Thorax 1986;**41**:707–736

Proceedings of the British Thoracic Society

The 1986 summer meeting of the British Thoracic Society was held on 18 and 20 June at Cheltenham Town Hall.

Interrelationships of physical disability, family knowledge of asthma and psychological stress in Bristol children

F CARSWELL, G HEK, E ROBINSON *Department of Child Health, Bristol University; Department of Community Nursing, Bristol and Weston Health Authority; School of Education, Bristol University* Two different general practices in Bristol agreed to a survey of their 2312 children aged 5-15 years. Sixty-five per cent of the families returned the initial postal questionnaire. Of these, 11.9 per cent had a child with asthma (one year symptomatic period prevalence). Comparisons were made in 86 asthmatic children (75% of the total found) between one week's record of PEF (peak expiratory flow, recorded up to four times/day) and asthma symptoms, structured questionnaires which utilised the rapid scaling technique to measure the parents' perception of their worry, confidence, knowledge and fear of their child's asthma and independent measurements of the family's theoretical knowledge of signs of attack severity and practical ability to use inhalers. There was an inverse correlation ($r = -0.33$) between the mean daily PEF and asthma symptoms. There was no detectable relationship between the mean PEF and the families' theoretical knowledge of asthma severity, but there were significant relationships between the families' worry and fear of attacks and their ability to judge severity of an attack. The results indicate that families have little objective knowledge of how to judge the most appropriate action for their child.

The role of primary school teachers in the supervision of childhood asthma

R HILL, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Management of asthma in school is clearly important. In a previous questionnaire survey of asthma management in primary schools certain problems were identified. We have investigated this more fully with a second questionnaire circulated to 224 teachers in a random sample of 28 primary schools in Nottingham. The questionnaire was returned by 155 teachers (70%). Class teachers, who are largely responsible for supervising medications (75%), usually found out about their pupils' asthma from parents (94% of respondents). Half the teachers had been shown how to administer inhalers, generally by parents or by the children. Only half the teachers were aware that a school nurse was attached to their school. Instruction in the care of childhood illnesses had been received by 34% of teachers, usually from teacher training (21%) and/or voluntary courses (20%). The majority of teachers (90%) would like more information on childhood disorders, particularly asthma, diabetes mellitus and epilepsy, and also on infectious diseases, hearing problems and first aid. Teachers preferred to learn from in-service discussions and demonstrations rather than from lectures and reading matter. These results suggest that improved teacher education and improved communication with the school health service would be well received by teachers and could benefit children with asthma.

Differences in the source of the house dust mite antigens sensitizing asthmatic and eczematous children

F CARSWELL, SJ THOMPSON *Department Child Health, Royal Hospital for Sick Children, Bristol* The specificity of the serum IgE against the faecal and body antigens of the house dust mite, *Dermatophagoides pteronyssinus* was compared in 65 children who had various combinations of asthma, eczema and rhinitis and in 10 normal children. Antibodies to the mite body were commoner in eczema (30 out of 33 subjects) than in asthma (13 out of 32 subjects) but all subjects who had antibodies to the body had IgE antibodies to the faecal particles. The higher prevalence of body antibody in eczema could have arisen because the allergen is absorbed through the skin in eczema. The faecal allergen is contained in faecal particles, which are 12 times smaller than the body. Although the mean size of the faecal particles is 18 μm sufficient may be inhaled to sensitise asthmatic subjects. This study provides the first evidence that the routes of natural sensitisation may be different in eczema and asthma.

Asthma in pregnancy

RJ WHITE, I COUTTS, C GIBBS, C MCINTYRE *Frenchay Hospital, Bristol* Studies of the behaviour of asthma in pregnancy have been largely retrospective and there is no uniformity in the conclusions. Thirty-one asthmatic women were followed during pregnancy and for six weeks of the puerperium. One was studied during two pregnancies. They measured their peak flow rate three times a week and recorded their bronchodilator usage and symptom score. Subjectively the women considered their asthma to have improved in 22 (71%) of the 32 pregnancies, two were worse and in seven (23%) there was no change. Analysis of the diary cards showed that in 10 pregnancies there was improvement during the third trimester when compared

with the second and that in 11 there was deterioration in the puerperium. Only one of the patients had severe asthma and she was one of the subjects in whom deterioration occurred. The remainder were classified as having mild or moderate asthma and the results suggest that in these patients improvement is likely to occur during their pregnancy, particularly in the last trimester, but that in approximately one-third of patients a deterioration post-partum may occur.

Occupational asthma due to unheated colophony

P BURGE, A WEILAND, AS ROBERTSON, D WEIR *Department of Thoracic Medicine, East Birmingham Hospital, Birmingham* Occupational asthma due to colophony is now a prescribed occupational disease only if exposure is to electronic soldering fumes containing colophony. There has been considerable dispute as to whether breakdown products of colophony during the heating at soldering temperatures (about 350°C) is a cause of the asthma or whether it is due to intact resin acids. Only a small proportion of the world's production of colophony is used for electronic soldering fluxes. We report the first case of occupational asthma due to colophony powder at room temperature. A worker developed occupational asthma while breaking up solid colophony with a hammer and later adding this to a bitumen mix. Occupational asthma was confirmed by serial measurements of peak flow. Bronchial provocation testing showed a dual, immediate and late asthmatic reaction following exposure to colophony dust at room temperature. Non-specific bronchial hyperreactivity to histamine was increased at the time of presentation and returned to normal when he left work, only to recur following a respiratory infection later.

Respiratory symptoms in coffee process workers and their relationship to bronchial hyperresponsiveness, atopy and sensitization to the green coffee bean

J BENNETT, P BAXTER, RJ DAVIES *Academic Department of Respiratory Medicine, St. Bartholomew's Hospital, and Employment Medical Advisory Service, Health and Safety Executive, London* Although allergic respiratory disease in coffee process workers is well recognised, few surveys of these individuals have been conducted, and none have measured bronchial responsiveness. We have conducted such a survey at a coffee processing plant near London. One hundred and ninety-seven workers (80% of the workforce) participated. A respiratory history was obtained by means of a computer administered questionnaire. Bronchial responsiveness to methacholine was measured by a tidal breathing method and the dose of methacholine producing a 20% fall in FEV_1 (PD_{20} FEV_1) was obtained. Skin prick testing was performed with 11 inhalant allergens, extract of green coffee beans (GCB) and histamine and saline controls. Atopy was present in 51% of individuals, bronchial hyperresponsiveness (BHR, defined as PD_{20} $FEV_1 < 6$ μmol) in 19%, a positive skin test reaction to GCB in 11.6% and work related lower respiratory symptoms (WRS) in 10.7%. WRS were more prevalent in atopic subjects ($p<0.05$) and subjects with a positive skin test reaction to GCB ($p<0.001$). There was no correlation between WRS and BHR alone, but those individuals with BHR and a positive skin test reaction to GCB were more likely to have WRS ($p<0.01$). Occupational asthma due to sensitization to the GCB (defined as WRS plus BHR and a positive skin test reaction to GCB) was identified in 2.7% of those studied.

Tuberculosis in NHS staff: is it a problem?

S CAPEWELL, AR LEAKER, AG LEITCH *Royal Victoria Dispensary, Edinburgh* During 1978-1983, 23 new cases of pulmonary tuberculosis (PTB) were notified among 22 077 NHS hospital staff working in the Lothian Area. The average annual incidence was thus $17/10^5$ overall with $21/10^5$ in nurses and $23/10^5$ in doctors, rates very similar to the local population of working age: $26/10^5$ in men and $13/10^5$ in women. However, the incidence of PTB in 300 medical laboratory technicians was appreciably higher at $111/10^5$ ($p<0.05$). Eight of the 23 cases were detected by pre-employment screening (chest radiograph and tuberculin test) and this practice, including BCG vaccination when indicated, should be continued. During employment, only five cases were detected by voluntary periodic chest X-ray screening and only two of these by the Mobile MMI Unit, a yield of approximately one case per 10 500 radiographs. Ten further cases of pulmonary tuberculosis presented with symptoms during the same period, however, and nine of these had smear or culture positive disease compared with only three out of the 13 detected by screening ($p<0.01$, Fisher). The intra-employment screening practised locally is therefore unproductive. We would suggest that maximum efforts should instead be concentrated on the annual chest X-ray screening of all hospital staff in the "high risk" groups.

Comparison of RHZ2/RH10 and RHE2/RH10 regimens in the treatment of tuberculous mediastinal lymphadenopathy

LP ORMEROD *Chest Clinic, Blackburn Royal Infirmary, Blackburn* A retrospective comparison of two regimens, RHZ2/RH10 (n = 37) and RHE2/RH10 (n = 32), used in the treatment of mediastinal lymphadenopathy is reported. The two groups did not differ in age or in pre-treatment or post-treatment values. The rate of improvement in serial radiographs was compared between the two groups, with each patient acting as his own control. There was no difference in frequency of initial gland enlargement at 1 month, but at 2 months RHZ2/RH10 had less enlargement ($p<0.05$). The rate of improvement was faster in the RHZ2/RH10 group from two-seven months treatment, being significantly better than RHE2/RH10 at two ($p=0.03$), five ($p<0.01$) and seven months ($p<0.02$). Pyrazinamide (25-40mg/Kg) appears superior to ethambutol 15mg/kg for the initial two months of treatment of tuberculous mediastinal lymphadenopathy.

Mortality from bacteriologically proved cases of tuberculosis as seen in a single hospital unit 1973-1984

F HOWELL, R O'LAOIDE, P KELLY, T HEALY, L CLANCY *Peamount Hospital, Newcastle, Co. Dublin* The Republic of Ireland has the highest incidence of and mortality from TB in these islands. In the study period, based on WHO methods for compiling mortality from TB, the figures were: nationally new cases of TB 12 063, deaths 1749 (15%), Peamount new cases of TB 4089 (32%), deaths 225 (5.5%). As many have questioned the validity of the WHO methods our study evaluated **all** deaths for the period (1354), of which 336 were TB related. In 95 TB was a remote event, in 149 TB was active but not the primary cause of death and in 92 TB was the true cause of death. This is a true death rate of 2.2%, the lowest reported. Most of the 92 were elderly, male, poor and smokers. The significant predictive factors were (i) bilateral extensive cavitatory disease 77%, (ii) patient referral delay mean 9.7 weeks, (iii) 1° referral delay mean 2.4 weeks, (iv) secondary referral delay mean 2.2 weeks, (v) the diagnosis was made in 91 cases prior to referral but only three had correct treatment at referral although 91% of cases were referred from the hospital services, (vi) of those dying from TB 50% were dead by the end of week two. The conclusions are:

1. This is the first study in these islands to look at the **true** mortality from TB and death certification simultaneously.
2. Our study shows that the international method of compiling mortality data is misleading and needs urgent revision.
3. Our study highlights the tragic consequences of an unacceptable delay in initiating correct treatment in extensive TB.

The clinical and radiological features of *Mycobacterium malmoense* infections in Scotland

AJ FRANCE, DT MCLEOD, MA CALDER, A SEATON *Chest Unit and Department of Microbiology, City Hospital, Edinburgh* Since 1982, *M malmoense* has been isolated from only 21 patients in Scotland (14 male, seven female; age 2-83, median 61 years). This constitutes less than one per cent of all patients with positive mycobacterial cultures. Features of the disease were obtained from case notes and radiographs of 20. Symptoms and radiological appearances were indistinguishable from pulmonary tuberculosis. Predisposing factors were found in 15. Chronic chest disease, predominantly chronic bronchitis and emphysema, was the most common factor. A previous report of 11 patients noted pneumoconiosis in seven (PA Jenkins and M Tsukamura, *Tubercle* 1979;**60**:71-76). In our series only one had coexisting pneumoconiosis. Despite *in vitro* resistance to rifampicin and isoniazid, all patients showed an early response to standard combination chemotherapy. Seven are bacteriologically cured, none has died of the infection but three have died of unrelated diseases; nine remain stable on chemotherapy and one has been lost to follow up. Of the nine who remain on treatment, four relapsed after a standard course and are now on a prolonged course of anti-tuberculosis drugs. The surprisingly good response to standard drugs may be explained by previous observations of *in vitro* testing to drugs in combination (J Banks and PA Jenkins, *Thorax* 1985;**40**:697-8).

What is the true incidence of disease due to opportunist mycobacteria?

PA JENKINS, R WILLIAMS *PHLS Mycobacterium Reference Unit, University Hospital of Wales, Cardiff* Infections with opportunist mycobacteria are not notifiable and it is therefore difficult to determine their true incidence. For the years 1981 to 1985 inclusive the Reference Unit was aware of, on average, 41 cases/year of pulmonary disease due to *Mycobacterium kansasii*, 30 due to the *M avium-intracellulare* complex, 21 due to *M xenopi* and 14 due to *M malmoense*. Since 1981 laboratories have been asked to notify such cases to the Communicable Diseases Surveillance Centre and they have been published in the Communicable Disease Report. The corresponding averages for each of the five years are *M kansasii* 50, *M avium-intracellulare* 16, *M xenopi* 24 and *M malmoense* nine. Because *M kansasii* is relatively easy to identify it is likely that laboratories did not bother to send all the isolates to the Reference Unit and hence the discrepancy. It is more difficult to explain the difference in the figures for *M avium-intracellulare* complex. The average figures for *M malmoense* do not reflect what appears to be a geniune increase in the incidence of infections due to this species over the five years. There were six known to the Reference Unit in 1981 and 25 in 1985. A similar picture is seen when one examines the incidence of cervical adenopathy in children due to opportunist mycobacteria.

BTS study of nine months' treatment with rifampicin and ethambutol in *Mycobacterium kansasii* pulmonary infection

IA CAMPBELL ON BEHALF OF BTS RESEARCH COMMITTEE *Sully Hospital, Sully, Penarth, South Glamorgan* In the current study of nine months' treatment with rifampicin and ethambutol in pulmonary infection with *M kansasii*, 75 patients were available for analysis at the end of treatment, 73% male. Initially 60% had a positive sputum smear. The organisms were resistant to isoniazid. Cavitation was present in 92%; 57% had disease of both lungs. Eleven patients received rifampicin (R) and ethambutol (E) only, 39 RE with isoniazid, 17 RE with isoniazid and pyrazinamide and eight RE with other drugs; 13 took drugs additional to RE for >3 months. There two deaths, neither due to *M kansasii*. One patient was a "failure of treatment" with positive cultures at months seven and eight. Cultures were positive in 8% at three months, 3% at seven months, 1% at eight months and none at nine months. At nine months 97% of the radiographs showed improvement although 47% were not considered to be healed. Clinical progress was assessed at three, seven, eight and nine months: 65 patients were always graded as satisfactory, nine were unsatisfactory on at least one assessment, in four because of *M kansasii*. Mean weight gain was 2.5 kg (SD 4.58).

Diaphragm dysfunction associated with brainstem pathology

A MIER, C BROPHY, M GREEN *Brompton Hospital, London* Diaphragm dysfunction has been reported secondary to lesions of the anterior horn cell, the phrenic nerve and diaphragm muscle itself. However, diaphragm weakness due to a brainstem lesion with normal phrenic nerve and diaphragm muscle function has not been described. Three patients aged 29, 33 and 64 years with dyspnoea were known to have Friedreich's ataxia, spinocerebellar degeneration and multiple sclerosis respectively. Transdiaphragmatic pressure (Pdi) was measured during maximal sniffs (sniff Pdi) and maximal inspirations (Pdi TLC). Phrenic nerve conduction time and twitch Pdi were measured during bilateral supramaximal phrenic nerve stimulation at 1 Hz. Pdi during the voluntary manoeuvres was reduced in all three cases: sniff Pdi 15, 35 and 42.5 cm H_2O respectively (NR>80); Pdi TLC 12.5, 12.5 and 20 cm H_2O (NR>25). By contrast, both phrenic nerve conduction time and twitch Pdi were normal. CT scans showed cerebellar and brainstem atrophy in the first case and cerebellar atrophy in the other two. It was concluded that connections to the respiratory centre localised in the brainstem were also affected by atrophy, resulting in compromised ability to achieve maximal co-ordinated diaphragm contraction during voluntary manoeuvres, whereas peripheral phrenic nerve and diaphragm muscle function were normal. We conclude that breathlessness due to diaphragm dysfunction may be associated with brainstem lesions.

Respiratory muscle function in hyperthyroidism before and after treatment

A MIER, C BROPHY, J WASS, M GREEN *Brompton Hospital and St. Bartholomew's Hospital, London* Patients with thyrotoxicosis may complain of breathlessness, which is usually attributable to cardiac dysfunction. Since skeletal muscle weakness is known to occur in hyperthyroidism we have assessed respiratory muscle strength in six patients before, and four patients after, treatment for thyrotoxicosis (mean (SD) T_4=215 (28) nmol/1). Vital capacity (VC), maximal static inspiratory (PImax) and expiratory (PEmax) mouth pressures and transdiaphragmatic pressures (Pdi) were measured. Phrenic nerve conduction time was recorded during percutaneous supramaximal phrenic nerve stimulation. Maximal voluntary contraction (MVC) of the quadriceps femoris muscles was assessed. Initially VC and PImax were reduced in five of the six patients and PEmax in four. Pdi was below normal in only one patient. Phrenic nerve conduction time was within the normal range, while MVC as reduced in all six patients. At reassessment two to three months later, there was a significant increase in muscle strength; VC, PImax, PEmax and MVC had increased in all patients. Phrenic nerve conduction time had also increased. Sniff Pdi rose by a mean of 27 cm H_2O. We conclude that global weakness of the inspiratory and expiratory muscles occurs in hyperthyroidism and that this weakness is reversible when the patient is rendered euthyroid.

Ribcage and abdominal motion during external negative pressure ventilation (ENPV) using cuirass respirators

WJM KINNEAR, JM SHNEERSON *Assisted Ventilation Unit, Newmarket General Hospital, Newmarket* The effect of cuirass respirators on ribcage and abdominal motion was studied with the Respitrace inductance plethysmograph in 14 subjects with nocturnal hypoventilation, mean (SD) age 56.0 (8.4) years. The Respitrace was calibrated with the isovolume manoeuvre. Subjects remained supine throughout the study and calibration was checked against a spirometer at each stage. Subjects were studied during spontaneous ventilation (SV) and during ENPV with a cuirass respirator at a rate of 15 breaths/minute with a peak suction pressure of -20cm H_2O. Four patients with paradoxical abdominal motion and two with paradoxical ribcage motion during SV had synchronous expansion during ENPV. Three subjects with synchronous expansion during SV developed paradoxical ribcage motion during ENPV. The ratio of ribcage to abdominal motion decreased during ENPV in four of the remaining five subjects. Five of seven subjects studied showed a fall in the ratio of ribcage to abdominal expansion with increasing suction pressure. Cuirass respirators increase the abdominal contribution to ventilation and correct paradoxical ribcage or abdominal motion. Restriction of the ribcage may produce paradoxical motion.

Breathing during sleep in patients with myotonic dystrophy and non-myotonic respiratory muscle weakness

D VEALE, BG COOPER, JJ GILMARTIN, CG GRIFFITHS, P HUDGSON, JW OSSELTON, TN STONE, TJ WALLS, GJ GIBSON *Department of Respiratory Medicine, Freeman Hospital and Regional Neurological Centre, Newcastle General Hospital, Newcastle upon Tyne* Abnormal central respiratory control has been suggested in myotonic dystrophy but the usual indices of ventilatory control are so influenced by muscle weakness that any additional central abnormality cannot be confidently inferred (Serisier *et al, QJ Med* 1982;51:205). We have therefore compared breathing during sleep in control subjects, seven myotonic patients and seven others with non-myotonic respiratory muscle weakness of comparable severity. The myotonic patients had more apnoeas than normal subjects ($p<0.05$), whereas the frequency in non-myotonic patients was similar to normal. Three myotonic patients fulfilled conventional criteria for the sleep apnoea syndrome; in one of these the apnoeas were predominantly obstructive and in the other two mainly central and they occurred in all sleep stages. Time weighted mean nocturnal Sao_2 in the myotonic patients (92.9% (SD 1.7%) was lower ($p<0.01$) than in normal subjects (95.5% (SD 1.4%) and on average they spent 12.8% of the time with $Sao_2<90\%$ compared with no desaturation below 90% in normal subjects ($p<0.01$). Mean Sao_2 in the non-myotonic patients was slightly less than normal (mean 94% (SD 1.1%), NS) and they spent an average 0.9% of the time with $Sao_2<90\%$ ($p<0.05$ compared with normal). The results suggest that sleep apnoea is common in myotonic dystrophy and not simply attributable to respiratory muscle weakness, supporting the

suggestion of disordered central ventilatory control in this condition.

