Thorax 1988;**43**:803P–868P

Proceedings of the British Thoracic Society

The 1988 summer meeting of the British Thoracic Society was held on 13–15 July at the University of Newcastle upon Tyne.

Value of serial peak flow recordings in the diagnosis of occupational asthma

BJ GRANEEK, R HAWKINS, AJ NEWMAN TAYLOR *Department of Occupational Medicine, Brompton Hospital, London* We have examined the pattern of change in serial peak flow recordings (SPFRs) in 53 patients who subsequently underwent specific bronchial provocation tests with occupational agents as part of the investigation into possible occupational asthma. These patients represented all those in whom both tests were performed out of a total of 411 patients seen during a five year period. SPFR data were reviewed by two observers independent of knowledge of the results of subsequent bronchial provocation tests. In 29 patients in whom inhalation tests with a specific occupational agent provoked an asthmatic response SPFRs demonstrated work related asthma (WRA) in 10 (34%), asthma without work relationship in 17 (59%), and no abnormality in two (7%). In 24 patients in whom specific inhalation tests provoked no asthmatic response SPFRs demonstrated asthma without work relationship in 15 (63%), no abnormality in seven (29%), and WRA in two (8%) in whom occupational asthma was subsequently diagnosed as being caused by an agent other than that tested in the inhalation tests. SPFR data were also examined in a further 15 patients in whom occupational asthma was diagnosed by the combination of a characteristic history and evidence of specific immunological response. SPFRs in these patients demonstrated WRA in four (27%), asthma without work relationships in nine (60%), and no abnormality in two (13%). These findings suggest that where SPFRs show WRA a diagnosis of occupational asthma can be made with confidence. Where they show asthma without clear relationship to work, it is not possible to exclude an occupational cause, and further investigations can be necessary. Where SPFRs do not demonstrate any abnormality it is very improbable that the patient has occupational asthma unless the patient is no longer exposed to the inducing cause of asthma.

A study of Spanish sepiolite workers

K MCCONNOCHIE, JP LYONS, C BEVAN, JC WAGNER *Department of Thoracic Medicine and MRC External Scientific Staff Team on Occupational Lung Diseases, Llandough Hospital, Penarth, South Glamorgan* Sepiolite is a naturally occurring fibrous clay which has a wide variety of commercial applications. It can occur as long thin lathe like crystals which have similar dimensions to asbestos fibres. This has prompted concern that both materials may have similar biological properties. Sepiolite has been processed at a site close to Madrid for the past 30 years. We report here a cross-sectional study of this workforce and mortality data for the total work population. All 218 current workers provided personal, occupational and smoking histories and all had a full-size chest radiograph. Data from previous environmental sampling were available to help derive measure of total exposure. Our study shows significant relationships between age and small opacities on the chest radiograph (as expected) but no relationship between years worked and chest radiographic appearance. There is a relationship between types of occupation and small opacities on the chest radiograph but this was less than the relationship with age. There appears to be no excess mortality in this population from lung cancer or other disease and no cases of mesothelioma have been reported. This supports the contention that exposure to sepiolite dust does not present a hazard.

Immunological reactivity to flour and grain mites in a UK bakery workforce

RD TEE, DJ GORDON, S ATKINSON, AJ NUNN, B CROOK, NM FARRER, D JOHNSON, G CROOK, JD DARBYSHIRE, BJ GRANEEK, ER HAWKINS, AW MUSK, KM VENABLES, AJ NEWMAN TAYLOR *Cardiothoracic Institute, Brompton Hospital, London, and Rothamsted Experimental Station, Harpenden, Herts* We have examined the immunological responses to grain mites and flour in 279 (88%) members of a UK bakery to identify the specific occupational causes of allergic disease. The study included a questionnaire, skin prick tests, bronchial reactivity and blood donation for specific IgE antibody measurements (RAST) (*Thorax* 1988;**43**:264P). Jobs were ranked from 0 to 10 according to dustiness and this correlated well with total dust measured in 79 personal air samples. Subjects were skin prick tested with *D pteronyssinus*, grass pollen, cat fur and 11 bakery related allergens, including grain mites. Forty per cent of subjects were atopic ($\geq$2 mm weal to one or more common allergens), 5% had a positive skin prick test to flour and 30% were positive to at least one of four grain mites. Two hundred and forty four sera were screened by RAST; 35% had $\geq$1% isotope binding to one or more of four grain mites, 22% to *D pteronyssinus*, 5% to mixed flour and 13% to wheat. Cross-reactivity studies between *L destructor*, *A siro*, *T longior* and *D pteronyssinus* showed that *L destructor* had individual specific epitopes. Logistic regression analysis showed that atopy was the most significant variable for both skin test and RAST positive responses to all bakery antigens. Additionally, a subject ever having been exposed to rank 6 or above was a significant

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factor for a positive skin test to wheat or flour. To verify if this high response to grain mites was due to exposure in a bakery, workers at a control site (salt factory) with no flour were studied. Forty one per cent were found to be atopic and 27% had a positive skin test to grain mites. A similar per cent of salt (12%) and bakery (9%) workers had a significantly positive RAST ($\geq$0·35 Phadebas RAST units) to grain mites. These responses imply that these mites are probably widely distributed in the environment and not a particular problem in bakeries.

Pulmonary manifestations of exposure to cobalt

DW CUGELL, WKC MORGAN, G PERKINS, A RUBIN *Departments of Medicine, University of Western Ontario Medical School, London, Ontario, Canada, and Northwestern University Medical School, Chicago, Illinois, USA* Seven subjects with cobalt induced parenchymal lung disease have recently been studied. All were involved in either the production of hard metal or were users of the finished product. Four subjects presented with intersititial fibrosis and were inititially diagnosed as cryptogenic fibrosing alveolitis. Only subsequently did the diagnosis become evident. In the other three subjects the initial presentation was of an hypersensitivity pneumonitis with low-grade fever, shortness of breath and fleeting radiographic abnormalities. All three subjects with hypersensitivity pneumonitis had restrictive pulmonary impairment and abnormal gas transfer but following cessation of exposure there was radiographic clearing and an improvement in their lung function and clinical condition. In two subjects, however, substantial restrictive impairment and a reduced diffusing capacity (transfer factor) persisted. Both showed persistent small lung volumes on their chest radiograph. One subject underwent magnetic resonance imaging and there was evidence of persistent alveolitis at a time when the chest radiograph had shown complete resolution of the parenchymal disease. Four subjects underwent bronchoalveolar lavage and the lavage fluid showed the presence of unusual multinucleate giant cells similar to those previously described in histological sections. The presence of these giant cells in lavage fluid is strong but not conclusive evidence of hard metal disease. Although hard metal disease is distinctly uncommon, early recognition is important if irreversible parenchymal damage is to be avoided.

Antibody response to inhaled antigens

C MCSHARRY, K ANDERSON, G BOYD *Department of Immunology, Western Infirmary, and Department of Respiratory Medicine, Royal Infirmary, Glasgow* Asthma among seafood process workers prompted a study of immunological hypersensitivity to prawn antigens aerosolised during processing. Twenty-six subjects with chest symptoms and 26 asymptomatic subjects individually matched for age and years of work exposure were assessed. The symptomatic group had significantly higher total serum IgE than the asymptomatic group (180 IU(ml *v* 88, p = 0·04) and higher prawn specific IgE antibody (3·8 RAST units *v* 0·1, p = 0·002). Total serum IgG and IgG antibody to the same prawn antigens were similar in both groups. The main factor affecting this antibody responsiveness was cigarette smoking. The smokers had significantly higher total IgE and IgE antibody (174 *v* 76, p = 0·029; 2·8 *v* 0·3, p = 0·012). The non-smokers had significantly higher total IgG and IgG antibody (12·9 mg/ml *v* 10·6, p = 0·003; 673 ELISA units *v* 291, p = 0·0004). Cigarette smoking would therefore appear to modulate the class of the serum antibody response to inhaled antigens.

Closed chest drainage without an underwater seal

HR MATTHEWS, JA MCGUIGAN *Regional Department of Thoracic Surgery, East Birmingham Hospital, Birmingham* Underwater seal chest drainage is effective but somewhat cumbersome and unsuitable for outpatient use. We have therefore tested an alternative system which combines a 1·5 l graduated plastic bag with a flutter valve connected to a standard intercostal tube. Eighteen patients aged 5–74 years have had bags attached for 1–35 days (mean 5·7 days). Fifteen patients had undergone thoracotomy for oesophageal and pulmonary procedures and three had not had chest surgery. Drainage material was blood and serum in 10 patients, two had serosanguinous fluid with air, two had air only, three had pus and air and one had a chylous effusion. Volume of fluid ranged from 20–4950 ml (mean 855 ml) with a maximum rate of drainage of 1500 ml/5 mins. The bag system was satisfactory in 17 cases but required replacement with an underwater seal attached to suction in one case with a chronically collapsed lung. Four patients with prolonged drainage of fluid and air were able to go home on closed drainage with bags for 2–20 days without difficulty. Our results indicate that this system is as satisfactory mechanically as a conventional underwater seal, but has the added advantage that it can be used on outpatients and in the emergency field situation.

Effective treatment of hypercalcaemia due to lung cancer by aminohydroxypropylidene diphosphonate

R FOX, SP HANLEY, R WEARS *Monsall Hospital, Manchester* Symptomatic hypercalcaemia associated with lung cancer is difficult to manage, with variable responses to drugs such as corticosteroids, calcitonin and mithramycin which are themselves toxic. Aminohydroxypropylidene disphosphonate (APD) has been shown to be effective in comparison with these agents in tumour induced hypercalcaemia (*Lancet* 1985;ii:907–910). We report our experience with APD in five male patients with lung cancer, aged 37–74 years, who presented with symptomatic hypercalcaemia, corrected calcium 3·1–3·72 mmol/l. Three patients had squamous cell carcinoma, one a large cell carcinoma, and in one no tissue diagnosis was obtained. None had metastatic disease clinically, on bone (n = 3) or liver scan (n = 1) when performed. All had a raised alkaline phosphatase (106–380 IU(l). Initially all patients were treated with intravenous 150 mM sodium chloride, diuretics (n = 4), corticosteroids (n = 2) but remained hypercalcaemic, corrected calcium 2·72–

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3·2 mmol/l. All patients then received intravenous APD 60 mg (n = 4) or 30 mg (n = 1), infused in 500 ml of 150 mM sodium chloride over 4–8 hours. All were normocalcaemic within 48–72 hours, corrected calcium 2·24–2·53 mmol/l, with symptomatic improvement, the treatment being well tolerated. After approximately three weeks, three patients received further doses of 30 mg of ADP, the remaining patients having died or deteriorated too much to prevent further treatment. Four of the patients have died, survival from first presentation ranging from 15 to 109 days. None had received radiotherapy or chemotherapy. We conclude that APD is effective in the treatment of hypercalcaemia associated with lung cancer, but that such hypercalcaemia indicates a poor prognosis.

