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Effect of oral corticosteroids on regional lung mucus clearance in stable asthma

JE AGNEW, JRM BATEMAN, D PAVIA, SW CLARKE Serial gamma camera images were used to assess lung clearance of ^{99m}Tc -labelled aerosol particles before and after four weeks' corticosteroid treatment in 12 stable asthmatics (8 men and 4 women; mean age $43 \pm \text{SD } 13$ years; mean FEV_1 , $69.2 \pm \text{SD } 20.1\%$ of predicted). Enteric-coated prednisolone, 15 mg daily for two weeks and then 30 mg daily for two weeks, was given orally as a supplement to the patients' usual bronchodilator therapy. FEV_1 and PEFr improved significantly ($p < 0.05$ Wilcoxon matched-pairs test); cough frequency decreased significantly ($p < 0.05$) and five patients who were initially sputum producers (mean 1.1 g/h) ceased to produce sputum after treatment. Regional mucus clearance was assessed by a newly introduced method (Agnew *et al.* In: Raymond C, ed. *Nuclear medicine and biology*, Paris: Pergamon, 1982: 2533), in which the distribution of inhaled ^{81m}Kr gas is used to assess the distribution of aerosol alveolar deposition so that clearance can be calculated relative to the amount of aerosol deposited on the ciliated airways. Clearance from inner and intermediate lung zones improved slightly despite a small increase in radioaerosol penetration and despite the reduced cough frequency. Peripheral zone clearance improved significantly ($p < 0.01$).

Erythromycin as a prophylactic agent in chronic bronchitis

G ANDERSON, ET PEEL, HV THOMAS Acute infective exacerbations of chronic bronchitis cause considerable morbidity and mortality each winter, and many lost days from work. Prophylaxis of such acute attacks would reduce suffering and make economic savings. We report a study, carried out over two winters, of the prophylactic effect of erythromycin on acute exacerbations of chronic bronchitis. In the first winter (study 1) 24 patients with chronic bronchitis (MRC criteria) were randomly allocated to take erythromycin stearate 500 mg or identical placebo for a continuous period of two months from 1 November 1979 to 31 December 1979. In the second study 35 different chronic bronchitics were similarly allocated for a three-month period from 1 December 1981 to 28 February 1982. In both studies patients were given an emergency supply of antibiotic (ampicillin or co-trimoxazole) to take for five days and an acute exacerbation was defined as the necessity to use this emergency supply. Patients recorded their chest infections and morning peak expiratory flow rate (PEFR) on a diary card. Fifty-nine patients entered the study. One on placebo and one on erythromycin died of acute infections during the study; the rest completed it.

Among the 32 receiving erythromycin there were 36 exacerbations—that is, 1.13 exacerbations per patient. There were 47 exacerbations among the 27 placebo patients (1.74 per patient). These represent a significant difference ($p < 0.05$). There was no change in the mean peak flow readings of either group. We conclude that erythromycin does have a prophylactic effect against acute infective exacerbations of chronic bronchitis.

Nocturnal hypoxia in obese women

MCP APPS, PG KOPELMAN DW EMPEY Sleep apnoea and nocturnal hypoxia occur in obese men, but are said not to occur in obese women. Some women who are obese have evidence of a hypothalamic disorder of prolactin, with no increase in response to insulin hypoglycaemia (non-responder, obese NR); others increase prolactin secretion with insulin hypoglycaemia (responder, obese R). We studied six obese NR (mean age 25, mean weight 110 ± 9 kg) and five obese R women (mean age 30, mean weight 96 ± 10 kg). They were observed during sleep for two nights. Airflow at nose and mouth was sensed with thermistors and movement of the chest and abdomen with inductance coils; oxygen saturation was measured with a Hewlett Packard ear lobe oximeter. Sleep staging was by standard methods. There were no apnoeic episodes in any woman. In the obese NR women mean Sao_2 was 97% awake, 94.5% asleep. There were episodes of desaturation during sleep, range Sao_2 84–90%, time $\text{Sao}_2 \leq 90\%$ 10 s—65 min. In the obese R women mean awake Sao_2 was 98%, asleep 95.5%. There were episodes of desaturation, range Sao_2 92–94%. Periods of hypoxia occur during sleep in obese women. The finding of a greater fall in Sao_2 in the obese NR women suggests that central factors may be involved.

Pneumococcal bacteraemia at Central Middlesex Hospital November 1981–March 1982

RA BANKS, RC GEORGE, MW MCNICOL During the winter of 1981–2 the number of positive blood cultures yielding *Streptococcus pneumoniae* represented an increase of 120% when compared with the mean for the preceding three winters. Sixteen patients had pneumococcal bacteraemia; two (aged 34 and 49 years) had meningitis and normal chest radiographs. Detailed data are presented from 14 patients (aged 35–92, mean 66 years) with radiological evidence of consolidation. Pre-existing respiratory or cardiac disease, or both, was present in 50%; four patients also had diabetes mellitus. Blood urea was initially raised in 11 patients and in the majority of the

survivors was probably due to dehydration. Four patients died, all within 72 hours of presentation; in three, with pre-existing disease, radiological evidence of consolidation was limited to one lobe. The highest blood urea concentrations and highest and lowest white blood cell counts were seen among the non-survivors. Sputum culture or counter-current immunoelectrophoresis, or both, of urine for pneumococcal antigen, performed in 12 patients, yielded positive results in only seven. Type 3 was the commonest serotype but all the isolates are represented in a commercially available vaccine. Pneumococcal bacteraemia is increasingly recognised (Young SE. *J Infect* 1982;5:19–26). Vaccination should be considered for patients with chronic illness.

Is disodium cromoglycate effective in asthma because it affects responses to platelet-activating factor (PAF-acether)?

GS BASRAN, CP PAGE, W PAUL, J MORLEY Disodium cromoglycate (DSCG) inhibits both immediate and late-onset airways obstruction induced by allergen inhalation. Inhibition of the late-onset response is assumed to be due to the capacity of DSCG to reduce airways hyperreactivity (Altounyan R. *Clin Allergy* 1980;10, suppl: 481–9). PAF-acether induces a biphasic inflammatory response in human skin, with a time-course reminiscent of allergen-induced responses (Basran GS, *et al. Thorax* 1982;37:787). We have therefore studied the effect of DSCG on PAF-acether-induced cutaneous responses. The study was performed in eight healthy volunteers (aged 20–32), who gave their informed consent. Wheal responses were induced by intradermal injection of PAF-acether (100 ng) alone or admixed with DSCG (250 µg). Flare and wheal areas were measured at 5 and 12 minutes respectively (immediate response) and then the injection areas were observed at intervals over the next 24 hours. In all eight subjects PAF-acether induced an immediate wheal-and-flare response, which resolved completely within 1 hour. In six of the subjects the immediate response was succeeded by an erythematous response, associated with hyperalgesia, around three hours after the PAF-acether injection. In all eight subjects DSCG significantly reduced the immediate wheal-and-flare response (37% and 63% inhibition; $p < 0.001$). Moreover, in the six subjects showing a delayed response to PAF-acether alone, there was no delayed response at sites treated with PAF-acether plus DSCG. These results suggest that DSCG may owe its therapeutic efficacy in asthma to its inhibitory effects on PAF-acether.

Tracheobronchial clearance during recovery from acute severe asthma

JRM BATEMAN, SP NEWMAN, NF SHEAHAN, D PAVIA, SW CLARKE Although tracheal mucus velocity is impaired in asymptomatic asthma and is further reduced after exposure to specific antigen (Mezey *et al. Am Rev Respir Dis* 1978;118:677–84), the effect on mucus clearance of an acute asthmatic attack is unknown. Using the *in vivo* radioaerosol technique (Thomson, Short. *J Appl Physiol*

1969;26:535–9), we have measured tracheobronchial clearance in seven patients (mean (\pm SEM) age 36 \pm 8 years) admitted to hospital with acute severe asthma. Three studies were performed, (1) 1–5 days, (2) 12–16 days, and (3) 2–4 months after admission. The results have been compared with those obtained from a control group of 21 healthy subjects (mean (\pm SEM) age 41 \pm 4 years), who inhaled the radioaerosol rapidly in order to attain a similar deposition pattern. Although lung function significantly ($P < 0.01$) increased in the asthmatic group after treatment with systemic corticosteroids and bronchodilators, alveolar deposition of radioaerosol was unchanged, and was similar to that in the control group. The mean (\pm SEM) tracheobronchial clearance of radioaerosol after 6 hours was similar in all three studies for the asthmatics—(1) 58 \pm 9%, (2) 52 \pm 8%, and (3) 61 \pm 9%—but was significantly increased in the control group (89 \pm 3%, $p < 0.01$). Mucociliary function is therefore impaired in acute severe asthma, and remains so over the subsequent two to four months.

Methacholine provocation tests in grain workers

AD BLAINEY, MJS COE, S OLLIER, RJ DAVIES Pulmonary disease resulting from grain dust has been recognised for many years, though its exact nature remains disputed. Asthmatic-type reactions following acute exposure to grain dust have been reported in both grain workers with symptomatic disease and normal subjects. The relationship between non-specific bronchial hyperreactivity and symptoms induced by grain dust remains unknown. We performed methacholine inhalational challenge testing on site in workers employed at a dockside grain storage facility. One hundred and thirty-three volunteer subjects (95% of the work force) participated in the study, and methacholine challenge was performed in 117. Sixteen were excluded because of severe pre-existing airways obstruction or intercurrent illness. A provocation concentration of methacholine producing a 20% fall in FEV_1 (PC_{20} — FEV_1) of greater than 10 mg ml⁻¹ (normal) was found in 75 subjects (64%) and a PC_{20} — FEV_1 of less than 2.5 mg ml⁻¹ (usually associated with symptomatic asthma) in 27 (23%). Age, duration of employment, smoking history, and atopic state did not differ significantly between these two groups but regular attacks of coughing, wheezing, and shortness of breath were significantly more frequent in those with a $PC_{20} < 2.5$ mg ml⁻¹ ($p < 0.02$), as were respiratory symptoms related to grain dust exposure that improved at weekends and holidays ($p < 0.05$).

Relationship between exercise tolerance, lung function, and mood in chronic airways obstruction

HA BOOKER, DJ HARRIES, JV COLLINS The mental state of patients disabled by breathlessness due to severe airways obstruction could be an important factor in determining their exercise tolerance. To see how anxiety and depression correlated with exercise tolerance and breathlessness we studied 103 patients with chronic airways obstruction. All patients had lung function tests, a standard question-

naire on anxiety and depression and two six-minute walking tests (6MWT) with Borg and visual analogue scales to rate perceived exertion and breathlessness respectively. Neither depression nor anxiety correlated significantly with the patients' perception of their breathlessness, with their assessment of the difficulty of the exercise task, or with any lung function indices. Those patients with bronchitis showed significant correlations between 6MWT and depression ($p < 0.01$) and between 6MWT and anxiety ($p < 0.001$) while there were no such significant correlations in the emphysema patients. We concluded that patients' beliefs concerning their own capabilities, their perception of their degree of breathlessness, and any mood disturbances must be considered in the assessment of their disability. These factors may be independent of clinical signs and lung function but will be of major importance in determining the patient's mobility and motivation, particularly in those with bronchitis.

Lung epithelial permeability changes after breathing a fine mist of distilled water but not after breathing cold air

C BORLAND, A CHAMBERLAIN, B MINTY, D ROYSTON, TIM HIGENBOTTAM The effect of distilled water fog and cold air on the lung epithelial permeability of nine non-smoking, non-asthmatic subjects was studied. Five of them also received normal saline fog. Subjects tidally breathed 80 litres from a Devilbiss 65 ultrasonic nebuliser for the fog challenge. They hyperventilated for three minutes from an adapted deep freeze for the cold air. Lung permeability was estimated as the clearance half time of ^{99m}Tc -DTPA from the lung (Jones JG, Minty BD, Royston D. *Br J Anaesth* 1982;54:705-21). No significant change occurred in FEV_1 . Mean net water gain (fog) = 6.3 ml. Mean net water loss (cold air) = 4.33 ml. Mean respiratory heat exchange (cold air) = -1.27 kcal/min. Challenges were compared by the paired t test. For distilled water fog clearance half time decreased by a mean of 22.4 minutes ($p < 0.05$). For cold air a decrease of 8.4 minutes (NS) and normal saline 0.66 minutes (NS) was observed. We conclude that distilled water fog increases lung permeability by an osmotic effect. Cold air has little or no effect. Cold air or fog provocation provides a rapid means of diagnosing asthma. Our observations indicate a difference in mode of action in normal subjects which may be relevant to the way in which these challenges provoke asthma. An increase in permeability arising during a therapeutic dose of ultrasonic nebulisers could be hazardous.

Effect on lung function of changes in intra-abdominal volume

A BUSH, A PEACOCK, J GABRIEL, DM DENISON In Britain one in five patients on dialysis uses continuous ambulatory peritoneal exchange. This requires frequent instillation and drainage of some two litres of fluid. We have examined the effects of this procedure on the respired and absolute lung volumes and carbon monoxide transfer characteristics in 20 patients undergoing such exchanges. Eighteen of the patients had no history of previous lung disease. The

changes seen on instilling 2.2 litres were: FEV_1 -0.1%; FVC -0.3%; TLC -1.1%; RV -7.4%; DLCO -2.5% (all expressed as % predicted values). None of these changes or the other derived values were statistically significant. We conclude that these aspects of lung function are insensitive to a two-litre change in abdominal volume. This was true even in the two patients with known lung disease, suggesting that this form of treatment could be extended to patients with respiratory disorders, to whom it is at present denied.

Route of antigen penetration of the respiratory membrane in sensitised rats

F CARSWELL, J MORRISSEY A rat model has been developed to study the immediate hypersensitivity reaction of the lungs to inhaled antigen (Carswell F, Oliver J. *Immunology* 1978;34:465-70). This reaction, which is analogous to the immediate reaction of asthmatic patients, involves IgE, mast cells, and nerves. Rats were exposed to an aerosol of the antigen (DNP, ovalbumin) containing ^3H -tritiated DNP for 10 minutes. The lungs and trachea were rapidly fixed by vascular perfusion with buffered glutaraldehyde. Tracheal sections had 12 mast cells/mm trachea, 15% of which were located in the respiratory epithelium. Autoradiography demonstrated that more antigen is taken up by the respiratory epithelium of the peripheral lung or trachea of sensitised than unsensitised rats. Statistical analysis shows a highly significant localisation of the radioactive antigen to the intercellular boundaries of the epithelium. Electron microscopy suggested possibly less "tight" intraepithelial junctions in sensitised rats after challenge. Our results provide substantial support for the belief that antigen penetrates the normally tight intraepithelial junctions and passes along the intercellular boundaries when a sensitised subject is challenged via the airways.