Sleep and oxygen saturation in erythrocytosis

MB ALLEN, L GROCCOT, P CHIPPING, K PROWSE *Departments of Respiratory Physiology and Haematology, City General Hospital, Stoke-on-Trent* It has been suggested (Editorial, *Lancet*, 1985;ii:925) that unexplained polycythaemia is an indication for sleep studies, based upon a study of 11 patients with erythrocytosis without features of polycythaemia rubra vera (PRV) (*Ann Intern Med* 1982;142:956-9). Six of these patients had severe arterial oxygen desaturation (<60%) during sleep, attributed in four to hypoventilation. We have studied six patients with erythrocytosis (mean RCM 40.4 ml/kg) of unknown origin, to assess the nature of respiratory problems during sleep. All were non-obese with an awake arterial oxygen saturation >92%, three were smokers, none had features of sleep apnoea syndrome; two patients with FEV_1 >2SD below predicted had respiratory symptoms. No patient was polycythaemic when overnight polysomnography was performed. The mean sleep period was 5.5 hours, four patients had occasional episodes of apnoea(A) or hypopnoea(H) with a mean A + H index of 2.2. Three patients showed significant arterial oxygen desaturation. In two symptomless patients the greatest fall was 7% from their baseline readings. The third patient, with an FEV_1 50% predicted and respiratory symptoms, had a 6% fall from her baseline value of 97%. The findings suggest that in patients with polycythaemia of unknown aetiology who have an arterial oxygen saturation > 92% polysomnography is unlikely to lead to a diagnosis.

Simple aspiration of pneumothorax

RM HIGGINS, DJ LANE *Osler Chest Unit, Churchill Hospital, Oxford* Simple aspiration has been adopted as treatment for many patients with pneumothorax, with a reported success rate of up to 70%. In order to review our experience with simple aspiration, all pneumothoraces treated in the Osler Chest Unit since February 1985 were reviewed. Forty-three patients with 52 pneumothoraces were seen, age range 9-83. Of 22 pneumothoraces treated with simple aspiration, only nine required no further treatment, three required aspiration more than once, nine were subsequently treated with intercostal tube drainage, and in one the cannula used for simple aspiration was left in situ for four days. Simple aspiration of nine pneumothoraces due to emphysema was successful in three patients. A "Leader Cath" (Vygon), usually used for central venous cannulation, was found to be more convenient than other flexible cannulae (eg "Medicut") for aspiration as it seemed less likely to kink or split. One patient with a persistent pneumothorax was sent home with an intercostal tube drain in situ, and a Heimlich flutter valve. Our experience suggests that simple aspiration may be used as treatment of pneumothorax, but may need to be repeated, or an intercostal tube drain may need to be inserted, in more than 50% of patients.

Paracentesis of carcinomatous pleural effusions through a fine silastic catheter

J SHAND, GT MCCREATH, RDH MONIE *Chest Clinic and Department of Radiology, Southern General Hospital, Glasgow* Carcinomatous pleural effusions occur not necessarily in the terminal phase of a patient's illness. To relieve symptoms, paracentesis is usually performed through an intercostal tube with an underwater seal drain, a procedure with potential hazards (Bristol *et al, Br Med J* 1983;286:348) and uncomfortable for the patient. Under ultrasonic control thirty-eight patients with such effusions had a soft polyethylene catheter (8Fr.Cystocath: Dow Corning) inserted into the largest loculus and up to one litre aspirated twice daily. Following complete aspiration confirmed ultrasonically, 27 had one of four sclerosing agents injected through the catheter before removal. The catheter was easily repositioned if required and all patients remained mobile (one outpatient). The median catheter time in situ was two days (range 1-14) and the mean volume aspirated 2.65 litres. Recurrence following pleurodesis occured in only one out of 27 effusions; in nine no pleurodesis was performed, mainly because the paracentesis was palliative in terminal care and two with pneumothoraces required large drains. Seven pneumothoraces occurred and three developed superficial skin infections around the catheter. The mean survival time in 26 was 225 days; twelve still survive. This method of paracentesis is safe and acceptable to patients.

Transbronchial aspiration of subcarinal lymph nodes in carcinoma of the lung

AD BLAINEY, M CURLING, M GREEN *Departments of Respiratory Medicine and Cytology, St. Bartholomew's Hospital, London* Assessment of mediastinal lymph node involvement in non-small cell carcinoma of the lung is important for surgical evaluation and prognosis, but difficult. A recent study from the USA reported that transbronchial aspiration of peribronchial lymph nodes via the fibreoptic bronchoscope revealed malignant involvement of these glands in a very high proportion (47%) of patients with carcinoma (Wang and Terry, *Am Rev Respir Dis* 1983;127:344-347). To evaluate this technique in clinical practice, we performed transbronchial needle aspiration of subcarinal lymph nodes in patients undergoing fibreoptic bronchoscopy for suspected carcinoma. The needle, in a sheathed catheter, is passed through the bronchoscope and inserted into the subcarinal area under direct vision, and material is aspirated for cytology. Malignant cells were aspirated from the subcarinal lymph nodes in four of 45 patients with histologically proved pulmonary neoplasm (8.8%). Three of these had squamous cell carcinoma and one had adenocarcinoma. In two patients with positive aspirates the carcinoma would have otherwise been resectable on clinical grounds. No complications of transbronchial needle aspiration were detected. This rapid, safe and simple technique reveals malignant subcarinal involvement in up to 10% of patients undergoing fibreoptic bronchoscopy for carcinoma of the lung, and may prevent uneccessary thoracotomy.

The effect of fibreoptic bronchoscopy on airway physiology

A PEACOCK, R BENSON-MITCHELL, R GODFREY *D Level East, Southampton General Hospital, Southampton* Several studies have shown that fibreoptic bronchoscopy can cause a decrease in Pao_2 but it is not known whether this is due to the premedication, the topical anaesthesia or the obstruction posed by the bronchoscope. We have studied the effects of each part of the procedure on spirometry and oxygen saturation (Sao_2) in 19 patients with lung disease and nine normal non-smokers. Each subject produced three flow-volume loops and the loop corresponding to the best FEV_1 was recorded. Sao_2 was measured by ear lobe oximeter. These measurements were repeated after premedication (Omnopon/Atropine) in seven patients and after topical anaesthesia to the bronchial tree (340 mg lignocaine) with and without the bronchoscope in the treachea in all patients and all controls. The premedication had no effect. In the normal subjects anaesthesia produced falls in FEV_1 10% (SE 1%), FVC 7% (SE 2%), PEF 14% (SE 2%), PIF 20% (SE 5%) and insertion of the bronchoscope caused further falls in FEV_1 5% (SE 1%), FVC 2% (SE 7%), PEF 18% (SE 30%) and PIF 3% (SE 4%). All these changes were significant ($p<0.01$). In the patients, anaesthesia produced falls in FEV_1 10% (SE 2%), FVC 10% (SE 3%), PEF 12% (SE 2%) and PIF 10% (SE 3%). All the changes were significant ($p<0.01$) but there was no further decrease when the bronchoscope was inserted. There were no significant changes in Sao_2 in normal subjects or patients. We conclude that the major effect of bronchoscopy on lung function is due to the topical anaesthesia and in patients with lung disease the insertion of the bronchoscope causes little additional obstruction.

The role of cervical mediastinoscopy in patients with superior vena caval obstruction

PH KAY, M AZARIADES, P GOLDSTRAW *Brompton Hospital, London* Cervical mediastinoscopy has been regarded as a hazardous procedure in patients with superior vena caval obstruction (SVCO). Since 1978 we have performed this procedure in 20 such patients. Biopsy specimens were taken from high in the mediastinum in all except one case. A tissue diagnosis was obtained in 18 patients (90%). In one patient excessive venous haemorrhage caused the procedure to be discontinued in favour of anterior mediastinotomy. In one of the four patients who had undergone previous empirical radiotherapy the tissue was too distorted to make a definite diagnosis. All patients required elective ventilation for one to two hours following the procedure. The ages of the patients assumed a bimodal distribution: five young patients (mean age 30) had lymphoma (three) or embryonic tumours (two); the 13 elderly patients (mean age 59) had primary lung tumours (five large cell, four small cell, four adenocarcinoma). Eight patients subsequently received radiotherapy, seven chemotherapy and five no treatment. Patient survival reflected the primary pathology. With experience cervical mediastinoscopy in the presence of SVCO is a safe procedure with a high yield of pathological tissue enabling definitive oncological management to be undertaken.

Is the Nd YAG laser ideal first line treatment for obstructing tracheal tumours?

PJM GEORGE, CPO GARRETT, MR HETZEL *Department of Chest Medicine, University College Hospital, London* We have treated 21 patients with tracheal tumours (10 primary and 11 secondary), using the Nd YAG laser under general anaesthesia. Fourteen patients presented with impending asphyxia. This was dramatically relieved in 11 cases and was associated with an immediate rise in peak expiratory flow (PEF) (mean improvement : 135%; range : 26-512%). This improvement provided time in which to select the most appropriate longer term management with tracheal resection (one case), tracheal stent (one), radiotherapy (seven), radiotherapy and laser treatment (three) or laser treatment alone (two). The remaining seven patients were treated electively with the laser and showed a mean improvement of 36% in PEF; further management has been with the laser alone. Eighteen patients were subsequently well enough to live independently at home. Nine patients with primary tumours are alive 62-500 days after initial laser treatment and one has died after 143 days. Five patients with secondary tumours remain alive at 29-321 days and six have died after 5-74 days (mean survival of 35 days). Laser treatment provides an ideal method of resuscitating patients with life threatening tracheal obstruction and enables further treatment to be carefully planned. In some cases, laser treatment alone provides adequate palliation.

Oesophageal intubation for broncho-oesophageal fistula — how effective is it?

AC DAVIDSON, BJM JONES, G MASKELL, DM GEDDES, ARW HATTFIELD *Departments of Thoracic Medicine, London Chest Hospital, and of Gastroenterology, London Hospital (Whitechapel), London* Broncho-oesophageal fistulae complicating bronchogenic or oesophageal carcinoma are extremely distressing and carry a prognosis of about one month. It has been suggested that such a fistula is an indication for palliative placement of an oesophageal prosthetic stent. In our joint experience these fistulae are uncommon, only four cases presenting in a two year period with primarily respiratory complications and accounting for six of 47 referrals for prosthetic stent insertion over the same time period. The fistula was confirmed radiologically and by bronchoscopy and oesophagoscopy in all patients. An Atkinson tube was placed across the fistula with standard techniques. Of the six patients (mean age 64 years, range 47-76), three had oesophageal and three bronchial primaries. Two had undergone radiotherapy prior to development of a fistula and all had severe coughing and choking on swallowing liquids and initially solids were tolerated poorly. Three patients were able to complete a course of palliative radiotherapy. Complications included: further fistula above prosthesis (one), distal tube displacement (two), tube blockage (one) and fatal

mediastinitis (one). Five patients survived longer than expected (44, 110, 127, 162, 191 days post intubation), although in the longest survivor the tube was removed at the patient's request and the fistula appeared to have closed spontaneously. Oesophageal intubation should be considered in patients with malignant broncho-oesophageal fistula for relief of symptoms and to allow time for other treatment modalities.

A single flush preservation technique for distant organ procurement for heart-lung transplantation

DK JONES, N CAVAROCCHI, TW HIGENBOTTAM, J WALLWORK *Papworth Hospital, Papworth Everard, Cambridge* By perfusing the donor's lungs with prostacyclin; flushing heart and lungs after removal with a solution of albumin crystalloid, donor blood, mannitol and prostacyclin; and finally transporting them in iced saline it is possible to obtain organs for transplantation from distant hospitals. We compared the postoperative alveolar-arterial oxygen difference measured up to 72 hours in five patients who received heart and lungs from donors in adjoining theatres (near procurement) with five patients where organs were transported from distant hospitals (distant procurement), and for 18 hours, in 13 patients who underwent routine coronary artery bypass grafting (CABG).

	$A\text{-}aO_2$ (kPa) geometric means									
Hours postop.	1	2	4	8	12	18	24	36	48	72
Near procurement	18*	10*	13*	9	11	10	8	11	12	14
Distant procurement	8*	8*	9*	8	7	6	5	6	7	3
CABG	30	31	26	20	17	14	—	—	—	—

* significantly lower than CABG ($p < 0.05$)

There was no difference in the incidence of alveolar shadowing on daily chest radiographs taken for a week postoperatively in the three groups. We now have a simple, safe system for distant organ procurement which gives excellent initial graft function.

Myasthenia gravis — a surgical experience

JF MORIN, KJ JEYASINGHAM *Department of Thoracic Surgery, Frenchay Hospital, Bristol* Over an eleven year period ending March 1986, five males and 25 females with an average age of 35 years (range 14-75) with generalised myasthenia gravis were admitted to a thoracic surgical unit for thymectomy. Myasthemia was associated with hyperthyroidism in two patients, with diabetes mellitus in one and with hypothyroidism in a patient who had previously had a thymic cyst removed. Of the 14 who had a routine CT scan of the mediastinum, only three showed enlargement of the thymus, shown later to be due to thymomas. In two of these, the routine chest radiograph showed an abnormal mediastinal shadow. Histologically five had a thymoma, 17 showed hyperplasia, and seven revealed normal thymic histology. In one a thymic cyst had previously been removed. Those with thymic hyperplasia were younger (average age 26) than the thymomatous group (average age 57), and the normal thymic group (average age 42). Two were able to discontinue their anti-cholinesterase drugs (one and four years after the operation). Eighteen had a significant reduction in their medication. In this preselected group referred for surgery the results of thymectomy were independent of the age of the patient, the duration of disease before surgery, and the histopathology of the gland. The surgery, which was carried out through an upper median sternotomy, entailed zero mortality, and assisted ventilation for over 24 hours was required in only two patients.

Wide surgical resection as the main treatment modality in primary chest wall tumours

A MERDAD, K JEYASINGHAM *Department of Thoracic Surgery, Frenchay Hospital, Bristol* Between April 1975 and February 1986, 74 patients underwent surgical resection for neoplasm involving the chest wall. Fifty-two patients had bronchogenic carcinoma invading the ribs, and two patients had a localized mesothelioma involving the ribs. These two groups have been excluded from further analysis for the purpose of this report. Twenty patients had primary chest wall tumours, and of these ten were benign. No operative mortality was encountered. Of the benign group, neural sheath tumours accounted for four whilst chondromata accounted for three. All ten patients have a recurrence free follow up of a mean of three years. Primary malignant tumours constituted 50%, with chondrosarcomata accounting for five. Three patients died during the follow-up period — at two months, five months and five years after surgery. The remaining seven are alive and free of disease with a mean follow-up of 4.2 years. In three of the five with malignant tumours who underwent preoperative biopsy the final histopathology was different. Based on preoperative histopathology two patients underwent preoperative radiotherapy and chemotherapy. In one of these patients the histology was revised from rhabdomyosarcoma to a low grade chondrosarcoma, not having shown any response to radiotherapy and chemotherapy over an 18 month period. We conclude that wide excision should constitute the primary modality of treatment in primary chest wall tumours.

The relationship between change in bronchial reactivity and change in respiratory symptoms in a community survey

J BRITTION, P BURNEY, S CHINN, O PAPACOSTA, A TATTERSFIELD *City Hospital, Nottingham, and St. Thomas's Hospital, London* We have previously reported seasonal variations in bronchial reactivity in the general population, with increased reactivity occurring in June and September, when asthma morbidity and mortality are usually increased. We now report the relationship between change in reactivity and change in respiratory symptoms in the same cohort of subjects. Histamine PD_{20} FEV_1 was measured and current respiratory symptoms assessed by questionnaire in 78 subjects in both September 1984 and March 1985. On both occasions PD_{20} FEV_1 was inversely correlated ($p < 0.001$, Spearman rank correlation) with the

reported severity and frequency of wheezing or tightness in the chest, and with the daily use of asthma medications. Change in PD_{20} between September and March could be estimated in 45 subjects. Although there was no significant overall mean change in PD_{20}, drug use or symptom scores in these subjects over this period, change in PD_{20} was inversely correlated within subjects both with the frequency of wheezing within the last month ($p<0.001$) and with daily medication use ($p<0.05$). This study suggests that within subjects change in bronchial reactivity does reflect changes in the severity of symptoms attributable to airflow obstruction.

Cadmium inhalation and emphysema

AG DAVISON, PM FAYERS, AJ NEWMAN TAYLOR, KM VENABLES, JH DARBYSHIRE, CAC PICKERING, H HOLDEN, NJ SMITH, H MASON, M SCOTT *The Brompton Hospital, London* Cadmium is commercially important and is present in cigarettes, but the chronic respiratory effects of inhaling cadmium remain controversial. We report the effects of cadmium fume inhalation in the largest and most complete occupationally exposed population studied to date. We studied (i) 101 of 102 men who were alive and had worked in a copper-cadmium alloy plant for one year or more since it opened in 1926, (ii) 96 unexposed controls matched for age, sex and occupational status from the same factory. Cumulative exposure to cadmium was estimated from company records and since 1951, from measured airborne levels. Smoking habits were similar in the two groups. Significant differences were found between the values for cadmium workers and expected values (the latter derived from regression equations for controls) for the measures FEV_1, — 194 ml ($p<0.05$); $FEV_1/FVC\%$, — 6.5% ($p<0.001$); TLCO, — 0.82 mmol/min/kPa ($p<0.001$); KCO, — 0.25 mmol/min/kPa/1 ($p<0.001$); Radiographic TLC + 461 ml ($p<0.001$); RV + 402 ml ($p<0.01$); RV/RTLC% + 2.9% ($p<0.02$). Cadmium workers first employed before 1950 and with high cumulative exposures showed the greatest reduction in FEV_1, $FEV_1/FVC\%$, TLCO, KCO. Eighteen per cent of cadmium workers had radiographic emphysema at independent assessment, compared with 7% of controls. These results are consistent with cadmium fume inhalation causing emphysema.

Pneumonia in the community: incidence, radiology and outcome

MA WOODHEAD, JT MACFARLANE, JS MCCRACKEN, DH ROSE, RG FINCH *Departments of Thoracic Medicine, Radiology and Microbiology, City Hospital, and Department of General Practice, University Hospital, Nottingham* We have studied lower respiratory tract infections (LRTI), in adults (16-79 years) in a suburban population of c.50 000 between 1st October 1984 and 30th September 1985. Twenty-nine general practitioners identified all their patients given antibiotics for LRTI. Of these 251 (5.6%) had pneumonia (defined as an acute LRTI associated with new localising chest signs on examination) and 236 were studied at home, without delay, by a visiting researcher (MAW). On average each GP saw nine pneumonia cases per year. The incidence of pneumonia was approximately 5/1000 population/year. An acute chest radiograph, performed in 234 cases, revealed fresh changes in 38%. Radiographs also showed other, unknown, significant diseases in 20 (8%) cases. There were seven deaths (3%), six in the 51 patients admitted to hospital (12%) and one in the 185 managed at home (0.5%). A parallel detailed study of all 87 patients with LRTI **without** focal chest signs, treated in one practice between 11th March and 30th September 1985 found only two (3%) with fresh radiographic changes. There were no deaths. New focal chest signs in patients wit LRTI are a good predictor of those with fresh radiographic change. Nearly 80% of all pneumonias are managed outside hospital and mortality in this group is very low.