Sedation for fibreoptic bronchoscopy: comparison of alfentanil with papaveretum and diazemuls

AR WEBB, JF DOHERTY, MR CHESTER, ARC CUMMIN, MA WOODHEAD, EM NANSONM, ST FLACK, FJC MILLARD *St James's Hospital, London* Sedation for fibreoptic bronchoscopy should produce optimal conditions for the operator, patient comfort and rapid recovery to allow early discharge home. We have compared a regimen producing "light" sedation with a more traditional "deep" sedation regimen. Seventy six patients undergoing fibreoptic bronchoscopy under topical anaesthesia were randomised to receive either light sedation with the short acting opiate alfentanil (median dose 1·1 mg, range 0·5–2·6 mg) or deep sedation with a combination of papaveretum (median dose 10 mg, range 5–15 mg) and diazemuls (median dose 8 mg, range 0–20 mg). The two techniques gave equally good operating conditions, although patients given alfentanil coughed less than those given papaveretum and diazemuls ($U = 2{\cdot}814$, $p < 0{\cdot}01$). Patients recorded their degree of apprehension on a visual analogue scale prior to sedation and the actual degree of comfort experienced after recovery. There was no significant difference between apprehension or comfort between the groups. This was despite a higher degree of amnesia for an irrelevant object shown during the bronchoscopy in the deeply sedated group ($\chi^2 = 21{\cdot}084$, $p < 0{\cdot}001$). Patients given alfentanil performed significantly better ($\chi^2 = 4{\cdot}321$, $p < 0{\cdot}05$) in a modified Romberg test (Kortilla K. *Anaesthesia* 1976;**31**:724–31) and a visualisation test (James F. *Anesthesiology* 1969;**30**:264–72) two hours after the bronchoscopy ($t = 3{\cdot}035$, $p < 0{\cdot}01$). Alfentanil produced good operating conditions, patient comfort, less cough and a more rapid recovery than the other regimen and is therefore an ideal sedative for fibreoptic bronchscopy.

Comparison of transcricoid and bronchoscopic routes for administration of local anaesthesia before fibreoptic bronchoscopy

WJM KINNEAR, L REYNOLDS, D GASKIN, JT MACFARLANE *City Hospital, Nottingham* We have compared two techniques for the administration of local anaesthetic prior to fibreoptic bronchoscopy. Twenty patients received 4 ml of 4% lignocaine by transcricoid injection. Another 20 patients received an identical dose of lignocaine injected in 2 aliquots through the bronchoscope onto the vocal cords. Each patient received the same intravenous premedication. Additional lignocaine was administered during the bronchoscopy at the discretion of the bronchoscopist. Bronchial biopsy samples were taken as clinically indicated, but no transbronchial biopsies were performed. The median number of coughs during the bronchoscopy was 2·5 (range 0 to 30) for the transcricoid route and 8·5 (range 2 to 30) for the bronchoscopic route of injection ($p < 0{\cdot}01$). Thirteen patients needed additional lignocaine after the initial bronchoscopic injection, compared to three patients after the transcricoid route. Radioisotope studies in two normal subjects revealed distribution of lignocaine in the trachea, main and lower lobe bronchi following the transcricoid injection, compared with predominantly laryngeal and oesophageal distribution following the bronchoscopic injection. The tolerance of the bronchoscopy by the patient and the time taken to complete the procedure were similar for both routes of administration. Eleven of 18 patients questioned about the transcricoid injection found it no more unpleasant than the intravenous injection of premedication, while seven found it slightly more unpleasant. No side effects were observed after injection by either route. Transcricoid injection of lignocaine prior to fibreoptic bronchoscopy is a simple technique which is well tolerated and produces more effective airway anaesthesia than injection through the bronchoscope.

Comparison of neuroleptanalgesia with a combination of papaveretum and diazepam as premedication for fibreoptic bronchoscopy

JFJ MORRISON, CA JAYAPRAKASAN, AG WARDMAN, RJ STEAD *Pulmonary Function Laboratory, Killingbeck Hospital, Leeds* Neuroleptanalgesia (N) with phenoperidine and droperidol has been shown to have several advantages over either papaveretum or diazepam given singly for fibreoptic bronchoscopy (FOB) (Morrison *et al. Thorax* 1987;**42**:223). However, it has not been compared with a combination of an opiate or a benzodiazepine which is used by 22% of UK bronchoscopists. We compared N with papaveretum and diazepam (P + D) in a double blind study in adults. Each patient received atropine 0·6 mg intramuscularly ½–1 hour before FOB, either alone or with papveretum 20 mgs according to randomisation. At the time of the FOB intravenous (IV) phenoperidine 2 mg and droperidol 10 mg or IV diazepam 10 mg (titred to dysarthria) was given. Doses were reduced by half if the patient was < 50 kg or > 60 years. The nose was sprayed with 10% lignocaine. Endobronchial anaesthesia with 2% lignocaine was standardised and extra medication of lignocaine or diazepam given at the operator's discretion. Arterial oxygen saturation was monitored by ear oximetry and oxygen at 2 l/min via nasal prong was routinely given. The patient characteristics and reason for FOB were similar in each group. Forty three patients received N and 41 P + D. N suppressed cough more than P + D ($p = 0{\cdot}03$) and produced less sedation ($p = 0{\cdot}02$). Patients found the FOB less unpleasant with P + D ($p < 0{\cdot}01$). After premedication there was no oxygen desaturation with N but a fall of 1·2% was seen with P + D ($p = 0{\cdot}02$). Despite supplemental oxygen a further 1·7% fall occurred with

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P + D ($p < 0.01$). during the FOB. The fall during the FOB with N was 1·5% ($p = 0.01$). Nasal anaesthesia was reported as being the worst part of the procedure by approximately one third of patients in each group. No significant differences were seen in scores of cooperation, additional medication amnesia, pain expectations, request for GA, sore throat or whether patients would undergo a repeat examination. No side effects were encountered. In conclusion both N and P + D are safe, acceptable regimens for FOB.

Diclofenac sodium: a valuable analgesic in postoperative thoracotomy pain

FC HAMDY, C CARTER, J RADCLIFFE, GK DAVIES, JAC THORPE *Cardiothoracic Unit, Northern General Hospital, Sheffield*

Immediate post-thoracotomy pain can be difficult to control and may require the administration of large doses of opiates with their accompanying side-effects, particularly of respiratory depression. Diclofenac sodium is a non-steroidal anti-inflammatory analgesic recently advocated for acute pain relief. Thirty nine patients selected from routine thoracotomy lists were studied: age range 21–76, 26 males and 13 females. Patients were randomly allocated to two groups. Group I (20 patients) received papaveretum (0·2 mg/kg) and prochlorperazine (12·5 mg) as premedication followed by 75 mg of diclofenac postoperatively and at 12 hourly intervals. Group II (19 patients) received the same premedication with placebo injections instead of diclofenac. In addition, all patients had access to intermittent injections of papaveretum when required. The total doses of opiates administered during the 48 hours following surgery were recorded and regular pain scores using the 100 mm visual analogue scale were measured. In group I the mean opiate dosage in 48 hours was 29·2 (SD 4·2) mg and in group II 62·6 (4·7) mg ($p < 0.0001$). The mean pain score in group I was 21·4 (2·3) and in group II 48·2 (3·7) mm ($p < 0.0001$). Our results show a marked reduction in opiate requirement and pain scores in the treated group, and demonstrate the effectiveness of diclofenac as a useful adjunct for post-thoracotomy pain control.

Early results of single lung transplantation in patients with end stage pulmonary fibrosis

PA CORRIS, DT MCLEOD, GJ FEATHERSTONE, JH DARK, CGA MCGREGOR *Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne*

Three patients underwent single lung transplantation for end stage pulmonary fibrosis. All were housebound on continuous, supplemental oxygen. Good early graft function enabled extubation at 11, 46 and 96 hours post-transplant and patients were discharged home after 5, 6 and 7·5 weeks. All patients had episodes of rejection before discharge based on a combination of symptoms, CXR infiltrates, the exclusion of pneumonia and prompt response to methylprednisolone. To date transbronchial biopsy (TBB) has given inconsistent results in diagnosing rejection. Two patients are well and living normal lives at nine and four months but our second patient has developed obliterative bronchiolitis (OB) and is severely limited requiring supplemental oxygen at six months. Maintenance immunosuppressive therapy comprises cyclosporin, azothioprine and prednisolone. Our first patient had two opportunistic pulmonary infections: herpes simplex pneumonia at four months, which resolved with acyclovir, and *Pneumocystis carinii* infection at six months, which resolved with co-trimoxazole. On each occasion she presented with dyspnoea and fever with a significant deterioration in TLCO and Pao_2, however, the chest radiograph and spirometric values were unchanged. Our second patient's recovery was complicated by phrenic nerve palsy but by three months he could walk five kilometres. Thereafter there was a slow but progressive decline in FEV_1, VC and TLCO and an open lung biopsy at five months confirmed OB. Our third patient presented with dyspnoea and fever at three months with a deterioration in FEV_1, VC, TLCO and Pao_2, although the chest radiograph remained unchanged. Lavage and TBB revealed *Aspergillus fumigatus* pneumonia, which responded to itraconazole and pulmonary function returned to the previous best within two weeks. We conclude that single lung transplantation is compatible with the restoration of good pulmonary function and normal lifestyle in patients with end stage pulmonary fibrosis but episodes of early pulmonary rejection and opportunistic infections are common.

Physiological characteristics of patients with pulmonary fibrosis before and after single lung transplantation

CR SWINBURN, CGA MCGREGOR, JH DARK, TN STONE, PA CORRIS *Cardiothoracic Unit, Freeman Hospital, Newcastle upon Tyne*

We have accepted six housebound, oxygen dependent patients with end stage pulmonary fibrosis for single lung transplantation. Mean (SD) FEV_1, VC, and TLCO were 1·5 (0·6) l, 1·8 (0·7) l and 1·6 (0·6) mmol min^{-1} kPa^{-1} respectively and Pao_2 at rest breathing air was 6·9 (1·1) kPa. Two patients had hypercapnia. All had raised mean pulmonary artery pressure (30 (9) mm Hg) and an elevated total pulmonary vascular (10 (4) units m^{-2}) but right ventricular function was preserved and resting cardiac index was normal (3·2 (0·6) l min^{-1} m^{-2}). Initially the six minute walking distance (6 MD) was only 158 (93) m on supplemental oxygen although this showed an improvement during a rehabilitation programme designed to optimise preoperative fitness. During formal progressive cycle ergometry the maximum work load achieved breathing 50% oxygen was 47 (20) watts at an excessive ventilation of 49 (17) l min^{-1} and heart rate of 149 (15) beats per minute. All showed a fall in arterial oxygen saturation during exercise. Three patients have undergone successful surgery and been discharged without supplemental oxygen. Two patients died awaiting suitable donor lungs. Six weeks postoperatively, pulmonary function was improved. Pao_2 (breathing air) and TLCO now averaged 11 kPa and 3·6 mmol min^{-1} kPa^{-1} respectively. Sequential radionuclide imaging of the lungs between one and six weeks after transplantation showed an early and unsustained preferential perfusion (average 79%) to the transplanted lung with a more variable distribution of ventilation. The 6 MD, now carried out breathing air, averaged 458 M and formal exercise testing again breathing air showed absent or minimal desaturation together with a fall in both ventilation and heart rate relative to work load in two patients.