Acupuncture point stimulation in bronchial asthma

SS CHU, SJ PEARCE In China electrical stimulation of acupuncture points is now widely used in management of asthma. To assess its effectiveness stimulation at the asthma points Ding Chuan, which are 2 cm on either side of the lower border of the 7th cervical spinous process, was compared with stimulation at the more lateral backache/mastitis points Jian Jing in a randomised double-blind cross-over trial; the subjects were nine adult volunteers with reversible airflow obstruction. Stimulation on two occasions a week apart was for 30 minutes with 0.5 v at 1.5 Hz, wire electrodes without jelly being used. The mean initial FEV_1 was 1.74l (56% predicted). Over the subsequent two hours there was no increase in FEV_1 after acupuncture stimulation at either site but the response to inhaled salbutamol was greater after active than control treatment ($p < 0.01$). For the week following stimulation the mean of three daily expiratory peak flows (PEFR) and the number of salbutamol inhalations did not on average differ between treatments. Thus electrical stimulation of the asthma relief points Ding Chuan may potentiate the

bronchodilator effect of salbutamol. This new observation merits further investigation.

Bronchial challenge: effect on regional lung function

HW CLAGUE, D AHMAD, MJ CHAMBERLAIN, WKC MORGAN, S VINITSKI Airway response during bronchial challenge is invariably documented by changes in ventilatory capacity but such tests give little information on the changes in regional lung function. We have studied regional ventilation and aerosol deposition in eight adult subjects before and after bronchial provocation with inhaled histamine to investigate whether alterations in airway calibre are important to subsequent aerosol delivery. Ventilation and aerosol deposition studies were performed in the sitting position using ^{133}Xe gas and $^{99\text{m}}\text{Tc}$ -sulphur colloid respectively. Prior to the administration of histamine radioaerosol scintiscans were abnormal in five subjects only, but following bronchoprovocation all subjects had abnormal scintiscans and showed significantly greater central deposition of radioaerosol. The decrease in aerosol penetrance was related to the percentage decrement in FEV_1 , indicating that the efficiency of aerodynamic filtration is dependent on the degree of airway narrowing. In addition, in six subjects the distribution of ventilation changed from predominantly basal to predominantly apical, suggesting that the airways response was greatest, at least initially, in the best-ventilated regions. This suggests a close relationship between regional ventilation and the site of deposition of histamine and may have implications for the delivery of aerosolised agents in general.

Fate of a standard dose of respirator solution

MICHELLE CLAY, D PAVIA, SP NEWMAN, SW CLARKE It is well known that only a small proportion of a nebulised aerosol reaches a patient's lung and this has caused criticism of this form of therapy. We therefore followed the course of nebulisation to partition the distribution of the dose. A standard dose, 0.5 ml (5 mg) of terbutaline (Bricanyl respirator solution) in 1.5 ml saline, was placed in five each of the Turret, Acorn, Upmist, and Inspiron mini-neb jet nebulisers. Nebulisation was performed at flow rates of 8 and 6 l/min until no further aerosol was produced. Both volume and concentration of solution remaining in the nebulisers were measured and amounted to 40–67% of the original dose. Of the aerosol nebulised, containing 33–60% of the dose, allowance was made for (1) the proportion of aerosol comprising droplets too large to be of therapeutic value ($> 10\mu\text{m}$) and (2) aerosol generated during exhalation ($> 50\%$). A maximum of 32% and 27% for flow rates of 8 and 6 l/min is available from the Turret, 20% and 18% from the Acorn, 20% and 15% from the Upmist, and 16% and 12% from the Inspiron mini-neb. There is almost a twofold difference in the quantity of drug available to the patient from the different makes of nebuliser.

Two-dimensional echocardiography in the preoperative assessment of patients with carcinoma of the bronchus

PA CORRIS, K JENNINGS, E NEVILLE, GN MORRITT, GJ GIBSON Cardiac invasion by tumour may prevent successful resection of bronchial carcinoma and its presence may not be recognised preoperatively. In a retrospective analysis of 100 consecutive thoracotomies unexpected cardiac involvement was found in nine cases and in six the tumour proved non-resectable. A prospective study was therefore carried out to assess the value of two-dimensional (2-D) echocardiography in diagnosing occult cardiac invasion. Forty-one patients with no clinical, radiographic, or ECG evidence of cardiac involvement had 2-D echocardiograms performed prior to planned thoracotomy and these were interpreted without knowledge of subsequent findings. In three cases the echocardiogram was of insufficient quality for a definitive report to be made. Five echocardiograms were interpreted as showing evidence of cardiac invasion (one pericardial, four left atrial). The extent and site of tumour invasion was confirmed at operation in three of the patients and at necropsy in one who died before surgery could be performed. In the fifth case the echocardiogram was thought to show left atrial involvement but this was not confirmed at operation. In all 33 patients whose echocardiograms were interpreted as showing no evidence of cardiac invasion this finding was confirmed at operation. The results suggest that 2-D echocardiography is a sensitive non-invasive method of excluding cardiac involvement in patients with carcinoma of the bronchus.

The abdominal electromyogram as an objective measure of cough intensity

ID COX, RCA OSMAN, DTD HUGHES, DW EMPEY In the study of cough the use of citric acid aerosols to stimulate coughing is widespread but the methods of defining a response have often been unsatisfactory, largely owing to lack of objectivity. Though attempts have been made to quantify cough, none has incorporated a measure of its intensity. Using abdominal muscle electromyograms (EMG) recorded from stick-on surface electrodes, we have developed a measure for an individual's cough that is objective in that the signals cannot be confused with other manoeuvres of the subject. They also give a measure of the intensity of the cough recorded. Simultaneous recordings of flow and volume have been performed during the recording of abdominal EMGs during 50 coughs in 10 subjects. There is good correlation between the peak of the flow and the peak of the filtered EMG (correlation coefficient 0.63) and also between the integrated EMG and the volume of the cough (correlation coefficient 0.79). Our results suggest that integrated abdominal EMG gives a valid and objective measurement of cough and also incorporates a value of the intensity of each cough. These results could be used to develop dose-response curves in the study of coughs.

Efficacy of inhaled methylxanthines as bronchodilators in asthma

MJ CUSHLEY, ST HOLGATE Methylxanthines are effective bronchodilators in asthma when given orally or parenterally but their efficacy by inhalation has not been established. In a randomised blind study, eight subjects with severe asthma (FEV_1 1.3 ± 0.1 l, $sGaw$ 0.4 ± 0.05 s⁻¹ kPa⁻¹, mean \pm SEM) inhaled on separate days the maximum tolerated concentrations of theophylline (Th 10 mg/ml), glycine theophyllinate (GTh 50 mg/ml), aminophylline (ATh 50 mg/ml), and diprophylline (DPr 125 mg/ml). The drugs were nebulised for 10 minutes and measurements of FEV_1 and $sGaw$ made at intervals for 30 minutes. The additional airway response to 200 μ g of inhaled salbutamol was then recorded. All four methylxanthines had an unpleasant, bitter taste. Salbutamol alone produced maximum increases from baseline of $45 \pm 9\%$ for FEV_1 and $157 \pm 24\%$ for $sGaw$. Th, GTh, ATh, and DPr all caused significant bronchodilatation ($p < 0.05$) with maximum increases of 17 ± 5 , 14 ± 5 , 16 ± 7 , and $27 \pm 3\%$ for FEV_1 and 37 ± 8 , 50 ± 15 , 71 ± 9 , and $56 \pm 14\%$ for $sGaw$ respectively. Peak bronchodilatation occurred within five minutes and, with the exception of DPr, this was not sustained beyond 25 minutes. Following the methylxanthines salbutamol produced a further increase in FEV_1 and $sGaw$ of $47 \pm 9\%$ and $175 \pm 30\%$ —not significantly different from the values obtained with salbutamol alone. Thus methylxanthines, at the doses administered, are effective bronchodilators by inhalation, but they are unpalatable and are considerably less potent than salbutamol.

Ultrastructure of bronchoalveolar lavage cells in pulmonary sarcoidosis

C DANIEL, A DEWAR, B CORRIN, M TURNER-WARWICK, J CHRETIEN To determine whether ultrastructural changes in mononuclear cells previously described in tissue granulomas are also evident in cells lavaged from the lung, lavage cells from 28 sarcoidosis patients were compared with lavage cells from 17 control subjects and with tissue granulomas from five sarcoid patients. Interactions between mononuclear phagocytes, especially subplasmalemmal linear densities, and between these cells and lymphocytes were observed in both the tissue granulomas and lavage specimens. Fully developed epithelioid cells were not identified in lavage specimens, but differences were nevertheless found between the lavage cells from sarcoidosis patients and control subjects: in particular, alveolar macrophages in sarcoidosis were larger and showed well-developed pseudopodia, marked polarity, less nuclear heterochromatin, and cytoplasmic granules which were larger and more numerous but less electron dense than normal. Lymphocytes were also enlarged and contained more lysosomes. It is concluded that, although there are only a few similarities between the cells of the granuloma and those obtained by bronchoalveolar lavage in sarcoidosis, there are noticeable differences between the lavage cells of sarcoidosis patients and of control subjects. In

sarcoidosis many of the lavage cells appear to be "activated" morphologically.

Why measure plasma theophylline levels?

PDO DAVIES, IA CAMPBELL, AG FENNERTY Nearly all reports published on slow-release theophylline preparations advocate measurement of plasma levels in order to achieve the "therapeutic range," 10–20 μ g/ml. A review of 70 papers of this literature reveals the following observations: (a) Many patients are unable to tolerate the side effects of theophylline in a "therapeutic range" of 10–20 μ g/ml. (b) Many patients are unable to tolerate side effects on doses less than 10 μ g/ml. (c) Some patients are able to tolerate levels above 20 μ g/ml. (d) The cost of each measurement is approximately £5. In a double-blind placebo-controlled crossover trial of slow-release theophylline conducted recently, seven patients achieved morning trough theophylline levels of 5–8 (mean 6.3) μ g/ml. With these levels they achieved 24% improvement in mean morning peak flow levels ($p < 0.01$). Other studies have also shown improvement in patients' airways obstruction with theophylline levels of 5–9 μ g/ml, though authors have tended to ignore this. In the same trial six of 27 patients initially started on the run-in period were unable to tolerate the theophylline with dosages insufficient to achieve plasma levels of above 10 μ g/ml. We suggest that therapeutic improvement is a better measure of satisfactory treatment than measurement of therapeutic levels. Indeed, determination to achieve a preconceived range of the latter can be counterproductive and may prevent a patient from benefiting from a potentially useful product.

Does the hyperventilation syndrome exist?

RICHARD DENT, DIANE YATES, TIM HIGENBOTTAM "Hyperventilation syndrome" is a term used to describe a symptom complex in which hypocarbia due to inappropriate overventilation is implicated. The symptoms may be multiple and include breathlessness and chest tightness (Evans, Lum. *Lancet* 1977; i:155–7). We present details of a group of 71 breathless patients referred from all over the country from October 1981 to July 1982 in whom the referring doctor had suspected hyperventilation. Of the 71 patients (30 male, 41 female; ages 14–59 years), 70% (50) gave a history compatible with a diagnosis of hyperventilation syndrome (Pincus. *Br J Hosp Med* 1978; 312–3). Fifty-five per cent were atopic (one or more positive prick tests) and 18% had a forced expiratory ratio of $< 75\%$ with significant improvement in function after bronchodilators. Peak expiratory flow charts showed excessive diurnal rhythm ($> 20\%$) in a further 14%. Three patients proved to have thyrotoxicosis. Appropriate treatment for the asthma or hyperthyroidism in 26 patients led to the disappearance of the original symptoms in all but two cases. The high percentage of patients with treatable underlying disease emphasises the need for careful assessment of "hyperventilators". Only 30% of this group were non-atopic and had no evidence of asthma or hyperthyroidism; the cause of their breathlessness remains unclear.

Retrospective analysis of patients with neurological respiratory failure treated with intermittent positive-pressure ventilation

JG DOUGLAS, GK CROMPTON, IWB GRANT Intermittent positive-pressure ventilation is now standard treatment for patients with severe respiratory failure associated with reversible neurological disease. The purpose of this retrospective study was to examine the indications for ventilation, management, and outcome in patients with neurological respiratory failure who required artificial ventilation in this unit over the 10 years 1972–81. Thirty-nine patients with neurological disease had presented with respiratory failure severe enough to need artificial ventilation, seven of whom required it on two occasions. The decision to undertake ventilation was usually based on a clinical impression of deteriorating respiratory effort and ineffective cough or inability to swallow (or both) because of pharyngeal paralysis. Ventilatory function tests and arterial blood gas studies were of limited value in assessing the need for ventilation. The most frequent complication was bronchopulmonary infection, which occurred in almost every patient, *Staphylococcus pyogenes* and *Pseudomonas pyocyanea* being the organisms most commonly isolated. In contrast, tracheostomy problems and pulmonary thromboembolism were infrequent, possibly reflecting a high standard of nursing care. Renal failure and hyponatraemia occurred in almost 25% of cases. Ten (25.6%) patients died during ventilation; eight of the deaths were attributable to the neurological disorder itself and only three to complications of intensive therapy.

Inhibition of antigen-induced bronchoconstriction in asthmatic subjects with disodium cromoglycate administered after antigen provocation

LS DUNLOP, NA MARTELLI, AF HENDERSON, JF COSTELLO Disodium cromoglycate inhibits the immediate allergic reaction in the lung when inhaled before antigen challenge, and Martelli and Usandivaras (*Thorax* 1977;32:684–90) showed that inhaled cromoglycate can inhibit the bronchoconstriction in progress after challenge with analgesics in analgesia-induced asthma. We investigated these observations further by studying the effect of inhaling cromoglycate shortly after antigen bronchial provocation challenge in atopic asthmatics. The bronchoconstriction observed in six patients with mild asthma, and monitored by measuring FEV₁, was significantly inhibited by two 20-mg capsules of cromoglycate inhaled two minutes after antigen provocation when compared with the effect of placebo capsules. There was no significant alteration in FEV₁ following inhalation of placebo or cromoglycate capsules alone, although two patients showed a slight bronchoconstrictor response to cromoglycate. It has been suggested that cromoglycate acts as a bronchodilator, but our results do not support this. Alternatively it may act on bronchial irritant receptors or have a direct effect on the bronchial muscle. Finally, there may be a sequential degranulation of mast cells and cromoglycate administered during antigen-induced bronchoconstriction prevents further degranulation. We conclude that inhalation of

cromoglycate after antigen challenge is effective in reducing the subsequent bronchoconstriction.