Pulmonary involvement in scleroderma: comparison with cryptogenic fibrosing alveolitis

EW ALTON, S KWAN, M TURNER-WARWICK *Brompton Hospital, London* It is often stated that fibrosing alveolitis, whether associated with one of the connective tissue diseases or of unknown origin (CFA), demonstrates identical clinical, radiographic and physiological features and carries the same prognosis. We have studied 10 patients having pulmonary involvement in association with scleroderma for a mean period of six years. In comparison to 94 patients of similar disease duration with CFA, those with scleroderma showed significantly less clubbing ($p<0.001$) and cyanosis ($p<0.05$) at presentation. A positive response to the antinuclear factor test was noted in 80% and rheumatoid factor in 40% in comparison to respectively 29% and 9% with CFA. Though lung function and the chest radiograph did not differ markedly, the five year survival was significantly increased from 45% to 83% in the group with scleroderma. To establish whether the strong female bias (8:2) amongst scleroderma patients or their younger mean age (45 years compared with 57 years) was responsible for the improved prognosis, 10 age and sex matched patients with CFA were studied. The survival of the scleroderma group remained significantly improved ($p<0.05$). With recent evidence showing a favourable response to D-penicillamine in scleroderma with lung involvement, as well as the improved prognosis noted here, differentiation of this group from patients with CFA may be of importance.

"Pulsed" intravenous methylprednisolone therapy for refractory sarcoidosis

AN WARRENS, PJ BARNES, PJ COLE, DZ MITCHELL *Departments of Thoracic Medicine and Clinical Pharmacology, Cardiothoracic Institute, and MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, London* Sarcoidosis may occasionally remain suboptimally suppressed or continue to progress despite daily high dose oral corticosteroid therapy. "Pulsed" intravenous methylprednisolone has been used in a variety of disorders, and recently with great success in a refractory

case of sarcoid polyneuropathy (RKA Allen, J Merory, *Aust NZ J Med* 1985;**15**:45). Accordingly we treated eight patients with difficult histologically proved sarcoidosis with a course of eight "pulses" of intravenous methylprednisolone 1 g per week. We simultaneously reduced the oral dose of prednisolone, until each was taking only 20 mg on alternate days. Seven of our patients showed considerable regression of their sarcoid activity after eight weeks. In one this represented an increase in visual acuity and a decrease in peripheral neuropathy. A second patient lost all radiological evidence of an intracerebral granuloma which had been associated with convulsions. Remarkably few adverse effects were experienced and only one patient showed significant increase in weight. Preliminary evidence suggests that disease activity remains under control after finishing the course of "pulsed" therapy. We suggest that this therapy offers a useful alternative for controlling disease activity in these difficult patients.

Fibrosing alveolitis (FCA): treatment with cyclosporin

EW ALTON, M JOHNSON, M TURNER-WARWICK *Brompton Hospital, London* Tissue lymphocytes are known to persist even at autopsy in CFA. Seven carefully monitored patients with fibrosing alveolitis, deteriorating despite high dose prednisolone and cyclophosphamide, were treated with 5 mg/kg of the lymphocyte suppressing agent cyclosporin A. Response was gauged by radiographic, physiological and breathlessness scores at monthly intervals. This report includes the decline noted in all parameters for 6 months before treatment and follow up to death. After one month, six of the seven patients noted marked improvement in exercise tolerance; the decline in both transfer factor and spirometry was halted, whilst the chest radiograph remain unchanged. One month later all parameters once again deteriorated and continued to do so with the longest survival period following treatment of ten months. To establish whether survival time was influenced by treatment, seven patients closely matched for this very advanced stage of disease, in terms of sex, age, disease duration, volumes, transfer factor and histology, were compared. The mean survival time for cyclosporin treated patients was doubled from 2.5 to five months. In view of increased awareness of heart-lung transplantation as a possible measure in these end stage patients, but in whom the wait for suitable organs often remains a determining factor, the increased survival even for short periods may be of crucial importance.

Chronic eosinophilic pneumonia — a long term follow up

MT NOLAN, MX FITZGERALD *Department of Respiratory Medicine, St. Vincent's Hospital, Dublin, Ireland* Chronic eosinophilic pneumonia (CEP) is a rare disorder, characterized by fever, weight loss, blood eosinophilia, diagnostic radiological and biopsy findings, and a prompt response to corticosteroids. There is little information concerning the natural history and treated course of CEP. We report the clinical and laboratory findings, together with long term follow up data on eight cases diagnosed without recourse to biopsy material. Mean follow up was eight years (range 1-12) and mean age was 42 years (range 19-52). Presenting features were fever and weight loss (five patients), wheeze (five patients), cough and sputum (five patients). Peripheral eosinophilia was present in all eight patients (mean eosinophil count 2403 — range 1100-5206), whereas atopic indices were positive in only three patients (↑ IgE and positive skin prick tests). Three patients had mild asthma before developing CEP. Radiography in all patients revealed characteristic fluffy peripheral shadows. Initial treatment with high-dose prednisolone produced resolution of symptoms within one week and of radiological changes within three weeks in all patients. Attempts to stop therapy resulted in relapse in seven of eight patients and maintenance therapy of prednisolone five mg (six patients) and 12.5 mg (one patient) has been required to prevent recurrence. One to twelve years following diagnosis all patients remain well and have normal spirometry. Our data suggest that the prognosis for patients with CEP is excellent, but long term low dose corticosteroids are required to prevent relapse.

The application of pattern recognition and signal processing techniques in the diagnosis of asbestosis

K ANDERSON, A LUK, J MCLEOD, F MORAN *Department of Respiratory Medicine, Glasgow Royal Infirmary, and University Department of Electrical Engineering, Glasgow* Previous research from this unit has suggested that breath sounds can be used to discriminate different forms of parenchymal lung disease (RB Urquhart *et al, Comput Biol Med* 1981;**11(3)**:129-39) and the procedure is by nature non-invasive (R Loudon and RLH Murphy, *Am Rev Respir Dis* 1984;**130**:663-73). Signal processing and pattern recognition techniques were applied to the lung sounds obtained when three groups of five subjects (with asbestosis and asbestos exposure and normal non-smoking subjects) were studied. Lung sounds were recorded during 10 deep tidal respiratory cycles from each lung base. The signals recorded on magnetic tape were then digitized and transformed to the frequency domain using the weighted segment overlapped averaging technique. Twenty features were extracted from the range 5-2000 Hz and projected onto a two dimensional space by applying the Kittler and Young transformation (a linear mapping technique). Three slightly overlapped clusters were observed. Inspection of the components of the two eigen vectors (of the matrix of the transformation) suggested that both the high and low frequency components are of importance. This may indicate that difference in breath sounds in addition to the presence of crackles may discriminate between the two groups. The technique potentially offers a new diagnostic aid for parenchymal asbestos disease.

Pulmonary infection or Kaposi sarcoma? A diagnostic role for fibreoptic bronchoscopy in the acquired immunodeficiency syndrome

PJV HANSON, JV COLLINS *St. Stephen's Hospital, London* Kaposi's sarcoma of the lung cannot be

differentiated clinically or radiologically from a number of opportunistic infections in patients with the acquired immunodeficiency syndrome. Furthermore it is rare to find pulmonary Kaposi's sarcoma without coexisting opportunistic infection. Fibreoptic bronchoscopy has a high diagnostic yield for *Pneumocystis carinii* pneumonia, the diagnosis being made more frequently before death than at necropsy. In contrast, pulmonary Kaposi's sarcoma is more commonly found at necropsy than was suspected before death. Many investigators have reported a very low diagnostic yield of pulmonary Kaposi's sarcoma by transbronchial biopsy perhaps owing to its multifocal pattern of distribution throughout the lung parenchyma and the absence of specific histological markers. Open lung biopsy has been repeatedly advocated as the only diagnostic procedure with an acceptable yield. We report four cases of pulmonary Kaposi's sarcoma from a series of eleven patients who underwent a total of thirteen fibreoptic bronchoscopy procedures in whom the diagnosis was made by transbronchial or endobronchial biopsy. We believe fibreoptic bronchoscopy is a useful procedure for the diagnosis of pulmonary Kaposi's sarcoma as well as opportunistic infection in the immunocompromised patient.

Diagnosis of lung cancer by a CA-50 radioimmunoassay inhibition test

MJ HERSHMAN, NA HABIB, R STEIN, CB WOOD (INTRODUCED BY JMB HUGHES) *Departments of Surgery, Royal Postgraduate Medical School, London, and Bristol Royal Infirmary* Cancer cells may secrete or express on their cell surfaces "fetal components" not normally present in adult cells, which may be detected in serum as "oncofetal antigens". Recently a new antigen, CA-50, has been isolated as a monosialoganglioside, which is shed into the serum and can be detected with a radioimmunoassay technique. CA-50 has been shown to be raised in 50-70% of patients with colorectal, pancreatic and liver cancer. This study assessed the significance of CA-50 in benign and malignant lung disease. Based on a normal population study a level of 17 units/ml is used as a cut off level between benign and malignant diseases. The serum CA-50 level was measured in 50 normal individuals and 28 with inflammatory lung conditions, including 10 TB, three sarcoid, six alveolitis, nine acute bronchitis + pneumonia. All normal subjects and 27 of 28 (96%) patients with benign lung conditions had levels below 17 units/ml with a mean value of 10.1 (SD 4.9). Twenty-one of 55 (38%) patients with lung cancer had raised serum levels (mean 32.3 (16.5)). Six of 13 (46%) squamous tumours were positive, compared with 14 of 24 (58%) oat cell tumours, one out of four adenocarcinomas, none of 12 large cell tumours and none of two lymphomas. These data suggest that CA-50 may have a role as a tumour marker for lung cancer since it has a high specifity and may perhaps be used in conjunction with other markers.

Pathology and physiology of the pulmonary circulation after long term domiciliary oxygen therapy (LTOT)

M WILKINSON, CA LANGHORNE, D HEATH, GR BARER, P HOWARD *Department of Medicine, University of Sheffield, and Department of Pathology, University of Liverpool* A detailed study of the pathology of the pulmonary vasculature was made in 10 patients who died of hypoxic cor pulmonale associated with severe chronic obstructive airways disease. Qualitative and quantitative measurements of the pulmonary vasculature were compared with physiological tests performed in the last year of life. Five patients received LTOT, and five did not. In muscular pulmonary arteries, highly distinctive changes of longitudinal muscle deposition in the intima were found. In pulmonary arterioles, medial muscularisation was combined with similar intimal changes to muscular pulmonary arteries. The extent of these changes did not correlate with arterial hypoxaemia or pulmonary haemodynamics. LTOT did not appear to influence the changes. The pathological appearances of hypoxic pulmonary vasoconstriction were less evident at death. They seemed more in keeping with an interaction of hypoxia and mechanical distortion of small airways. LTOT did not arrest the changes and will probably be of only temporary therapeutic benefit.

A new technique for measuring alveolar surface and the assessment of microscopic emphysema

D LAMB, A MACLEAN, DC FLENLEY *Department of Pathology, University Medical School, and Department of Respiratory Medicine, City Hospital, Edinburgh* Emphysema is an increase in air space size; normal alveoli average 0.25 mm, and macroscopic emphysema assessment requires a 1 mm air space, which involves a fourfold loss of alveolar surface area. Measurement of alveolar surface area would be a sensitive measurement of early emphysema. We have devised a method which assesses alveolar wall surface area per unit volume (AWUV as mm^2/mm^3) from measurements of alveolar perimeter per unit area on histological sections using an IBAS2 automatic analyser. Measurements were made on random fields (18-35) from 12 random blocks from each of 46 resected lobes fixed by standard inflation with formol saline. Measurements were controlled for compression and shrinkage artefacts. Perimeter measurements per unit area were converted to AWUV by the formula AWUV = alveolar perimeter $(mm/mm^2) \times 4 \div Pi$. AWUV range was 8.8-27.4 with most cases exhibiting normal distribution. Variation in AWUV did not correlate with parameters for body size or lung volume and did not relate to area of lung slices occupied by macroscopic emphysema measured by direct planimetry. We believe this variation in AWUV reflects the presence of microscopic emphysema which precedes macroscopic emphysema. Values of AWUV correlate with quantitative CT scan and with tests of gas transfer, suggesting that this degree of emphysema is of clinical significance

Pleural thickening and skeletal deformity in thoracoplasty — the relationship with ventilatory failure

NR MOORE, MS PHILLIPS, JM SHNEERSON, CDR FLOWER, AK DIXON *Department of Radiology, Addenbrooke's Hospital, Cambridge, and Chest Unit, Papworth Hospital, Cambridgeshire* Hypercapnic respiratory failure is a late complication of tuberculosis treated by thoracoplasty. Why it develops in some patients only is unknown. We studied 32 patients by computed tomography (CT) of the thorax and arterial blood gas analysis while awake. Ventilatory failure was defined as a $Paco_2 > 5.9$ kPa. CT was performed on a third generation system using 8 mm thick slices with a 15 mm slice interval. The CT studies were reviewed without knowledge of the blood gas results. The maximal pleural thickening of operated and non-operated sides was recorded for every image. Skeletal deformity was assessed by two methods. The apical vertebra of the scoliosis was determined from plain radiographs. The corresponding CT image was selected; the skeletal deformity angle was measured and the extraskeletal cross sectional areas of operated and non-operated sides of the thorax were compared. The $Paco_2$ correlated with mean total pleural thickening, and with pleural thickening of the non-operated side. Linear regression analysis suggested that mean total pleural thickening > 7 mm was associated with ventilatory failure. There was no correlation between skeletal deformity and $Paco_2$.

Quantitative CT scan and CO transfer can estimate the size of directly measured distal airspaces which defines emphysema in smokers

GA GOULD, A MCLEAN, W MACNEE, MD HAYHURST, AT REDPATH, PM WARREN, JJK BEST, D LAMB, DC FLENLEY *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, and Department of Pathology, Edinburgh* Emphysema is defined as distal airspace enlargement, but internal surface area ranged from 40 to $98m^2$ in 29 inflation fixed lungs without macroscopic emphysema (*Thorax* 1967;22:483). We have studied 48 smokers (FEV_1 1.0-4.4 l) undergoing resection for lung cancer, measuring lung function and radioabsorbence by quantitative CT scan, and air space size as alveolar wall/unit volume (AWUV). After inflation 12 random blocks from the lateral 2/5ths of each lung/lobe were embedded in glycol methacrylate and 18-35 random fields (mag $\times$ 63) examined by image analyser to yield a stable running mean AWUV. Mean AWUV for the five fields with lowest values (AWUV/L5F) measured the maximal severity of emphysema. Mean AWUV ranged from 10 to $28mm^2/mm^3$ and in 39 cases with $< 5\%$ macroscopic emphysema from 14 to $28mm^2/mm^3$. AWUV correlated with both TLCO ($r = 0.72$) and Kco ($r = 0.66$) but correlation improved with AWUV/L5F (TLCO $r = 0.78$; Kco $r = 0.84$). The EMI number defining the lowest fifth percentile in the CT scan correlated with AWUV ($r = 0.63$) and AWUV/L5F ($r = 0.75$), but correlation improved ($r = 0.77$) with the use of CT scan data from the lateral lung field only. We conclude: (1) Airspace size (AWUV) varies widely in smokers, even without macroscopic emphysema. (2) Transfer factor correlates with AWUV, without discontinuity when macroscopic emphysema appears. (3) Quantitative CT scanning can identify and measure early emphysema in man during life.

Narrow section computed tomography in diffuse lung disease

B STRICKLAND *Brompton Hospital, London* In CT scanning the image is composed of pixels approximately 1×1 mm in section but commonly 10 to 15 mm deep. A single density value is alloted to each pixel equivalent to the mean for the corresponding volume of tissue. This averaging process introduces blur proportional to the depth of the CT slice. If narrow (3 mm) slices are used and the density window is adjusted as for bone, the scans are much sharper and less ambiguous, giving very clear pictures of compact and diffuse lesions together with more accurate estimates of their physical densities. Inspiratory scans are used to identify areas of defective filling or unusual opacity. Expiratory scans are used to identify areas of defective emptying or tissue destruction. Repeat scans in the prone position redistribute lung weight and fluid volume, revealing lesions not apparent in the supine position. This allows us to identify fine fibrosis before it is apparent on conventional chest radiographs. The same is true of emphysematous obstruction, bronchial wall thickening and isolated small opacities.

General practitioner (GP) referrals for static miniature chest radiography — indications and diagnostic yield

FG SIMPSON, JFJ MORRISON, NJ COOKE, SB PEARSON *Leeds Chest Clinic, 74 New Briggate, Leeds* One thousand two hundred and five consecutive GP referrals for chest radiography to a unit based at Leeds Chest Clinic were studied prospectively. Chest physicians read the films and saw patients recalled. Final diagnosis and outcome at one year were correlated with information provided at referral. Seventy-three per cent of radiographs were normal; 16% showed abnormalities not clinically relevant. One hundred and thirty-two (11%) patients were recalled. In 37 the abnormality had resolved when the patients was seen. Sixty-one patients were seen only once. Fifty-five (5% of requests) had significant pathology: 22 malignancies including 15 primary lung tumours, 15 pneumonias, 14 cardiac lesions and five uses of active tuberculosis (one with carcinoma). Fifty-one of these were aged over 40. Radiographs in the under-40s and those with non-respiratory symptoms had a very low yield. Yield was highest (13%) in the over-60s and those with haemoptysis, cough, dyspnoea, wheeze and weight loss. At one year nine of the 15 lung cancer patients had died; only one had had surgery. A similar study by radiologists (Guyer and Chalmers, *J R Coll Gen Pract 1983;*253:477) showed a higher recall rate with less differentiation of clinically unimportant abnormalities. Chest clinic based radiography still provides an efficient service to GPs. Efficiency could be improved by more selective referral.

Circulating mediator and catecholamine concentrations during the refractory period in exercise induced asthma

NG BELCHER, R MURDOCH, N DALTON, PJ REES, TJH CLARK, TH LEE *Guy's Hospital, London* We have measured circulating mediator and catecholamine concentrations in seven asthmatics who were subjected to two bouts of cycle ergometer exercise separated by one hour. The maximum fall in FEV_1 was 20% (20%) 7% 1%) (mean (SEM), n = 7) after the first and second exercise, respectively. Venous blood was sampled before exercise and at five, 15, 30 and 60 minutes after each exercise task for measurements of serum neutrophil chemotactic activity (NCA), plasma histamine and catecholamine levels based on microchemotaxis and radioenzymatic techniques. NCA increased in all patients after exercise, ranging from 100% to 1400% and there were no significant difference in NCA release between the two tasks. Gel filtration chromotography using columns of ultragel A demonstrated that the NCA detected after the first and second exercise tasks had molecular sizes of 600 000 daltons. Plasma histamine concentrations increased from 3.4 (0.36) mmol/1 to 6.1 (2.0) mmol/1 and from 2.3 (0.36) mmol/1 to 5.9 (2.6) mmol/1 after the first and second exercise tasks respectively. Plasma noradrenaline concentrations increased from 1.9 (0.5) mmol/1 to 2.7 (0.8) mmol/1 and from 2.1 (0.5) mmol/1 to 2.8 (0.5) mmol/1 after the first and second exercises respectively. The levels had returned to baseline by 15 minutes. There was no significant change in plasma adrenaline concentrations after each exercise. These findings suggest that the refractory period in EIA is not caused by mediator depletion or by protection of the airways through catecholamine release.

Circulating adrenaline concentrations during exercise in normal subjects and patients with exercise induced asthma (EIA)

KE BERKIN, G WALKER, GC INGLIS, SG BALL, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow* Circulating adrenaline may be important in the control of airway calibre. When infused to produce circulating concentrations similar to those found during exercise, adrenaline causes bronchodilation (KE Berkin *et al, Clin Sci* 1986, in press) and may inhibit mast cell degranulation (RP Orange *et al, Fed Proc* 1971;**30**:1725). A failure of the usual increase in plasma adrenaline during submaximal exercise has been implicated in the pathogenesis of exercise induced asthma (PJ Barnes *et al, Thorax* 1981;**35**:435). The severity of exercise may be important in determining the adrenaline response. Six normal subjects (N) and six asthmatic patients (A) underwent a standard maximal exercise test. Exercise time (mean (SE)) was 17.8 (1.1) min (N) and 16.3 (0.1) (A); peak heart rate was 199 (2) beats/min (N) and 190 (11) beats/min (A). Specific airways conductance and FEV_1 fell by 46% (7%) and 20% (5%) respectively in asthmatic patients after exercise. Basal plasma adrenaline concentrations (nmol/1) were 0.05 (0.03) (N) and 0.12 (0.04) (A) and increased to 2.7 (1.2) (N) and 1.6 (0.8) (A) at peak exercise. Noradrenaline concentrations (nmol/1) increased from 2.0 (0.7) (N) and 1.9 (0.8) (A) to 14.3 (2.1) (N) and 13.7 (5.2) (A) at peak exercise. The increase in adrenaline and noradrenaline in A showed no statistically significant difference from the increases in N. A reduced sympatho-adrenal response to exercise does not appear to be an important mechanism in the pathogenesis of EIA.