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Characteristic histological changes associated with rejection in recipients of heart-lung transplants

JA HUTTER, TW HIGENBOTTAM, JP SCOTT, CAC CLELLAND, BA OTULANA, S STEWART, J WALLWORK *Papworth Hospital, Cambridge* Combined heart-lung transplantation (HLTx) is complicated in the long-term by the development of disabling and frequently fatal Obliterative Bronchiolitis (OB) (*Lancet* 1986;i:517–9), thought to be the consequence of chronic lung rejection (*Transplant Proc* 1987;**19**:1052). Regular monitoring of lung function and Transbronchial Lung Biopsy (TBB) via a fibreoptic bronchoscope in our institute, has been associated with a low prevalence of OB, three patients out of 35 transplanted over the last three years. A total of 110 TBB have been undertaken in our patients. Thirty four sets of biopsies were obtained when there was a clear clinical diagnosis of rejection with no evidence of infection. Fifteen routine biopsies were taken when the patients were well. The presence on multiple sections of perivascular infiltrates, alveolar interstitial infiltrates and bronchial mucosal inflammation was compared between the rejection group and the routine group.

	Perivascular lymphocytic infiltrates	*Alveolar interstitial infiltrates*	*Bronchial mucosal infiltrates*
Rejection (n = 34)	79%	62%	79%
Routine (n = 15)	0%	13%	27%

In comparison, 103 endomyocardial biopsies (EMB) in the first 17 HLTx recipients showed a focus of moderate rejection in only one specimen. On no occasion did EMB influence patient management. We conclude that histological diagnosis by TBB but not EMB is valuable in the HLTx recipient and may be significant in the prevention of obliterative bronchiolitis.

Pulmonary function monitoring allows early diagnosis of lung rejection in heart-lung transplantation

BA OTULANA, TW HIGENBOTTAM, JP SCOTT, C CLELLAND, JA HUTTER, J WALLWORK *Departments of Respiratory Physiology and Surgery, Papworth Hospital, Cambridge* Acute pulmonary rejection, diagnosed by transbronchial lung biopsy, is common after heart-lung transplantation and is usually unassociated with cardiac rejection. Diagnosis can be difficult but is aided by histology. The biopsy specimens in rejection, unlike normal, show extensive perivascular lymphocyte infiltrates. To determine the value of monitoring pulmonary function in deciding when to biopsy the lung we have compared values of spirometry, lung volumes and gas transfer for carbon monoxide at the time biopsy confirmed rejection with values recorded when routine and normal biopsy specimens were obtained. All 34 patients transplanted since 1984 were studied regularly after surgery and when symptomatic. Routine biopsies were made when patients were well at three months and annually. The results of chest radiographs were compared with lung function changes.

	Mean (SD) % predicted			
	FEV	*VC*	*TLC*	*TLCO*
Rejection episodes (n = 34)	64·1(21·5)	61·3(18·5)	83·9(20·9)	52·3(14·6)
Routine biopsies (n = 20)	101·0(24·4)	88·5(15·0)	101·6(10·8)	65·8(16·8)

In rejection the greatest change was observed in FEV_1, mean fall 20% and rising by 17% after augmented immunosuppression (intravenous methylprednisolone 0·5–1 g daily for three days). By contrast the chest radiograph was normal in 40% of the rejection episodes. From these observations regular monitoring of FEV offers a means of deciding when to undertake diagnostic lung biopsy and can be used to assess efficacy of augmented immunosuppression.

Natural history of obliterative bronchiolitis in heart-lung transplant recipients

JP SCOTT, TW HIGENBOTTAM, JA HUTTER, S STEWART, BA OTULANA, J WALLWORK *Papworth Hospital, Cambridge* Thirty five patients have received combined heart-lung transplants (HLTx) in our institute over the last three years. All have had regular monitoring of pulmonary function (FEV_1). When values fell or the patient developed respiratory symptoms, they underwent transbronchial lung biopsy (TBB) through a fibreoptic bronchoscope. In addition routine biopsies were performed at three months and annually when the patients were well. A total of 32 episodes were confirmed by biopsy and subsequent improvement on augmented immunosuppression (0·5–1·0 g methyl prednisolone administered for three days). Three patients have died with obliterative bronchiolitis (OB), a common complication in HLTx (*Lancet* 1986;i:517–9), thought to result from chronic rejection. The remaining patients with OB died at 33, 14 and 11 months after transplantation. They experienced more frequent rejection, one episode every 13 weeks compared with one every 34 weeks in the remaining 32 patients. Each had episodes of rejection recurring within two weeks. After each episode, and unlike in fit patients, FEV_1 failed to return to normal with the augmented immunosuppression. At necropsy, in addition to OB extensive pulmonary vascular disease was found and in two patients severe coronary occlusive disease with myocardial infarcts were present and were the probable cause of death. These observations suggest that frequent, incompletely treated episodes of acute rejection lead to OB. There is also an association between occlusive pulmonary vascular disease and occlusive coronary disease of heart-lung transplants consistent with the view that both may be the consequence of chronic rejection.

Importance of cytomegalovirus in heart-lung transplantation

JA HUTTER, TW HIGENBOTTAM, JP SCOTT, T WREGHITT, J WALLWORK *Papworth Hospital, Cambridge* Thirty three patients have received heart-lung transplants at Papworth Hospital, Cambridge, since 1985. The preoperative cytomegalovirus (CMV) status of the recipient and the CMV

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status of the donor have been studied. Cytomegalovirus was diagnosed on serological, culture and histological criteria on tissue obtained at necropsy or obtained via a fibreoptic bronchoscope. CMV disease was classified as lethal, severe, moderate or mild according to established criteria. Eighteen patients (mean age 26 (SD 10·2) years) were seronegative for CMV prior to transplantation. Eight of these received organs from seropositive donors; all but one developed primary CMV classifed as lethal in three, severe in three, and moderate in one. All patients surviving primary CMV received Guanciclovir (Wellcome) in addition to prophylactic hyperimmune globulin given from the time of transplantation. The patients who died from primary CMV had been treated with acyclovir alone or in combination with Foscarnet. Ten seronegative patients have received organs from seronegative donors. Three have developed primary blood product acquired CMV classified as mild. Reactivation of CMV has occurred in seven of 15 recipients (mean age 34 (SD 7·5) years) but this was associated with mild symptoms in only one patient. We recommend that CMV negative recipients should only receive organs from CMV negative donors. This has been our policy since 1986. If, however, a CMV mismatch occurs we suggest that hyperimmune globulin is given prophylactically and Guanciclovir started as soon as there is any suggestion of CMV disease.

Effect of Iloprost (prostacycline analogue) on lung preservation in canine lung transplantation

HSR HOSKER, T HOOPER, P MCARDLE, RT PEASTON, CGA MCGREGOR, PA CORRIS *Departments of Respiratory Medicine and Cardiothoracic Surgery, Freeman Hospital, Newcastle upon Tyne* We have previously shown that bronchoalveolar lavage (BAL) is useful in characterising the extent of injury associated with ischaemic preservation prior to lung transplantation (Locke T *et al. Thorax* 1987;**42**:227). In this study we have evaluated the effect of Iloprost (Schering Ltd) on lung preservation in a dog model of unilateral transplantation. In one group (n = 5) donor animals received Iloprost by intravenous infusion (20 ng/kg/min) prior to flushing the pulmonary artery with modified Euro Collins solution (20 ml/kg) containing Iloprost (20 μg/litre). A control group (n = 5) received Euro Collins solution alone (20 ml/kg). The donor left lung was then excised and stored at 4°C for six hours, then transplanted into a healthy recipient animal. After 24 hours' reperfusion at a fixed Fio_2, dogs were killed and the transplanted lung was removed and lavaged. The pneumonectomy specimen from each recipient animal was lavaged to provide control data. Acute lung injury was assessed by BAL neutrophil counts and protein concentration. There were significant differences between control and transplanted lungs in both neutrophil counts (mean (SD) control 54·8 (55·9) $\times$ 10^6/l; transplant 272·7 (264) $\times$ 10^6/l; $p < 0.05$) and protein concentration (control 1·74 (1·53) g/l; transplant 5·65 (4·08) g/l; $p < 0.02$). There were no significant differences between Iloprost and non-Iloprost treated transplant lungs in terms of BAL neutrophil counts (Iloprost 216 (136) $\times$ 10^6/l; non-Iloprost 329 (361) $\times$ 10^6/l) or protein concentration (Iloprost 6·34 (2·55) g/l; non-Iloprost 4·96 (1·67) g/l). BAL eosinophil and lymphocyte counts did not distinguish between control and transplant groups or between Iloprost and non-Iloprost groups. The degree of acute lung vascular injury following lung preservation with Euro Collins solution as assessed by BAL was not modified with the addition of Iloprost.

Reproducibility of spirometric values between pneumotachygraph and spirometer compared with intrasubject variability

CM ROBERTS, KD MACRAE, WA SEED *Department of Medicine, Charing Cross and Westminster Medical School, London* Spirometric values derived from the pneumotachygraph and spirometer are used interchangeably in many clinical situations. We assessed the comparability of these two systems during a period of laboratory upgrading when both a pneumotachygraph (Vertek 5000 VR, Hewlett Packard) and dry rolling seal spirometer (CPI 5000 IV, Gould) were in use. Twenty subjects performed forced vital capacity manoeuvres on both systems on different days. The highest values for forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEF) were taken independently from the first three technically accurate maximum efforts. Intrasubject variability was tested in 20 subjects, who performed similar manoeuvres on the spirometer on two separate days. Statistical analysis of the two groups consisted of correlation coefficient (R), variance (F), paired *t* test (T) and probability value (p) with 95% confidence intervals (CI). All p values for F were < 0.1. The statistical results are shown below.

Pneumotachygraph with spirometer					
FEV_1	1·252 (F)	0·984 (R)	0·638 (T)	0·532 (p)	±0·369(CI)
FVC	1·046	0·990	0·219	0·829	±0·308
PEF	1·169	0·934	0·502	0·624	±1·630
Intrasubject variability					
FEV_1	1·107 (F)	0·948 (R)	0·626 (T)	0·539 (p)	±0·221(CI)
FVC	1·066	0·997	0·396	0·696	±0·271
PEF	1·351	0·966	1·093	0·288	±1·526

These results suggest that differences in measurements derived from the two systems are largely the result of intrasubject variability. The reproducibility of PEF is poorer with larger confidence intervals, reflecting its great dependence on effort.

Spirometric values derived from a contemporary British population

CM ROBERTS, AJ WINNING, KD MACRAE, WA SEED *Department of Medicine, Charing Cross and Westminster Medical School, London* There are few published UK normal ranges for spirometry and most of these consider either a single sex (Hall *et al. Thorax* 1979;**4**:359; Cotes *et al. Br Med J* 1966;i:1016) or a narrow age range (Fowler *et al. Thorax* 1987;**42**:173) and have included cigarette smokers as normal subjects. European and North American series also fall short of ideal standards. We have carried out a study to provide contemporary reference values from a British population. One

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hundred and seventy nine healthy, lifelong non-smokers without current or previous respiratory symptoms were recruited. There were 96 women, mean age 44·6 years, mean height 1·64 m, and 83 men, mean age 44·9 years, mean height 1·77 m. Subjects performed forced expiratory maneouvres with a pneumotachygraph or dry rolling seal spirometer. Highest values for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), expiratory peak flow (PEF) and flow rate at 50% of vital capacity (FEF_{50}) were recorded. Statistical analysis showed acceptable skew and kurtosis and multiregression analysis was used to produce prediction equations which are given below with correlation coefficients (R) and standard deviations.