Immunological studies of antigen-induced late asthmatic reactions

SR DURHAM, TH LEE, TG MERRETT, JOSEPHINE MERRETT, MJ BROWN, R CAUSON, AB KAY We recently demonstrated that high-molecular-weight neutrophil chemotactic factor (NCF) was released into the circulation following the late phase as well as the early antigen-induced asthmatic responses and that the time course of appearance paralleled the fall in FEV₁. We now report that in four subjects studied there was also an increase in venous plasma histamine in both early-phase and late-phase reductions in FEV₁. Four asthmatics giving isolated immediate reactions had only a single early peak of histamine, with no further marked rises up to nine hours. In all subjects the time course of appearance of histamine and NCF was similar. We have also measured the concentrations of allergen-specific IgG₄ antibodies but have been unable to confirm the findings of Gwynn *et al* (*Lancet* 1982;i:254–6), who concluded that IgG₄ was associated with the late-phase response. There was no difference in the frequency of positive allergen-specific IgG₄ antibodies between those subjects who developed isolated early reactions and the patients who gave a dual response following bronchial provocation. These results, taken together with the lack of evidence of complement (C3 and C4) activation following the late-phase reaction, suggest that mast cell-associated mediators rather than immune complexes are involved in the pathogenesis of late reactions.

The larger bronchi in cryptogenic fibrosing alveolitis

C EDWARDS, A CARLILE In cryptogenic fibrosing alveolitis there is progressive effacement of distal air spaces by fibrous tissue, while at the same time bronchioles and smaller bronchi dilate. Eventually the characteristic end-stage "honeycomb lung" develops. Physiological measurements indicate restrictive and diffusion defects, and sometimes obstruction of small bronchi. The abnormalities relating to the periphery of the lung are so dramatic that little attention has been paid to the larger airways, even though casual observation of the major bronchi in such cases gives the impression of an increase in gland and muscle. A morphometric study of the main, lobar, and segmental bronchi in nine cases of fibrosing alveolitis is described. The quantity of gland was significantly higher than in a group of normal controls, and was similar to that of a group of chronic bronchitics. The quantity of muscle was also increased, with levels in the segmental bronchi higher than in the chronic bronchitics. The cause of these changes is uncertain, but it seems likely that they are due to proximal extension of repeated and persistent infection of the lung parenchyma.

The pathology of byssinosis

C EDWARDS, A CARLILE Although byssinosis affects many workers in the cotton industry, its pathology has only

recently been studied in detail. We present the postmortem findings in the hearts and lungs of 86 patients receiving industrial benefit for this condition. Morphometric analysis of the main, lobar, and segmental bronchi showed that the proportions of gland and muscle were increased. In over 60% of cases the lungs were normal on gross examination, and in the remainder there were varying degrees of panacinar and centrilobular emphysema. Microscopic changes in the lung parenchyma were non-specific, and no different from those to be expected in a group of patients exposed to a polluted industrial atmosphere. Ventricular weights did not suggest an increased incidence of pulmonary or systemic hypertension; there was no consistent alteration in the pulmonary vasculature. It is concluded that there are no characteristic parenchymal lesions in byssinosis. The bronchial changes are indistinguishable from those of chronic bronchitis.

Clinical experience with the oxygen concentrator

TW EVANS, JL WATERHOUSE, P HOWARD Patients with hypoxaemia and chronic airways obstruction derive benefit from long-term domiciliary oxygen therapy. The oxygen concentrator is the most economical method of delivering low-flow oxygen but has to be used for at least 15 hours per day to maintain clinical efficacy. Sixteen concentrators fitted with hidden time clocks have now been used for at least six months. Patients were visited by a technician every three months at home and were seen in between in the outpatient clinic. After six months patient usage averaged 11.6 hours per day against the recommended 15 hours. Two machines of one make were found, unknown to the patient, to be producing inadequate oxygen. Three other machines required preventive maintenance at the time of the home visit. Long-term domiciliary oxygen using the oxygen concentrator is an effective means of delivering low-flow oxygen but requires regular clinical and technical visits at not less than three monthly intervals.

Occupation and lung cancer in a naval dockyard area

MJB FAREBROTHER, RF HELLER, IM O'BRIEN, A AZZOPARDI, TP TELFER, M YOUNG Previous employment in a naval dockyard with occupational exposure to asbestos may predispose to lung cancer. A study was designed to see what proportion of the lung cancer found in a community in which a large part of the population has worked in a naval dockyard could be attributed to this occupational exposure. All the cases of lung cancer newly presenting over two years within two local authorities surrounding a large naval dockyard were matched with one or two controls from the same population newly presenting with other illnesses to the same doctors. Matching was performed according to age, sex, and cigarette smoking history. Detailed occupational histories were obtained by one observer. Twenty-three per cent of the 135 male lung cancer patients had worked in the dockyards compared with 28% of the 236 male controls: the length of employment was not significantly different, nor was any known exposure to asbestos. Employment in the naval dockyards was thus not

a major factor in the causation of lung cancer in this community. An unexpected finding was that nine of the cases and only two of the controls had worked in local cement works; this difference was significant ($p < 0.01$) and should be explored further.

Effects of virus infections on pulmonary mucociliary clearance in man

CS GARRARD, R LEVANDOWSKI, TR GERRITY, DB YEATES We have investigated pulmonary mucociliary clearance during the course of acute, naturally acquired upper respiratory tract infection in eight previously healthy volunteers. Measurements of tracheal mucus velocity (TMV) and whole lung mucociliary clearance of an inhaled 8- μ m (MMAD)^{99m}Tc-labelled Fe₂O₃ aerosol were made for 4-7 hours with a tracheal multidetector probe and a gamma camera. Viral cultures of throat washings yielded influenza A virus from four volunteers, rhinovirus from one, respiratory syncytial virus (RSV) from one, and no viral organisms from two. Clearance studies were performed within 48 hours of the onset of symptoms, at one week, and again at 12-16 weeks. TMV for the initial and one-week studies in the subject with rhinovirus and the two uninfected subjects were 5.3 ± 2.4 mm/min (mean \pm 1 SD) and fell within the normal range. TMV could not be measured in the four subjects with influenza, however, during the initial studies owing to complete absence of boluses of radioactivity moving up the trachea. Absence of boluses was still noted in two of these four influenza subjects at one week. The subject with RSV showed a low TMV of 2.0 mm/min initially and absence of boluses at one week. When boluses were absent the recorded frequency of cough was greatly increased. When normal TMV was observed cough was absent or rare. TMV in the four influenza subjects and the one RSV subject had returned to normal in the studies at 12-16 weeks (4.3 ± 1.2 mm/min). Whole-lung mucociliary clearance was measured in three of the four influenza subjects. Within 48 hours of the onset of symptoms the time for 50% whole-lung clearance (t₅₀) was prolonged (280 minutes) in one subject with less than three coughs per hour. In the other two subjects, who had more than three coughs per hour, t₅₀ was 112 and 120 minutes (within the normal range for our laboratory). At one week t₅₀ was prolonged to 244 and 194 minutes in the two subjects who coughed less than three times per hour and in the subject who coughed more than three times per hour t₅₀ was 30 minutes. Values for t₅₀ in all three influenza subjects had returned to normal by 12-16 weeks (112, 120, 86 minutes). Results indicate that influenza A and RSV infection disrupt normal tracheal transport and that mucus is removed by spontaneous coughing. In influenza subjects with frequent cough whole-lung mucociliary clearance was maintained at or above normal rates.

Assessment of "pulmonary oedema" in the critically ill

RJD GEORGE, RA BANKS, JF RIORDAN, MW McNICOL The critically ill hypoxic patient with radiological evidence of dif-

fuse pulmonary infiltration is common and presents problems in diagnosis and management. We studied 13 patients (mean age 51 years) with adult respiratory distress syndrome (ARDS), comparing provisional diagnoses based on examination, chest radiograph, and central venous pressure (CVP) with the diagnoses following measurement of pulmonary wedge pressure (PCWP) and cardiac output (Q) using a Swan-Ganz catheter. PCWP was predicted correctly in only two of the 13 patients. In six, serial measurements over 48 hours showed no constant relationship between CVP and PCWP. Eight out of nine patients with elevated CVPs had pulmonary hypertension (pulmonary artery end-diastolic pressure/PCWP gradient > 8 mm Hg) and all had septicaemia. Q was predicted correctly in six patients. In the remaining seven Q was underestimated in six, all of whom also had septicaemia. In nine of the 13 patients the main diagnoses were correct, but eight had additional significant haemodynamic abnormalities. Our findings suggest that an elevated CVP in these patients may reflect pulmonary hypertension due to hypoxaemia or sepsis rather than an adequate circulating blood volume. We conclude that in patients with adult respiratory distress syndrome errors in diagnosis and management will be made unless PCWP and Q are measured directly.

Premenstrual exacerbation of asthma

CJ GIBBS, II COUTTS, OC FINNEGAN, R LOCK, RJ WHITE Forty-nine (43%) out of 114 asthmatic women questioned observed a variation in their asthma during the menstrual cycle and in 37 the worsening occurred premenstrually. A second, more detailed questionnaire was sent to the same patients. Thirty-six of 91 responders reported premenstrual worsening and in 27 this occurred before most periods. Nearly all the asthmatics experienced some symptoms of premenstrual tension (PMT) but the asthmatics with premenstrual worsening did not have more premenstrual symptoms and there was no particular symptom related to the premenstrual deterioration. The group with premenstrual asthma did not take aspirin more frequently for PMT than the other group, nor did their use of the oral contraceptive pill differ. Serial peak flow measurements were made over three consecutive months. In some patients this deterioration was confirmed and the drop in peak flow was sometimes marked, whereas in others who had reported a deterioration in their asthma no change was detected. We conclude that worsening of asthma premenstrually is a common phenomenon, but whereas in some patients this exacerbation is due to increased airflow obstruction in others there may be a change in perception of their asthma.

Survey of physicians' attitudes to management of pulmonary sarcoidosis

GJ GIBSON A questionnaire was completed by 191 of 232 consultant members of the BTA on their usual practice in management of patients with pulmonary sarcoidosis and diffuse radiographic shadowing. For patients who had tri-

val or no respiratory symptoms at presentation only eight physicians would usually institute corticosteroid treatment on diagnosis. When the remaining physicians were asked about subsequent management of a patient who continued to have no respiratory symptoms, abnormal or deteriorating pulmonary function carried more weight than the chest radiograph in the decision to start treatment. Nevertheless, 29% of respondents would usually give steroids if the chest radiograph failed to improve after a period of observation, and the proportion rose to 69% if radiographic shadowing increased. The physicians' usual starting doses of prednisolone varied from 10 to 80 mg daily, with a mode of 30 mg; 80% aimed at a narrow dosage range for maintenance therapy, between 5 and 12.5 mg daily. The considerable variation in the management of patients whose respiratory symptoms do not "demand" early treatment reflects uncertainty as to whether treatment aimed at optimising the chest radiograph appearance improves long-term outcome. The research committee of the BTS has therefore set up a prospective study to address this problem.

Abnormalities of chest wall motion in patients with chronic airflow obstruction

JJ GILMARTIN, GJ GIBSON Indrawing of the lateral margin of the ribcage during inspiration is a common observation in patients with airflow obstruction, but other abnormalities of chest wall movement are less often recognised. We have studied 40 patients with varying degrees of chronic airways obstruction (FEV₁ 9–69% predicted) and hyperinflation (FRC 116–324% predicted). The patients were clinically stable outpatients but were otherwise unselected. Their chest movements were noted during clinical examination in the upright posture. Changes in anteroposterior (AP) diameters of ribcage (RC) and abdomen and lateral RC diameters at two levels were then measured using magnetometers during tidal breathing sitting and supine. Paradox was defined as a change in any diameter of opposite polarity to the simultaneous change in volume. Only five of the 40 patients had normal chest wall motion. Three main types of abnormality were found but 13 subjects had two or more patterns. Lateral paradox was present in 31 of the 40 and was recognised clinically in all except one. In the supine posture the degree of paradox was usually less. Eleven patients had paradox of RCAP and nine had abnormal abdominal motion. Neither of these was easily recognisable by observation. There were no significant differences in the severity of airways obstruction or hyperinflation between the groups of patients showing paradox and those with normal movements. Neither AP nor lateral RC displacement correlated with the severity of airflow obstruction or hyperinflation, but the larger the FRC (% predicted) the smaller the increase in abdominal AP diameter during tidal inspiration.

"Fog"-induced bronchoconstriction is inhibited by sodium cromoglycate but not lignocaine or ipratropium

DAVID GODDEN, SARAH JAMIESON, TIM HIGENBOTTAM The effect of ipratropium bromide, sodium cromoglycate, lig-

nocaine, and isotonic saline on the bronchial response to inhalation of ultrasonically nebulised distilled water was studied in a group of normal and asthmatic subjects. Each subject was studied on four occasions on separate days, in random order. A standard challenge, involving inhalation of increasing volumes of "fog"—from 10 to 80 litres—was performed following treatment with each agent. Ipratropium 1 mg and sodium cromoglycate 20 mg were administered by nebuliser. Lignocaine was applied by atomiser in a dose sufficient to anaesthetise the nasopharynx, and isotonic saline was similarly applied as a control. FEV₁ values before and after treatment and after each dose of fog were plotted against cumulative dose. The threshold dose for each challenge was taken as the point at which FEV₁ fell below the 95% confidence interval (Dunnett CN. *Biometrics* 1964;**31**:482–91). Cough frequency was recorded during each period of fog breathing, and was significantly higher in normal subjects than asthmatics. Bronchoconstriction did not occur in normal subjects and was significantly inhibited by sodium cromoglycate, but not lignocaine or ipratropium, in the asthmatic group. The results suggest that bronchoconstriction in response to fog inhalation may be a mast-cell-mediated phenomenon. Ipratropium lessened cough in normal subjects but this could have occurred by chance.

Failure of isoprenaline to stimulate human respiratory tract cilia in vitro

M GREENSTONE, P COLE Beta-agonists have been reported to accelerate pulmonary mucociliary transport in healthy subjects and patients with chronic airflow obstruction. It is not clear whether this is due to stimulation of cilia or alteration in the physicochemical properties of mucus. To determine whether β-agonists could stimulate human

Effects of isoprenaline sulphate in varying concentrations on tracheal ciliary beat frequency (CBF)

Mean CBF (Hz) ± SD	Control	Isoprenaline (mol/l)				
		10 ⁻⁸	10 ⁻⁷	10 ⁻⁶	10 ⁻⁵	10 ⁻⁴
"Fast"	13.52 ± 0.91	13.86 ± 0.81	14.07 ± 1.08	14.16 ± 0.49	14.38 ± 1.04	13.60 ± 0.91
"Random"	8.92 ± 1.03	8.68 ± 0.83	8.75 ± 0.76	8.89 ± 0.87	8.63 ± 0.82	10.11 ± 1.11

respiratory tract cilia, nasal cilia were obtained from 20 normal subjects by brushing the inferior turbinate. Nasal cilia are easily accessible and their beat frequency is a reflection of tracheal ciliary beat frequency (CBF) (Rutland *et al. Am Rev Respir Dis* 1982;**125**:100–5). CBF was measured at 37°C with a photometric method (Rutland *et al. Lancet* 1980;ii:564–5). Control samples were compared with those to which isoprenaline sulphate had been added in concentrations varying from 10⁻⁸ to 10⁻⁴ molar. For each specimen CBF was estimated on 10 vigorously beating cilia ("fast") and on 20 randomly selected cilia which included more slowly beating cilia ("random"). Comparison of control values with isoprenaline-treated cilia by analysis of variance showed that under these conditions isoprenaline

had no effect on human cilia in vitro, in contrast to the stimulatory effect reported in animal models (Verdugo *et al. J Appl Physiol* 1980;**48**:868–71). The implications of these findings are discussed.