Anticholinergic blockade of propranolol induced bronchoconstriction

PW IND, CMS DIXON, RW FULLER, PJ BARNES *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, and Department of Clinical Pharmacology, Cardiothoracic Institute, Brompton Hospital, London* The mechanism of propranolol induced bronchoconstriction (PIB) remains unclear. Previous uncontrolled studies suggested that atropine antagonised bronchoconstriction induced by intravenous propranolol in asthma (McNeil *et al,* 1968; Grieco *et al,* 1976). We conducted a randomised, double blind, placebo controlled study of the effect of a new anticholinergic agent, oxitropium bromide, on bronchoconstriction induced by inhaled propranolol. Six subjects with mild atopic asthma, five male, mean age 29 (range 24-34) years, were studied on four days. On days one and two they received increasing concentrations of propranolol or methacholine by nebuliser (Minineb) until sGaw fell by >35%. A cumulative dose-response curve for inhaled isoprenaline was then constructed. On days three and four oxytropium 200 μg or matched placebo was inhaled 30 min prior to propranolol. Mean baseline sGaw did not differ significantly on the four days. Geometric mean PD_{35} for methacholine was 0.34 μmol and mean dose of propranolol was 5.4 μmol. Oxitropium significantly increased sGaw compared with placebo. Propranolol reduced mean sGaw by 39% after placebo compared with one per cent after oxitropium ($p<0.001$). PIB was associated with airway beta blockade. Geometric mean dose of isoprenaline for 50% increase in sGaw after methacholine was 8 compared with 111 μg after propranolol. Anticholinergic receptor blockade by oxitropium inhibits PIB, the idea that supporting cholinergic pathways play a part in PIB.

Investigation of the mechanism of action of phenylephrine and methoxamine in asthmatic airways

J CROSSLEY, J BRITTON, A TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We have previously shown that the alpha adrenoceptor agonists phenylephrine and methoxamine have different effects on the airways. Phenylephrine caused bronchodilatation in 10 subjects with asthma whilst methoxamine caused more variable responses but an overall mean trend towards bronchoconstriction in the same subjects (*Thorax* 1985;**40**:715). We have now investigated the mechanism of action of these drugs in seven subjects wth mild asthma. In a randomised double blind design subjects ingested either propranolol (40 mg), prazosin (1 mg) or placebo one hour before a cumulative inhalation dose-response study with either phenylephrine (dose range 0.038-2.5 mg) or methoxamine (0.15 to 10 mg). A saline control was given in

place of methoxamine after oral propranolol. Phenylephrine caused similar dose related bronchodilatation after both placebo and prazosin but not after propranolol. Methoxamine caused dose related bronchoconstriction after placebo, and similar though non-significant bronchoconstriction after prazosin. There was no relationship between the maximum bronchoconstriction caused by methoxamine and that caused by propranolol. These studies demonstrate that phenylephrine causes bronchodilatation in asthmatic airways by beta adrenergic agonism. The results for methoxamine are less conclusive, but suggest that it probably causes bronchoconstriction by alpha agonism.

Pulmonary tuberculosis treated by thoracoplasty: the outcome after 30 years

MS PHILLIPS, WJM KINNEAR, JM SHNEERSON *Papworth Hospital, Papworth Everard, Cambridge* In 1985, using information provided by the Office of Population Censuses and Surveys, we attempted to trace the 171 patients with pulmonary tuberculosis treated by thoracoplasty at Papworth Hospital between January 1951 and December 1953. Thirteen could not be traced. Sixty-five have died; death certificates were available for 61. Ninety-three were alive. Questionnaires were sent to these patients and to their general practitioners. Replies were received from 87 patients (93.5%) and 88 general practitioners (94.5%). Forty-nine patients (56.2%) admitted to a productive cough, 44 (50.5%) to breathlessness, 40 (46.0%) to wheezing and six (6.9%) to recent haemoptysis. Nineteen (21.8%) had none of these symptoms. Fourteen received bronchodilators, two oral steroids and four domiciliary oxygen. Eighteen (19.6%) attend a chest clinic. Four deaths were due to uncontrolled tuberculosis. All occurred before 1962. Since 1960, pulmonary tuberculosis has recurred in four patients. Three have developed extrapulmonary disease. Five have received chemoprophylaxis. Nineteen patients died from cardiorespiratory failure. Eight survivors have required hospital admission for ventilatory failure within the past five years. Examination of 140 available case records show that these 27 patients were older at operation with more extensive disease. They more frequently had a contralateral artificial pneumothorax and right sided thoracoplasty.

Quality of life during chemotherapy for small cell carcinoma of the lung

DM GEDDES, SG SPIRO, RH SOUHAMI, P HARPER, J TOBIAS *Brompton Hospital, London* Quality of life in patients with small cell carcinoma of the lung was assessed by daily diary card in the course of a randomised controlled trial of chemotherapy (CT). The trial compared four cycles with eight cycles of CT (cyclophosphamide, vincristine and etoposide) and so allowed a comparison of matched patients with and without CT. This was done by examining the treatment period when one group received cycles five to eight and the other had completed CT. Patients scored eight variables (sickness, vomiting, appetite, general well-being, mood, pain, activity, sleep) on a four point scale every day. Fifty-three patients entered the study and 39 of these completed diary cards; 12 died or relapsed during the study period. The findings were:

1. A significant worsening of sickness and related variables during CT which persists in mild degree throughout the inter treatment period.
2. An overspill of the adverse effects of CT to unrelated variables, such as mood and general well-being, which is pronounced at the time of treatment but lasts until the next cycle.
3. A worsening of side effects and unrelated variables with successive courses of CT.
4. A transient increase in sickness and vomiting during prophylactic cranial irradiation.

Restriction fragment length polymorphism of the alpha$_1$-antitrypsin gene in chronic lung disease

NA KALSHEKER, I HODGSON, GL WATKINS, JP WHITE, HM MORRISON, RA STOCKLEY *Departments of Medical Biochemistry and Respiratory Medicine, University of Wales, College of Medicine, Cardiff, and Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* Deficiency of alpha$_1$-antitrypsin is associated with pulmonary emphysema and bronchiectasis. However, most patients with these diseases have normal alpha$_1$-antitrypsin (α_1-AT) and the aetiology of their disease is unknown. Abnormalities of α_1-AT are detected by measuring serum concentrations or by isoelectric focusing which detects changes in the charge of the protein. However, changes in amino acid composition not affecting concentration or electrophoretic charge will not be detected by these methods. Specific DNA probes provide a more sensitive tool to study the α_1-AT gene, including portions that are not transcribed (introns). The latter may regulate expression of the protein. We have used a genomic clone — α_1pAT 6.5 (Leicht *et al*, Nature 1982;**297**:655) and a cDNA clone — α_1pNJ (Rogers *et al, Biochem; Biophys Res Comm* 1983;**116**:375) to study DNA from 101 control subjects, 63 patients with emphysema (14 with α_1-AT deficiency) and 42 patients with bronchiectasis. A Taq I restriction site in the 3^1 flanking region of the gene was absent in five of the control subjects and two of the α_1-AT deficient subjects. However, nine of the emphysema patients and eight of the bronchiectatic subjects showed this variation. This was significantly different from the control population ($p<0.01$ and $p<0.01$ respectively). The results suggest that abnormalities of genes closely related to the α_1-AT gene may predispose to some forms of emphysema and bronchiectasis.

Palatopharyngoplasty in the treatment of snoring and obstructive sleep apnoea

PJ REES, M KING, MJ GLEESON, CL WENGRAF *Guy's Hospital and Hither Green Hospital, London* A number of treatments are now available for the treatment of obstructive sleep apnoea, but none is completely satisfactory. We have assessed the effects of palatopharyngoplasty in eight patients. All were loud

snorers and four had significant obstructive sleep apnoea. Of those with apnoeas, one had tried protriptyline and two positive nasal airflow with little success. All patients were studied during sleep preoperatively and those with obstructive apnoea were restudied one to six months postoperatively. Snoring was abolished or markedly reduced in all subjects, judged by subjective criteria. Daytime sleepiness was present preoperatively in six patients and improved in all of them. The four with obstructive sleep apnoea had nocturnal desaturations of at least 5% reduced from a mean of 23 per hour (range 11-46) preoperatively to seven per hour (range 4-12) postoperatively. The best results were seen in the most severely affected patient (46 per hour to four per hour). Adverse effects of the operation were a local infection in one patient and occasional nasal regurgitation in three patients. Palatopharyngoplasty is an effective treatment for troublesome snoring. It reduces apnoeic episodes and oxygen desaturation in obstructive sleep apnoea, but better criteria for selection for operation are required.

Daily purulent sputum production without bronchiectasis

ND GARBETT, DC CURRIE, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* Fifteen patients (M = 6, F = 9, age 16-46 years) who have presented to the Host Defence Clinic in the last five years with daily purulent sputum production of longer than six months' duration, were found to have no known cause for this symptom and no evidence of bronchiectasis on a bronchogram. Three had childhood pneumonia, one associated with whooping cough. The median duration of daily purulent sputum production was three years (range 1-20 years). Nine had frequent or continuous purulent rhinorrhoea and five reported intermittent wheeze. Ten had never smoked, two had an insignificant smoking history and three had smoked significantly. FEV_1 was normal in 14. Sputum cultures have grown *Haemophilus influenzae* in nine, *Pseudomonas aeruginosa* in five, and *Staphylococcus aureus* in four on some occasion. We have treated this group of patients as though they had generalised bronchiectasis — including home physiotherapy, topical nasal corticosteroids, inhaled bronchodilators, inhaled corticosteroids, and antibiotics for exacerbations. Six patients responded well to this regimen, a further three with the addition of continuous antibiotics, but six have not responded. Chronic bronchitis is an inappropriate label for these patients in view of their daily purulent sputum production, persistent nasal symptoms, early age of onset, the presence of *Pseudomonas aeruginosa* in the sputum of five, and a "never smoked" history in 10. The pathophysiological basis of disease in these patients is unknown but may become apparent as the natural history develops.

The reliability of physical signs in examination of the respiratory system

MA SPITERI, D COOK, S POCOCK, SW CLARKE *Department of Thoracic Medicine, Royal Free Hospital, London* Clinical examination of the respiratory system still maintains an important place in undergraduate and postgraduate teaching. We fear however, that emphasis continues on the teaching of obscure chest physical signs, which tend to take precedence over more discriminating ones. Accordingly, we studied observer agreement on the presence or absence of physical findings in a variety of respiratory diseases. Twenty-four patients with stable, well defined clinical features were divided into six sets, each consisting of four patients. Each patient was examined by four physicians assigned to that set. All 24 examiners possessed the MRCP diploma. Findings were recorded as present or absent in a standard questionnaire. Using statistical analysis, we found clubbing, wheezing, crackles, percussion note and vocal resonance to be the top five most reliably elicited signs. At the other extreme, there was very little agreement on cricosternal distance, tracheal deviation, cyanosis, tachypnoea and whispering pectoriloquy in descending order. We believe that a ranking order of the reliability with which chest signs are elicited is essential to teaching clinical chest medicine at all levels. It should deter from the use of obscure, imprecise physical signs which were important in a bygone age.

The place of high frequency jet ventilation in thoracic surgery: an improvement in postoperative recovery

M NEVIN, JR PEPPER, C WILLIAMS, JP VAN BESOUW *St. Helier Hospital, Carshalton, Surrey* Sixty-five patients, statistically matched for age, sex and preoperative cardiorespiratory status, undergoing thoracic surgery were randomly allocated to one of two groups, each receiving a total intravenous anaesthetic technique. The first group received a conventional method of ventilation (double lumen endobronchial tube), the second high frequency jet ventilation (HFJV) via an endotrachial tube, both utilising high inspired oxygen concentrations (60%). At predetermined points, perioperatively, arterial blood gases, mean arterial blood pressure, heart rate and peak inspiratory airways pressure were recorded. Postoperatively, all patients received oxygen via mask (35% for 24 h), physiotherapy and opiate infusion. The incidence of postoperative chest infections (clinical and bacteriological), chest drain volumes, and length of postoperative stay in hospital were recorded. All data obtained from the two groups was analysed statistically using a Students *t*-test. Results showed the jet ventilator group to have a significantly reduced mean hospital stay ($p<0.05$), which can be attributed to a lower incidence of postoperative chest infection ($p<0.01$) and significantly improved arterial blood oxygen tensions at four and 24 hours and seven days postoperatively ($p<0.05$).

Assessment of fitness for surgery in patients with chronic obstructive disease

JF NUNN, JS MILLEDGE, D CHEN, C DORE *Division of Anaesthesia, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex* Although much has been written about preoperative pulmonary function testing,

there is a dearth of information on the interpretation of results in patients with impaired lung function, particularly in respect of the outcome after surgery. A retrospective analysis has been undertaken of 42 patients with severe chronic obstructive airway disease undergoing elective general surgery. All patients had an FEV_1 of 1.0 litre or less. Preoperative assessment of their respiratory state was critically analysed to determine the relative value of different indices of function in predicting their outcome. No patient died. Thirty-eight of the 42 patients had uneventful anaesthetic and surgery together with a normal postoperative period with no significant pulmonary complications. Four patients were given artificial ventilation in the postoperative period. The best predictor of the requirement for postoperative ventilation in patients dyspnoeic at rest was an arterial Po_2 of less than 9.5 kPa or, in patients not dyspnoeic at rest, of less than 6.0 kPa. Other patients are unlikely to need artificial ventilation during the postoperative period.

Does compliance with inhaled therapy by asthmatic patients matter?

CP HORN, P HILL, E ESSEX, GM COCHRANE *Chest Clinic, New Cross Hospital, London* A prospective study of the value of active management of asthmatic patients has been undertaken in two general practices. Urine salbutamol levels were measured to determine patient compliance (Colthup *et al, J Chromatogr* 1985;**345**:111-118). Ten patients improved significantly, FEV_1 increasing by a mean of 47 (SD 34.4) per cent over nine months. In these patients the mean urine salbutamol level rose from 584.8 (442) to 1757 (1797) ng/l. A further ten patients failed to improve, mean FEV_1 falling to 95.4 (9.0) per cent of the baseline value. Four of these patients appeared to be complying, mean urine salbutamol level rising from 399 (335) to 2104 (2466) ng/l. However the other six patients were underusing their therapy, urine salbutamol levels varying between zero (three patients) and 350 ng/l. (mean 110 (145) ng/l.) These results suggest that poor patient compliance is a major cause of persistent morbidity from asthma.

The effect of particle size of bronchodilator aerosols on lung distribution and pulmonary function

DM MITCHELL, M SOLOMON, S TOLFREY, M SHORT, SG SPIRO *Department of Thoracic Medicine, University College Hospital, London* The particle size of bronchodilator aerosols may be important in determining the site of deposition in the lung and their effect. We have studied the distribution of ^{99m}Tc-DTPA labelled aerosols of two different particle sizes of (1.4) and 5.5 (2.3) μm (mass median aerodynamic diameter and geometric standard deviation) delivered from a jet nebuliser in eight chronic stable asthmatics using gamma camera imaging. There was no significant increase in peripheral lung deposition with the aerosol of smaller particle size in any of the patients. The bronchodilator effect of the two aerosols was then determined by cumulative dose response studies. To avoid large saturating doses, thereby masking any possible differences in effect due to aerosol size, each patient inhaled small precisely determined incremental amounts of salbutamol (25 μg-250 μg total lung dose) via a nebuliser on two separate occasions. Spirometry was measured 30 minutes after each dose. Bronchodilation was equally effective with either aerosol at each dose of salbutamol. There is, therefore, no difference in distribution within the lung or difference in bronchodilator effect between an aerosol of small (1.4 μm) particle size and an aerosol of 5.5 μm in patients with severe but stable asthma.

Factors affecting the plasma pharmacokinetics of inhaled sodium cromoglycate (SCG)

R RICHARDS, AG RENWICK, CR DICKSON, ST HOLGATE *Medicine I, General Hospital, Southampton* Ten normal subjects attended on four occasions separated by at least three days. A spinhaler was attached to a rolling seal spirometer with an integral resistor. The subjects inhaled from RV to TLC at three flow rates (maximum 100 l/min and 50 l/min) and were asked to hold their breath for 10 seconds. On the fourth occasion the maximum flow rate was repeated without breath hold ($n = 7$). Fourteen patients undergoing diagnostic bronchoscopy had 1 mg of SCG (0.5 ml nebuliser solution) placed in a second generation bronchus. In all cases blood samples were taken and analysed by radioimmunoassay. The inhaled SCG was rapidly absorbed ($t½ = 1.75$ min, SEM 0.51), reaching maximum in 13.2 min (SEM 1.7), then decreased with a $t½ = 166.3$ min (SEM 19.43). Maximum concentration achieved (cmax) and area under the curve (AUC) were significantly greater at maximum flow rate ($p<0.05$). The presence or absence of breath hold made no difference. Direct deposition of 1 mg via a bronchoscope gave similar cmax and AUC to 20 mg inhaled at maximum flow rate. However the terminal $t½$, 62.2 min (SEM 9.56), was shorter than following inhalation ($p<0.05$). Inspiratory flow rate is the major factor in determining delivery of powdered SCG to the lungs, and should be an important consideration in clinical practice.

Does hydroxychloroquine have a steroid sparing effect in chronic steroid dependent asthma?

JA ROBERTS, JA ELLIOT, A GUNNEBERG, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow, and Department of Medicine, Heathfield Hospital, Ayrshire* There is a small group of asthmatic patients who require oral prednisolone to control their symptoms and even then their asthma control may be poor. A recent report suggested that hydroxychloroquine (HCQ) had a significant steroid sparing effect in a patient with severe chronic asthma (Goldstein, *Am Rev Respir Dis* 1983;**128**:100). We have examined this finding in a group of nine steroid dependent adult asthmatic patients (6F:3M) (aged 29-58). Their mean FEV_1 (%predicted (SEM)) was 49.8 (7.7). The study was a randomised double blind crossover comparison of HCQ (400 mg/day) with placebo. Each patient received HCQ or placebo for two months. Following a washout period of two weeks, crossover to the

other treatment was made and the second drug was given for two months. Mean (SEM) oral prednisolone dose was not significantly different during HCQ treatment (7.9 (2.4) mg) compared with placebo treatment (7.0 (2.5) mg) or with the pretrial period (10.5 (1.7) mg). There was no difference between symptom score, inhaler use or peak expiratory flow measurements between the HCQ and placebo treatment periods. These results demonstrate that HCQ does not have a steroid sparing effect in adult asthmatics with chronic steroid dependent asthma nor does it improve subjective or objective control of asthma symptoms.

Changes in FEV_1 and disturbances of cardiac rhythm in severe airways obstruction: a comparison of nebuliser and Nebuhaler

RM HIGGINS, WOCM COOKSON, GA CHADWICK, G MCCARTHY, S JOHN, DJ LANE *Osler Chest Unit, Churchill Hospital, Oxford* In order to compare the relative efficacy of beta agonist administration by nebuliser and Nebuhaler, 20 patients with severe chronic airways obstruction (mean age 71.1 (SEM 1.5) years) were given terbutaline 4 mg or placebo through nebuliser and Nebuhaler in a double blind study. The mean FEV_1 rose from 0.68 (SEM 0.06) litres to 0.74 (SEM 0.06) litres after nebuliser administration of terbutaline ($p<0.0005$), but there was no significant change when terbutaline was delivered by Nebuhaler or after placebo. In 12 subjects cardiac rhythm was analysed to assess whether terbutaline administration was arrhythmogenic. There was no sinus tachycardia after adminstration of terbutaline. Nine subjects experienced fewer than five supraventricular or ventricular ectopic beats per minute in the entire study period. Two subjects experienced short runs of artrial fibrillation after terbutaline administration. The effect was more marked after nebuliser than Nebuhaler in both subjects. This was not related to changes in oxygen saturation. The Nebuhaler appears less efficient than a nebuliser at delivering terbutaline to patients with severe chronic airflow obstruction. Supraventricular dysrythmias after terbutaline adminstration may be less marked after Nebuhaler.