		SD	*r*
FEV_1	(male) (3·961Ht) − (0·033 age y) − 1·558	0·51	0·83
	(female) (3·321Ht) − (0·025 age) − 1·394	0·39	0·83
FVC	(male)(6·628Ht) − (0·028 age) − 5·377	0·64	0·79
	(female)(4·321Ht) − (0·023 age) − 2·379	0·49	0·78
FEV/FVC	(male)126·252 − (21·476Ht) − (1·242 age)	6·88	0·50
	(female)88·134 − (0·172 age)	6·74	0·43
PEF	(male)(15·317Ht) − (0·062 age) + 2·945	1·25	0·72
	(female)(4·087Ht) − (0·05 age) + 2·945	1·10	0·70
FEF_{50}	(male)6·456 − (0·044 age)	1·41	0·31
	(female)5·556 − (0·0038 age)	1·05	0·55

These equations provide predicted values higher than those of older British studies but similar to those of recently published European and North American series.

Role of γ aminobutyric acid (GABA) in human respiration: a study using vigabatrin

AG FENNERTY, EM RIMMER, J BOULTON, A RICHENS *Departments of Thoracic Medicine and Clinical Pharmacology, Llandough Hospital, and University Hospital of Wales, Cardiff* Animal studies have shown that Ventriculocisternal infusion of GABA causes respiratory depression (Kneussl MP *et al. Am Rev Respir Dis* 1986;**133**:1024–9) and that GABA levels rise with hypercapnia (Hoop B *et al. Am Rev Respir Dis* 1985;**132**:248–53). It is speculated therefore that GABA may have a role in the control of respiration. Since systemically administered GABA does not pass the blood-brain barrier its effect on human respiration is unknown. Vigabatrin is an innovatory antiepileptic drug which increases brain GABA by inhibiting its breakdown by the enzyme, GABA transaminase (Rimmer EM, Richens A. *Lancet* 1984;i:189–90) and provides a unique opportunity to study the effects of GABA on human respiration. Seven fit subjects, two female, mean age 30 years (range 26–36), took 3 g of vigabatrin or matched placebo daily for three days, with a 14 day washout period, in a randomised double blind crossover study. The dose chosen is known to have a significant antiepileptic effect in man (Rimmer and Richens). There was no significant difference between the CO_2 ventilatory response two hours after placebo (mean 1·65 (SEM 0·72) l/min/mm Hg) and vigabatrin (1·82 (1·05) l/min/mm Hg). Reduction in platelet GABA transaminase activity confirmed a pharmacological effect in subjects taking vigabatrin. This preliminary study using a pharmacologically active dose of vigabatrin as a means of enhancing brain GABA concentrations has failed to show an effect of GABA on the CO_2 ventilatory response in fit human subjects.

An increase in allergen dose can induce a late asthmatic response (LAR) in previous single early responders

CKW LAI, ST HOLGATE *Department of Immunopharmacology, University of Southampton* Allergen challenge provokes two types of bronchoconstrictor response, the early asthmatic response (EAR, maximal fall in FEV_1 >20% in the first hour) and the LAR (maximal fall in FEV_1 3-h (Lmax) >15%). It is still not clear why the LAR only occurs in some atopic asthmatics but not in others. In an attempt to investigate if the LAR is dose-dependent, we have used a short acting β_2 agonist rimiterol to convert single early responders to dual responders with allergen challenge. On two separate days at least two weeks apart eight atopic asthmatics with only single early response to allergen were challenged with allergen (day 1, D1) and then allergen preceded by the inhalation of 400 μg rimiterol 10 min earlier (day 2, D2), allowing for a greater allergen dose to be given. On both days changes in airways calibre were followed as FEV_1 prechallenge and 8 h postchallenge airways responsiveness as the cumulative provocation concentration of methacholine causing a 20% fall in FEV_1 ($PC_{20}M$). Prechallenge $PC_{20}M$ were similar on the two days (0·58 mg/ml on D1, 0·83 mg/ml on D2; $p > 0·25$). On D2 rimiterol increased the dose of allergen inhaled by a geometric mean of 8·9-fold without altering the magnitude of the EAR (mean (SEM) 35·8 (3·9)% on D2 and 35·4 (3·5)% on D1; $p > 0·9$). However, five subjects were converted to dual responders with Lmax of >15% from premedication value. For the group as a whole Lmax increased significantly from 5·4 (2·2)% on D1 to 17·8 (3·3)% on D2 ($p < 0·05$). However, the change in $PC_{20}M$ eight hours after allergen challenge did not differ significantly on the two days ($p > 0·6$). These results indicate that (1) it is possible to induce a late asthmatic response in a subject who previously demonstrated only an early response by increasing the dose of allergen inhaled, and (2) this late bronchoconstrictor response is not accompanied by a change in non-specific bronchial responsiveness.

Effects of dietary supplementation with fish oil on the asthmatic responses to antigen

JP ARM, CE HORTON, TJH CLARK, TH LEE *Guy's Hospital, London* The effects of dietary supplementation with fish oil on neutrophil biochemistry and function and immediate and late asthmatic responses to antigen have been studied in 15 atopic asthmatic subjects. Nine subjects received 18 capsules a day containing 3·2 g of eicosapentaenoic acid (EPA) and 2·2 g of docosahexaenoic acid, and eight subjects received identical capsules containing olive oil, for 10 weeks in a double blind fashion. Following dietary supplementation

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with fish oil, but not following placebo, there was a greater than 10 fold increase in neutrophil EPA content, neutrophil chemotactic responses to FMLP were markedly depressed, and there was a mean 47% inhibition of LTB4 generation by neutrophils stimulated by A23187. There were no significant changes in the dose of antigen causing a 35% fall in airways specific conductance (PD_{35}), the extinction dose of antigen on skinprick testing (ED AG), the histamine PD_{35}, or total serum IgE following either placebo or fish oil. The antigen PD_{35}, the histamine PD_{35}, the ED AG and the total serum IgE were 1·5 μg, 0·48 μmol, 0·034 g% and 176 IU/ml (geometric means) respectively before and 1·8 μg, 0·42 μmol, 0·014 g% and 281 IU/ml respectively after dietary supplementation with fish oil. By comparison there was a significant ($p < 0.005$) attenuation of the late asthmatic response to inhaled antigen following ingestion of fish oil but not placebo. The mean (SEM) maximal fall in airways specific conductance during the late asthmatic response decreased from 56 (2)% before treatment to 36 (2)% following the fish oil supplemented diet.

Relation between T lymphocytes, activated eosinophils, and human late phase skin reactions

AJ FREW, AB KAY *Cardiothoracic Institute, London* Using the late phase skin reaction (LPSR) as a model of allergic asthma we have studied the migration and activation of eosinophils and lymphocytes. LPSR was introduced in 25 atopic subjects by intradermal challenge with 30 BU *Dermatophagoides pteronyssinus* or grass pollen extract. The diameter of the LPSR was measured at six hours and skin biopsies were obtained after six, 24 or 48 hours (10 subjects at each timepoint). A panel of monoclonal antibodies was used to determine the phenotypes of infiltrating leukocytes. Activated eosinophils (stained with the monoclonal EG2) were found in virtually all the allergen challenged sites. Perivascular accumulation of T lymphocytes was observed, which decreased gradually in intensity by 48 hours. The majority of the T lymphocytes were $CD4^+$ and some bore IL-2 receptors. Small numbers of $CD8^+$ cells were also seen but with no statistical difference from control sites. At all three timepoints the number of $EG2^+$ cells and $CD4^+$ cells were significantly correlated with the size of the preceding LPSR. At six and 48 hours the number of $EG2^+$ cells was the closest cellular correlate of LPSR size ($r = 0.71$ and 0·81 respectively; $p < 0.01$) followed by the number of $CD4^+$ cells. At 24 hours the order was reversed with $CD4^+$ cells most closely correlated ($r = 0.84$, $p < 0.001$). These findings show that activated eosinophils are present at sites of allergic inflammation and also that $CD4^+$ T lymphocytes are attracted to these sites. Both these cell types may therefore contribute to the pathogenesis of chronic allergic inflammation.

Blood cortisol concentrations do not correlate with the late asthmatic response or associated changes in blood eosinophils

SR DURHAM, J KEENAN, WOCM COOKSON, CF CRADDOCK, MK BENSON *Osler Chest Unit, Churchill Hospital, Oxford*

Fourteen asthmatics underwent two inhalation challenges with allergen and allergen diluent (control). The challenges were performed at midday and in random order with an interval of 14 days. We previously reported increases in airway histamine responsiveness which preceded the late asthmatic response (*Thorax* 1987;**42**:711) and correlated with the size of the late response and associated changes in blood eosinophils (*Thorax* 1988;**43**:237P). In view of a report that metyrapone pretreatment ("medical adrenalectomy") accentuated the late response in dogs (Sasaki H *et al. Am Rev Respir Dis* 1987;**136**:1459) we assessed whether alterations in endogenous cortisol concentrations might influence the late reponse or eosinophil counts in humans. Mean (SEM) serum cortisol concentrations (μmol/l) on the control and allergen days were as follows:

	9.30 am (before)	*3 pm (3 h)*	*9 pm (9 h)*	*9.30 am (24 h)*
Control	555·7 (68·4)	356·4 (37·8)	143·8 (20·5)	470·8 (82·9)
Allergen	481·4 (66·7)	330·2 (47·8)	176·3 (37·6)	484·9 (63·0)

Highly significant ($p < 0.0001$) decreases in cortisol levels were observed on both days. Cortisol concentrations after allergen did not differ significantly from corresponding control day values, and did not correlate with the size of the late response (mean FEV_1% decrease 18·7 (4·1)) or the associated changes in airway histamine responsiveness or blood eosinophils. We conclude that after allergen challenge serum cortisol concentrations exhibited normal diurnal variation and were unrelated to the late asthmatic response or associated changes.

Allergen induced late reactions and cellular infiltration in the upper respiratory tract

S LOZEWICZ, E GOMEZ, S CHALSTREY, D GATLAND, Y HARMANYERI, RJ DAVIES *Department of Respiratory Medicine, St Bartholomew's Hospital, London* It is well recognised that an early phase allergic reaction occurs in the nose but it remains uncertain whether there is a late increase in nasal airways resistance (NAR) comparable to that seen in the lower airways. In order to assess the nasal late phase reaction we studied 41 patients with seasonal allergic rhinitis to grass pollen. One nostril was challenged with a solution of mixed grass pollens (Bencard Ltd, Brentford) and measurements of NAR made until biopsy specimens of the nasal mucous membrane were taken under local anaesthetic from the ipsilateral and, as a control, contralateral inferior turbinate. Biopsy samples were taken at one of the following times after allergen: 0 (baseline) (n = 7), ½ h (n = 6), 1 h (n = 6), 2 h (n = 5), 4 h (n = 6), 8 h (n = 5), and 24 h (n = 6). Cell counts were made of mast cells, basophils, eosinophils, and neutrophils in the epithelium and lamina propria. In six of the patients we measured NAR for 4 hours following provocation of one nostril with grass pollen as described above, and compared the results with those occurring in the same six patients after isotonic saline challenge on a control day. Following allergen all of these

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patients demonstrated an immediate and subsequently a late increase in NAR such that in each patient the maximum NAR achieved 2–8 hours after challenge was at least 50% greater than on the control day. The median values of maximum NAR during the period 2–8 hours were 2·1 and 0·65 kPa. l^{-1}. s for the allergen and controls days respectively ($p < 0·02$). These results suggest that a late increase in NAR frequently follows nasal provocation by allergen.