Safer insertion of chest drains

JE HARVEY, JB BRISTOL Prepacked plastic cannulas with their own metal trocar (for example, Argyle) have become popular for the insertion of chest drains. Sudden penetration of the trocar is a recognised risk of using such an assembly and, although this has seldom been reported, the majority of intrathoracic and upper abdominal organs have at some time been penetrated (Walesby RK. *Br J Hosp Med* 1981;**25**:198–201). We have surveyed the current practice of respiratory physicians and thoracic surgeons in the Wessex and South-western Regional Health Authorities with regard to the insertion of chest drains. Out of 19 physicians and six surgeons (92% response), 18 used prepacked Argyle drains, though 14 expressed reservations about their use, chiefly with regard to the risk of overpenetration. Thoracic surgeons in particular were concerned about the hazards of an Argyle-type assembly and favoured the use of a Tudor Edward's trocar and cannula. After preliminary measurements of chest wall thickness in cadavers we have devised a guard for use with Argyle trocars, consisting of a stainless steel tube with a distal protective flange. Passed down the centre of the guard the trocar and cannula protrude 7 cm beyond the flange — a distance that can be varied by using molybdenum washers. Experience over 18 months with all grades of staff has shown that this guard makes for both easier and safer insertion of Argyle-type chest drains.

Effect of nifedipine on bronchoconstriction induced by inhalation of cold air

AF HENDERSON, RW HEATON, JF COSTELLO The effect of nifedipine (20 mg sublingually) on the bronchial response to cold air was studied in a group of eight asthmatics and a group of eight normal subjects. Eucapnic hyperventilation with dry, subfreezing air was performed for three minutes by each subject, with a minute volume of 30 × FEV₁ for normal subjects and half that for the asthmatics. In the normal subjects there was no difference in the falls in FEV₁ and sGaw produced by cold air inhalation on the placebo and nifedipine pretreatment days. In asthmatic subjects, however, significant protection with nifedipine was demonstrated. The maximum recorded fall in FEV₁ was reduced from 13 ± 2% (SEM) to 4 ± 2% (p < 0.005) and the maximum fall in sGaw was reduced from 35 ± 5% (SEM) to 17 ± 4% (p < 0.002). It is suggested that these results present further evidence for a different mechanism of response to cold air in asthmatic and normal subjects.

Primary malignancy of intrathoracic organs in young adults

MS HENDY, HR MATTHEWS, DE STABLEFORTH The subject of intrathoracic malignancy in young adults has received little

or no attention in the literature and the possibility of malignancy is not generally thought of when a young adult presents with chest symptoms. From January 1977 to April 1982 22 patients aged 15–40 years have been referred to one thoracic surgeon in a general hospital thoracic unit. Thirteen patients had common tumours of the lung and oesophagus, but nine had unusual tumours of the lung, pleura, thymus, trachea, and mediastinum. The tumours were adequately resectable in only five patients. Of the 22 patients, 13 are already dead and only one of these survived one year. Of the nine surviving patients, six have definite tumour and only three have any real possibility of long-term survival (14%). The average interval between the onset of symptoms and diagnosis was 8.3 months and there were several instances of delay in diagnosis. It is unlikely, however, that this had any effect on the ultimate prognosis, as the tumours appeared to be of a virulent nature. The occurrence of such cases, about one every three months, raises the question of whether the incidence is increasing in this age group.

Randomised study of intrapleural *Corynebacterium parvum* versus tetracycline for malignant pleural effusions

D HONEYBOURNE, BC LEAHY, SG BREAR, KB CARROLL, TB STRETTON, N THATCHER This study was designed to compare the effects of instillation of intrapleural *Corynebacterium parvum* or tetracycline in the palliative treatment of malignant pleural effusions due to primary or secondary lung tumours. Twenty-six patients were randomly allocated to one of two treatment groups. The effusion was aspirated to dryness and then 7 mg of *C parvum* in 20 ml of saline (group A) or 500 mg of tetracycline in 20 ml of saline (group B) was instilled. If the effusion recurred radiographically and caused symptoms of dyspnoea then it was reaspirated and the same treatment repeated. If the effusion then recurred again the treatment was deemed a failure. Success was defined as no recurrence of the effusion causing symptoms within one month of the last treatment. One patient in each group died before the one-month assessment could be made. There were 14 patients in group A, of whom success was established in 11 (79%), and 12 in group B, of whom seven were a success (58%). Pyrexia, nausea and vomiting, and chest pain were assessed in the two groups. The only difference between the groups seemed to be an almost invariable transient pyrexia in group A, which was uncommon in group B.

Immunological abnormalities and circulating endotoxin in bronchiectasis

MA HORAN, BC LEAHY, RA FOX, TB STRETTON Chronic bronchial suppurative has been found to be associated with raised immunoglobulin levels, circulating autoantibodies, and immune complexes. In order to investigate possible mechanisms for these abnormalities we have studied eight men and 16 women with bronchiectasis. Gram-negative organisms were found in the sputum of 23 of the subjects. Forty per cent (10 subjects) had elevation of immunoglobulin levels and 60% (15 subjects) had circulating

autoantibodies. Twenty-five per cent (six subjects) had both raised immunoglobulin levels and circulating autoantibodies. Eighty-eight per cent (21 subjects) had mild-to-moderate increases in the level of C-reactive protein. With the *Limulus* amoebocyte lysate test endotoxin was detected in 50% (12 subjects). Endotoxin was found only in patients with an immunological abnormality and was more likely to be detected in those with both elevated immunoglobulins and circulating autoantibodies. It is suggested that endotoxin may trigger the formation of autoantibodies and elevations of immunoglobulin levels in patients with bronchiectasis.

Comparison of four spirometers

ALE HUGHES, CA HUGHES, DTD HUGHES A comparative study was made of four spirometers — the Pulmonaire (P), Puritan-Bennett (PB), Vicatest (VT), and Vitalograph (VG). They were considered from the point of view of volume range and accuracy, linearity of volumetric calibration, accuracy of timing, activation volume, and inertia and resistance to air flow. A comparative biological calibration was performed by using 100 subjects covering a wide range of vital capacity. Linear regression analyses were made that could be used to convert and compare readings taken from the different spirometers. The accuracy of the reading charts and the convenience of use of each type of spirometer were also assessed. The PB and VG spirometers proved the easiest to operate and also had the most accurate chart paper and the lowest inertia and resistance to air flow. All except the PB had a linear volumetric calibration, but only the VG had a really accurate timing system. Activation volumes were difficult to compare since the method of activation varies between spirometers. The clinical comparison, however, revealed little difference between the vital capacity and FEV₁ recorded on the different spirometers. The regression analyses are presented and discussed. The PB and VG spirometers proved the most satisfactory, though their volume range was only 7 or 8 litres compared with 10 for the other two.

Deaths in patients with pulmonary tuberculosis notified in the Medical Research Council 1978–9 survey

MJ HUMPHRIES, SP BYFIELD, KM CITRON, JH DARBYSHIRE, W FOX, AJ NUNN A study has been made of the treatment of patients notified during the 1978–9 Medical Research Council tuberculosis survey in England and Wales. All adult patients of white or Indian subcontinent (Indian, Pakistani, or Bangladeshi) ethnic origin with previously untreated pulmonary tuberculosis but without an extrapulmonary lesion were selected for follow-up. A surprising finding was that 160 (12%) of the 1309 patients surveyed had died during their course of chemotherapy. Whereas 154 (15%) of the 1019 white patients died, only six (2%) of the 290 Indian subcontinent patients died. Of the 154 white patients, 47% died from tuberculosis according to their death certificates (part I) and 30% died with tuberculosis as a contributing factor (part II). The majority — namely, 69% of those who died from tuberculosis —

died in the first month. Further, 88% of the 154 deaths occurred in patients aged 55 years or more, approximately half dying from tuberculosis. Among patients with extensive disease radiographically, death from tuberculosis occurred in over 20%. Clearly, death from tuberculosis is still a problem in England and Wales.

Use of tyramine to probe pulmonary noradrenaline release in asthma

PW IND, AJI SCRIVEN, CT DOLLERY The contribution of the sympathetic nervous system to human bronchomotor tone is uncertain. Beta-receptor antagonists produce bronchoconstriction in asthmatics, suggesting sympathoadrenal tone; but circulating catecholamines are normal and β -receptor responsiveness is reduced. We have investigated neuronally released noradrenaline (NA) by incremental infusions of tyramine, an indirectly acting sympathomimetic. Six asthmatic subjects (five atopic, five male) aged 45 ± 4 years, FEV₁ 71 ± 7.0 , VC 89 ± 8.0 , and PEF_R $67 \pm 8.0\%$ predicted (mean \pm SEM), were studied. A 30-minute control saline infusion was followed by four 15-minute infusions of 5.0-30.0 $\mu\text{g}/\text{kg}/\text{min}$ tyramine. At the highest dose systolic blood pressure rose 31 ± 7.6 mm Hg, heart rate fell 13 ± 1.2 beats/min, and plasma NA (by double-isotope radioenzymatic assay) increased from 2.50 to 4.86 nmol/l. Mean plasma adrenaline, FEV₁, FVC, and PEF_R, however, did not change significantly. One subject became wheezy and her FEV₁ fell by 0.65 l during infusion of 30 $\mu\text{g}/\text{kg}/\text{min}$ tyramine. Salbutamol (200 μg) given intravenously increased heart rate by 17 ± 3 beats/min, and FEV₁, FVC, and PEF_R by 34%, 24%, and 32% respectively above the baseline. The failure of neuronally released NA, in concentrations great enough to raise the plasma level by 94%, to produce bronchodilatation argues against a major contribution of the sympathetic nervous system to final airway diameter in asthma.

Effect of the water-soluble gaseous fraction of tobacco smoke on phagocytosis and morphology of human peripheral blood neutrophils: comparison of normal and emphysematous subjects

PK JEFFERY, H ROMANO, D HUTCHISON, H BAUM Peripheral blood neutrophils were obtained from venous blood of nine normal individuals and 11 patients with emphysema. Leucocytes were separated with 6% dextran, resuspended in MEM, and incubated at 37°C for 120 minutes with either latex solution (0.22 μm or 1.1 μm IgG opsonised spheres) or a solution of the water-soluble gas fraction of tobacco smoke (WSGF), or both. Cells were then processed for and examined by electron microscopy. Comparison of normal and emphysematous subjects showed that (i) the mean numbers (about 52%) of cells which show evidence of phagocytosis are similar; (ii) the mean number of latex particles per cell is significantly higher in the emphysema group and there is a higher proportion than normal of cells with a high latex "load"; (iii) the numbers of intracellular lysosomal granules are similar; and (iv) there are no significant morphological differences. In normal subjects

WSGF (i) inhibited phagocytosis by 50%; (ii) did not alter either the mean number of latex spheres per cell or their normal frequency distribution; (iii) decreased the mean number of lysosomal granules per cell; (iv) caused a rounding of cells, loss of filopodia, and a three-fold increase in cell vesiculation. In emphysematous subjects WSGF (i) inhibited phagocytosis by 40%; (ii) decreased the mean number of latex spheres per cell and particularly of those cells with high latex "load"; (iii) decreased the mean number of lysosomal granules per cell to much the same extent as in the normal subjects; and (iv) caused similar morphological changes. When given alone latex decreased the mean number of lysosomes per cell; the effect was significantly greater in those peripheral blood neutrophils taken from patients with emphysema than in those from normal subjects. These results indicate there are basic differences in the phagocytic capabilities of peripheral blood neutrophils of normal and emphysematous subjects and in their responses to the water-soluble gaseous fraction of tobacco smoke.

Low-dose dihydrocodeine and breathlessness in chronic airflow obstruction

MA JOHNSON, AA WOODCOCK The acute administration of dihydrocodeine (1 mg/kg) to patients with chronic airflow limitation improved exercise tolerance and reduced breathlessness. Chronic administration of dihydrocodeine in similar dosage produced unacceptable side effects. We have therefore investigated a low-dose intermittent regimen for efficacy and side effects. Eighteen patients with severe breathlessness due to chronic airflow obstruction completed a randomised placebo-controlled double-blind cross-over trial to examine the effect of dihydrocodeine 15 mg on breathlessness, disability, and exercise tolerance. There were three periods of one week each. During the first two weeks patients were instructed to take dihydrocodeine 15 mg or placebo 30 minutes prior to exercise as required up to three times daily. During the third week patients received either dihydrocodeine or placebo on alternate days. During the weekly dihydrocodeine period patients were more mobile (daily pedometer distance increased by 16.8%) and less breathless (daily visual analogue score of breathlessness reduced by 17.8%). This benefit was confirmed by treadmill testing at the end of each treatment period, when maximum distance walked was 16.5% higher and breathlessness 11.8% less with dihydrocodeine than with placebo. Similar benefit in breathlessness occurred during alternate-day therapy. No adverse effects were encountered. Dihydrocodeine 15 mg 30 minutes prior to exercise offers significant benefit to this group of patients.

Effect of intermittent positive-pressure ventilation during exercise on endurance and inspiratory muscle function

MA JOHNSON, AA WOODCOCK, DM GEDDES Respiratory muscle fatigue has been implicated in respiratory failure. In order to assess the role of the respiratory muscles in limiting exercise tolerance we have studied six patients

with chronic airflow obstruction who performed exercise with and without intermittent positive-pressure ventilation (IPPV) supplied by the Bird ventilator. The patients exercised on a horizontal treadmill at 60% of a previously determined maximum work load. Maximum inspiratory (Pi max) and expiratory (Pe max) mouth pressures were measured before and immediately following exercise, which was continued to exhaustion. The Pi max was 36.3 cm H₂O at rest and fell by 27% following normal exercise. After exercise with IPPV the mean Pi max fell by only 13%. The IPPV increased the mean treadmill distance achieved by 9%. The patients with the greatest improvement in exercise tolerance with IPPV also showed the greatest improvement in postexercise Pi max. Pe max fell by 19% following normal exercise and this was not altered by IPPV. Inspiratory muscle fatigue may contribute to disability by limiting exercise tolerance.