Nebuliser or Nebuhaler for COAD?

MB ALLEN, E PUGH, RSE WILSON *Department of Respiratory Physiology, City General Hospital, Stoke-on-Trent, and Royal Shrewsbury Hospital, Shrewsbury* The Nebuhaler (NH) is an alternative method of delivering large doses of β agonists, and is as effective as wet nebulisation (NL) in adult asthma. We have compared NH and NL therapy in chronic bronchitis and emphysema (CB + E). Thirteen patients, mean age 64.5 (43-73) years, FEV_1 0.7 (SD 0.35) l, FVC 1.68 (0.56) l and reversibility 7.6% (7.5%) were randomised to receive 10 mg terbutaline qds from either NL or NH for two weeks before crossing over to the alternative delivery system. Symptom scores, side effects and twice daily PEF were recorded on diary cards. Ten patients completed the study, three withdrawing because of palpitations (one) or tremor (two) associated with NH use, one patient having completed the NL regimen with no side effects. There was no difference in PEF between treatments but the NL significantly improved cough and wheeze ($p<0.05$ χ^2 test). When compared with the run in period both treatment regimens improved symptom scores and the NH significantly increased morning PEF ($p<0.05$, t test). Tremor, palpitations and restlessness were more frequent after NH use. Three patients considered the NH easier to use but only two preferred this delivery method. The Nebuhaler is a cheaper, portable alternative to domiciliary NL therapy in the management of patients with CB + E but may be associated with side effects and low patient acceptability.

Acute effects of oral theophylline on trapped gas volume in chronic bronchitis

H CHRYSTYN, BA MULLEY, MD PEAKE *Pontefract General Infirmary and University of Bradford* Airflow limitation is usually described as 'reversible' or 'irreversible' based on changes in peak expiratory flow (PEF) or forced expiratory volume in one second (FEV_1). We studied the acute effects of oral theophylline in 18 clinically stable patients (one female) mean age 60.2 years (range 53-73 years) with chronic bronchitis (MRC criteria) and a mean baseline FEV_1 of 29.2% of predicted (range 12.1-50.6%). PEF, FEV_1 forced vital capacity (FVC) and total lung capacity using plethysmography (TLC_{Box}) and helium dilution (TLC_{He}) were measured before and 2.5 hours after a mean dose of theophylline syrup of 382 (273-545) mg/l when the mean serum theophylline concentration was 9.89 (7-12.5) mg/l. There was no change in FEV_1 or FVC and only a 12% mean increase in PEF ($p<0.1$). In contrast the trapped gas volume (V_{TG} i.e. TLC_{Box} minus TLC_{He}) fell from 1.97l (SD 0.88l) to 0.92 (0.77l) ($p<0.001$) owing largely to an increase in TLC_{He}. The fall in V_{TG} reflects improved distribution of ventilation, presumably resulting from small airway dilatation not reflected in spirometric changes. Further work is needed in this area before patients are described as having 'irreversible' disease or theophyllines are discarded as of no value in their management.

Effects of theophylline on cardiac rhythm in patients with hypoxaemic chronic airways obstruction

CA KELLY, PA CORRIS, PC ADAMS, A MURRAY, GI GIBSON *From the Regional Cardiothoracic Centre and Department of Medical Physics, Freeman Hospital, Newcastle upon Tyne* Intravenous aminophylline may produce cardiac arrhythmias (Dutt *et al, Europ J Respir Dis* 1983;**64**:264-270) but the effects of chronic oral therapy on cardiac rhythm are unclear. Eight patients (five smokers, three ex-smokers, mean age 66) with severe chronic airways obstruction (mean (range) FEV_1 0.75 (0.6-1.0)l) and hypoxaemia (mean oxygen saturation 89.4% (85%-91%)) had 24 hour electrocardiograms recorded by ambulant Holter monitoring before and during treatment with slow release theophylline. No patient had overt heart disease and none had previously received theophylline. The dose was adjusted until a therapeutic plasma level was achieved

(range 6.2-20.1 mg/l). Other treatment remained unchanged throughout the study. The pretreatment recordings showed a very variable degree of ectopic activity. During treatment there was a significant increase both in the maximal heart rate from a median (range) of 110 (105-180) to 140 (110-200) per minute ($p<0.01$*), and in the frequency of ventricular ectopic beats (VEB) from 16 (2-493) to 46 (1-1369) per 24 hours ($p<0.05$*). There were no episodes of ventricular tachycardia and no patient noted palpitations. There were no significant changes in numbers of supraventricular ectopic beats or episodes of supraventricular tachycardia. A marked increase in VEB occurred only in patients with baseline ectopics and with plasma theophylline levels >10 mg/l, and was unrelated to initial FEV_1, oxygen saturation or smoking status.

*Wilcoxon rank test

Placebo responses in corticosteroid trials in chronic airflow obstruction

RI GOVE, AS ROBERTSON, PS BURGE *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* One hundred and seven patients with adult onset chronic airflow obstruction (CAO), excluding those with a clinical diagnosis of asthma, underwent a double blind, randomised, crossover trial of prednisolone 40 mg a day, inhaled beclomethasone dipropionate 500 μg tds and placebo. Each treatment was given for two weeks with a two week washout phase between each. Responders were identified by a $\geq$20% rise in FEV_1, FVC or mean peak flow during the second week of treatment. A significant order effect on the response to placebo compared with baseline was noted ($2p<0.01$) but not on the two active treatments. Responders to placebo were 6%, 22% and 30% respectively when the placebo phase was first, second and third. Of the 42 patients who responded to active treatment (compared with baseline), 15(36%) had a placebo response. This group did not differ from the remaining responders in any parameter other than their FEV_1 + FVC reversibility to salbutamol, which was significantly ($2p<0.025$) greater. Whatever the mechanism of action of corticosteroids in CAO, the effect seems to persist for more than four weeks after they have been stopped in some patients. A carry over effect lasting four weeks makes placebo controlled trials of corticosteroid in CAO with random treatment order impracticable in clinical practice.

Physiological emphysema and corticosteroid responsiveness in chronic airways obstruction (CAO)

RI GOVE, AS ROBERTSON, PS BURGE *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* Patients with CAO and a marked degree of physiological emphysema on lung function testing are often excluded from corticosteroid trials on the basis that they are unlikely to respond. The degree of physiological emphysema and pressure dependent collapse in the flow-volume loop were examined in 107 patients with adult onset CAO. All patients underwent a double blind, randomised crossover study of 40 mg prednisolone/day, beclomethasone dipropionate 500 μg tds and placebo, each given for two weeks with a two week washout phase between each and responders identified. Physiological 'emphysema' was defined as TLC>120% predicted, RV>150% predicted and KCO<60% predicted. The ratio of inspiratory to expiratory flow at 50% of the vital capacity (I:E50) was calculated and an 'expiratory collapse' pattern was identified, where I:E50>10. Nineteen patients had 'emphysema' as defined physiologically. A corticosteroid response was no more common in those without 'emphysema' than in those who satisfied the criteria ($\chi^2=0.91$;NS). Nor was there any difference in the number of patients with 'emphysema' in each group (responders 24% and non-responders 16%: $\chi^2=0.36$; NS). The mean I:E50 values were similar in the two groups and 12 patients from both responders and non-responders had I:E50>10. The mean TLC, RV and KCO values were also similar although the responders had significantly lower FEV_1, FVC and mean PEF values (all $2p<0.025$). The results suggest that the changes in lung function usually associated with marked emphysema do not militate against a response to corticosteroids in CAO.

Peripheral neurophathy with almitrine

MB ALLEN, C CHANDRASEKERA, K PROWSE *Department of Respiratory Physiology, City General Hospital, Stoke-on-Trent* We have studied 25 patients with COAD participating in a controlled double blind trial of almitrine 100-150 mg daily (A) or placebo (P) for one year. Twenty-three were assessed neurologically at 0,6 and 12 months with neurophysiological studies before and after the trial in 12 patients (5A 7P). Twenty-three patients (10A 13P) completed the study. Two withdrew because of severe peripheral neuropathy (PN) at five and nine months, both having high blood almitrine levels. After one year four patients, all receiving almitrine, had symptoms of PN with variable sensory changes and loss of ankle jerks. Thus, 6/12 (50%) patients developed PN in the absence of other obvious causes, with little improvement when almitrine was stopped. Neurophysiological studies were performed by one observer (CC) and interpreted without knowledge of blood gases. Four patients had abnormal results before treatment (1P 3A). At the end of the study there had been no changes in the placebo group but four of the patients receiving almitrine had clinical PN confirmed neurophysiologically. In three cases there had been progression of the initial abnormality. We have found a high frequency of PN in patients treated with almitrine for one year, but careful dose regulation and prior neurophysiological testing may help reduce the prevalence.

Effects of prostacyclin on pulmonary hypertension due to pulmonary vascular disease and chronic obstructive lung disease

DK JONES, M FITZPATRICK, TW HIGENBOTTAM *Department of Respiratory Physiology, Papworth Hospital, Papworth Everard, Cambridge* Eighteen patients with pulmonary

hypertension due to pulmonary vascular disease (PVD) — 10 with primary pulmonary hypertension (PPH) and eight with recurrent thromboembolism (RTE) — and five patients with chronic obstructive lung disease (COLD) received an infusion of prostacyclin (PGI_2). In PVD, PGI_2 at a dose (mean (SD)) of 6.4 (1.8) ng/kg/min increased mean cardiac index (CI) from 1.92 (0.6) to 2.35 (0.6) l/min/m^2 ($p<0.001$). Mean PVR decreased from 1629 (697) to 1315 (552) dyn s cm^{-5} ($p<0.001$). Mean SVR fell from 1736 (418) to 1179 (213) dyn s cm^{-5} ($p<0.001$). There was no effect on mean pulmonary artery pressure (PAP) or mean arterial oxygen saturation (Sao_2 sat). The effects of PGI_2 were the same in PPH and RTE. It can be argued that because mean PAP did not fall and SVR fell more than PVR, PGI_2 did not cause pulmonary vasodilation (Rich *et al, Am Heart J* 1983;**105**:115-125). However, in the COLD patients, PGI_2 at a dose of 4.7 (1.5) ng/kg/min caused a fall in Sao_2 sat from 76 (14) to 69 (16) ($p<0.05$). Ten patients with PVD exercised and reached a cardiac output (CO) of 4.3 (0.71) l/min — similar to the CO of 4.3 (0.82) l/min reached during PGI_2 ($p>0.6$). However the exercise PAP of 85 (24) mm Hg was higher than the PAP during PGI_2 of 66 (22) mm Hg ($p<0.005$). PGI_2 causes pulmonary vasodilation in PVD and COLD.

Effect of "mucolytic" agents in Young's syndrome

M GREENSTONE, D CURRIE, D PAVIA, J AGNEW, P PELLOW, W HENDRY, S CLARKE, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital; Royal Free Hospital; and St. Bartholomew's Hospital, London* Young's syndrome (recurrent sinopulmonary infection and obstructive azoospermia) is associated with impaired mucociliary clearance in the upper and lower respiratory tracts but *in vitro* ciliary function and structure is normal (Greenstone *et al, Thorax* 1984;**39**:702). To evaluate whether modification of mucus properties was beneficial in this condition, eight subjects with Young's syndrome (mean (SD) age 37(2) years) received N-acetylcysteine 200 mg tds, ambroxol 60 mg bd, carbocysteine 750 mg qds and bromhexine 16 mg qds in random order for a period of eight weeks each. All patients had characteristic findings at exploratory scrototomy (Hendry, *Br J Urol* 1981;**53**:664) and had undergone epididymovasostomy. Full lung function tests, tracheo-bronchial clearance (measured by a non-invasive radioaerosol technique) and seminal analysis were performed after each treatment. There was no overall improvement in any of these parameters with treatment when compared with control values. Whilst an underlying abnormality of epithelial secretions may be responsible for the clinical features of Young's syndrome, short term "mucolytic" therapy was unable to effect any demonstrable benefit to airways obstruction, mucociliary clearance or sperm count.

The effect of volume history on maximal airflow in bronchial asthma during spontaneous and induced airflow obstruction

TK LIM, RH INGRAM JR, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* We compared maximal expiratory airflow at 40% vital capacity from residual volume on maximal and partial flow-volume curves (M/P $\dot{V}40$ ratios) in asthmatic subjects during spontaneous and induced airflow obstruction. The M/P $\dot{V}40$ was considered to be an index of relative parenchymal and airways hysteresis (*J Appl Physiol* 1985;**59**:1590-1596). In 46 asthmatic patients attending an outpatients clinic we recorded baseline spirometry and M/P $\dot{V}40$ ratios. Their mean (SD) FEV_1%P (percent predicted FEV_1) and M/P $\dot{V}40$ ratios were 64% (37) and 0.74 (0.3) respectively. There was a positive correlation between FEV_1%P and M/P $\dot{V}40$ ($r=0.632$). We compared the M/P $\dot{V}40$ ratios in six stable, mild asthmatics after bronchoprovocation with cold air had reduced their FEV_1%P < 50% and 19 chronic asthmatics with baseline FEV_1%P < 50%. The mean (SD) M/P $\dot{V}40$ ratios in spontaneous and acutely induced obstruction were 0.58 (0.04) and 1.40 (0.17) respectively ($p<0.0001$). During induced bronchial obstruction in the mild asthmatics mean M/P $\dot{V}40$ rose from 1.11 (0.37 SD) to 1.40 (0.17). We conclude that in bronchial asthma (1) airways hysteresis predominates during acutely induced bronchoconstriction and (2) parenchymal hysteresis predominates in spontaneous obstruction.

Steady state responses to hypercapnia and added deadspace in awake and sleeping dogs

JR STRADLING, L KOZAR, S ANDREY, EA PHILLIPSON *Department of Medicine, University of Toronto, Canada* Previous studies on ventilatory responses to CO_2 showing a reduced response during rapid eye movement sleep (REMS) were performed using short rebreathing techniques and delivering a progressive stimulus. This may be like the asphyxic insult of obstructive apnoeas, but unlike the situation in chronic hypoxic lung disease. We have used two steady state, ventilatory stimulants: added deadspace and 200ml of extra inhaled CO_2 given by the Fenn-Craig technique (which delivers a constant volume of CO_2 during inspiration, irrespective of the rate and depth of breathing). Ventilation, its subdivisions and endtidal P_{CO_2} were measured in six chronically tracheotomised dogs, trained to sleep in the laboratory. In each dog on at least two separate days steady state data (2-10 min) were collected under controlled conditions and after ventilatory stimulation (order randomised) during wakefulness (W), slow wave sleep (SWS) and REMS.

	Control		*Deadspace*		*Control*		*Added CO_2*		
	$\dot{V}$	PCO_2	$\dot{V}$	PCO_2	$\dot{V}$	PCO_2	$\dot{V}$	PCO_2	(V as l/min, PCO_2 as mm Hg)
W	3.8	38.0	5.9	39.5	3.5	37.4	6.0	42.2	
SWS	3.5	38.2	5.3	40.2	3.4	37.4	6.0	41.7	
REMS	4.6	37.2	6.9	39.9	4.0	37.3	6.2	42.2	

These results show that in these dogs REMS has not reduced the steady state response to either added deadspace or added CO_2 compared to either SWS or wakefulness.

Effect of hypoxia on platelet size

JA WEDZICHA, FE COTTER, DW EMPEY *The London Hospital, Whitechapel, London* Larger platelets, as reflected by an increased mean platelet volume (MPV), are haemostatically more active (CB Thompson *et al, J Lab Clin Med* 1983;**101**:205-13). We measured the MPV in 20 patients with chronic airflow obstruction and hypoxaemia, but not on long term oxygen therapy (mean (SD) Pao_2 7.39 (0.60) kPa; Pao_2 6.26 (0.94) kPa; FEV_1 0.76 (0.23) l) and in 15 patients without hypoxaemia (Pao_2 9.88 (1.04) kPa; Pao_2 5.04 (0.54) kPa; FEV_1 0.94 (0.37) l). The mean MPV was significantly higher in the hypoxic group (9.41 (0.86) fl) than the non-hypoxic subjects (7.83 (0.60) fl; $p<0.001$); however the platelet count was similar in the two groups. The MPV was correlated with the Pao_2 in the hypoxic patients ($r = -0.62$; $p<0.01$). Twelve hypoxic patients were treated for 24 hours with supplemental oxygen, 4 l/min, the Pao_2 rising from 7.27 (0.88) kPa with air to 9.58 (1.59) kPa with oxygen. The mean MPV fell from 9.47 (1.06) fl with air to 8.96 (0.80) fl ($p<0.05$) in the hypoxic patients, but there was no significant change in the MPV in nine non-hypoxic patients after oxygen therapy. Serial sampling in the hypoxic group showed that changes in the platelets occurred at the end of the treatment period. Platelet size, activity and turnover are increased in hypoxic lung disease and this may contribute to pulmonary vascular damage. Supplemental oxygen may partially reverse these changes by modifying platelet size.

Effect of inspired oxygen concentration on effective pulmonary blood flow measured by an inert gas rebreathing method in ventilated patients

DF TREACHER, TK COWELL, RD BRADLEY *Intensive Care Unit and Bioengineering Department, St. Thomas' Hospital, London* Breathing pure oxygen theoretically reduces pulmonary shunt fraction ($\dot{Q}s/\dot{Q}t$) and increases predicted effective pulmonary blood flow ($\dot{Q}c$ pred) provided cardiac output ($\dot{Q}t$) does not fall: $\dot{Q}c\ pred = \dot{Q}t\ (1-\dot{Q}s/\dot{Q}t)$. However in ventilated patients an increase in inspired oxygen concentration (Fio_2) was observed to reduce $\dot{Q}c$ measured by the argon/freon inert gas rebreathing method ($\dot{Q}c$ a/f) previously described (Treacher *et al, Clin Sci* 1985;**68**:6p). This observation was investigated in seven patients after uncomplicated cardiac surgery. All patients were ventilated using a Siemens Servo ventilator with $Fio_2 < 0.5$. $\dot{Q}t$ was measured and mixed venous blood sampled using a thermodilution balloon catheter positioned in the pulmonary artery. The Po_2 and So_2 of mixed venous and arterial blood and the Po_2 and Pco_2 of inspired, end tidal and mixed expired gas were measured and four estimations of $\dot{Q}c$ a/f were made. Fio_2 was increased to >0.9 and all measurements were repeated after 30 minutes. $\dot{Q}s/\dot{Q}t$ and $\dot{Q}c$ predicted were calculated using standard formulae. Results are presented as mean (1 SEM) and analysed using Student's paired *t* test. Pao_2 increased from 73 (7) to 295 (45) mm Hg and $\dot{Q}c$ a/f fell from 3.9 (0.2) to 3.3 (0.2) l/min ($p>0.005$). $\dot{Q}t$ fell from 5.1 (0.3) to 5.0 (0.3) l/min (NS) and $\dot{Q}c$ pred increased from 4.2 to 4.3 l/min (NS). In ventilated patients increasing Fio_2 from < 0.5 to > 0.9 produced no significant change in $\dot{Q}t$ but significantly reduced $\dot{Q}c$ a/f.