Does an increase in non-specific bronchial responsiveness precede the late asthmatic response following allergen challenge?

OP TWENTYMAN, ST HOLGATE *Medicine 1, Southampton General Hospital, Southampton* Bronchial hyperresponsiveness is increased following late asthmatic bronchoconstrictor reactions after allergen challenge. We have examined the temporal development of the increase in airways responsiveness to histamine after allergen challenge in 17 atopic asthmatic subjects (8F, 9M), baseline FEV_1 >65% predicted, challenged with inhaled grass pollen or *D pteronyssinus*. All medication was withheld for six hours prior to each challenge. Bronchial responsiveness to histamine was measured 15 hours and one hour before and 1·5, 3·5, 5·5 and 7·5 hours after challenge with a dose of allergen producing a >20% fall in FEV_1 in the immediate reaction. Immediate bronchoconstriction resulted in a 30·1 (2·9)% mean (SEM) fall in FEV_1 from baseline at 20 min. FEV_1 improved to within 7·6 (2·8)% of baseline at 1·5 hours and 4·8 (1·9)% of baseline at 3·5 hours. The late bronchoconstrictor response followed causing a progressive decline in FEV_1. At 7·5 hours FEV_1 had fallen 23·9 (4·4)% from baseline. A 1·2 (−2·0 to +2·6) (mean (range)) fold decrease in responsiveness between the first and second baseline measurement was not significant. Responsiveness increased 1·5 (−2·3 to +2·5), 1·9 (−2·33 to +3·6), 2·6 (−2·3 to +5·6) and 3·3 (−1·5 to +6·0) fold respectively at 1·5, 3·5, 5·5 and 7·5 hours after allergen. The increase in responsiveness reached significance ($p < 0·05$) compared with the first baseline measurement 3·5, 5·5 and 7·5 h after allergen. In conclusion, increased bronchial responsiveness develops progressively after allergen challenge, is significant at 3·5 h and precedes late bronchoconstriction. Late bronchoconstriction may reflect these events rather than initiate them.

Value of computed tomography in unexplained haemoptysis

AB MILLAR, A BOOTHROYD, D EDWARDS, MR HETZEL *Departments of Thoracic Medicine and Radiology, Whittington Hospital, and University College and Middlesex School of Medicine, London* It is well known that in many cases of haemoptysis (perhaps as many as 30%) no cause is found. We have therefore assessed the value of computed tomography (CT) scanning in patients in whom other investigations have failed to give a diagnosis. We studied 22 consecutive patients who presented with haemoptysis, and in whom conventional chest radiographs were normal. Each patient underwent fibreoptic bronchoscopy, which was either normal or showed only blood in the bronchial tree. CT examination of the thorax was then performed. CT scan abnormalities were present in 15 (69%) of patients, of whom three (19%) had blood in the endobronchial tree at bronchoscopy. Three patients had arteriovenous malformations and three patients had bronchiectasis, one of whom also had a bronchogenic carcinoma. Four had pulmonary nodules suggestive of carcinoma and one had a pulmonary nodule, which was a metastatic malignant melanoma. One patient had a focal area of consolidation and two others had shadowing suggestive of intra-alveolar blood. A further patient had minor abnormalities on his chest radiograph which were consistent with alveolar bleeding. CT showed dramatic cystic changes. There were found at open lung biopsy to be due to histocytosis X. We conclude that computed tomography is an essential investigation in all cases of haemoptysis when the chest radiograph and fibreoptic bronchoscopy are normal since it will lead to a diagnosis in a substantial proportion of patients.

Role of computed tomography scanning in the evaluation of suspected asbestos related lung disease

S LOZEWICZ, R REZNEK, M HERDMAN, J DACIE, A MACLEAN, RJ DAVIES *St Bartholomew's Hospital, London* Computed tomography (CT) has been shown to be more sensitive than chest radiography in the detection of both pleural and pulmonary lesions associated with asbestos exposure (Katz D *et al. Clin Radiol* 1979;**30**:207). However, the role of CT of the chest in evaluating suspected asbestos related lung disease is not defined. We have studied 27 men with a history of asbestos exposure by lung function testing, high kilovoltage posteroanterior and left lateral chest radiographs, and chest CT. Eighteen of the subjects were randomly selected asbestos workers who had been referred for routine assessment under the Control of Asbestos at Work Regulations 1987. Their age range was 19–51 (mean 30·8) years and the duration of exposure to asbestos in this group ranged from one month to 30 years (mean 5·1 years). CT demonstrated pleural plaques in only one of these patients but these were evident on chest radiography. CT demonstrated minimal interstitial lung shadowing in only one patient and this was not evident on chest radiography. In five patients with suspected pleural shadowing on chest radiography no abnormality was seen on CT. A separate group of nine patients was studied, all of whom had been referred for the evaluation of respiratory symptoms. Their age range was 45–78 (mean 59·7) years and the duration of asbestos exposure varied from 20 to 30 (mean 18·1) years. All of these patients demonstrated pleural thickening on chest radiography, which was confirmed by CT. Five of these patients demonstrated interstitial lung shadowing on CT, which was evident on chest radiography in only one case. These results suggest that CT scanning is unlikely to be useful in routinely screening individuals exposed to asbestos. However, when used selectively for those with pleural changes on chest radiography it may be useful in refuting or confirming the presence of pleural disease, or demonstrating unsuspected pulmonary interstitial shadowing.

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Role of magnetic resonance imaging (MRI) in thoracic malignancy

P GODDARD, J CATTERALL *Bristol Royal Infirmary* Early reports established a role for MRI in the investigation of thoracic malignancy. Gamsu *et al* (*Radiology* 1983;**147**:473) showed two main advantages over CT in the mediastinum: ease in distinguishing between lymph nodes and vascular structures and very high contrast between lesions and fatty tissue. Fifteen patients with proved thoracic malignancy were studied by MRI. The malignancies included carcinoma of the bronchus, mesothelioma and lymphoma. A variety of scanning sequences and planes were employed. The ability to scan in any desired plane proved to be an advantage. If direct comparison with chest radiography was desired the coronal plane was very useful. If comparison with CT was necessary the transverse plane was indicated. The sagittal plane was difficult to interpret in the chest but was the most useful plane for studying the spine. MRI can be effectively used to confirm or refute the presence of large lymph nodes in the mediastinum and this can be particularly useful in patients with carcinoma of the bronchus. The normal lung parenchyma is of low proton density. Solid pulmonary lesions are more readily studied than was originally thought. Magnetic resonance imaging is also useful for studying the pleura and chest wall.

Characteristic computed tomography appearances of pulmonary alveolar proteinosis

CR MURCH, DH CARR *Brompton Hospital* Seven patients with pulmonary alveolar proteinosis have been examined by computed tomography (CT) of the thorax. The appearances are similar in all patients, and unlike pulmonary shadowing seen in other diseases. The CT appearances correlate well with histology and demonstrate septal thickening within lung affected by pulmonary alveolar proteinosis. These characteristic CT appearances suggested the diagnosis in one of the patients, which was subsequently confirmed by lung biopsy.

Narrow section computed tomography in the diagnosis of bronchiectasis

NC MUNRO, JC COOKE, DC CURRIE, B STRICKLAND, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, and Department of Radiology, Brompton Hospital, London* Computed tomography (CT) using 10 mm slice width has the low sensitivity of 66% (*Thorax* 1987;**42**:272) by comparison with bronchography in the diagnosis of bronchiectasis. To determine whether CT using narrow sections would be more sensitive we compared CT scans using 3 mm slice width at 10 mm intervals with bronchograms in 27 consecutive patients with chronic sputum production referred for diagnosis. The films were read separately in a blind, randomised fashion by two pulmonary radiologists. For each segment the presence or absence of proximal and distal bronchial dilatation on CT and/or bronchogram was noted, as well as, on the bronchogram, the presence of mucus, "stripping," or mucus plug and, on the CT scan, proximal and distal wall thickening and parenchymal disease. In the 498 segments examined the CT scans were interpreted as showing bronchiectasis in 46 out of 55 bronchographically bronchiectatic segments (84% sensitivity) and in 80 out of 364 bronchographically non-bronchiectatic segments (18% "false positives"). However, only 15 of these 80 segments were entirely normal on the bronchogram: one was underfilled and the remainder displayed "bronchitic" changes (*Thorax* 1978;**42**:278). We conclude that 3 mm slice width CT scanning is useful in the investigation of chronic sputum production but bronchography may still be necessary when surgery is being considered.

Bronchial lavage and biopsy findings before and after allergen challenge in mild atopic asthma

RC BEASLEY, JA ROBERTS, WM ROCHE, ST HOLGATE *Immunopharmacology Group, Southampton General Hospital, Southampton* In this study we have examined the cell content of bronchial lavage fluid (BL) and mucosal biopsy specimens in eight atopic asthmatic subjects (age 19–26 years, mean FEV_1 99·4% of predicted, PC_{15} meth 1·13 (range 0·16–7·2) mg/ml) and four non-asthmatic controls, age 27–42 years, mean FEV_1 105% predicted, PC_{15} meth >27 (range 16–>32) mg/ml. Regular treatment for the asthmatics consisted of none (2) and salbutamol alone (6). Subjects were premedicated with nebulised salbutamol, ipratropium bromide and local lignocaine. A fibreoptic bronchoscope was passed and a 30 ml bronchial wash undertaken from one lung and two or three mucosal biopsy specimens taken from 3rd–4th generation airways of the other lung. At least three weeks after the first procedure five asthmatic subjects underwent bronchial challenge with HDM allergen, with early falls in FEV_1 from 27–38% and late phase falls of 25–39%; while three asthmatics underwent methacholine challenge with %fall in FEV from 31–41%. A second bronchoscopy with lavage and biopsies was then undertaken 17 hours post-challenge in all eight asthmatics. The lavage and biopsies were coded prior to examination. In the first lavage, the asthmatics had more eosinophils ($p < 0·05$) and epithelial cells ($p < 0·01$) but fewer lymphocytes ($p < 0·05$) than controls. For the whole group the epithelial cell count correlated inversely with PC_{20} ($r = 0·68$, $p = 0·015$). In the asthmatics but not in controls there was extensive epithelial fragility, subbasement membrane collagen deposition and mucosal infiltration with eosinophils, degranulated mast cells, lymphocytes and macrophages. Electron microscopy showed the eosinophils to be highly activated, and eosinophil, monocyte and platelet adherence to venular endothelial cells. No major differences were apparent between lavage and biopsy findings before and 17 hours after allergen and methacholine challenge. We conclude that extensive acute and chronic inflammatory changes are present in the airways of patients with mild asthma.