Peak flow patterns in wheezy children

IDA JOHNSTON, HR ANDERSON, S PATEL Little is known about the patterns of peak expiratory flow rate (PEFR) among wheezy children in the community. We have therefore studied a group of 64 children with current or recent wheeze sampled from a cross-sectional survey of asthma in 5000 Croydon school children aged 9. Using a mini Wright peak flow meter, PEFR was measured at 8 am, 4 pm, and 9 pm for 12 days. Mean PEFR was below predicted normal in 73% and < 80% of predicted normal in 24%. A significant morning dip was seen in 41%. By cosinor analysis, 71% of the group reached the lowest point of their circadian PEFR rhythm between 12 midnight and 8 am, though in only 22% was the rhythm statistically significant. The amplitude of the rhythm as a percentage of the mean was $12.0 \pm 9.5\%$ (SD) for the group as a whole and $20.3 \pm 12.7\%$ for those with a significant rhythm. Variability irrespective of rhythm was measured for each day as the difference between the highest and lowest values as a percentage of the day's highest reading and as a percentage of the day's mean. Over the 12-day period the means for these indices of variability were $14.9 \pm 7.8\%$ and $17.9 \pm 10.1\%$ respectively. The timing of the rhythm is similar to that derived from hospital-based studies of adults, but the levels of variability seen are considerably lower.

Prevalence of asthma and rhinitis in a Sudanese community seasonally exposed to a potent airborne allergen (the "green nimitti" midge) *Cladotanytarsus lewisi*

AB KAY, CM UNA MACLEAN, AH WILKINSON, MO GAD EL RAB The period prevalence rates for asthma and rhinitis were studied in a Sudanese village close to the Nile (Kalakla), where the inhabitants are seasonally exposed to very large numbers of non-biting midges (the "green nimitti" midge, *Cladotanytarsus lewisi*—Diptera: Chironomidae). The results were compared with those in a control village some distance from the river where this midge nuisance does not occur. Of the 5262 persons

enumerated in Kalakla, 4.9% suffered from asthma compared with 3.2% of the 2634 in the control area. For allergic rhinitis the rates were 6.7% for Kalakla and 1.5% in the control town. The percentage of patients with the combination of asthma and allergic rhinitis was four times greater in the affected area. These differences were all highly statistically significant. The patient's own subjective assessment of provoking agents and the higher incidence of symptoms during the winter months (the "green nimitti" season) indicated that seasonal exposure to chironomids was a major aetiological factor in asthma and rhinitis in Kalakla. These epidemiological findings support previous immunological data which indicated that the "green nimitti" midge is a potent seasonal allergen, and that repeated exposure results in a very high incidence of allergic rhinitis as well as increasing significantly the indigenous asthmatic population.

Mediators of hypersensitivity, immunoglobulins, and eosinophils in atopic and non-atopic asthma

TH LEE, T NAGAKURA, MJ BROWN, R CAUSON, AB KAY Although the distinction between atopic and non-atopic bronchial asthma has long been emphasised, these two "types" of asthma have many features in common. We have measured several allergy associated variables in 28 skin-test-positive (atopic) and 25 skin-test-negative (non-atopic) asthmatic subjects. Seven of the atopic and six of the non-atopic asthmatics with exercise-induced asthma were subjected to a treadmill exercise task. Following this procedure both patient groups had comparable elevations in the concentrations of plasma histamine and serum high-molecular-weight neutrophil chemotactic factor (as assessed by Sephadex G-200 chromatography). There were no significant differences in the percentage of sputum eosinophils or in the concentrations of sputum IgE between the atopics and non-atopics, although in both groups these were considerably higher than those found in the sputum of a control population (young smokers with symptoms). There were also no differences in sputum or serum IgA, IgG, or IgM concentrations between atopic asthmatics, non-atopic asthmatics, and smokers. These findings support the view that (a) the release of mast-cell-associated mediators can be independent of the atopic state and (b) appreciable local IgE production and eosinophilia occur in the airways of non-atopic asthmatics.

Comparison of efficacy and adrenal suppression produced by alternate-day, daily, and twice-daily prednisolone regimens for chronic asthma

WAC McALLISTER, M HETZEL, P EMEREY, CR GOTHAM, JV COLINS The principal aim in the use of corticosteroid treatment is to find a balance between maximum therapeutic efficacy and minimum side effects. As hypothalamic pituitary adrenal suppression is diminished by an alternate-day regimen we compared it with two daily regimens to assess whether therapeutic efficacy could be maintained as well as reducing adrenal suppression. Ten chronic stable asthmatics on long-term prednisolone therapy were studied double blind during an alternate-day, a twice-daily, and a

daily regimen lasting three weeks each. With the help of placebo preparations the same number of tablets was administered twice daily and the total steroid received was the same throughout. Peak flow records and symptoms were recorded at home by the patient. At the end of each three-week period a clinical assessment was made and plasma prednisolone, plasma cortisol, and urinary free cortisols were measured over the treatment period (24 or 48 hours). Asthma was equally well controlled on all regimens. Adrenal suppression was least on alternate-day therapy, with low normal function on both days. Cortisol diurnal variation was not lost on daily therapy; however, continuous suppression occurred on twice-daily therapy. Chronic stable asthma can be controlled on alternate-day therapy with diminished risk of side effects. Twice daily treatment is unnecessary and more harmful.

Adverse prognostic factors in pneumonia

JT MACFARLANE In the Trent Region the mortality for adults (ages 12–79 years) admitted to hospital with pneumonia (excluding bronchopneumonia) is 16–20%. Factors associated with a poor prognosis in 127 consecutive adults hospitalised with pneumonia have been studied. The adverse effects of increasing age, co-existing disease, and the cause of the pneumonia have already been reported. In the history and physical examination only confusion, hypotension, and atrial fibrillation carried a poor prognosis. Leucopenia ($\leq 10000 \times 10^9/l$) and lymphopenia ($\leq 1000 \times 10^9/l$), a raised blood urea (≥ 7.0 mmol/l), hypoalbuminaemia (≤ 25 g/l), abnormal liver function test results, and hypoxia ($PaO_2 \leq 6.6$ kPa) were significantly commoner in patients who did badly. Adverse radiographic features included multilobe involvement and no improvement in the second radiograph taken after admission. The use of four criteria, including (a) confusion, (b) leucopenia or lymphopenia, (c) raised urea, and (d) hypoxia, appeared useful for identifying those patients on admission who subsequently did badly. Seventy-eight per cent (14/18) of patients who died had three or four of these factors, compared with 63% (15/24) of those who had a complicated course and 9% (7/75) of those who made an uncomplicated recovery. Only 19% of patients with three or four of the factors made an uncomplicated recovery, compared with 84% of those with less than three. The identification on admission of patients likely to do badly will help in their management.

An index of disproportionate disability in chronic bronchitis

GJR McHARDY, AD MORGAN, D BUCHANAN, DF PECK We have recently shown that exercise tolerance in chronic bronchitis is influenced by the attitudes and beliefs which patients hold concerning their illness. We have now derived an index of disproportionate disability from measurements of forced vital capacity (FVC) and distance walked in 12 minutes (12-MD) in 50 patients. The index was calculated by converting the values of FVC and 12-MD into standard scores related to the mean and stan-

dard deviation for each quantity. A constant was added to eliminate negative values. The transformed 12-MD scores were divided by the transformed FVC scores to obtain the index. An index more than 1 suggests that the subject was able to walk further than expected from the measurement of FVC and an index of less than 1 that the walking distance was low in relation to FVC. This index was significantly positively correlated with beliefs that treatment would be successful, would take much effort, or would be new. It was negatively correlated with age. A low value of the index was also significantly correlated with high scores for perceived exertion in the 12-MD test. The study emphasises that disproportionate breathlessness is best thought of as a continuum rather than a dichotomy and that a full assessment of psychological factors needs to be made in any assessment of disability.

Acute and chronic effects of pirbuterol on pulmonary and right ventricular haemodynamics in chronic hypoxic cor pulmonale

W MACNEE, CG WATHEN, QF XUE, WJ HANNAN, DC FLENNLEY Preliminary reports have suggested that pirbuterol a β_2 -sympathomimetic may improve cardiac function in cor pulmonale. To determine whether this was a result of pulmonary vasodilatation or a direct inotropic effect, we have compared the effects of intravenous sodium nitroprusside (SNP), a known vasodilator (dose range 1.5–5 mg/hour), with those of oral pirbuterol (22.5 mg) on pulmonary haemodynamics (measured by Swann-Ganz catheter), using gated equilibrium radionuclide angiography, in patients with chronic hypoxic cor pulmonale resulting from chronic bronchitis and emphysema (FEV_1 0.67 ± 0.13 l (\pm SD), PaO_2 7.08 ± 0.41 kPa, $Paco_2$ 6.6 ± 0.2 kPa). SNP reduced mean pulmonary artery pressure (PAP) by 16% without significant change in cardiac output or RVEF, resulting in a fall in PVR (407 \pm 49 dyn s cm^{-5} ; $p < 0.01$). After return to a stable state was achieved oral pirbuterol produced maximum effects 90 minutes thereafter, when heart rate had increased by 6%, blood pressure was unchanged, and mean PAP had fallen from a control value of 31 ± 2 to 26 ± 3 mm Hg ($p < 0.05$), with a rise in cardiac output (4.53 ± 0.26 to 5.47 ± 0.24 l/min; $p < 0.01$) resulting in a fall in PVR (407 ± 49 dyn s cm^{-5} ; $p < 0.01$). Initial RVEF was 0.45 ± 0.02 , which rose to 0.54 ± 0.03 90 minutes after pirbuterol, stroke volume (SV) also increasing from 52 ± 4 to 57 ± 4 ml ($p < 0.05$). Oral pirbuterol in a dose of 15 mg in six similar patients with chronic bronchitis and emphysema produced similar changes in PVR, RVEF, and SV. Nine of the above patients received oral pirbuterol 15 mg three times daily for six weeks, which produced a fall in PAP (43 ± 3 to 34 ± 2 mm Hg; $p < 0.05$) and the increase in RVEF shown acutely was sustained after six weeks' treatment with the drug (RVEF control 0.45 ± 0.02 , RVEF pirbuterol six weeks 0.52 ± 0.03 ; $p < 0.05$). Oral pirbuterol vasodilates the pulmonary circulation without increasing hypoxaemia in patients with chronic hypoxic cor pulmonale; but the increase in right ventricular ejection fraction may also be

mediated by an inotropic action. These acute effects are sustained after six weeks treatment with the drug.

Sniffs as a test of diaphragm function

J MILLER, J MOXHAM, M GREEN It is claimed that measurement of transdiaphragmatic pressure (Pdi) is the most accurate method of assessing diaphragm function. The manoeuvre most commonly used has been the maximum static inspiratory effort (PI Max), but De Troyer and Estenne (*Thorax* 1981;**36**:169) have shown that the range of normal values is unacceptably wide (18–137 cm H₂O). We aimed to confirm this normal range in a similar group of subjects and concurrently to evaluate the sniff as a test of diaphragm function. A group of untrained healthy subjects, mean age 31.4 years, with normal pulmonary function underwent transdiaphragmatic pressure measurements using oesophageal and gastric balloons during sniffing and PI Max. Subjects were asked to sniff maximally and sharply from FRC and encouraged until a plateau value of sniff Pdi was obtained. PI Max manoeuvres from residual volume against a closed shutter were performed repeatedly to reach a plateau. A conventional mouthpiece and noseclip were used and the pressures sustained for one second recorded. Our results confirm the wide normal range for Pdi PI Max (range 30–164 cm H₂O, mean \pm SD 102.4 \pm 37.7, n = 27) but in the same subjects sniff Pdi values were higher (p < 0.001) and the range narrower (range 94–168, mean \pm SD 133.9 \pm 23.4). The sniff is a spontaneous manoeuvre easily performed by subjects and readily repeatable without causing fatigue and it avoids mastering of noseclip and mouthpiece. It may have a practical role in the quantification of diaphragm function.

Effect of inhaled antihistamine and antiallergic drugs on plasma mediator levels during the immediate asthmatic reaction induced by allergen provocation

DJR MORGAN, D CUNDELL, I MOODLEY, RJ DAVIES Allergen-induced asthma has been reported to be associated with rises in circulating levels of histamine and neutrophil chemotactic factor (NCF). The prior administration of sodium cromoglycate (SCG) in some studies not only inhibited the asthma but also the rises in NCF. In this study 10 atopic asthmatic subjects were pretreated on four occasions in a double-blind fashion with either inhaled SCG, clemastine, ketotifen, or placebo. Thirty minutes later each subject underwent bronchial provocation testing (BPT) with the inhaled allergen to which they were sensitive; the dose of allergen was that which had previously been shown to induce a 20% fall in forced expiratory volume in one second (FEV₁). Venous plasma histamine was measured before and for one hour after BPT with the double-isotope radioenzymatic assay. No significant change in histamine levels was found at any time after BPT. Serum NCF was similarly monitored and measured by a modified Boyden technique. A significant rise in NCF, occurring at the time of maximum fall in FEV₁, was found in all groups (p < 0.02). The administration of SCG and ketotifen significantly inhibited the

immediate asthmatic reaction after BPT when compared with placebo (p < 0.005, p < 0.02), but no significant inhibition of NCF occurred in any of the groups. We conclude that there is no evidence from this study of circulating levels of histamine and NCF and the effect of drugs to support the hypothesis that mast-cell activation is important in the pathogenesis of allergen-induced asthmatic reactions in man.

Effect of aminophylline on human diaphragm and limb muscle contractility

J MOXHAM, J MILLER, CM WILES, D NEWHAM, RHT EDWARDS, M GREEN The contractile properties of the human diaphragm are similar to those of limb muscles: following inspiratory loading forces at low stimulation frequencies (< 30 Hz) can be reduced for prolonged periods (low-frequency fatigue) (Moxham J, *et al. Thorax* 1981;**36**:164–8). It has recently been reported that aminophylline at therapeutic concentrations can improve diaphragm contractility and reverse low-frequency fatigue in man (Aubier *et al. N Engl J Med* 1981;**305**:249–52). To investigate this further we have studied the effect of aminophylline on the contractile properties of both the human adductor pollicis muscle and the diaphragm. The adductor pollicis was studied in three normal subjects: aminophylline (6 mg/kg infused over 30 minutes) did not change maximum voluntary contraction force, twitch tension, the frequency:force curve, or relaxation rate and did not influence the development or resolution of low-frequency fatigue (mean theophylline level 14.2 mg/l, range 11.5–16.8 mg/l). To assess diaphragm contractility transdiaphragmatic pressure (Pdi) twitches in response to supramaximal stimulation of the right phrenic nerve were measured in four normal subjects before and during aminophylline infusion (6–7.5 mg/kg, mean level 13.8 mg/l, range 8.5–20.2 mg/l). Aminophylline did not increase twitch Pdi. Thus we have been unable to demonstrate any direct effect of aminophylline at therapeutic concentrations on the contractility of adductor pollicis or diaphragm in man.