Supplementary oxygen during exercise in COAD patients — a dose response study

R LEACH, RJD GEORGE, AC DAVIDSON, DM GEDDES *London Chest Hospital, London* The effect of supplemental oxygen at flow rates of 2, 4 and 6 l min^{-1} (adjusted to a total flow of 6 l min^{-1} with cylinder air) upon endurance, minute ventilation and visual analogue scoring for breathlessness during steady state exercise on a cycle ergometer (50% max work load) was determined. Eight COAD patients (age 53-70 years, mean (SD) FEV_1 0.84 (0.19) l, Pao_2 65.0 (9.7), $Paco_2$ 43.3 (9.1) mm Hg) were studied when in a stable state under standardised conditions. The differing flow rates of oxygen were randomly tested. Endurance was progressively increased by supplemental oxygen (min to exhaustion, air 5.6 (2.6), O_2 2 l min^{-1} 8.1 (4.4), $p<0.01$; O_2 4 l min^{-1} 9.1 (4.3), $p<0.002$; O_2 6 l min^{-1} 10.2 (5.9), $p<0.01$) and was associated with a marked reduction in breathlessness (mean decrease at 2 min, 47% at 2 l min^{-1}, 42% at 4 l min^{-1}, 74% at 6 l min^{-1}; at 4 min, 21% at 2 l min^{-1}, 20% at 4 l min^{-1}, 31% at 6 l min^{-1}). Desaturation (ear oximeter) and the fall in Po_2 (transcutaneous) on exercise was partially prevented by oxygen at 2 l min^{-1} and abolished at 4 and 6 l min^{-1}. These beneficial effects would not have been predicted by the increase in six minute walking distance with supplemental oxygen (2 l min^{-1}).

Perception of dyspnoea during and after exercise

J MOORE-GILLON, R GEORGE, D GEDDES *London Chest Hospital, London* We investigated the possibility that the relationship between dyspnoea and minute ventilation ($\dot{V}_e$) during exercise may differ from that during recovery after exercise. Ten healthy naive subjects (six female, four male; 22-33 years) performed a progressive exercise test on a bicycle ergometer, breathing through a mouthpiece. Instantaneous $\dot{V}_e$ was calculated every six seconds by on line analysis of the signal from a vane ventilometer. After three minutes at rest exercise commenced, workload increasing every one minute until subjects were unable to continue. Measurement of $\dot{V}_e$ continued until it fell to pre-exercise baseline. Every 30 seconds during rest, exercise and recovery subjects scored dyspnoea on a 10 cm visual analogue scale. Maximum ventilation ($\dot{V}_{e\ max}$) coincided with maximum dyspnoea, occurring at discontinuation of exercise. Dyspnoea was compared at 10, 25, 50 and 75% $\dot{V}_{e\ max}$ during exercise with dyspnoea at the same levels of ventilation during recovery, using Wilcoxon's signed rank sum test. At 10, 25 and 50% $\dot{V}_{e\ max}$ subjects felt significantly more dyspnoeic during recovery than whilst exercising ($p<0.05$ in each case). Dyspnoea at 75% $\dot{V}_{e\ max}$ during recovery was not significantly different from that during exercise. If these findings are also applicable to dyspnoeic subjects with lung disease, then their capacity for exercise might be limited by anticipation of distress during recovery as well as by dyspnoea experienced during the exercise itself.

The extent of pulmonary emphysema as assessed non-invasively by CT scan in life does not relate to pulmonary haemodynamics during rest or exercise

W BIERNACKI, KF WHYTE, GA GOULD, A BELLONE, DC FLENLEY *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* Emphysema, defined pathologically as in increase in size of air spaces distal to terminal bronchioles, cannot be accurately assessed clinically, by plain radiology, or by respiratory function. We have recently developed a new quantitative CT scan method which can diagnose, locate, and quantitate emphysema in man in life (Hayhurst *et al, Am Rev Respir Dis* 1985;131:A71). We have used this method to explore the relationship between pulmonary haemodynamics and the extent of emphysema in 20 patients with chronic air flow obstruction (age 54-72 y, FEV_1 0.35-3.92 l, VC 1.3-4.46 l, arterial Po_2 5.07-12.0 kPa, Pco_2 4.4-7.3 kPa, Kco % predicted 21-108%). We found no correlation between either pulmonary haemodynamic measurements or right ventricular ejection fraction (by gated blood pool angiography (Xue QF *et al,* Thorax 1983;38:486-493)) and quantitative assessment of emphysema by this method, either at rest or on exercise. However, FEV_1 was correlated with abnormalities in pulmonary haemodynamics. We conclude that the degree of airways obstruction, which relates both to the amount of emphysema and the severity of any "bronchitis," is a major factor leading to haemodynamic change, possibly also associated with hypoxia.

Effect of preconditioning regimens on pulmonary function following bone marrow transplantation

T SUTEDJA, JF APPERLEY, L JONES HG KENNEDY, L HOPPER, JM GOLDMAN, JMB HUGHES *Department of Medicine and MRC Leukaemia Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London* Spirometry (FEV_1 and vital capacity) and the single breath carbon monoxide diffusing capacity (TLco) were measured before and at intervals (up to 24 months) after bone marrow transplantation (BMT) for chronic granulocytic leukaemia. In Group I (n = 24) daunorubicin 60 mg/m^2, cyclophosphamide 60 mg/kg (×2) and total body irradiation (TBI) (1000 cGy in five fractions) were given before BMT and prednisone (100 mg × 5) and cyclosporin (for six months) after BMT. In Group II (n = 22) the same regimen was used (latterly 1200 cGy was given in six fractions) with the addition of ex vivo T-cell depletion of donor marrow with Campath I. In those patients who were studied through to 24 months (Group I n = 8, Group II n = 12) the TLco (as % of pre-BMT value) reached a nadir of 75% (SD 4%) and 69% (SD 17%) at six months in Groups I and II respectively, recovering to 89% (SD 16%) and 97% (SD 8%) at 24 months. Changes in vital capacity were similar but smaller. FEV_1/VC ratios were always normal. The incidence of significant graft versus host disease (GVHD) was 83% in Group I and 11% in Group II. The recovery of function from six to 24 months post-BMT was significant in both groups and was greater in recipients of T-cell depleted marrow (Group II). The relatively severe conditioning regimens used for BMT appear to be well tolerated by the lung.

Influence of smoking habit on changes in carbon monoxide transfer coefficient over ten years in middle aged men

A WATSON, H JOYCE, L HOPPER, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* There is little information on longitudinal changes in CO transfer coefficient (T_L/V_A BTPS). We have measured T_L/V_A mmol min^{-1} kPa^{-1} l^{-1} in 1975 and 1985 in middle aged men by the single breath method; all values were corrected to a haemoglobin concentration of 14.3 g/dl. In 1975 T_L/V_A averaged 97% predicted in never-smokers (n = 42, age 37.2 y), 99% predicted in ex-smokers (n = 21, age 41.9 y) and 85% predicted in smokers (n = 42, age 42.0 y) of > 15 cigarettes/day. Mean decreases in T_L/V_A in 1975-85 however were similar in all three groups. Seventeen men who were smokers in 1975 became sustained ex-smokers between 1975 and 1977. In these men T_L/V_A averaged 89% predicted in 1975 but 102% predicted in 1985.

T_L/V_A Mean (SEM)	Never-smokers	Ex-smokers 1975-85	Ex-smokers 1977-85	Smokers >15 cigs/day
T_L/V_A 1975	1.62(0.03)	1.60(0.05)	1.44(0.05)	1.36(0.04)
T_L/V_A 1985	1.51(0.04)	1.51(0.03)	1.50(0.04)	1.25(0.06)

Thus by age 40 years T_L/V_A was lower in smokers than in never-smokers but this difference did not increase over the following 10 years. Ex-smokers have similar values to never-smokers even when T_L/V_A is known to have been slightly reduced while smoking. The differences are considerably larger than can be explained by CO back pressure and indicate that other mechanisms than increase in size of terminal air spaces are involved in the lower values in smokers.

Response and acclimatisation of smokers to low nicotine, low tar cigarettes: puff and inhaled smoke volume measurements

G WOODMAN, SP NEWMAN, SW CLARKE *Department of Thoracic Medicine, Royal Free Hospital, London* Ten symptomless smokers (median of usual cigarettes (Ucig): tar 16.5 mg, nicotine 1.4 mg) were monitored over a six-week period to investigate their response and acclimatisation to a low tar (3.76 mg), low nicotine (0.59 mg) test cigarette (Tcig). The inhaled smoke volume was measured by tracing the smoke with the inert gas $^{81}Kr^m$. Puffing indices were recorded using a Filtrona smoking analyser. Subjects were monitored at two weekly intervals: at the beginning of a control period (C) (Ucig), at the beginning and end (T1 and T2) of a test period (Tcig) and at the end of a return period (R) (Ucig). Apart from a small change in puff duration, cigarettes were smoked in the same way during C and R. The table shows median volumes (in ml) for the group.

Index (ml)	Visit C	T1	T2	R	Difference between visits CvsT1	CvsT2	T1vsT2
MPV	39.8	60.9	55.5	39.5	p 0.05	p 0.05	NS
TPV	494	796	861	515	p 0.05	p 0.05	NS
MISV	24.8	19.9	20.7	20.2	NS	NS	NS
TISV	329	335	294	269	NS	NS	NS

Mean and total puff volume (MPV and TPV) increased with the Tcig but did not change from T1 to T2. There was no significant difference (NS) in the mean and total inhaled smoke volumes (MISV and TISV) or cigarette consumption throughout the study. It is concluded that when switched to a low tar, low nicotine cigarette smokers regulate the amount of smoke inhaled by increasing their puff volumes but do not increase their daily consumption.

Time course of end expired carbon monoxide concentration (CO) is important in studies of cigarette smoking

DM WINTONIUK, G WOODMAN, RG TAYLOR, SW CLARKE *Departments of Physiology and Thoracic Medicine, Royal Free Hospital and School of Medicine, London* Twenty healthy regular smokers each smoked one cigarette of their usual brand, not having smoked for two hours. CO was measured by an Ecolyzer 2000 series analyser before smoking (pre-S), immediately after smoking (post-S), every one minute for five minutes and then 10 minutes up to one hour. End expired air was sampled after a 20s breath-hold following maximum inspiration (Jones *et al, J Lab Clin Med* 1958;**51**:553). Control studies showed that neither ventilatory changes during smoking nor sampling frequency affected CO. The median (range) CO was: pre-S 11(5-25.5) ppm, post-S 26(14.5-44) ppm and CO boost (post-S − pre-S) 13.5(4.5-27) ppm. The pre-S CO was not related to the CO boost ($r_s = 0.14$, $p > 0.05$) but was related to the post-S CO ($r_s = 0.67$, $p < 0.01$). The %CO boost after smoking declined with an initial fast phase and then a slow phase in all subjects. Exponential curves were fitted to the mean %CO boost values for the group by least squares regression analysis. The fast phase (0-5 minutes) had a half life of 6.3 minutes; the slow phase (5-60 minutes) had a half life of 69.3 minutes. (Regression equations: fast phase %CO boost = 89.12 exp (−0.11t), $0 \leqslant t \leqslant 5$ minutes, r = 0.94; slow phase %CO boost = 57.37 exp (−0.01t), $5 \leqslant t \leqslant 60$ minutes, r = 0.99). The time taken for a fall to 50% of the boost was 13.5(1-36) minutes, and was independent of both CO boost and post-S CO. CO fell almost twice as much in the first five minutes after smoking as in the next hour. These results show that CO after smoking depends on time elapsed and provide a basis for optimum CO sampling in epidemiological and smoking studies.

Is tracheobraonchial clearance affected by temazepam?

MA SPITERI, D PAVIA, MT LOPEZ-VIDRIERO, JE AGNEW, SW CLARKE *Department of Thoracic Medicine, Royal Free Hospital, London* While tracheobronchial clearance is reduced in normal subjects during sleep (Bateman *et al, Clin Sci Mol Med* 1978;**55**:523-527), it is not known whether hypnotic drugs have any effect on the clearance rate in awake, healthy subjects. To investigate this we looked at the effect of 10 mg of temazepam (5 ml syrup) on eight healthy volunteers (mean age 30 years), six female, two male; mean height 1.64 m; mean weight 64 kg) in a double blind study. Two of our subjects were light current smokers. Five μm diameter ^{99m}Tc-labelled polystyrene particles were inhaled in a controlled manner (Pavia *et al, Thorax* 1985;**40**:171-5) and total lung radioactivity measured every 30 minutes for six hours and then at 24 hours. There was no significant change in pulmonary function in our subjects; however, tracheobronchial clearance was impaired in the first three hours after drug ingestion ($p < 0.05$). These results are of importance in clinical practice as temazepam and other more potent hypnotics are widely prescribed to healthy subjects as well as patients. While we do not discount their potential hypnotic value, we suggest caution in their administration, especially in ill patients, whose clearance may already be impaired.

The effect of filtration on absolute and differential cell counts in fluid obtained at bronchoalveolar lavage (BAL)

CA KELLY, C WARD, G BIRD, DJ HENDRICK, EH WALTERS *Newcastle General Hospital, University of Newcastle on Tyne* Mucus in BAL fluid can interfere with cell function studies and its removal may be desirable. However no consensus exists on the practice of filtering BAL fluid and there are no data on its effect on cell counts. One ml samples were taken for absolute and differential cell counts from 18 BAL specimens before and after filtration through a 200 μm^2 steel mesh. The volume of mucus removed was measured. Two independent observers performed both absolute cell counts (ACC) and differential counts on each sample. Mean (SD) values are shown expressed as cells $\times 10^8$/l.

		ACC	Macrophages	Neutrophils	Lymphocytes
Absolute counts	Pre	2.66 (2.0)	2.27 (2.0)	0.08 (0.1)	0.31 (0.3)
	Post Filtration	2.18 (1.4)*	1.72 (1.5)*	0.09 (0.1)	0.37 (0.4)
Differential counts (%)	Pre		82 (14)	4 (4)	14 (7)
	Post		76 (16)*	5 (4)	19 (9)

*$p < 0.01$ Paired *t*-test

The volume of mucus removed correlated with both ACC ($r = 0.85$, $p < 0.01$) and change in ACC ($r = 0.76$, $p < 0.05$) and was greater in smokers (n = 11), who had higher ACC (3.52 ± 2.2) than non-smokers (1.36 (0.6); $p < 0.01$). In three other patients with bronchiectasis and very high neutrophil counts, filtration reduced numbers of both macrophages (3.34 (1.8) to 1.30 (0.6)) and neutrophils (22.8 (11.9) to 16.6 (8.2)). We conclude that filtration may diminish cell counts in BAL fluid and affect the differential cell count by, in most cases, disproportionately removing macrophages. Standardisation of this procedure is important if results from different centres are to be meaningfully compared.

Pulmonary cellular defence: alteration of alveolar macrophage function following inhalation injury

AJ POLLOK, CG GEMMELL, CJ CLARK, JF MCMILLAN, WH REID, D CAMPBELL *University Departments of Anaesthesia and Medical Microbiology and Regional Burns Unit, Glasgow Royal Infirmary, and Department of Respiratory Medicine, Hairmyres Hospital, East Kilbride* A combination of smoke inhalation injury and skin burns (>25% BSA) carries a serious prognosis. Patients die of ARDS or its sequelae. BAL was undertaken in 13 smoke inhalation victims (CO-Hb > 10%), seven with skin burns alone (>20% BSA) and 19 controls (seven non-smokers and 12 smokers). AM chemiluminescence (CI) was measured with luminol as substrate and activity expressed as counts/s/10^5 cells. CI was measured (mean (SEM)) before (CI_{spont}) and after (CI_{stim}) the addition of a phagocytic stimulus. There was no significant difference in CI_{spont} between the 0 h (46 (19)), four h (250 (130)) and 24 h (448 (180)) samples from the smoke inhalation patients and the smoking controls (46 (20)). Patients with burns alone (18 (8)) demonstrated a significantly reduced CI_{spont} when compared with the smoking controls ($p<0.05$). Following stimulation a significant increase in CI_{stim} was seen in the four h (613 (248)) and 24 h (706 (226)) samples from the smoke inhalation patients when compared with the 0 h sample (150 (100)) ($p<0.05$) or the smoking controls (69 (27)) ($p<0.001$). CI_{stim} from the burns alone patients (19 (7)) was significantly depressed when compared with either control group ($p<0.05$). These results suggest the presence of a 'primed' AM population. Membrane instability or particle ingestion may lead to the inappropriate release of free radicals resulting in the pathophysiological lesion implicated in ARDS.

Lymphocyte induced macrophage abnormality in pulmonary sarcoidosis

LW POULTER, DA CAMPBELL, RM DU BOIS *Departments of Immunology and Thoracic Medicine, Royal Free Hospital and School of Medicine, London* Immunocytological analysis of lavage cells from 12 patients with untreated pulmonary sarcoidosis was performed to determine whether functionally distinct subsets of macrophages were present. Initially, Mc Abs specific for dendritic cells (RFD1), mature macrophages (RFD7) and Class II MHC antigens (RFDR1) were used to determine the phenotype of macrophage like cells in the BAL fluid. *In vitro* experiments then investigated the role of autologous lymphocytes maintaining the expression of the surface antigens on these macrophage like cells. These studies revealed that large numbers of cells with a "dendritic cell" phenotype (RFD1+ RFD7−) were present in sarcoid lavage fluid when compared with normal BAL fluid and that some of these cells showed concurrent expressions of macrophage antigens (RFD1+ RFD7+). By culturing the macrophage like cells with or without autologous lymphocytes the presence of the lymphoid cells was found necessary to maintain the expression of these abnormal phenotypes. The culture of BAL adherent cells alone resulted in the modulation of RFD1 and RFD7 antigens within 3 days. When the autologous lymphocytes were readmixed with these cells the proportions expressing RFD1, RFD7 and RFDR1 antigens remained constant. As cells phenotypically identical to the BAL cells have been shown to be involved in sarcoid lung granulomas it is postulated that the lung inflammation may involve a change in function of the non-lymphoid cells resulting from lymphocyte/macrophage interaction.

Patients with cryptogenic fibrosing alveolitis have an increased bronchoalveolar elastase burden

I DOWNING, W SCOTT, DC FLENLEY, AP GREENING *Rayne Laboratory, Department of Respiratory Medicine, University of Edinburgh* In cryptogenic fibrosing alveolitis (CFA) tissue damage by neutrophil proteinases may be important. We have determined the elastase 'burden' and anti-elastase activity in bronchoalveolar lavage fluids (BALF) from 18 CFA patients and 25 control subjects. Elastase activity and elastase inhibitory capacity were measured radiometrically using ^{3}H-elastin and porcine pancreatic elastase (PPE). $Alpha_1$-proteinase inhibitor ($alpha_1$-Pi) and $alpha_1$-Pi/elastase complex were measured by ELISA (the latter a gift from Merck). BALF from controls had no free elastase activity and all had elastase inhibitory capacity (mean 1.24 μg PPE inhibited/ml; range 0.28-4.57). BALF from 4/18 CFA patients had free elastase activity (0.45-14.45 μg PPE equivalent activity/ml) and from 5/18 patients had no elastase inhibitory capacity. Immunoreactive $alpha_1$-Pi was present in BALF from all controls (0.16-24.85 μg/ml; mean 3.67) but was higher in CFA BALF (0.90-33.21 μg/ml; mean 10.96), owing probably to increased transudation from plasma. BALF $alpha_1$-Pi/elastase complex levels were increased in CFA patients (5.7-4036.0 ng/ml; median 51.03) compared with controls (0-36.7 ng/ml; median 3.77 : $p<0.01$). These data suggest an increased bronchoalveolar elastase burden in CFA. It is uncertain whether this reflects or determines disease activity.

The effect of *Haemophilus influenzae* lipopolysaccharide on human respiratory epithelium *in vitro*

R WILSON, D SYKES, A RUTMAN, S ZAMZE, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London; and Unit of Infectious Diseases, Department of Paediatrics, John Radcliffe Hospital, Oxford* It has been suggested that the cell wall lipopolysaccharide (LPS) of *Haemophilus influenzae* may be an important virulence factor. The LPS of one type a and one type b strain of *H influenzae* was extracted and purified prior to assessment of its effect on human nasal epithelium obtained by a brushing technique (J Rutland, PJ Cole, *Lancet* 1980;ii:564-5). The LPS of both *H influenzae* types, dissolved in PBS (50 μg/ml and 500 μg/ml), did not slow ciliary beat frequency measured photometrically compared with controls in PBS alone. A sample of nasal epithelium was divided into three portions. The first was immediately fixed in glutaraldehyde, the second incubated in PBS alone at 37°C for four hours, and

the third similarly incubated but with LPS of both *H influenzae* types (10 μg/ml and 100 μg/ml dissolved in PBS) before fixation. Each sample was processed for examination by transmission electron microscopy. PBS alone was without effect but LPS caused extrusion of both ciliated and unciliated cells from the epithelium (more prominent at 100 μg/ml than 10 μg/ml), although ciliary ultrastructure was unaffected. LPS purified from the transformant strain Rb^+I69 was very rough, lacking all core sugars except 2-keto-3-deoxyoctonic acid. It was more potent in extruding epithelial cells than the above preparations, suggesting that the lipid-A moiety of LPS is important in mediating disruption of respiratory epithelium.

