven index cases of tuberculosis were notified during the five year period 1977–81. Of these, 131 (14%) were detected by routine contact procedures; none had presented with symptoms and disease was consequently detected at an earlier stage with fewer being sputum smear positive (11% *v* 28%, $p < 0{\cdot}001$). The 131 cases were found by screening 5416 contacts of other index cases, an overall yield of 2·4%. The highest yield was 18% in close contacts of sputum smear positive (S+C+) index cases, the yield in contacts of other respiratory and non-respiratory index cases was less than 2%. The incidence of new cases in contacts with previous BCG vaccination was significantly lower than in the non-vaccinated group (1·2% *v* 2·8%, $p < 0{\cdot}001$). The workload involved in screening contacts in this series could have been halved by restricting screening to all contacts of S+C+ index cases and only close contacts of other index cases, but this would have resulted in missing 26 of the new cases amongst contacts over the five year period. Contact procedures remain valuable in the detection of new, asymptomatic cases of tuberculosis in the Edinburgh area. Particular efforts should be directed towards contacts of S+C+ patients, children, Asians, and those without BCG vaccination.

Notices

Cor pulmonale and the pulmonary circulation

A one day symposium on cor pulmonale and the pulmonary circulation will be held at the Postgraduate Medical Centre, East Birmingham Hospital, on 31 October 1984. The programme will include a guest lecture by Professor Alain Lockhart (France), president of SEPCR. Further details are available from Miss Megan Wood, postgraduate secretary, East Birmingham Hospital, Birmingham B9 5ST (021-772 4311 ext 4259).

School of Clinical Perfusion Sciences: postgraduate diploma

The postgraduate diploma course of the School of Clinical Perfusion Sciences, St Thomas's Hospital, will consist of a two year block release of one week in four. The first year, based at St Thomas's Hospital, will concentrate on the basic sciences of anatomy, physiology, pharmacology, haematology, microbiology, engineering, and materials science. The second year will be based at the Brompton and Hammersmith Hospitals and will concentrate on the clinical aspects of perfusion. The entrance requirements are three years' experience as a practising perfusionist and the HNC/HND/HTec or degree or equivalent qualification. Perfusionists with other qualifications who have contributed to perfusion sciences will also be considered for this course. Applications should be sent to the Secretary, Mr R Hobbs, School of Clinical Perfusion Sciences, St Thomas's Hospital, London SE1 7EH.