Margination of human leucocytes in the lung: influence of exercise and catecholamines

AL MUIR, M CRUZ, B MARTIN, A BELZBERG, JC HOGG Microscopic studies have shown that leucocytes either circulate freely in the blood or appear to adhere to the vascular endothelium, from which they may re-enter the circulation in a process of continuous exchange. This "marginated pool" of cells in believed to play an important part in leucocyte kinetics and the lung is thought to be a major site. Recently endothelial damage by adherent neutrophils has been incriminated in the aetiology of the adult respiratory distress syndrome and also in the aetiology of emphysema. To determine the factors controlling demargination of leucocytes, we studied six normal subjects and showed that upright exercise caused a greater leucocytosis than supine exercise at the same work load (900 kpm/min). Although greater changes in heart rate and blood pressure

were produced by intravenous infusions of noradrenaline and isoprenaline (2 µg/min), the greatest leucocytosis was produced by adrenaline. When indium-111-labelled neutrophils were given to four normal subjects 20–25% were retained in the lung when compared with technetium-99m-labelled red blood cells. These retained white cells were subsequently released from the lungs and taken up by spleen and liver. The release from the lungs was increased by exercise and catecholamines and was associated with an increase in the total white count and indium-labelled white cells in the peripheral blood. Our observations suggest that the leucocytosis produced by exercise and catecholamines is not directly mediated by the sympathetic nervous system and we suggest that the increase is caused by an increased velocity of flow in pulmonary vessels, causing a decrease in the "marginating pool".

Exercise-induced late asthmatic reactions

T NAGAKURA, TH LEE, NIKI PAPAGEORGIOU, Y IIKURA, AB KAY Two adults and 13 children with exercise-induced asthma (EIA) gave late-phase in addition to immediate reductions in FEV₁ following treadmill exercise. The late reactions developed 4–10 hours after exercise and, in each instance, were associated with wheezing or chest tightness or both. Neutrophil chemotactic activity (NCA) was measured in the two adults and 11 of the children and in all these subjects the reductions in FEV₁ were accompanied by an increase in NCA. In contrast, a further four adults giving a single early fall in FEV₁ following exercise had only an initial elevation in NCA, with no subsequent increase for the remaining 24-hour period. The NCA released during exercise-induced early-phase and late-phase reactions appeared to be identical since (a) following gel filtration on Sephacryl S-400 both were associated with molecules of approximately 600 000 daltons; (b) both eluted as single peaks of activity following anion exchange chromatography on DEAE-Sephacel (0.15 mol NaCl, pH 8.1); and (c) both had an isoelectric point of 6.5 as determined by chromatofocusing on Polybuffer Exchanger 94. These observations suggest that certain individuals with EIA develop late-phase reactions, which, as in antigen-induced bronchoconstriction, are accompanied by the release of NCA.

Is there any place for a routine chest x-ray examination in a diabetic clinic?

E NEVILLE, WMG TUNBRIDGE There is a well-recognised association between pulmonary tuberculosis and diabetes mellitus. Modern management of both conditions necessitates reappraisal of the value of a routine chest x-ray examination in diabetes. A mass miniature radiograph (MMR) was performed on all diabetics attending the clinic in a three-month period. A large posteroanterior chest radiograph was obtained where clinically indicated. These two groups of radiographs were compared with radiographs requested selectively in the same three months of the preceding year. The results of radiographs on all new diabetic patients in a four-year period were also assessed.

Four hundred and twelve MMRs were obtained, of which 79 (19%) were abnormal. In the same period of time eight of 25 (32%) large films were abnormal, and in the preceding year nine of 63 (14%). MMR abnormalities included 29 (7%) with cardiomegaly due to hypertensive or ischaemic heart disease, 25 (6%) with evidence of old inactive tuberculosis, 13 (3%) showing pleural reactions, four (1%) which were interpreted as showing "tumours," four (1%) showing emphysema, two cases of interstitial fibrosis, and one each of hiatal hernia and retrosternal goitre. Two of the "tumours" were large pulmonary arteries, one was a longstanding pulmonary nodule, and one represented pre-symptomatic tuberculosis confirmed by percutaneous aspiration biopsy. Apart from this case, the MMR abnormality frequently caused further investigations but did not lead to alteration of a single patient's management. The useful return of this survey was one in 412 (0.2%) MMRs and even large chest radiographs were relatively unhelpful in clinical management. We do not recommend routine chest radiography in diabetic patients.

Do particle size and airway obstruction affect the deposition of pressurised inhalation aerosols?

SP NEWMAN, M KILLIP, D PAVIA, F MORÉN, SW CLARKE Particle size is probably the most important factor determining the deposition of stable particles inhaled during steady breathing. Little, however, is known about the deposition of different-sized particles released from pressurised metered dose inhalers (MDIs) and inhaled during a single breath. Particles of Teflon labelled with ^{99m}Tc, having a mass median aerodynamic diameter of 3.2 µm (geometric standard deviation (GSD) 1.2) or 6.4 µm (GSD 1.2), have been inhaled from MDIs in 26 studies in 20 patients with varying degrees of airway obstruction (FEV₁ 27–120% predicted). Whole-lung deposition was unchanged by the difference in particle size, being 13.9 ± 1.3 (mean ± SEM) % of the dose (n = 18) for the smaller particles and 12.8 ± 1.4% of the dose (n = 8) for the larger particles. Alveolar deposition was also similar for the two particle sizes (4.5 ± 0.6% and 3.6 ± 0.4% of the dose respectively). There was little relation between the results of tests of airway calibre (FEV₁, MMEF, PEFR, and Vmax25) and either whole-lung deposition or alveolar deposition. It is concluded that the particle size of pressurised aerosols may be less important than the size distribution of the propellant droplets released from the canisters, and that pressurised aerosols may penetrate to the lung periphery in patients with both mild and severe airway obstruction.

Evaluation of two transcutaneous carbon dioxide monitors

CG NICHOLL, JR STRADLING, D COVER, JMB HUGHES We have investigated the initial warm-up times, response times, and accuracy of the Radiometer Copenhagen (R-C) transcutaneous PCO₂ (PtCCO₂) electrode and the Hewlett-Packard (H-P) PtCCO₂ infrared sensor in normal subjects and patients. Both devices were used according to manufacturers' recommendations. The time taken to reach a steady reading following application to the skin was

recorded. In normal subjects the response times to step changes in end-tidal P_{CO_2} (P_{tCO_2}) were recorded. Steady-state comparisons were made between P_{tCO_2} and P_{aCO_2} (or P_{etCO_2} in normal subjects), $n = 111$ (R-C) and $n = 34$ (H-P). P_{tCO_2} correlated well with P_{aCO_2} and P_{etCO_2} (H-P, $r = 0.95$; R-C, $r = 0.95$); but the slopes and intercepts were different (H-P, $P_{tCO_2} = 0.94 \times P_{aCO_2} + 9.3$ mm Hg; R-C, $P_{tCO_2} = 1.39 \times P_{aCO_2} + 6.2$ mm Hg). Warm-up times were similar (normal subjects: H-P = $11.7 \pm SD 4.0$ min, R-C = $8.1 \pm SD 1.0$ min; patients: H-P = $17.2 \pm SD 6.4$ min, R-C = $15.4 \pm SD 6.0$ min). Full response to a step change in P_{etCO_2} was $6.5 \pm SD 1.7$ min for the H-P and $5.2 \pm SD 1.9$ min for the R-C. Abrasion of the skin, as recommended for the H-P, greatly improved the response time of the R-C. Both devices follow changes in P_{aCO_2} with accuracies and response times that are adequate for most clinical purposes. They represent a significant advance in non-invasive monitoring.

Effects of almitrine on interregional distribution of ventilation and perfusion in chronic bronchitis

P NUNN, YT WANG, M MYERS, JR STRADLING, JMB HUGHES Almitrine, a new respiratory stimulant, increases P_{aO_2} in chronic airflow obstruction apparently out of proportion to changes in ventilation or P_{aCO_2} . Rigaud *et al* (*Rev Franc Mal Resp* 1980;8:605-16) have shown striking changes in regional blood flow distribution, using lung scans, with improvement in regional ventilation-perfusion (\dot{V}_A/\dot{Q}) matching after almitrine. In this study six patients with chronic airflow obstruction (four male, two female; mean age 64 years; P_{aO_2} $6.9 \pm SD 0.95$ kPa, P_{aCO_2} $7.0 \pm SD 0.93$ kPa, FEV_1 $0.53 \pm SD 0.15$ l, VC $1.85 \pm SD 0.4$ l) were given almitrine bismesylate orally (3 mg/kg) or placebo on two days one week apart. Resting ventilation (impedance plethysmography (Respirace)), arterial oxygen saturation (S_{aO_2} , oximetry) and the regional distribution of ventilation, perfusion, and \dot{V}_A/\dot{Q} (inhalation and intravenous infusion of krypton-81m and intravenous injection of ^{99m}Tc -HSA macroaggregates) were measured with the subjects seated, by means of a gamma camera, before and 90 minutes after almitrine or placebo. The mean improvement in S_{aO_2} (+ 5.7) was greater after almitrine than after placebo (- 1.1). Minute ventilation decreased 20% after placebo but only 1% after almitrine and tidal volume decreased by 11% and 5% respectively. \dot{V}_A/\dot{Q} images were created by a computer but no significant difference between drug and placebo was found by visual inspection. In addition, the left lung was divided into 10 horizontal slices and regional \dot{V}_A/\dot{Q} computed. No significant difference between control, almitrine, and placebo was found using Student's paired *t* test. The average position of the left lung, derived from analysis of the picture element rows of the ventilation scans, was significantly higher after almitrine than after placebo (paired *t* test). Plots of $\log \dot{V}_A/\dot{Q}$ against fractional \dot{V} or \dot{Q} have so far shown no consistent changes after almitrine. We conclude that the redistribution of ventilation towards the upper zones after oral almitrine may lead to improved interregional \dot{V}_A/\dot{Q} matching.

Propranolol-lignocaine interaction in the lung

JA PANG, TR WILLIAMS, JP BLACKBURN, D HOLT Many drugs are concentrated by the lungs, especially after intravenous administration. This provides ample opportunity for drug interaction, which may lead to alterations in pharmacokinetics. We have previously shown that lung uptake of injected propranolol is enhanced by general anaesthetic agents. The possibility of interaction between propranolol and the local anaesthetic-antidysrhythmic drug lignocaine is investigated. Lung uptake of propranolol was measured by comparing the ratio of ^{14}C -propranolol (0.2 mg) to indocyanine green (1.875 mg) injected into the right atrium with the ratio of their concentrations in aortic blood collected over the duration of the first-pass dye outflow curve (Pang JA, *et al. J Appl Physiol* 1982;52:393-402). Measurements were made in three dogs before and during administration of lignocaine through a leg vein (100 mg bolus followed by 2 mg/kg/min infusion). The fraction of the injected dose of propranolol taken up after a single passage through the lungs was $52.5\% \pm SD 11.7\%$ ($n = 12$) before lignocaine, and $78.3\% \pm SD 9.9\%$ ($n = 14$) during lignocaine infusion ($p < 0.002$). This corresponded to a 37% reduction in the concentration of propranolol in the arterial sample (from 151.8 ± 43.6 to 96.1 ± 30.4 g/l). There was no significant change in resting cardiac output, mean PA pressure, P_{O_2} and P_{CO_2} during infusion of lignocaine, although mean aortic pressure fell from 123 ± 15 to 108 ± 7 mm Hg. We conclude that lignocaine increases single-pass lung uptake of propranolol, thereby reducing the arterial concentration of the injected beta-blocker. Drug interaction in the lungs may be an important but neglected consideration in therapeutics.

Neutrophil activation during exercise-induced asthma

NIKI PAPAGEORGIOU, TH LEE, MARY CARROLL, AB KAY We recently demonstrated that high-molecular-weight neutrophil chemotactic factor (NCF) was released into the circulation during exercise-induced asthma (EIA). Since chemotactic factors "activate" leucocytes in vitro, as shown by increased expression of surface membrane markers and release of lysosomal enzymes, we attempted to establish whether neutrophil activation occurs in vivo following EIA. Using the rosette technique we observed a time-dependent increase in the numbers of complement (C) (nine patients) and IgG(Fc) (four patients) neutrophil receptors following exercise. NCF peaked at 15 minutes whereas receptor increase was continuing even at 1 hour. In contrast, asthmatic subjects who did not develop EIA following the same exercise task had no significant increase in either C or IgG(Fc) rosettes. Prior administration of disodium cromoglycate (DSCG) to five patients with EIA inhibited both the increase in rosette formation and the elevation in NCF and the fall in peak flow. These studies suggest that neutrophils are activated following EIA and that these effects are inhibited by DSCG. These observations may have particular relevance to the inflammatory events associated with airways narrowing.

Food-induced asthmatic reactions

NIKI PAPAGEORGIOU, TH LEE, T NAGAKURA, DG WRAITH, AB KAY We have studied four atopic subjects (that is, skin-test positive to common inhalants) who gave convincing clinical histories of food-induced asthma. In three subjects cow's milk was incriminated, whereas one subject wheezed and had rhinitis following the ingestion of soya milk. All were skin-test and RAST negative to the foods in question. Following ingestion of the appropriate milk, under controlled conditions in a single-blind manner, each subject gave a reproducible and dose-dependent increase in airflow limitation. Three patients (cows' milk two and soya milk one) had immediate reactions, inhibitable with oral disodium cromoglycate (DSCG), which was associated with maximal decrease in PEFr approximately 30 minutes following food challenge. The fourth individual developed an isolated late reaction with maximal airways obstruction three hours after milk ingestion, which was blocked by prior administration of oral beclomethasone dipropionate but not DSCG. The wheeze in subjects with the early reactions was accompanied by a rise in the circulating neutrophil chemotactic activity (NCA), whereas these changes were not observed in the individual with the isolated late reaction. These observations indicate that controlled, objective measurements can be made in patients with food-induced asthma.