Relation between cell number and activity and PAF-acether in bronchoalveolar lavage (BAL) fluid

SC STENTON, EN COURT, CA KELLY, P GOADY, WP KINGSTON, DJ HENDRICK, EH WALTERS *Newcastle General Hospital, University of Newcastle upon Tyne, Department of Pharmacology, Sunderland Polytechnic* We have previously reported (*Br J Clin Pharmacol* 1987;**24**:258P) the presence of PAF-acether in BAL fluid from some asthmatic subjects but not from control subjects. We have now looked at a number of parameters to see how asthmatics with PAF-acether in their BAL fluid might differ from those without. BAL was performed in a middle lobe segment using three × 60 ml aliquots of sterile buffered saline in 28 consecutive asthmatic subjects undergoing routine diagnostic bronchoscopy. Total cell counts (Neubauer counting chamber) were measured, the aspirate centrifuged and the supernatant stored for later PAF-acether assay. Differential cell counts (Wright Giemsa) were performed on resuspended cells and neutrophil and macrophage metabolic activity was assessed by means of latex stimulated luminol and lucigenin enhanced chemiluminescence respectively. PAF-acether was extracted from 2·5 ml aliquots with chloroform/acetone and measured by means of a guinea pig platelet bioassay. Where samples appeared to contain PAF this was further identified using thin layer chromatography. PAF-acether was found in BAL fluid from eight of the asthmatic subjects (median 2·9, range 0·5–7·1 nmol/l where PAF-acether was present) and from no controls. Multiple regression analysis showed associations between the presence of PAF-acether and low BAL neutrophil counts in association with high lymphocyte counts ($p < 0·05$), and with macrophage metabolic activity ($p < 0·05$). The presence of PAF was not associated with bronchial responsiveness (PD_{20})FEV_1 to methacholine), age, atopy (skinprick tests), smoking status or neutrophil metabolic activity.

Does a cell mediated immune reaction contribute to asthma?

LW POULTER, C BURKE, E GALLAGHER, J KIDNEY *Department of Immunology, Royal Free Hospital and Medical School, London, Department of Thoracic Medicine, James Connelly Hospital, Dublin* Eight patients with clinically stable asthma (all non-smokers, $PC_{20}/FEV_2 > 2$ standard deviations outside normal, $\Delta FEV_1 > 400$ ml) underwent bronchial biopsies after informed consent. The biopsy samples were snap frozen and 6 μm sections cut on a cryostat maintained at −30°C. The sections were air dried, fixed in chloroform acetone (1:1) for five minutes and stored at −20°C until use. The presence and distribution of immunocompetent cells was analysed by immunohistological methods employing a panel of monoclonal antibodies. In all asthmatics but in no normal controls an inflammatory infiltrate was seen as a diffuse distribution of mononuclear cells throughout the lamina propria with some clustering of cells just below the epithelium. The inflammatory cells were both lymphocytes and macrophages, the former being predominant in the cell clusters and the macrophage like cells being predominant in the lamina propria. Monoclonal antibodies to CD4 and CD8 antigens demonstrated a ratio of 1:1 in 5/8 cases with 3/8 cases showing a majority of CD8+ cells. Double staining with McAbs showed that most of the CD8+ cells were CD5− and UCHL1+ indicating a direct involvement of resident intraepithelial lymphocytes in the reaction. The majority of macrophage like cells were RFD7+ mature macrophages, but RFD1+ dendritic cells were associated with lymphocyte clusters just below the epithelium. All macrophage like cells expressed HLA-DR antigens and in some areas the epithelial cells were also strongly HLA-DR positive. These results are consistent with the presence of an ongoing cell mediated immunological reaction in the bronchial wall of patients with clinically stable asthma.

Circulating markers of oxygen derived free radical production in acute asthma

ER CHILVERS, M WHYTE, H GARRATT, R FINK, PW IND *Department of Medicine, RPMS, Hammersmith Hospital, London, and Department of Clinical Chemistry, West Middlesex Hospital* Oxygen derived free radicals generated by activated alveolar macrophages, leucocytes and mast cells, have been proposed as important mediators of airway inflammation (Raphael GD, Metcalfe DD. *Eur J Respir Dis* 1986;**69**:44). To evaluate their potential role in asthma we have measured the serum concentration of phospholipid esterified 9,11- and 9,12-linoleic acid isomers, linoleic acid sensitive circulating markers of free radical activity (Fink R *et al. Lancet* 1985;ii:291), in six patients (two males; aged 19–42) with acute asthma. Measurements were made by HPLC with simultaneous assay of 9,11-linoleic acid and 9,12-linoleic acid with a diode array detector. Patients were studied at 0, 6, 12, 24 and 48 hours and 4–6 weeks following admission. Initial blood samples were taken prior to any drug administration or oxygen therapy. On admission, the mean heart rate was 104 (SEM 6·1) beats/min, systolic BP 123 (6) mm Hg, peak expiratory flow rate (PEF) 103 (41) l/min, respiratory rate 31 (4·5)/min and arterial Po_2 9·5 (1·4) kPa. On review at 4–6 weeks all patients were free of audible wheeze and mean PEF was 309 (54) l/min. Mean concentrations of 9,11-linoleic acid and 9,12-linoleic acid on admission were normal at 18·3 (3·3) μmol/l and 1143 (120) μmol/l (ratio 1·6 (normal range 1·0–2·0)). At 4–6 weeks mean concentrations were 19·2 (3) μmol/l and 1372 (49) μmol/l (ratio 1·4). In only one subject was an abnormally high ratio found, and this returned to normal at four weeks. This study does not support a major role for oxygen derived free radical generation in acute asthma, although the presence of efficient local scavenger systems may exist in the airways.

Histamine responsiveness of rabbit bronchial smooth muscle after exposure to activated human neutrophils

LG MCALPINE, EP WILSON, JC MCGRATH, NC THOMSON *Department of Respiratory Medicine, Western Infirmary, Glasgow, Autonomic Physiology Unit, Institute of Physiology, University of Glasgow* Asthma is associated with an inflammatory infiltrate in the bronchial wall and with airway hyperresponsiveness to histamine. The products of activated neutrophils have been implicated as a cause of that hyperre-

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sponsiveness. We examined the effect of zymosan activated human neutrophils on the histamine responsiveness of rabbit bronchial smooth muscle in vitro. Smooth muscle rings prepared from rabbit second order bronchi were suspended under 1 g initial tension in an organ bath containing Krebs-Henseleit solution aerated with 5% CO_2 in O_2 at 37°C. A cumulative concentration response curve (CCRC) to histamine (0·03–1000 μM) was performed on all preparations after which untreated preparations were used as time controls and others exposed to the supernatant of activated human neutrophils. Neutrophils were prepared from heparinised whole blood, suspended in Krebs-Henseleit solution at 2×10^7/ml and activated by incubation for 30 min at 37°C with opsonised zymosan. The supernatant was used to replace the Krebs-Henseleit solution in the organ baths of test preparations. A second histamine CCRC was performed after five minutes' exposure of the tissue to this supernatant without further washing. Time controls showed a shift to the right of the CCRC to histamine: pD2 (mean (SEM))—1st CCRC = 5·57 (0·12), 2nd CCRC = 5·24 (0·10); $p < 0·05$. The addition of the supernatant from activated neutrophils did not alter the resting tension. The histamine CCRC (pD2 1st CCRC = 5·48 (0·10), 2nd CCRC = 5·26 (0·10)) was not altered by the supernatant from activated neutrophils when corrected for the effect of time. In conclusion, the products from zymosan activated human neutrophils do not influence the in vitro histamine responsiveness of rabbit bronchial smooth muscle.

Effect of oral terfenadine, alone and in combination with flurbiprofen, on adenosine 5'-monophosphate induced bronchoconstriction in non-atropic asthma

GD PHILLIPS, ST HOLGATE *Medicine 1, Southampton General Hospital, Southampton* Inhaled adenosine and adenosine 5'-monophosphate (AMP) cause bronchoconstriction in atopic and non-atopic asthma by a mechanism believed to involve preformed mediator release from airway mast cells and/or an interaction with neural reflexes. In this study the effect of oral terfenadine 180 mg (T), flurbiprofen 100 mg (F), and the drug combination (C) on AMP induced bronchoconstriction was investigated in eight non-atopic asthmatic subjects, mean age 53·8 (SD 5·6) years, in a randomised, double blind, placebo controlled study. The provocation concentrations of histamine and AMP required to produce a 20% decrease in FEV_1 (PC_{20}) were determined to be 2·5 (0·2–16·3) and 50·1 (1·5–841) mg/ml respectively, representing a potency difference of 17·8 fold on a molar basis. In subsequent time course studies T and C, but not F, ablated the bronchoconstrictor response to inhalation of the PC_{20} histamine. T and F inhibited AMP-provoked bronchoconstriction by 49·8 (5·5)% ($p < 0·01$) and 31·9 (7·9)% ($p < 0·01$) respectively when areas under the FEV_1-time curves are compared with placebo, the difference between the two treatments not being significant ($p = 0·06$). C inhibited the response to AMP by 60·0 (8·3)% ($p < 0·01$), this being significantly greater than with F ($p < 0·01$) but not T. These data implicate both histamine and cyclo-oxygenase products in the bronchoconstrictor response to AMP.

T lymphocyte activation in acute severe asthma is accompanied by a rise in serum concentrations of interferon and the soluble interleukin-2 receptor

CJ CORRIGAN, AB KAY *Department of Allergy and Clinical Immunology, Cardiothoracic Institute, Brompton Hospital, London* We previously described activated CD4+ T lymphocytes (T-LC) in peripheral blood in severe asthma (ASA), suggesting that cell mediated immunity has a role in the pathogenesis of this disease (*Thorax* 1988;43:238P). These observations have been extended by studying serum concentrations of two proteins elaborated by activated T-LC (γ-interferon (γ-IFN) and the shed receptor for interleukin-2 (IL-2R). We compared ASA (n = 21) with control groups (normal, mild asthma and chronic obstructive airways disease). Peripheral venous blood was drawn on admission to hospital and in some instances, one week later; control subjects were sampled once only. γ-IFN was assayed by solid phase radioimmunoassay and IL-2R by an enzyme linked immunoassay. Significantly elevated concentrations of both γ-IFN and IL-2R ([γ-IFN], [IL-2R]) were found in ASA on admission as compared with all three control groups ($p < 0·01$). Patients restudied after one week of treatment showed a significant reduction in [IL-2R] ($p < 0·02$). [γ-IFN] concentrations were also reduced. There was a linear correlation between [IL-2R] in the ASA patients and the peak expiratory flow rate (% predicted) ($p < 0·01$). These observations provide further evidence that cell mediated immunity is a feature of the pathogenesis of ASA.

Improving pulmonary drug aerosol delivery

SHL THOMAS, CM PAGE, TO NUNAN, DM GEDDES *St Thomas' Hospital and Brompton Hospital, London* Equipment used to inhale aerosols produced by jet nebulisers is inefficient as only a fraction of the aerosol is deposited in the lungs. Considerable amounts are lost uninhaled to the atmosphere. With the aim of reducing this loss, an inhalation system was designed which incorporated a storage chamber to conserve aerosol formed during exhalation for delivery at the subsequent inhalation. The effects of this modification were investigated in a three way study involving eight healthy subjects comparing two different storage chamber manifolds (SCM1 and SCM2) with a conventional inhalation system. The aerosol formed by an Acorn nebuliser filled with 3 ml ^{99m}Tc colloidal albumin solution, and driven by 6 l/min compressed air until dry, was inhaled via each apparatus on separate occasions. After inhalation the fate of the aerosol was determined by scintiscans of the lungs, stomach, and oropharynx, and the filter placed the expiration port of the apparatus. The results showed a reduction in aerosol deposition on the filter, and an increase in deposition on the apparatus and in the lungs. In comparison with conventional apparatus mean improvements of 128% (SCM1, $p = 0·078$) and 125% (SCM2, $p = 0·023$) were seen in pulmonary deposition. We conclude that this modification offers substantial advantages for treatment of patients using jet nebulisers.