Effect of bacterial products on ferret tracheal ciliated epithelium

A BARKER, A RUTMAN, R WILSON, G TAYLOR, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* Beating of cilia in isolated strips of human nasal epithelium obtained by brushing is slowed when they are exposed to certain bacterial products *in vitro* (R Wilson, D Roberts, PJ Cole, *Thorax* 1985;**40**:125). In order to move towards determining the *in vivo* significance of this observation we have first asked whether intact ciliated preparations (ferret tracheal rings) exhibit similarly slowed beating when exposed at 37°C *in vitro* to pH adjusted products of *Pseudomonas aeruginosa* (PA) and *Haemophilus influenzae* dissolved in phosphate buffered saline (PBS) compared with PBS alone as control. Ciliary beat frequency (CBF) was determined by a photometric technique (J Rutland, PJ Cole, *Lancet* 1980;**ii**:564). Partially purified PA pigment caused ciliostasis and epithelial disruption in dilutions of 1:15 and 1:24, and 26% slowing of CBF at 1:360 ($p<0.001$, Student's t test). Synthetic pyocyanin and 1-hydroxyphenazine (1-HP) pigments of PA were shown to be indistinguishable from authentic biological pigments. Synthetic pyocyanin reduced CBF significantly ($p<0.001$): 56% at 50 μM, 18% at 25 μM. 1-HP acted similarly ($p<0.001$): 41% reduction of CBF at 57 μM, 15% at 25 μM, 19% at 12 μM. All slowing was seen by 30 min and was still present at 6 hours. *H influenzae* culture filtrates caused a smaller reduction in CBF, which had disappeared after three hours' incubation. We interpret these results as strengthening the case that these bacterial products significantly decrease mucociliary clearance.

Pseudomonas aeruginosa* phenazine pigments in the sputum in chronic bronchial sepsis (CBS) inhibit human ciliary beat frequency *in vitro

DA SYKES, R WILSON, D WATSON, G TAYLOR, J MACDERMOT, PJ COLES *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London; and Department of Clinical Pharmacology, Royal Postgraduate Medical School, London* Purulent sputum from patients with CBS slows the beating of human nasal cilia *in vitro* (Smallman *et al, Thorax* 1984;**39**:663). At least two factors contribute to this cilioinhibitory activity: one a serine proteinase, the other chloroform extractable (Sykes *et al, Thorax* 1986; in press). Using a photometric technique measuring human nasal ciliary beat frequency (Rutland and Cole, *Lancet* 1980;**ii**:564), we have studied sputum sols (SS) from four patients with daily purulent sputum production which possessed cilioinhibitory activity unaffected by α_1 anti-proteinase but removed by chloroform extraction. *Pseudomonas aeruginosa* was isolated from all four sputum samples. Each SS was dissolved in 5% acetic acid, purified with C_{18} Sep Pak (Waters Associates, Cheshire) and submitted to high performance liquid chromatography (Nova Pak column) eluting with an acetonitrile:water: trifluoroacetic acid gradient. The eluate was monitored by ultraviolet absorbance (UVA) (280 and 254 nm) and aliquots were tested for cilioinhibitory activity using the photometric technique. Cilioinhibition correlated with those UVA peaks compatible with the *Pseudomonas aeruginosa* phenazine pigments pyocyanin and 1-hydroxyphenazine. Mass spectrometry confirmed the identity of these cilio inhibitory pigments.

A more sensitive method for quantitation of elastolytic activity in purulent sputum

DC CURRIE, SA AFFORD, D BURNETT, RA STOCKLEY, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London; and General Hospital, Birmingham* Neutrophil elastolytic activity of sputum is a measure of local host response to the colonising microbial load in patients with purulent sputum and it may cause progressive bronchial damage in such patients. Using microtitre plates, we have modified a fluorescein-elastin (FE) technique (Macgillivray *et al, Clin Chim Acta* 1981;**111**:289-294) to detect elastolytic activity (EA) equivalent to 0.02 mg/l porcine pancreatic elastase (PPE). Two hundred μl of diluted standard (PPE) or sputum in buffer was added to each well containing 1.6 mg of washed and dried FE. The plate was covered and incubated at 37°C for 16 hours. The reaction was stopped and the fluorescence measured (excitation wave length 468 nm, emission 512 nm). EA was measurable in the sol of 43/46 different purulent sputum specimens from 33 patients by our FE method and ranged from 0.02 to 45 mg/l. By contrast, EA was measurable in only three using elastin-agarose diffusion plates. Each sputum specimen was assessed for the proportions of thick and thin phases in the whole specimen, proportion of purulence (opaque and coloured part) in the thick phase and the colour and degree of colour of the purulent portion. For 27/46 specimens with $\geqslant$75% purulence overall, the mean (SE) EA was 8(2) mg/l, which was significantly greater than that of 19/46 less purulent specimens (2(0.4) mg/l, $p<0.01$, unpaired t test). The more sensitive FE method allows objective monitoring of EA during treatment of chronic bronchial sepsis and will complement our detailed assessment of the macroscopic appearance of the sputum.

Specificity of murine cytotoxic T-cells to respiratory syncytial virus

PJM OPENSHAW, MJ CANNON, BA ASKONAS *National Institute for Medical Research, London* Although respiratory syncytial virus (RSV) is the commonest single cause of hospitalisation of infants in the western world, a successful vaccine has yet to be developed. Two serogroups of RSV can be distinguished by antigenic variants of the envelope attachment glycoprotein (G) or fusion protein (F). Serum antibodies to these proteins follow natural infection, but confer little protection. T-cells may contribute to viral clearance, but also to the pathogenesis of RSV bronchiolitis. BALB/c mice were infected intranasally with 10^5 PFU of group A RSV. After three weeks, splenocytes were co-cultured *in vitro* with autologous cells infected with serogroup A or B virus, which stimulated RSV specific cytotoxic memory cells. At five days RSV specific cytotoxicity (T_c) was assessed against P815 cells ('targets') infected with serogroup A or B RSV in a ^{51}Cr release assay. Targets were lysed equally regardless of the RSV serogroup used to stimulate the cultures. Cells infected with recombinant vaccinia virus coding for G protein (serogroup A) expressed G antigen on the surface, but were not lysed. We conclude that T_c are crossreactive between serogroups of RSV, and that G protein is not recognised by T_c cells. The role of other proteins awaits definition.

Local production of alpha interferon in cytomegalovirus pneumonitis

AML LEVER, HJ MILBURN, JE GRUNDY, P PRATT, PD GRIFFITHS, RM DU BOIS *Departments of Virology and Thoracic Medicine, Royal Free Hospital, London* Alpha interferon (α_1IFN) is released by most tissues in response to virus infection, whereas gamma interferon (γIFN) is released only by immunologically committed T-cells in response to specific antigenic stimulation. We have looked at α and γIFN levels in serum and bronchoalveolar lavage (BAL) fluid from 13 patients who developed CMV pneumonitis following organ transplantation to determine whether CMV stimulates local IFN production, to characterise any IFN produced and to see whether its presence is of prognostic significance. Four patients had coinfection with *Pneumocystis carinii*. Three patients had α IFN detectable in BAL fluid and in serum; in one of these γIFN was also present in BAL fluid. All three of these patients died. No IFN was detected in BAL fluid or serum from the remaining 10 patients and only two of these died. The mean duration of illness before diagnosis in the IFN positive group was 18.3 days (range 14-27), but only 5.6 days (2-14) in the IFN negative group. All patients were treated with CMV hyperimmune globulin, and high dose septrin where appropriate, when infection was diagnosed. We conclude that in immunosuppressed patients with CMV pneumonitis the presence of α IFN in BAL fluid and serum correlates with late diagnosis and poor prognosis.

High dose total body irradiation (TBI) and subsequent cytomegalovirus (CMV) pneumonitis in patients receiving bone marrow transplants (BMT)

HJ MILBURN, JP GROB, HG PRENTICE, JE GRUNDY, RM DU BOIS *Departments of Thoracic Medicine and Haematology, Royal Free Hospital, London* This study investigates whether high dose irradiation used as pre-BMT conditioning predisposes to the development of interstitial pneumonitis. From February 1983 to November 1985 55 patients with haematological malignancies at various stages of their disease have received T cell depleted bone marrow from HLA matched (n = 50) or partially matched (n = 5) sibling donors. Pre-transplant conditioning consisted of cyclophosphamide and TBI (n = 42) or cytosine arabinoside, cyclophosphamide and TBI (n = 13). Sixteen patients developed interstitial pneumonitis and nine of these had CMV infection diagnosed by bronchoalveolar lavage. Eight of the nine had significant titres of CMV antibody in serum prior to BMT. Of a total of 30 patients with positive CMV serology pre-BMT, 15 received a total irradiation dose to the lungs of >715 cGy and 11 of the 15 developed interstitial pneumonitis (eight due to CMV), while only one of 15 who received lower lung doses developed pneumonitis (none due to CMV) ($p<0.001$). By contrast, only four of 13 seronegative patients who received >715cGy to the lungs developed interstitial pneumonitis (one CMV) and none of the 12 seronegative patients who received <715cGy to the lungs developed pneumonitis. We conclude that high dose irradiation predisposes to interstitial pneumonitis in general and to CMV in particular, especially in patients previously seropositive.

Pulmonary complications of AIDS: a review of 90 English cases

RJ SHAW, CA ROWLAND-HILL, J PARKIN, S FOSTER, EE KEAL, AJ PINCHING *St. Mary's Hospital, London* Ninety patients (mean age 39, range 21-72) with AIDS (89M, 1F) have been treated at one London centre. Pulmonary complications occurred in 59. Thirty-nine had pneumocystis pneumonia (PCP) with a second episode in nine. In 32 PCP was the initial illness, but in 10 it was associated with another respiratory pathogen (CMV eight, *Mycobacterium Xenopi* one, histoplasma one) and in three with Kaposi sarcoma (KS). Treatment with high dose cotrimoxazole led to clinical recovery in 29 of the 39 first episodes. Nine of the 10 fatalities occured in patients with additional pathology. Of the 29, thirteen have subsequently died (mean survival 10 months) but one of the survivors is alive at 26 months. *Mycobacterium* tuberculosis was identified in 10 patients (nine from the chest), and was found at presentation in six. Atypical mycobacteria were isolated from 13 patients (seven from the lung), including *M avium intercellulare* (five), *xenopi* (five), *flavescens* (one), untyped (three). Infection occurred later (with a mean of six months after the diagnoses of AIDS). Endobronchial KS was common, but respiratory complications of parenchymal KS occurred in one case. Nineteen patients had a pyogenic pneumonia and two developed chronic purulent bronchitis. One patient had a fatal candida pneumonia, two had adenovirus

isolated during a pneumonia, and in two *Cryptococcus* was grown. This series illustrates the wide variety of pulmonary complications of AIDS, and suggests an important role for respiratory physicians in their management.

Radiological clearing after pneumonia

CK CONNOLLY, B FARR, BDW HARRISON FOR THE BTS RESEARCH COMMITTEE *Friarage Hospital, Northallerton* In the BTS pneumonia Study, pneumonia was defined as "an acute illness with radiological pulmonary shadowing, which was at least segmental or present in more than one lobe, and which was neither pre-existing nor of other known cause" (thus excluding carcinoma). This presentation describes the rate of resolution of the radiographs and factors influencing it. The possible influence of all recorded features was considered as previously described for death. Univariate analysis showed failure to clear at six weeks, was associated with age, non-employment, smoking, pre-existing respiratory disease, dyspnoea, vomiting at admission ($p<0.01$), and treatment for incidental illness ($p<0.05$). Relevant investigations were a low serum albumin ($p<0.01$), abnormal liver function, hypoxaemia and more than one lobe involved ($p<0.05$). With multivariate analysis, giving preference to age, only age ($p<0.01$), low serum albumin ($p<0.01$) and more than one lobe involved ($p<0.05$) remained significantly correlated. Radiographs were clear in 15% on discharge, and in 55% of those seen at six weeks. Life table analysis suggested that 75% of radiographs showed resolution of pneumonic features at 100 days and 83% at 157 days (the date of the last reported clearing). Stratification by age showed that resolution occurred before six weeks in the lowest quartile (aged under 32), but took up to four months in older age groups. Radiography at discharge is probably too early to be useful in patients progressing satisfactorily.

Haemophilus pneumonia in hospitalised patients

MB ALLEN, K PROWSE *Department of Respiratory Physiology, City General Hospital, Stoke-on-Trent* *Haemophilus influenzae* pneumonia occurs rarely in the UK (*Br. J Dis Chest* 1985;79:95-7) but may produce community acquired pneumonia. It is commoner in the USA, where there is an association with chronic lung disease and other medical problems. To determine the features of *Haemophilus influenzae* pneumonia case notes of hospitalised patients with positive blood cultures over a five year period were examined. Forty-eight positive cultures were obtained; 40 neonates and infants were excluded and one patient, aged 60 years, with vasculitis died of septicaemic shock but had no respiratory symptoms, so these are not considered further. Two patients aged 17 and 18 years had respiratory signs and symptoms on the right side but no radiological evidence of consolidation. The five remaining patients, mean age 68, had respiratory signs and symptoms for one to seven days, with radiological evidence of consolidation, which was localised to the right lower lobe in four. Only one patient had underlying chronic chest disease (chronic obstructive lung disease and tuberculosis). Four of the five patients, mean age 74, one of whom died, were clinically shocked with marked hypotension. *Haemophilus* isolates in all seven patients were sensitive to cotrimoxazole and tetracycline but three were resistant to ampicillin. *Haemophilus influenzae* is an important cause of pneumonia, which, contrary to previous reports, is not always associated with chronic chest disease or underlying medical problems. In the elderly, shock and hypotension may occur but prompt antibiotic treatment appears effective.

Outbreak of legionnaires' disease at Glasgow Royal Infirmary: early containment by rapid diagnosis

JH WINTER, AC MCCARTNEY, RJ FALLON, ABM TELFER, JK DRURY, IJ REECE, MC TIMBURY *Departments of Respiratory Medicine, Microbiology, Anaesthetics, Peripheral Vascular Surgery and Cardiothoracic Surgery, Glasgow Royal Infirmary, and Department of Laboratory Medicine, Ruchill Hospital, Glasgow* An outbreak of legionnaires' disease involving 17 patients occurred at Glasgow Royal Infirmary in the last quarter of 1985. Legionnaires' disease was first suspected when pneumonia occurred in a second patient housed in a high dependency unit; within 48 hours a firm diagnosis of legionnaires' disease had been made in two patients by the demonstration of *L pneumophila* serogroup 1 using the direct fluorescent antibody technique in bronchial aspirate obtained at bronchoscopy; within 72 hours two further cases had been similarly diagnosed and the areas associated with a high risk of legionnaires' disease had been closed. Ten patients and one surgeon developed severe disease; five patients died. Patients received therapy with erythromycin and ciprofloxacin and/or rifampicin. The application of the direct fluorescent antibody test to specimens obtained at bronchoscopy was responsible for the rapid diagnosis of legionnaires' disease, the prescription of appropriate antibiotic therapy and the early containment of this outbreak. It is suggested that these techniques should be included in investigation of patients involved in an outbreak of pneumonia.

Community acquired staphylococcal pneumonia (SP) in the Trent region

J RADVAN, MA WOODHEAD, JT MACFARLANE *Department of Thoracic Medicine, City Hospital, Nottingham,* We have reviewed, retrospectively, 51 adult patients with SP. *Staphylococcus aureus* (SA) was cultured from sputum (37), blood (10), treacheal aspirate (seven), lung (seven), pleural fluid (one) and splenic aspirate (one). Half of the patients were young (24 (47%) < 45; eight (16%) < 25 years) and 24 (47%) were previously fit. Cases were commoner in late winter. Chest infection or 'flu' was stated in only 20 of 34 (59%) GP diagnoses. Of 23 prior antibiotic courses only five were active against SA. Clinical features were generally unremarkable. Seventeen (33%) patients died (<8 55% years old), mostly within a week. From six of these influenza virus was isolated. Seventy per cent of survivors were in hospital for more than a fortnight. Admission features associated with death were drowsiness

($p<0.005$), confusion ($p<0.001$), leucocyte count $<11\times10^9/l$ ($p<0.05$), urea >7 mmol/l ($p<0.001$) and bacteraemia ($p<0.01$). Pneumothorax occurred in five. Of eleven requiring assisted ventilation eight (73%) died. Of 13 necropsies eight showed lung cavitation, seven ulceration and inflammation of the large airways, one metastatic abscess and one bacterial endocarditis. In seven cases SA was isolated again five or more days after the start of effective therapy. The management of any severely ill pneumonia patient should include anti-SA chemotherapy. This should be prolonged if SP is confirmed.

Use of totally implantable system for venous access in cystic fibrosis

RJ STEAD, FR DUNCAN, TI DAVIDSON, ME HODSON, JC BATTEN *Department of Cystic Fibrosis, Cardiothoracic Institute and Brompton Hospital, and Academic Surgical Unit, Royal Marsden Hospital, London* Difficulty with venous access is common in those patients with cystic fibrosis (CF) who are frequently treated with intravenous antimicrobials for bronchopulmonary infections due to *Ps. aeruginosa*. The 'Port-a-Cath' system (Pharmacia), a stainless steel chamber with an injection port connected to a silicone catheter, has been implanted in nine such patients (8F, 1M; median age 22, range 13-38 years). As a percentage of predicted normal their median (range) FEV_1 was 32 (17-47), FVC 30 (26-62) and weight 90 (79-94). Peripheral venous access had become unsatisfactory in all, and five had previously had cannulations via the neck. The implantation was performed under local anaesthetic in eight patients and general in one. Following cannulation of a central vein the other end of the catheter was tunnelled subcutaneously to the portal site on the chest wall. Six patients had no post- operative complications. In one the portal was later resited because of pain, and in a second the catheter was repositioned after it migrated proximally in the vein. A third patient experienced pain around the portal requiring pethidine for one week. The system has been used for domiciliary antimicrobial chemotherapy in eight patients, and for parenteral feeding in five. It is initially expensive, but in carefully selected patients functions well and appears to have advantages over alternative means of central venous access.

Response to salbutamol in adult patients with cystic fibrosis related to recovery from acute exacerbations of pulmonary infection

BK ASSOUFI, RJ STEAD, CM ROBERTS, ME HODSON, JC BATTEN *Brompton Hospital, Cardiothoracic Institute, London* Airflow limitation is characteristic of cystic fibrosis (CF) but response to bronchodilators is unpredictable. To investigate the relationship between response to β_2 agonists, bronchopulmonary infection and airflow obstruction, we studied 11 patients (5M, 6F; median age 23, range 16-29 years) receiving intravenous chemotherapy for infection with *Pseudomonas aeruginosa*. Peak expiratory flow (PEF), forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured at the beginning and end of inpatient treatment, before and after nebulised salbutamol (5 mg in 2 ml 0.9% saline). There was a significant increase in mean values for each variable compared with baseline following salbutamol on both days one and 10 ($p<0.01$). The mean percentage change following salbutamol on days one and 10 respectively for PEF was 16.1 and 7.4, for FEV_1 12.6 and 8.6, and for FVC 16.0 and 9.0. The mean preinhalation values for each variable increased during treatment but this increase did not reach statistical significance. No correlation was found between baseline lung function and percentage change following salbutamol on either day one or day 10. As a group, the patients with CF responded to salbutamol but the response tended to decrease with recovery from acute bronchopulmonary infection.