Azlocillin versus carbenicillin used in the treatment of bronchopulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis

ARL PENKETH, MARGARET E HODSON, H GAYA, JC BATTEN There are few randomised controlled trials of chemotherapy for pseudomonas infection in cystic fibrosis in the literature, and there is debate over the criteria for assessment of response. The usual features of infection—pyrexia, raised white cell count, or ESR, may not be present, and it is often difficult to see new changes on a chest radiograph which is already severely abnormal. *Pseudomonas* itself is never eradicated from the sputum for any length of time. We report a randomised comparative trial on azlocillin and gentamicin compared with carbenicillin and gentamicin in cystic fibrosis patients chronically infected with *Pseudomonas aeruginosa*. The clinical response was measured by respiratory function tests and patients assessed their own response on a visual analogue scale. The sputum penetration of antibiotics used was also studied. The 10 patients in each group were comparable in terms of age, sex, and respiratory function at entry to the trial. Both regimens produced significant improvement in respiratory function over 10 days. Mean FEV₁ in the azlocillin group increases from 1206 ml to 1760 ml ($p < 0.001$). In the carbenicillin group mean FEV₁ increased from 1116 ml to 1619 ml ($p < 0.001$). Significant improvements in PEFr, FVC, and visual analogue scale score were also seen but there was no significant difference between the antibiotic regimens. Despite high serum levels sputum penetration of antibiotics was poor.

Defective serum-killing of *Pseudomonas aeruginosa* in cystic fibrosis

ARL PENKETH, TL PITT, MARGARET E HODSON, JC BATTEN Most strains of *Pseudomonas aeruginosa* from the sputum of cystic fibrosis patients are sensitive to the bactericidal action of normal human serum. We have investigated the bactericidal activity of cystic fibrosis serum from 61 adult patients against autologous and heterologous strains of pseudomonas. Cystic fibrosis serum had similar bactericidal activity to normal human serum against a reference panel of strains. Six cystic fibrosis sera had a selective inability to kill autologous strains of pseudomonas, which were sensitive to normal human serum and to sera from other cystic fibrosis patients. These six sera had normal levels of complement and immunoglobulin and were bactericidal to other strains. A titratable blocking factor was present in these sera which interfered with the bactericidal action of normal human serum on the patients' own strain. This factor was present in the IgG-containing fractions of serum obtained by ion-exchange chromatography, but was not removed from the serum by absorption with the pseudomonas strain, suggesting that it is not bound to a locus on the bacterial cell. A possible mechanism for the selective "resistance" of a strain of pseudomonas for the serum of its cystic fibrosis host is the development of blocking antibody (IgG) against natural bactericidal IgM.

Relationship of phenotype changes in *Pseudomonas aeruginosa* to the clinical condition of patients with cystic fibrosis

ARL PENKETH, TL PITT, MARGARET E HODSON, JC BATTEN Cystic fibrosis patients chronically infected by *Pseudomonas aeruginosa* may remain relatively well for many years, but some deteriorate inexorably once colonised. Routine sputum bacteriological examination cannot identify the latter group. One hundred and nine strains of *P aeruginosa* from 49 cystic fibrosis patients were compared with 87 strains from other sputa and 118 from specimens other than sputum. Three phenotype characteristics—loss of O serotype, expression of a new somatic antigen, and serum sensitivity—were found to be significantly more frequent in the cystic fibrosis strains ($p < 0.001$ in each case). These three features were significantly associated with each other (r values 0.627–0.720). Cystic fibrosis strains were classified in terms of these features and the category of organisms from each patient was related to his clinical condition, assessed by lung function tests, Shwachman score, and frequency and duration of hospital admissions. Relatively fit patients, recently colonised by pseudomonas, had organisms similar to those from the environment. Patients colonised by pseudomonas for many years had strains with all three phenotype changes. The patients with organisms exhibiting one or two changes were most severely affected by the disease, with significantly worse respiratory function and clinical score, more time in hospital, and a high mortality. Of these variants may represent a critical stage in the progression of cystic fibrosis.

Tuberculous pericardial effusion: associated radiological features, AAFB isolation, results of treatment with modern chemotherapy

DK PILLAI, DA JONES, PR FARROW, MJ GOLDBERG, JB COOKSON We discuss 19 cases of tuberculous pericarditis. Two presented with calcific constriction and proceeded to surgery. Seventeen had pericardial effusions. Fifteen patients (nine male) were of Asian origin, mean age 34 years (SD \pm 13), and two were caucasian (one male), aged 68 and 69 years. All chest radiographs showed a cardiothoracic ratio $>$ 50%, and 14 had additional abnormalities—namely, pleural effusion (7), enlarged intrathoracic lymph nodes (5), and apical lung infiltrates (2). Fifteen had documented Heaf tests; all except two were strongly positive. The diagnosis was confirmed in 10 by isolation of AAFB, four from pericardial fluid and six from other sites—namely, excised pericardium, sputum, lymph nodes, urine, ascitic fluid, and gastric washings. Seven were presumptive clinical diagnoses; all these responded to antituberculous treatment. Fourteen were treated with a rifampicin-containing regimen—(ethambutol, isoniazid, rifampicin) (11) and streptomycin, isoniazid, rifampicin (3). Thirteen also received corticosteroids. None had an elevated bilirubin concentration before treatment. Four (mean cardiothoracic ratio 83%) developed jaundice, which resolved when rifampicin was withdrawn. The remaining 10 (mean cardiothoracic ratio 62%) discontinued treatment after a mean 12-month period, a shorter time has been usual hitherto. One developed constriction within two months of treatment; nine have remained well for one to seven years after chemotherapy.

Acute airway changes induced by coughing

PJ REES, TJH CLARK During inhalation challenge procedures coughing often occurs in an unpredictable way. We have examined the effects of such coughs on subsequent assessment of airway calibre. We examined the effects of voluntary coughs on specific conductance (sGaw) in normal, atopic, and asthmatic subjects before and after bronchoconstriction with histamine. Before histamine there were only small changes in sGaw with coughing. After bronchoconstriction 32% of coughs resulted in significant bronchodilatation within the first 30 seconds. The cough was divided into two components of a deep inhalation and a cough without preceding inhalation. These were studied in a similar manner in four normal, four atopic, and four asthmatic subjects. Before histamine sGaw changes were again small. After bronchoconstriction with histamine full inhalations always produced a temporary increase in sGaw. Modified coughs without deep inhalations most often produced a temporary further decrease in sGaw. One other atopic subject was unable to complete the study because a full inhalation produced marked and prolonged airway narrowing. These results show that the main effects of coughs on airway smooth muscle result from the deep inhalation, which usually produces transient bronchodilatation. In challenge studies coughs are likely to affect airways resistance measurements over the following 30–60 sec-

onds, while occasional individuals show prolonged changes.

Alveolar-capillary barrier permeability to ^{99m}Tc -DTPA following cardiopulmonary bypass

D ROYSTON, BD MINTY, JG JONES, J WALLWORK, TIM HIGENBOTTAM Pulmonary oedema due to altered permeability is an uncommon but well recognised problem following cardiopulmonary bypass. We have studied a group of nine patients with normal left ventricular function undergoing coronary artery surgery with cardiopulmonary bypass. To examine alveolar barrier function we measured the rate of clearance of a hydrophilic solute ^{99m}Tc -DTPA (MW 492 daltons) from lung into blood (Jones JG, *et al. Br J Anaesth* 1982;54:705–21). A permeability index is expressed as half-time clearance of ^{99m}Tc -DTPA from lung into blood ($T_{1/2\text{LB}}$, min). Measurements were performed before operation and at 2, 24, and 48 hours and 5 and 7 days post-operatively. In addition we measured alveolar-arterial oxygen tension difference during the breathing of 40% oxygen, and arterial blood was taken for estimation of thromboxane B_2 and complement with its active metabolites, because these have been postulated as mediators in pathogenesis of acute respiratory distress syndrome (Reines *et al. Lancet* 1982;ii:174–5; Hammerschmidt *et al. Lancet* 1980;ii:947–9). In all patients a reduction was observed in $T_{1/2\text{LB}}$ by the second hour post-operatively, from a mean pre-operative value of 49 ± 5.5 (SEM) mins to 24 ± 4.5 mins ($p < 0.001$). Over the subsequent six days of the study there was a gradual improvement in $T_{1/2\text{LB}}$ towards the patients control value. These observations have clear implications for preoperative and postoperative assessment of such patients.

Possible role for anaerobic bacteria in acute exacerbations of chronic bronchitis

D SIEGLER, S REILLY, KD PHILLIPS, AT WILLIS We have evaluated the possible role of anaerobic bacteria in acute exacerbations of chronic bronchitis requiring admission to hospital. In addition to the conventional therapy for such exacerbations, alternate patients were given metronidazole 400 mg three times daily orally for seven days. Of 48 patients available for final analysis, 28 received metronidazole, with 20 matched controls. Sixty-seven per cent of the sputum specimens obtained at admission contained anaerobic bacteria and 10% *Haemophilus influenzae*. Seventeen of 21 (81%) of sputum cultures positive for anaerobes on admission were cleared by metronidazole; two of 11 (18%) not receiving metronidazole were cleared. Bronchial secretions obtained at bronchoscopy from smokers not in acute exacerbation contained only scanty anaerobes. Our findings suggest an important and hitherto unexplored role for anaerobic bacteria in some acute exacerbations of chronic bronchitis.

Effects of long-term high-dose beclomethasone on adrenal function

MJ SMITH, ME HODSON Studies of adrenal function have been performed on 54 asthmatic patients who were taking high doses of inhaled beclomethasone dipropionate in the range 500–2000 $\mu\text{g}/\text{day}$. Basal plasma cortisol levels and short tetracosactrin stimulation tests were performed on all patients and in 15 of them diurnal cortisol levels and 24-hour urinary free cortisol excretion were also measured. The majority of the basal plasma cortisol levels were within the normal range. The mean \pm SEM value for the patients taking 1000 $\mu\text{g}/\text{day}$ was 410 ± 32 nmol/l, compared with the control mean of 430 nmol/l. The mean value of patients taking 2000 $\mu\text{g}/\text{day}$ was significantly lower at 215 ± 36 nmol/l ($p < 0.01$) but still within the normal range. Fifty-one of the 54 patients had 30-minute responses to tetracosactrin within the normal range, although the mean rise in plasma cortisol was again significantly lower in the patients taking 2000 $\mu\text{g}/\text{day}$ ($p < 0.01$). Diurnal plasma cortisol variation was normal in all 15 patients studied. Twenty-four-hour urinary free cortisol excretion was normal in patients taking up to 1500 μg of beclomethasone per day (mean 115 ± 12 nmol/24 hours) but was reduced in those taking 2000 $\mu\text{g}/\text{day}$ (mean 57 ± 9 nmol/24 hours) indicating some degree of adrenal hypofunction at this dose.

High-dose beclomethasone in the treatment of asthma

MJ SMITH, ME HODSON The effects of long-term high-dose inhaled beclomethasone dipropionate (BDP) administered by an aerosol inhaler containing 250 $\mu\text{g}/\text{metered dose}$ (BDP 250) have been studied retrospectively in 293 asthmatic patients who were poorly controlled on standard doses of beclomethasone or who required continuous oral corticosteroid therapy. The dose of BDP ranged from 500 to 2000 $\mu\text{g}/\text{day}$ and the mean duration of follow-up was 20 months. One hundred and sixty two patients were receiving continuous maintenance oral corticosteroids when BDP 250 was commenced and 131 patients were receiving either intermittent courses (86) or none at all (45). Two per cent of the patients receiving continuous oral corticosteroids were able to stop them altogether and a further 39% were able to reduce their maintenance dose. The mean \pm SEM daily oral steroid maintenance dose fell from 12.0 ± 0.6 mg on standard doses of BDP to 6.0 ± 0.4 mg on BDP 250 ($p < 0.001$). Clinical assessment of the effects of high-dose BDP on asthma control showed improved control in 62%, no change in 37%, and deterioration in 1%. The number of severe asthma attacks per year fell significantly and there was a marked increase in the number of patients having no severe exacerbations ($p < 0.001$). The incidence of oropharyngeal candidiasis was not significantly greater on high-dose BDP than standard doses (11% and 9% respectively) and in some patients who developed recurrent oral candidiasis on standard-dose BDP this resolved following reduction in the frequency of inhalations when they used the BDP 250 inhaler.

Causes of progressive massive fibrosis of coalminers

CA SOUTAR, HPR COLLINS The chest radiographs of 112 coalminers with progressive massive fibrosis (PMF) have been classified by one reader into six types based on the appearances of the large opacities. The lifetime exposures of these men to mixed respirable coalmine dust, and to its quartz component, were compared with those of control subjects without PMF, matched for age and starting category of simple pneumoconiosis. Overall the men with PMF had been exposed to more mixed dust than the controls. For the different types of PMF, only men with the commonest type of PMF (large shadows of homogenous radiodensity) could be shown to have been exposed to more mixed dust than the controls. For another type of PMF, in which the large opacities appeared to consist of conglomerations of "r"-type small rounded opacities, the quartz exposure was much higher than in control subjects, suggesting that in this type of PMF quartz was an important causative factor.

Nasal mucociliary clearance in patients attending a nose clinic

PJ STANLEY, MA GREENSTONE, L MACWILLIAM, PJ COLE Nasal mucociliary function was assessed in 345 patients attending Brompton Hospital nose clinic. Nasal mucociliary clearance (NMCC) was measured by recording the time taken to experience a sweet taste after a particle of saccharin was placed on an inferior nasal turbinate (Rutland J, Cole PJ. *Thorax* 1981;36:654). Thirty-five apparently healthy subjects acted as controls. Sixty-nine patients had an NMCC time of >60 minutes. The remaining patients, who tasted within 60 minutes, had a mean transport time of 21.1 ± 0.6 (SEM) minutes, which was significantly longer than the mean of the healthy controls (14.0 ± 0.9 (SEM) minutes) (Mann-Whitney U test, $p < 0.001$). A higher proportion of patients with concomitant chest disease (55/230 (24%)) than of patients with rhinitis alone (14/115 (12%)) had an NMCC of >60 minutes (χ^2 test $p < 0.02$). Of these 69 patients with a grossly prolonged NMCC, three had clinical Kartagener's syndrome and their ciliary dyskinesia was confirmed by ciliary beat frequency (CBF) assay (Rutland J, Cole, PJ. *Lancet* 1980;ii:564), and a further two patients with bronchiectasis but no dextrocardia also had dyskinetic cilia. NMCC was prolonged in patients with rhinitis, especially those with concomitant chest disease. Nasal ciliary beat frequency measurements on such patients will reveal dyskinesia when present.