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Effect of high frequency oscillations on the pulmonary aerosol deposition rate

SHL THOMAS, JA LANGFORD, DM GEDDES *London Chest Hospital, London* Superimposing high frequency oscillations (HFO) on normal tidal breathing may have important effects on the pulmonary deposition of inhaled aerosols. To investigate these, dynamic pulmonary scintiscans were made while five patients with chronic airflow obstruction (CAO) and four normal subjects inhaled a ^{99m}Tc DTPA aerosol under control circumstances and with HFO at 8, 16, and 24 Hz. The slopes of time-activity curves constructed for pulmonary regions of interest were used as measures of pulmonary deposition rates (PADR), following correction for blood background and pulmonary DTPA clearance. In separate experiments the effects of HFO on the deposition of aerosol on the apparatus and oropharynx, and on particle size characteristics, were also measured. All frequencies of HFO reduced total and peripheral PADR in both subject groups. Reductions from control were largest with HFO at 8 Hz (normals: 31 (SEM 44)%, $p < 0.005$; CAO patients: 59 (29)%; $p < 0.005$). With HFO a greater proportion of total PADR occurred in peripheral lung in the CAO patients. HFO reduced deposition on the oropharynx and increased it on the apparatus. Particle sizes reaching the mouthpiece were reduced with HFO. We conclude that HFO reduces PADR by increasing deposition of larger particles on the apparatus. Although improved peripheral aerosol distribution may occur as a result, no clinical benefits would be expected if this method was used during drug administration.

Bronchodilator response and deposition patterns in response to nebulised particles with different breathing patterns in patients with chronic stable asthma

BMZ ZAINUDIN, SEJ TOLFREE, M SHORT, SG SPIRO *Departments of Chest Medicine and Medical Physics, University College Hospital, London* The effect of different breathing patterns of inhaled nebulised aerosol on deposition patterns and bronchodilator responses within the lungs were studied in eight patients with chronic stable asthma. Salbutamol solution (2·5 mg) labelled with technetium-99m human serum albumin was nebulised by an Acorn nebuliser. Particles with a mass median aerodynamic diameter (MMAD) of 4·8 μm were produced for inhalation by tidal breathing (study 1), six tidal breaths followed by three deep breaths (study 2) and six tidal breaths followed by three deep breaths, each with a five second breath hold at total lung capacity (study 3). Each subject continued each breathing pattern for four minutes. Aerosol deposition was assessed by gamma camera imaging and lung function by the measurement of PEF, FEV_1 and FVC. The total inspired volume during the four minutes of inhalation was greatest in study 2. The mean (SEM) values for the total inspired volumes were 31·1 (2·2) l for study 1, 40·8 (4·2) l for study 2, and 33·0 (2·6) l for study 3, and the percentages of total lung deposition of radioaerosol were 10·9 (1·4)%, 12·7 (1·3)% and 11·9 (1·2)% respectively; but these differences were not significant. The distribution patterns of aerosol within the lungs were similar. There were no significant differences in the percentage change of PEFR, FEV_1 and FVC 30, 45 and 60 minutes after inhalation of the aerosol. This study shows that inhaling a nebulised aerosol by tidal breathing (the simplest method) is as efficient as tidal breathing with deep breaths with or without a breath hold.

Influence of size and inspiratory flow rates on the efficiency of a spacer: in vitro study

BMZ ZAINUDIN, M BIDDISCOMBE, SEJ TOLFREE, M SHORT, SG SPIRO *Departments of Chest Medicine and Medical Physics, University College Hospital, London* We studied the effect of spacer size and inspiratory flow rate on aerosol deposition in vitro. A plastic cone spacer whose size could be varied from 650 to 1350 ml internal volume was constructed. A multistage cascade impactor with a throat extension was used as a model of the human respiratory tract. The percentage of aerosol deposited in stages 2 and 3 of the impinger was taken to represent the percentage that would be deposited within the lungs. Technetium-99m labelled teflon particles with a mass median aerodynamic diameter of 3·0 μm were produced with a May-spinning disc generator, and were incorporated into a commercial canister containing micronised salbutamol and freon propellants. The radiolabelled aerosol was actuated into a pear shaped spacer of the following sizes: 650 ml (19 × 8·2 cm), 750 ml (22 × 8·2 cm), 1050 ml (27 × 8·2 cm) and 1350 ml (32 × 8·2 cm) and inhaled at 0·5, 0·75, and 1·0 litres per second on different occasions. The radioactivity deposited in the spacer and impinger was measured by a whole body monitor. Our results showed that in general, the percentage of aerosol deposited in the "lung" increased with the spacer size and with increasing inspiratory flow rate ($p < 0.001$ for both spacer size and flow rate). The percentage of aerosol impacted and remaining in the spacer was lower with an increase in spacer size and/or flow rate ($p < 0.001$ for both spacer size and flow rate). The highest "lung" deposition (35·6 ± 3·3%) was achieved when the aerosol was inhaled through the largest spacer (1350 ml) at 1·0 litres per second ($p < 0.001$) and this was associated with the smallest percentage of aerosol remaining within the spacer (55·2 (3·6)%; $p = 0.003$). These in vitro results suggest that a larger spacer size can improve aerosol deposition in the lung provided the flow rate employed is effective in emptying the particles from the spacer.

Comparison of asthmatic patients' ability to use a metered dose inhaler (MDI) and a powder inhaler (PI) during relapse

S LAWFORD, J HILL *Warwick Hospital, Warwick* The MDI is usually the inhaling device prescribed for asthma and previously many studies have demonstrated a need for better education of both patients and their doctors in their use (Patterson and Crompton. *Br Med J* 1976;i:76; Frew and MacFarlane. *Practitioner* 1984;**278**:883). One hundred consecutive patients referred to an asthma clinic because of poor control had their MDI technique assessed. All had previously used both MDI and PI (rotahaler) and had also been shown the correct technique by either the general practitioner or a hospital doctor. The assessment was based on the steps detailed in the manufacturer's insert for each device. Only 15 MDI users used the device correctly when in relapse. The

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commonest error was in coordinating actuation with inhalation (74); 54 failed to hold the breath after inhalation and 50 failed to breathe out fully before inhalation; seven held the inhaler upside down and 12 at a distance from the mouth, and 22 failed to shake it. Of the 85 who failed to use the MDI correctly, 73 (85·9%) used the PI faultlessly. The commonest error (in 11) was failure to load the inhaler in the vertical position (12·9%), with eight patients failing to breathe out adequately prior to inhalation (9·4%) and six failing to hold breath adequately afterwards (7%). Only one patient failed to breathe deeply enough to agitate the powder capsule and one patient allowed the dose to be lost by carelessness after dividing the capsule. When asthma is in relapse, failure of hand breath coordination appears to be the most important factor in poor MDI usage. Separation of the hand action and inspiration as occurs in powder devices overcomes this fundamental difficulty and these observations, taken in conjunction with the current recognition of the harmful environmental effects of freon propellants, would seem to suggest that perhaps powder devices ought to become devices of first choice.

Drug delivery in man from Turbohaler, a new multidose dry powder inhaler

SP NEWMAN, F MORÉN, E TROFAST, N TALAEE, SW CLARKE *Royal Free Hospital, London; Hospital Pharmacy, Helsingborg, Sweden; AB Draco, Lund, Sweden* A new multi-dose dry powder inhaler, delivering 200 metered doses of 0·5 mg terbutaline sulphate, is now available (Turbohaler, Astra Pharmaceuticals). We have developed a radiotracer technique permitting the simultaneous assessments of aerosol deposition and clinical efficacy from Turbohaler. The radionuclide ^{99m}Tc, dissolved in chloroform, was added to a spheronised formulation of micronised terbutaline sulphate, and the chloroform allowed to evaporate. In vitro tests with a multistage liquid impinger showed that the radiolabel was distributed uniformly among different particle size fractions, and hence acted as a marker for the drug. A single metered dose was inhaled by ten asthmatic patients (mean (SEM) forced expiratory volume in one second (FEV_1) 48 (8)% predicted) and deposition in the lung comprised 14·2 (2·1)% of the dose. 71·6 (3·0)% of the dose was deposited in the oropharynx; the remainder was either retained on the mouthpiece (13·7 (2·1)%) or exhaled (0·5 (0·2)%). Gamma camera scans showed that radiolabel was present in both central and peripheral lung zones. FEV_1 increased from 1·40 (0·24) l to 1·77 (0·24) l ($p < 0·01$) 20 minutes after inhalation. The inhaled flow rate was 45 to 70 l/min and did not correlate with the degree of airway obstruction. These findings suggest that delivery of drug from Turbohaler is similar to that measured previously from a pressurised metered dose inhaler (Newman *et al. Thorax* 1981;**36**:52–5).

Metered dose inhaler (MDI) technique, 1988

S OWEN, S ANDREW, A WOODCOCK *Wythenshawe Hospital and Manchester Royal Infirmary, Manchester* Recently considerable emphasis has been placed on MDI technique. Has the message got through? Eighty patients were intercepted at Hospital and Community pharmacies when they were collecting prescriptions for metered dose inhalers. Patients came from four sources, general practice (n = 20), surgical outpatients (n = 20), general medical outpatients (n = 20) and respiratory outpatients (n = 20). Inhaler technique was scored using an eight point system by a single observer (SA) and assessed an effective (7–8 points), moderatively effective (5–6 points) or ineffective (0–4 points). Patients also responded to a simple questionnaire (table).

	n	*Effective*	*Moderately effective*	*Ineffective*
General practice	20	5	5	10
Surgical	20	8	5	7
General medical	20	9	4	7
Respiratory	20	13	7	0

Respiratory patients were significantly better at using their inhalers effectively ($p < 0·005$). Twenty six out of 80 patients had never received inhaler tuition. Patients who had received tuition were significantly more likely to have effective technique (29/54; 54%) than those who had not (6/26; 23%) ($p < 0·005$). Patients taught by hospital doctors had better technique than those taught by GPs (14/19 versus 7/24 $p < 0·05$). More respiratory patients were receiving inhaled steroid therapy (15/20; 75%) than the other groups (18/60; 30%). However, 12/15 respiratory patients on inhaled steroids believed that these drugs were "acute relievers" of asthma. Despite recent publicity, in outside respiratory clinics fewer than half of patients use MDIs incorrectly and a third received no tuition at all. In the respiratory clinic MDI technique is better, but emphasis needs to be now placed on increased knowledge on the mode of action of asthma therapy.

Computer training system for metered dose inhalers

PJ CHOWIENCZYK, PJ REES, GM COCHRANE *Guy's Hospital, London* Bronchodilation produced by inhalation of beta agonist from a metered dose inhaler is maximal when the inhaler is activated at the start of a long, slow inhalation, followed by a period of breath holding. Many patients, and especially children, find this difficult to achieve. We have developed a computer system incorporating a placebo inhaler with a flow sensor and a microswitch to detect activation. This system can be used to assess inhaler technique in terms of flow rate during activation and breath holding time. Our results show that most patients inhale at flow rates several times the optimal. We have used the modified placebo inhaler to develop a computer "game" to train subjects, particularly children, in the correct use of a metered dose inhaler. Inspiratory flow through the inhaler controls the movement of a "ball" on the computer display. "Skittles" along a marked path are knocked down when the inhaler is correctly activated and inhalation occurs at the appropriate flow rate. In 10 doctors/respiratory function technicians who regularly taught patients how to use inhalers only two were found to have optimal techniques. One of these two participated in a randomised controlled trial to assess the

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computer training game. The training game was found to be as effective as teaching by this technician in instructing eight year old children in the use of an inhaler.