Pregnancy in cystic fibrosis

RJ STEAD, ME HODSON, JC BATTEN *Department of Cystic Fibrosis, Brompton Hospital and Cardiothoracic Institute, London* Of 156 female patients who have attended our adult CF clinic, nine have had a pregnancy beyond 28 weeks' gestation. All had typical clinical features of CF with sweat sodium concentration >70mmol/1 and bronchopulmonary disease, and seven had exocrine pancreatic insufficiency. At conception, the patient's median (range) age was 26 (21-43) years, and as a percentage of predicted normal FEV_1 was 61 (35-84), FVC was 78 (35-96) and weight was 95 (73-121). There was a tendency for pulmonary function to deteriorate in the third trimester, but most patients appeared to regain this within six months of delivery. The median gestation was 37 (29-40.5) weeks. In one case premature labour occurred at 29 weeks and the infant had cerebral palsy. The other infants were healthy, although four weighed less than the 25th percentile for gestational age. Two of the mothers successfully breast fed; milk obtained from them and colostrum from a third patient had broadly normal osmolalities and concentrations of electrolytes and calcium. One patient died 5.5 years following delivery, but the other eight have survived a median 5.3 (1.5-10.7) years to date. Pregnancy in patients with cystic fibrosis can be advised only in the fittest patients but with careful management the outcome may be satisfactory.

Treatment of distal intestinal obstruction syndrome in patients with cystic fibrosis

AC DAVIDSON, NK HARRISON, DM GEDDES *London Chest Hospital, London, and Brompton Hospital, London* Cleghorn *et al* recently reported the use of intestinal lavage in the treatment of distal intestinal obstruction syndrome (DIOS) in cystic fibrosis (CF) (*Lancet* 1986;I:8). We report our own experience in a further seven patients. Initial presentation in one patient was with subacute bowel obstruction. He had no past history of DIOS or evidence of malabsorption requiring pancreatic supplements. The remaining six patients were taking pancreatic supplements to control steatorrhoea. Two also required H_2 blockers. Three had documented normal faecal fat excretion on treatment. In all six, previous

manifestations of DIOS included recurrent abdominal pain. Two also suffered recurrent subacute bowel obstruction and two others frequently had a palpable mass in the right iliac fossa. All had radiographic evidence of inspissated faeces in the colon and two had features of small bowel dilatation. Between three and 10 litres of lavage fluid was administered either orally or by nasogastric tube. Treatment was well tolerated in each case and resulted in the passage of large amounts of faecal material. All patients reported improvement in symptoms and colonic clearance was usually confirmed radiographically. Time spent in hospital was short (2-5 days in six patients). Symptoms of DIOS have not recurred in six patients after one-two months follow-up. One patient required repeat treatment. We conclude that intestinal lavage is a safe and effective treatment of DIOS.

Oral gastrografin in the treatment of meconium ileus equivalent in cystic fibrosis

SM O'HALLORAN, J GILBERT, O MCKENDRICK, H CARTY, D HEAF *Alder Hey Children's Hospital, Liverpool* Of the 67 patients attending the cystic fibrosis (CF) clinic, 25 (37%) had meconium ileus equivalent (MIE) at some time. During one year 14 children had 40 episodes (one to nine per child) despite prophylaxis with N-acetyl cysteine and lactulose. Compared with CF patients with no history of MIE ($n=42$), MIE patients were significantly older (mean age 11.7 years vs 6.6 years in controls, $p<0.01$) and more often admitted to hospital (mean 1.86 vs 0.78 admissions/year, $p<0.05$) and had worse Schwachman scores (mean 74 vs 85 in controls, $p<0.05$). Pseudomonas chest infection (42% vs 14% in controls) and meconium ileus at birth (28% vs 9% in controls) were more common in the MIE group. Thirty-seven episodes of MIE were treated with oral gastrografin. Thirty responded to a single dose, six required a second dose and one required a gastrografin enema. Twenty-nine episodes were treated as outpatients. All patients found oral gastrografin more acceptable than other agents and greatly preferable to enema treatment. Oral gastrografin is simple, safe, effective and can be given to outpatients.

Eosinophils and mast cells in bronchoalveolar lavage in mild asthma: relationship to bronchial hyperreactivity

AJ WARDLAW, SANDRA DUNNETTE, GJ GLEICH, JV COLLINS, AB KAY *Cardiothoracic Institute, Brompton Hospital, London, and Mayo Clinic, Rochester, Minnesota, USA* We have performed bronchoalveolar lavage on 15 mild asthmatic patients (eight symptomatic, seven asymptomatic) and 12 non-asthmatic controls (four hayfever, eight non-atopic). There were significantly more eosinophils, mast cells and epithelial cells in the symptomatic asthmatic group compared with the non-asthmatics. These changes were even more marked when asthmatics with hyperreactive airways ($PC_{20}<4$ mg/ml) were compared with subjects with normoreactive airways. There were no differences between the asymptomatic asthmatics and the non-asthmatic subjects. Neutrophils were not elevated in the asthmatic subjects but were significantly greater in a 'bronchial' wash compared with a 'bronchoalveolar' wash in both asthmatics and non-asthmatics. Major basic protein (an eosinophil granule protein, MBP) was measured in lavage fluid from 15 subjects. Amounts of MBP recovered in lavage fluid were significantly greater in the hyperreactive asthmatic compared with normoreactive subjects ($p<0.01$) and correlated significantly with the percentage of eosinophils in the bronchoalveolar lavage fluid ($p<0.001$). This study supports the view that increased bronchial hyperreactivity may be mediated by eosinophil derived granule products. The mast cell counts, although raised, are similar to the counts found in other disease groups (Wardlaw *et al, Clinical Allergy* 1986;**16**:in press) and may be increased as a result of the inflammation present in asthma rather than predisposing to it.

Prostaglandins (PG), thromboxane (Tx) and leukotriene C_4 (LTC_4) generation by the human eosinophil stimulated by calcium ionophore (A23187) and unopsonised zymosan (ZYM)

R MAHAUTHAMAN, LJF YOULTEN, B SPUR, TJH CLARK, TH LEE *Guy's Hospital, London* The definition of physiological stimuli for mediator generation by the eosinophil (EOS) is critical to the elucidation of the role of this cell in pulmonary eosinophilias and in bronchial asthma. We have therefore compared the generation of the cyclo-oxygenase products PGE_2, $PGF_2\alpha$, and TxA_2 and the lipoxygenase product LTC_4 by EOS stimulated by ZYM and by A23187 in a dose and time dependent manner. Mediators were quantitated by radioimmunoassay; PGI_2 and TxA_2 were measured as the stable metabolites 6-keto-$PGF_1\alpha$ and TxB_2 respectively. Activation of 1×10^6 EOS by ZYM under optimal conditions produced no detectable PG and 1.6 (0.8) ng LTC_4 (mean (SEM), $n=4$); 40-60% of LTC_4 was cell associated. There was no correlation between the per cent cell associated LTC_4 and the quantities of LTC_4 produced or the time of incubation with ZYM. Optimal activation of 1×10^6 EOS with A23187 produced 0.8 (0.4) ng PGE_2, 0.9 (0.2) ng TxB_2 and 204.0 (38.6) ng LTC_4 ($n=6$); $<10\%$ of LTC_4 was cell associated. $PGF_2\alpha$ and 6-keto-$PGF_1\alpha$ were undetectable. Authenticity of the immunoreactive LTC_4 was confirmed by the elution of a single immunoreactive peak after RP-HPLC at the retention time of synthetic LTC_4. Thus the generation of LTC_4 exceeds that of PG in EOS activated by both ZYM and A32187. Further, activation of EOS by a physiological phagocytic stimulus leads to the production of 1/100th the quantities of LTC_4 generated by a secretory agonist, A23187, and the generated LTC_4 is substantially cell associated.

The monokine interleukin-1 (IL-1) augments leukotriene B_4 (LTB_4) generation by human neutrophils (PMN) stimulated by unopsonised zymosan (ZYM)

TH LEE, E IRVINE *Department of Medicine, Guy's Hospital, London* The pathology of severe asthma is characterised in part by the infiltration of airways with

granulocytes and mononuclear cells. Since interactions between these cells may enhance bronchial inflammation, we have studied the capacity of the monokine IL-1 to enhance generation of the pro-inflammatory mediator LTB_4 by PMN activated by ZYM, a phagocytic stimulus. IL-1 was affinity purified and the levels of LTB_4 released into supernatants and those associated with cells were quantitated by a specific radioimmunoassay. Identity of LTB_4 was confirmed by the elution of a single immunoreactive peak after RP-HPLC at the unique retention time of synthetic LTB_4. The augmentation of ZYM induced LTB_4 generation was IL-1 dose and time dependent. Generation of LTB_4 induced by 8×10^8 ZYM particles increased from 1.2 (0.3) ng/10^7 cells in the absence of IL-1 to a maximum of 6.1 (1.3) ng/10^7 cells (mean (SEM), n = 5) after preincubation of PMN with 10 units IL-1 at 37°C for 10 min. Greater than 90% of the enhancement was observed in the cell associated component of generated LTB_4 with only minimal change in the levels of LTB_4 which were released. Augmentation of LTB_4 generation (200-600%) by IL-1 treated PMN occurred over the full dose range of ZYM (2 to 8×10^8 particles), and was evident when PMN were activated by 8×10^8 ZYM particles for periods of five to 30 min at 37°C. The positive pro-inflammatory interaction between monocytes and PMN provides a mechanism for the amplification of the inflammatory responses in the airways in bronchial asthma.

Comparative activities of leukotriene (LT)B_4 and LTB_5 in enhancing complement receptors (CR1 and CR3) in human neutrophils

JP ARM, TJ SETHI, NM EISER, *MJ WALPORT, TH LEE *Departments of Medicine and Respiratory Medicine, Guy's Hospital, and Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Eicosapentanoic acid (EPA) is abundant in fish oil lipids and is metabolised to LTB_5. LTB_5 is a weaker chemotactic agonist than LTB_4. We have compared the capacity of LTB_4 (10^{-10} to 10^{-7}M) and LTB_5 (10^{-8} to 2.0×10^{-6}M) to enhance the expression of CR1 and CR3 on human neutrophils using monoclonal antibodies to the receptors, a fluorescein conjugated anti-mouse IgG and flow cytometry as described by Fearon (1983). There was a dose dependent increase in CR1 and CR3 to a maximum of 300% and 350% of basal levels respectively at 10^{-8}M LTB. LTB_5 also produced a dose dependent increment of CR1 and CR3, but the maximal increase was less than that observed for LTB_4, being 250% and 200% respectively at 10^{-6}M LTB_5. The concentration of LTB_4 eliciting half maximal response (EC50) was 10^{-9}M for both CR1 and CR3. The concentrations of LTB_5 eliciting the same increase in CR1 and CR3 produced by the EC50 LTB_4 were 1.6×10^{-7}M and 6×10^{-7}M respectively. Thus LTB_5 is a weak and partial agonist, not only in its chemotactic activity for human neutrophils, but also in its capacity to enhance complement receptors. These results support the view that dietary supplementation with EPA has anti-inflammatory potential and may be useful in the treatment of the inflammatory components of bronchial asthma.

Human *in vitro* bronchial smooth muscle responses to leukotriene D_4 in relation to the quantity of muscle

JA ROBERTS, IW RODGER, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow* Hypertrophy and/or hyperplasia of airway smooth muscle may contribute to hyperresponsiveness in asthma. If so, the quantity of smooth muscle present in *in vitro* bronchial strips should be related to *in vitro* airway smooth muscle responsiveness as assessed by maximum agonist induced tension. To investigate this we obtained thoracotomy specimens from 11 patients and prepared four bronchial strips from each. These were assessed for sensitivity (expressed as EC_{50}) and maximum induced tension to LTD_4. At the end of the experiment the tissue was weighed and then preserved and stained. The smooth muscle content of each strip was assessed at four levels and a mean percentage of smooth muscle calculated. From this and the tissue weight the quantity of smooth muscle present was calculated. The *in vitro* sensitivity ranged from 1.4×10^{-9} to 3.0×10^{-8} μmol/l. The maximum tension generated ranged from 275 to 2300 mg and the percentage smooth muscle ranged from 1.13 to 16.41. Smooth muscle quantity was related to maximum tension generated ($r=0.65$, $p<0.05$) but not to EC_{50} ($r=-0.08$, $p>0.05$). These results suggest that the hypertrophy and/or hyperplasia of smooth muscle reported in the airways of patients with asthma may contribute to *in vivo* airway responsiveness to constrictor agents.

The inhibitory effect of terfenadine on bronchoconstriction induced by adenosine monophosphate and allergen

P RAFFERTY, CR BEASLEY, ST HOLGATE *Southampton General Hospital, Southampton* Adenosine is a naturally occurring purine mucleoside that has been shown to produce bronchoconstriction in asthmatics. Recent *in vitro* work demonstrated that adenosine enhanced antigen induced release of preformed mast cell mediators without affecting the production of newly generated mediators. We have investigated this possibility *in vivo* by assessing the effect of H_1 receptor blockade on bronchoconstriction induced by histamine, adenosine monophosphate (AMP) and allergen. Nine subjects with mild, atopic asthma underwent inhalation challenge tests on six separate days using doses of the three agonists previously shown to produce a 30% fall in FEV_1. The tests were performed three hours after treatment with terfenadine 180 mg or matched placebo. Histamine and AMP both produced rapid bronchoconstriction, reaching a maximum within five minutes and returning to within 10% of baseline after 25 minutes. Terfenadine abolished the bronchoconstrictor response to histamine and reduced that to AMP by 86% (SD 8.1%). In contrast allergen produced bronchoconstriction that was slower in onset and was sustained over the 45 minutes of observation. Terfenadine partially inhibited the bronchoconstrictor response to allergen by 50% (10%). These results are in keeping with the suggestion that the bronchoconstrictor response to AMP is due to enhancement of the release of preformed mediators without increasing the formation of newly generated mediators.

The effect of H_1-receptor blockade on exercise induced asthma (EIA)

OP TWENTYMAN, ST HOLGATE, P HOWARTH *Medicine 1, Southampton General Hospital, Southampton* There is conflict over the role of mast cells in EIA. We have studied the effect of H_1-receptor blockade on eight asthmatic subjects (4M, 4F), mean (SEM) age 27.6 (3.8), who underwent two identical treadmill exercise tests before and after 14 days' treatment with astemizole 10 mg/day. On the two days prior to each exercise test the PC_{20} methacholine (eight subjects) and PC_{10} histamine (five subjects) were determined. There was no significant difference in either the mean resting FEV_1 (2.9 vs 2.9 l) or in the mean respiratory heat exchange (3.7 vs 3.8 kcal) between the two exercise days. Six subjects were protected against EIA with mean maximum falls in FEV_1 of 23.0% (7.4%) before and 9.2% (7.2%) after astemizole ($p<0.05$). Mean PC_{20} methacholine was not significantly different before (0.29 mg/ml) and after (0.30 mg/ml) astemizole. The mean PC_{10} histamine was displaced by a factor of 12.9 from 0.31 mg/ml to 5.47 mg/ml by astemizole. These results show that histamine may be important in the development of EIA in some patients. This is further evidence that EIA is a heterogeneous condition that can be mediated via different mechanisms (*Thorax* 1985;**40**:481-487), including mast cell degranulation.

The symptoms of bronchial hyperresponsiveness in schoolchildren

RD CLIFFORD, ST HOLGATE, M RADFORD *Medicine 1, General Hospital, Southampton* In children the symptoms of asthma are diverse. A respiratory questionnaire was sent to parents of 3000 Southampton schoolchildren aged seven and 11 years. Four hundred from selected symptom groups were invited for methacholine bronchial provocation and skin prick testing with house dust mite, cat fur and grass pollen extracts. The highest dose of methacholine was 6.4 μmol. The response for both parts of the study was 84%. Between seven and 11 years the current prevalence of wheeze remained at 12% but the prevalence of cough fell from 32.5% to 21%. Skin prick testing differentiated two groups of children. Eighty-four per cent of allergen exposed atopic children who responded to methacholine had symptoms — 58% had wheeze compared with 7% of non-responders, whilst the rest had cough or symptoms in response to environmental agents. In contrast one third of parents of non-atopic methacholine responders denied symptoms and only 9.8% admitted to wheeze; cough was the only symptom more prevalent in this group — 33% compared with 18% of non-responders. Whilst in atopic children wheeze was a highly specific indicator of bronchial hyperresponsiveness, in children without wheeze no other symptom or symptom combination has so far been found to differentiate methacholine responders from non-responders.

Neutrophil chemotactic activity in acute severe asthma

DR BUCHANAN, O CROMWELL, AB KAY *Department of Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* Serum neutrophil chemotactic activity (NCA) was measured in patients with acute severe asthma and compared with mild asthma, stable chronic irreversible airflow obstruction and asymptomatic atopic individuals with other non-infective lung conditions (nine patients in each group). Concentrations of NCA were related to a standard chemoattractant (the synthetic bacterial analogue f-met-leu-phe, 10^{-8} M). NCA was significantly elevated ($p<0.001$) in acute severe asthma compared with controls. Longitudinal studies were undertaken on 12 patients with acute asthma on admission, during treatment, and on discharge from hospital (days 0, 3 and 7 approximately). There was a highly significant reduction in serum NCA activity on day 7 as compared with day 0 ($p<0.01$) and this fall correlated inversely with improvement in lung function. The physiochemical characteristics of serum NCA from acute asthmatics resembled those of high molecular weight NCA (HMW-NCA) previously observed in allergen and exercise induced asthma. However, there was more heterogeneity in terms of molecular size ($>1\times10^6$ K, 450-600 K, 100 K, 40-45 K and <20 K) as assessed by fast protein liquid chromatography on Superose 6PG. These data support the concept that HMW-NCA occurs in the natural disease in its acute form as well as in clinical models.

Food antibodies in asthma

SE CHURCH, R FINN, RMR BARNES, AJ WILLIAMS *Royal Liverpool Hospital, Liverpool* The role of food in asthma remains undefined. In an attempt to clarify the situation further we have studied serum antibodies (IgG by ELISA) to gliadin, milk and ovalbumin in a hospital population of 30 asthmatics and compared results with a local blood donor population (BDP) of 262 subjects. We found that eight (27%) asthma patients had one or more of these food antibodies compared with 9.2% of BDP ($p<0.05$). Of these eight patients four had antibodies to gliadin, five to ovalbumin and six to milk. The clinical and immunological features of those asthma subjects with food antibodies (FA) have been compared with those of subjects without (NFA). There was no significant difference between FA and NFA for: age (mean 45 vs 46 years), sex, duration of asthma, history of rhinitis/eczema, food induced gastrointestinal/respiratory symptoms, prednisolone therapy, skin prick tests (inhalants and foods), total blood eosinophilia and total serum and RAST IgE. The finding of an increased prevalence of food antibodies in asthma is of interest but these patients (FA) were not distinguishable clinically or immunologically from the remaining asthma patients (NFA). However the role of these antibodies in asthma may be relevant and warrants further investigation.

Increased permeability of the trachea in sensitised rats after aerosol challenge

F CARSWELL, S MUKHERJEE, P HEAP *Department of Child Health, Royal Hospital for Sick Children, and University Department of Anatomy, Bristol* More antigen penetrates the tracheal epithelium of rats when they have been sensitised prior to challenge via the airways. The present study examines the mechanism of this increased penetration by measuring the passage of (electron dense) lanthanum into the respiratory epithelium. Rats were sensitised by injection with DNP_{19}, ovalbumin (DNP-OA) or saline. The rats were challenged for 10 minutes with an aerosol of DNP-OA, bovine gamma globulins or saline. Within one minute of completion of challenge the trachea was immersed in fixative containing 1% lanthanum nitrate. Tissues were processed for electron microscopy. The lanthanum concentration in the epithelium was measured directly from electron micrographs by planimetric analysis of the intercellular boundaries and by X-ray static probe microanalysis. The proportion of lanthanum stained cell boundaries was greater in the tracheas from the DNP-OA sensitised and challenged group than in the other experimental groups ($p<0.05$). X-ray microanalysis confirmed that more lanthanum was present in the tracheal epithelium of these rats ($p<0.05$). The quantity of lanthanum penetrating correlated ($r=0.743$) with the severity of the mechanical respiratory response. The results show that antigen challenge of sensitised rats leads to increased penetration along the intercellular boundaries of the epithelium. This intercellular route could be used by antigen or released agonists to produce subepithelial activation.