Treatment of obstructive sleep apnoea with nasal continuous positive airway pressure

JR STRADLING In 1981 Sullivan *et al* (*Lancet* 1981; i: 862–5) reported that continuous positive airway pressure (CPAP), applied via intranasal cannulas sealed with silicone rubber, abolished obstructive sleep apnoea. Later reports (Sullivan *et al*. *Am Rev Respir Dis* 1982;125:107) have suggested that following several weeks of this overnight therapy the patients may be cured and no longer

need the CPAP. Three patients with classical obstructive sleep apnoea (cyclical pharyngeal obstruction throughout the night leading to recurrent hypoxia with arousal and daytime sleepiness) have been studied with two CPAP systems. One uses small, cuffed endotracheal tubes in the nares and the other a paediatric anaesthetic mask strapped over the nose alone. Both systems are supplied with air by a quiet pump generating a maximum pressure of 19 cm H₂O. The mouth can act as the expiratory pathway but in one subject who would not mouth breathe an overflow valve was fitted. The pump and mask are freely available and require only trivial modification. Sleep apnoea in all three patients was completely abolished with dramatic resolution of their disabling sleepiness and other symptoms. This system represents a real alternative to tracheostomy and, as in one of our cases, can also be used during a waiting period for operative treatment such as tonsillectomy.

Bronchoalveolar lavage in the diagnosis of diffuse pulmonary shadowing

PR STUDDY, RM RUDD, AR GELLERT, S UTHAYAKUMAR, G SINHA Bronchoalveolar lavage (BAL) was performed at fiberoptic bronchoscopy in 79 patients with diffuse radiographic pulmonary shadowing and in 20 control subjects undergoing investigation for respiratory symptoms without radiographic shadowing. The highest percentages of cells other than macrophages found in BAL fluid from the controls were 11% for lymphocytes (L) and a total of 10% for neutrophils (N) and eosinophils (E). The table shows the cell profiles and eventual diagnoses in 79 patients.

Cell profiles and diagnoses in 79 patients

	Sarcoi- dosis	Fibrosing alveolitis	Pneumo- coniosis	Bacterial infection	Tubercu- losis
L > 11%	21	4	0	1	6
N + E ≤ or > 10%					
L ≤ 11%	3	13	5	19	0
N + E > 10%					
L ≤ 11%	5	1	0	0	1
N + E ≤ 10%					

with increased lymphocytes differed from those with normal lymphocytes but increased neutrophils plus eosinophils in diagnoses ($p < 0.001$, χ^2 test). Although different diseases can have similar cell profiles BAL has diagnostic value in some situations. For example, in the presence of clinical and radiographic features suggesting an estimated 80% probability of sarcoidosis elevated BAL lymphocytes increase the probability of sarcoidosis to 95% while normal lymphocytes reduce it to 56% (predictive values calculated by Bayes's theorem). In the presence of radiographic shadowing suggesting bacterial pneumonia but with an estimated 20% chance of tuberculosis normal BAL lymphocytes with increased neutrophils reduce the probability of tuberculosis below 1%, while increased lymphocytes raise it to 81%. Culture of lavage fluid may later

provide a definitive diagnosis. BAL has diagnostic value in the investigation of diffuse pulmonary shadowing if the cell profile is considered in conjunction with other information.

So it's easy to interpret pulmonary functions tests

PM TWEEDDALE, MF SUDLOW, GK CROMPTON, GJR MCHARDY Ability to interpret the results of standard pulmonary function tests is a required part of the training of all chest physicians, but tends to be thought of as an easy, repetitive chore, largely based on comparison of the patients' values with the predicted normal. We have put before an audience of seven senior and 12 junior chest physicians straightforward choices of interpretation on 21 questions derived from standard measurements of ventilatory capacity, lung volumes, and carbon monoxide transfer obtained from seven patients with common conditions who had recently attended the laboratories. Unanimous agreement on interpretation was found in the two cases where all the results conformed to the accepted pattern for that type of disorder. In the other five cases the results did not so conform and unanimity was lost. We uncovered different meanings given to conventional terms (such as "restrictive" or "overinflation") and interpretations tended to give more weight to trends than to the size of deviations from predicted values. Examples will be shown to stimulate the society to consider whether some terms need to be abolished, and whether findings of clinical significance are not being obscured by a tendency to recognise only a very limited number of "acceptable" patterns of abnormality.

Are PEFr records a reliable way of diagnosing asthma?

KM VENABLES, PS BURGE, AG DAVISON, AJ NEWMAN TAYLOR We have developed a method for computer-plotted graphical presentation of PEFr records. There are no objective criteria to validate diagnoses of asthma using these graphs. We examined the independent assessments made by three "blind" observers on 61 graphs and estimated between-observer and within-observer agreement and the reasons for agreement. In 90% of graphs at least two observers agreed—completely in 54% and within two points on a four-point asthma assessment scale in 21%. Within-observer agreement was complete in 76%–90% of 29 duplicated graphs, and within two points on the scale in 90–100%. The median number of "variable" days (within-day PEFr variation of at least 15%) was 10.0 in 21 records classified by observers as asthma, and 0.0 in 26 records classified as normal. Graphs with either high or low mean PEFr were difficult to assess, as were those containing one to three "variable" days. In the latter group some graphs were classified as asthma on between-day variability and others as normal because "variable" days were isolated phenomena. Despite the subjectivity of these assessments observer agreement is good. Mathematical analysis of PEFr records must be sophisticated to reproduce the complex diagnostic criteria used by human observers.

Comparative study of erythromycin and ampicillin/amoxycillin as initial therapy for adults admitted to hospital with pneumonia

MJ WARD, RG FINCH, JT MACFARLANE, DH ROSE Although ampicillin is the most popular antibiotic used for treating community-acquired pneumonia, erythromycin has several theoretical advantages because of its spectrum of cover. In a double-blind trial we compared ampicillin (500 mg intravenously, six hourly for two days followed by oral amoxycillin 500 mg four times a day for seven days) to erythromycin (300 mg intravenously six hourly for two days followed by oral erythromycin 500 mg four times a day for seven days) for treating consecutive adults admitted to hospital with primary pneumonia. Ninety-one patients were available for analysis and the clinical course for 42 patients (mean age 53 years; 29 male) treated with ampicillin/amoxycillin was similar to the 49 patients (mean age 48 years; 35 male) in the erythromycin group. Two-thirds of patients in both groups made an uncomplicated recovery and fall in temperature, symptomatic improvement (assessed by detailed daily symptom charts), and rate of radiographic clearance were similar. Adverse reactions were uncommon, although infusion-related phlebitis occurred significantly more often with erythromycin. A complicated or delayed recovery or fatal outcome in the remaining third of patients was principally related to the cause of the pneumonia. Bacteraemic or antigenaemic pneumococcal pneumonia, legionnaires' disease, other bacterial pneumonias, and psittacosis carried a poor prognosis.

Effect of posture on the sympathoadrenal response to theophylline infusion

JB WARREN, C TURNER, N DALTON, A THOMPSON, GM COCHRANE, TJH CLARK Clinical observation suggested that the side effects of theophylline were potentiated by upright posture. The effect of posture on the sympathoadrenal response to theophylline was therefore studied in six normal subjects. On three separate occasions they received an intravenous infusion of either theophylline (6 mg/kg) while supine, theophylline (6 mg/kg) while standing, or saline as placebo while standing. With the subjects standing theophylline caused tremor, a peak pulse rate of 99 ± 6 beats/min and an elevation of plasma cyclic AMP from 9.3 ± 0.7 to 15.1 ± 1.7 nmol/l (mean \pm SEM). There was a small, but statistically significant, elevation of plasma adrenaline, noradrenaline, and glucose concentrations. The elevation in plasma catecholamines was insufficient to explain the sympathomimetic effects of theophylline or the rise in plasma cyclic AMP. Theophylline had little or no effect with the subjects supine. The mean peak theophylline concentration following infusion was significantly higher with the subjects upright than when supine (18.3 v 12.4 mg/l, $p < 0.025$). Analysis of individual data suggests that differences in plasma levels of theophylline are unlikely to account for the increased effects seen on standing. The mechanism of action of theophylline cannot be explained by increased secretion of catecholamines alone. Theophylline appears to amplify the increased sympathetic

activity associated with standing and this may be by phosphodiesterase inhibition.

Isovolaemic haemodilution by erythrapheresis for polycythaemia secondary to hypoxic lung disease

JA WEDZICHA, FE COTTER, MCP APPS, RM RUDD, AC NEWLAND, DW EMPEY We compared the effects of erythrapheresis, a new method of isovolaemic haemodilution, and placebo apheresis in a single-blind manner on exercise capacity and mental alertness in eight patients (seven men, one woman) with polycythaemia secondary to chronic obstructive bronchitis with hypoxaemia (mean FEV₁ 1.0 l, mean PaO₂ 7.2 kPa). Apheresis was performed with a Haemonetics V50 blood processor and on the first occasion blood was returned to the patient after circulating through the machine (placebo apheresis). Two days later a mean of 655 ml of packed red cells were removed, plasma was returned to the patient and blood volume was restored with human plasma protein fraction. After erythrapheresis the mean microhaematocrit fell from 0.50 to 0.49 ($p < 0.01$). The mean blood viscosity decreased significantly at high and low shear rates ($p < 0.01$). There was no change in the platelet count. After erythrapheresis the mean six-minute walking distance was significantly greater (455 m) than before treatment (364 m; $p < 0.01$) or after placebo apheresis (390 m; $p < 0.05$). Three tests of mental alertness were used. The scores were significantly better after treatment than before ($p < 0.01$) or after the placebo procedure ($p < 0.05$). Scores were not significantly different before and after placebo apheresis. Erythrapheresis was well tolerated with no complications. Exercise capacity and mental alertness were improved with symptomatic benefit in all patients.

Reversibility of airways obstruction

AA WOODCOCK, MA JOHNSON Asthma is often regarded as "reversible" airways obstruction. The accepted degree of reversibility that constitutes asthma varies between 10 and 20% of FEV₁. The adoption of the terms COPD, CNSLD, COAD, etc, has meant that chronic bronchitis and emphysema have become synonymous with "irreversible" airways obstruction and patients with this diagnostic label may consequently be undertreated with bronchodilators.

Reversibility of airways obstruction in asthma, chronic bronchitis/emphysema and sarcoidosis

u	Degree of reversibility (mean \pm SD)		Reversibility of FEV ₁		
	FEV ₁	FVC	>15%	>10%	>5%
Asthma	20.3% (19.2)	12.1% (11.2)	54%	67%	78%
Chronic bronchitis/emphysema	9.1% (14.4)	10.4% (12.2)	32%	43%	62%
Sarcoidosis	3.3% (5.8)	0.4% (5.3)	2%	10%	33%

Our study investigated reversibility of FEV₁ and FVC response to 200 µg of inhaled salbutamol in patients with a forced expiratory ratio < 60%, labelled by clinicians as asthma (n = 481) or chronic bronchitis/emphysema (n = 356) and in a control group with sarcoidosis (n = 294). While reversibility in chronic bronchitis and sarcoidosis was normally distributed in asthma it was skewed and the asthma group could be split into two normally distributed populations (asthma group 1 mean 8.1% ± 9.1%, n = 238; asthma group 2 mean 27.8% ± 16%, n = 247). Asthma, chronic bronchitis, and emphysema all had significantly greater reversibility of FEV₁ than sarcoidosis, in which it approximates to that seen in normal subjects (2.5% ± 3.9; n = 75 Watanabe *et al. Am Rev Respir Dis* 1974; 109: 550). We conclude that although there is a difference in reversibility between the two populations with asthma and chronic bronchitis/emphysema there is a considerable overlap even at levels of reversibility greater than 15%. The use of diagnostic labels which imply differences in reversibility is a great oversimplification which can lead to inadequate treatment.

Theophylline prescribing, serum levels, and toxicity

AA WOODCOCK, MA JOHNSON, DM GEDDES Prescriptions of slow-release theophylline preparations have risen five-fold in the last five years at the Brompton Hospital. Since March 1981 1913 serum theophylline assays have been performed (86.4% inpatients 13.6% outpatients). The number of assays per month rose three-fold following a postgraduate lecture in February 1982 (60–199 per month), but the proportion of assays in each of three groups (group A < 10 mg/l; group B 10–20 mg/l; group C > 20 mg/l) remained unchanged (A v B v C; 49% v 43% v 8%). Theophylline prescribing was assessed retrospectively in 50 stable outpatients randomly selected from each of groups A and B and the 13 stable outpatients in group C. Oral theophylline dosage differed between the groups (8.6 ± 3.2 mg/kg/day v 12.1 ± 4.1 v 17.6 ± 6.6; A v B v C (mean ± SD)) but there was considerable overlap between the range of dosage in each group. Side effects were equal in groups A and B but greater in group C (for example, nausea: 26% v 24% v 62%). Other factors related to toxic

levels (group C) were abnormal liver function (36%), diuretic therapy (46%), and duplicate prescribing of different theophylline preparations (23%). All group C patients but only 30% of group A patients had subsequent dosage adjustments. Serious toxicity (serum theophylline > 25 mg/l) occurred in a total of 28 patients (six outpatients and nine inpatients on infusion, 12 inpatients on oral therapy). Three patients had fits (two died) and one was successfully resuscitated after cardiac arrest. Two further patients who were admitted to other hospitals with fits (one died) were suspected of aminophylline toxicity but the theophylline assay was not available. We conclude that theophyllines are difficult to use, with considerable side effects, morbidity, and mortality. Theophylline levels are mainly used to detect toxicity in inpatients and rarely to individuals dosage in outpatients. Unsuspected toxicity in outpatients may be responsible for a considerable hidden morbidity.

Cycling for patients with chronic airways obstruction

AA WOODCOCK, MA JOHNSON We have studied cycling in seven patients with severe chronic airflow limitation disabled by breathlessness. Patients were able to cycle three to four times further than they could walk in six minutes, which is greater than the increase seen in normal subjects. Patients travelled significantly further on a lightweight tricycle (1147 metres ± 197) than on a heavy "NHS" tricycle (833 ± 192 metres) or a bicycle (1055 ± 278 metres) or walking (289 metres ± 75). Patients were also less breathless after riding the lightweight tricycle (visual analogue score 6.8 ± 2.2) than the NHS tricycle (8.1 ± 0.8) or the bicycle (7.6 ± 2.8) or walking (7.9 ± 2.7) despite having travelled the greatest distance. Oxygen consumption during cycling was less than half that during walking at an equivalent speed. Patients quickly adapted to the lightweight tricycle, which had the advantages of lightness and stability. Patients could adopt a good breathing posture and if they became breathless could stop to recover without dismounting. The improvement in exercise tolerance on a cycle is considerably greater than that achieved by conventional medical treatment, and we believe that a lightweight tricycle has potential in rehabilitation.

Correction

Jejunal bypass of the cardia for benign stricture

We regret that in the January issue the list of contents gave the title of the paper by J Borrie and RW Bunton incorrectly. It should be "Jejunal bypass of the cardia for benign stricture: report of six cases," as on page 31.