Patterns of compliance with inhaled anti-asthma therapy

CR HORN, GM COCHRANE *Department of Thoracic Medicine, Guy's Hospital, London* Compliance with a rigid regimen of inhaled anti-asthma therapy has been assessed in a prospective study in general practice. One hundred and sixty two patients were followed for nine months. Salbutamol usage was determined by counting returned rotacaps and inhaled steroid (BDP) usage by weighing aerosol canisters. It was possible to assess compliance in 62% of the total number of "patient-weeks" in which salbutamol was prescribed and 68% of patient-weeks for BDP. Patients took between none and approximately twice the prescribed dosages of both salbutamol and BDP, with overall means of 92% and 82% respectively. Less than 80% of the prescribed dosage of salbutamol was taken in one quarter of patient-weeks but under compliance with BDP occurred in 40%. Overall patients were under compliant with both salbutamol and BDP concurrently 52% of the time assessed. More than 120% of the prescribed dosage of salbutamol was taken in 10% of patient-weeks; overuse of BDP occurred in 16% of patient-weeks. However, simultaneous overuse of both drugs occurred in less than 20% of weeks assessed. Under-compliance with salbutamol rose steadily from 27% to 43% during the first five months of the study but then fell to virtually disappear. During the final three months over one third of the patients took more than 120% of the prescribed number of salbutamol rotacaps. Compliance with BDP remained little changed throughout the study, roughly one half of patients taking the correct number of puffs at all stages. Over compliance rose only from 10% to 20%.

Use and abuse of inhaled corticosteroids

EA KAY, A BERNSTEIN *University Department of Pharmacy and Department of Medicine, Hope Hospital, Salford* Inhaled corticosteroids are frequently used in the management of asthma. We report a questionnaire study to determine prescribing patterns and patients' use and knowledge of inhaled corticosteroids. Several problems were identified. Forty patients, selected at random, receiving inhaled corticosteroids were interviewed. Questions included: patient knowledge of mode of action, side effects, duration and efficacy of treatment and compliance. Case notes were reviewed for diagnoses and history of steroid responsiveness. Diagnosis included asthma (22), chronic bronchitis and emphysema (11) and other (7). Eleven patients appeared to be receiving inhaled corticosteroids inappropriately, because they had no objective or subjective evidence of response to steroids. Only 19 patients admitted compliance, nine used it "as required," four used more and three less than prescribed, and five discontinued therapy. The prescribed frequency of use varied considerably and did not seem to affect compliance. Patients had little knowledge of the purpose of treatment. Only 14 knew it was slow acting. Sixteen believed rapid relief of breathlessness could be obtained with an additional puff of corticosteroid. Patients had no knowledge of potential side effects, but 11 had suffered adverse effects. Only 27 had had their inhaler technique checked. Twenty three considered the inhaled corticosteroid helpful. Questions on the preparation were posed by 17 patients. These results suggest that some patients and some doctors have limited knowledge of inhaled corticosteroids.

Relation of methacholine PD_{20} and peak flow variability measurements to respiratory symptoms in a community population

BG HIGGINS, JR BRITTON, S CHINN, TD JONES, PGJ BURNEY, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham, and Community Medicine Department, St Thomas's Hospital, London* We have measured bronchial reactivity to methacholine and peak expiratory flow (PEF) variability and related both to respiratory symptoms in a sample of 97 subjects selected at random from a small town and 126 subjects selected because of wheeze in the last year. Reactivity was measured as the provocative dose of methacholine causing a 20% fall in FEV_1 ($PD_{20}M$) by the method of Yan *et al* (*Thorax* 1983;**38**:760–5) with methacholine doses up to 24·5 μmol. PEF variability was expressed as amplitude % mean (AM—highest—lowest/mean daily reading). One hundred and fourteen subjects had a measurable PD_{20} whereas a measure for AM was obtained in all 223 subjects. Both $PD_{20}M$ $<24{\cdot}5$ μmol and AM were associated with wheeze, dyspnoea, and a diagnosis of asthma ($p < 0{\cdot}001$ for $PD_{20}M$, χ^2 test, and $p < 0{\cdot}001$ for AM, t test). Discrimination between wheezers with a diagnosis of asthma and non-asthmatics without wheeze was assessed as described by Armitage (*Statistical methods for medical research*, 1st ed, 1971:436) and was better with PD_{20} measurements ($\Delta = 2{\cdot}09$) than AM ($\Delta = 1{\cdot}57$). The frequency of wheezing episodes was related to both $PD_{20}M$ and AM (analysis of variance, $p < 0{\cdot}0001$ for both indices). PD_{20} and AM values correlated significantly ($r = -0{\cdot}478$, $p < 0{\cdot}0001$). Thus $PD_{20}M$ and PEF variability expressed as AM showed similar relationships to respiratory symptoms in this community sample: PEF measurements could provide an alternative to challenge tests in some surveys of respiratory morbidity.

Non-specific bronchial hyperresponsiveness in an unselected group of young Irish adults

HE MALONE, JS MCCORMICK, JS PRICHARD *Department of Medicine, Trinity College Building, Saint James's Hospital Dublin* The population distribution of non-specific bronchial responsiveness in normal subjects has received relatively little attention compared with that in asthmatics. This study measures its prevalence in a non-selected group of 102 young Irish adults (17–34 years) who did not have asthma. All underwent spirometry, a histamine provocation test, skinprick tests for type I sensitivity, and blood analysis for IgE. Information on adult and childhood respiratory

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problems was obtained by direct and parental questionnaires. The level of bronchial responsiveness was judged by the histamine aerosol concentration producing a 20% fall in FEV_1 (PC_{20}). Thirty four per cent of this normal group of young people constricted below 16 mg/ml and 16% below 8mg/ml. Sixty one per cent had cutaneous hypersensitivity and 19% had elevated IgE. Bronchial hyperresponsiveness was positively associated with cutaneous hypersensitivity ($\chi^2 = 5{\cdot}98$, df = 1; $p < 0{\cdot}05$) and with a history of hayfever ($\chi^2 = 10{\cdot}15$, df = 1; $p < 0{\cdot}01$) but not with serum IgE levels ($\chi^2 = 0{\cdot}006$, df = 1; $p > 0{\cdot}10$). These results suggest that in non-asthmatics skin reaction, nasal responsiveness and bronchial responsiveness may all be influenced by a common factor which is not serum IgE. Finally, although the subjects were all healthy adults and without current respiratory symptoms, bronchial hyperresponsiveness correlated strongly with childhood wheeziness ($\chi^2 = 10{\cdot}15$, df = 1; $p < 0{\cdot}01$).

Relation between airway reactivity, wheezing and lung function in gold miners

RL COWIE *Ernest Oppenheimer Hospital, Welkom, South Africa* Airway reactivity (AR) was assessed in 1197 gold miners by measuring the forced expiratory volume in one second (FEV_1) before and 10 minutes after salbutamol 200 μg by inhalation. AR was defined by a difference of more than 10% between the pre-salbutamol and post-salbutamol FEV_1. At an interview immediately preceding the lung function measurement respiratory symptoms were recorded. A total of 139 mean (12%) had evidence of AR and 272 men (23%) stated that they had wheezed. A history of wheezing was only 29% sensitive and 78% specific in detecting AR and had a positive predictive value for AR of 15%. The other symptoms which might have had a relation with AR, nocturnal dyspnoea and variable dyspnoea, each had a positive predictive value for AR of 14%. A history of wheezing was associated with tobacco smoking, but the presence of AR was not shown to be associated with any of the personal nor occupational variables evaluated in the study. Both the history of wheezing and AR had significant effects on the best FEV_1 while dyspnoea at night and variable dyspnoea had no independent effect on the FEV_1 after we had controlled for dyspnoea on effort. The mean FEV_1 was 91% of predicted (*American Thoracic Society*, 1982) for men without wheeze and without AR, 85% for men with either wheeze or AR and 79% for men with both wheeze and AR. Wheezing and AR appear to be separate entities but each predict a significant ($p < 0{\cdot}001$) reduction in the FEV_1.

The natural history of bronchial hyperresponsiveness

CJ TRIGG, JB BENNETT, M TOOLEY, MF D'SOUZA, RJ DAVIES *St Bartholomew's Hospital, London, and Canbury Medical Centre, Kingston, Surrey* The significance of the high prevalence of bronchial hyperresponsiveness (BHR) in the population is uncertain. Studies carried out by this department showed that 23% of a general practice population had BHR—that is, the cumulative dose of methacholine required to provoke a 20% fall in forced expiratory volume in one second (PD_{20} FEV_1) was <11 μmol. The prevalence of asthma in this population was only 5·07%. The majority of these patients were not identified as suffering from respiratory disease; indeed, a five year retrospective study of the general practice notes of these patients showed that attendance with respiratory complaints was not increased in this group. One hundred and twenty patients from the original general practice survey have reattended after an interval of 18–36 months for repeated investigations, including methacholine bronchial provocation testing, skin test responses to six common inhalant allergens and respiratory symptom questionnaires. Only 24 of the original 40 patients were found repeatably to have BHR and nine new cases were detected. There was also a significant increase in skin test positivity ($p < 0{\cdot}001$), not correlated with baseline bronchial responsiveness or change in bronchial responsiveness. The change in bronchial responsiveness was not correlated with smoking history, change in lung function or respiratory symptoms. These large changes in bronchial responsiveness suggest that there is a shifting group of individuals within a population who may be found to have BHR, perhaps depending on seasonal/environmental influences. We are investigating this hypothesis in a three year prospective study repeating the above tests at four month intervals.

Bronchial responsiveness in the elderly

L DOW, P VENN, ST HOLGATE *Department of Immunopharmacology, University of Southampton* In an epidemiological study of respiratory symptoms bronchial responsiveness and allergy in the elderly 2775 people over 65 years completed a respiratory questionnaire. Three hundred randomly selected subjects attended for spirometry, bronchial challenge with methacholine, skin tests, blood eosinophil count and serum IgE determination. Challenges were performed on 180 subjects aged 65–88 years with doubling doses of methacholine up to 6·4 μmol or until a greater than 15% fall from the post-saline value had been obtained. The PD_{20} was calculated by linear regression and bronchial responsiveness was defined as a PD_{20} $<6{\cdot}4$ μmol methacholine. Forty nine subjects were found to be hyperresponsive. Substantial differences were found between baseline FEV_1 (hyperresponders mean $FEV_1 = 1{\cdot}91$, range 1·15–2·70, non-responders mean $FEV_1 = 2{\cdot}38$, range 1·15–4·00; $p < 0{\cdot}001$) and the % predicted FEV_1 (hyperresponders mean % predicted $FEV_1 = 107$, non-responders mean % predicted $FEV_1 = 128$; $p < 0{\cdot}001$). No differences were found when the incidence of positive skinprick test responses to *Aspergillus fumigatus*, cat fur, *Dermatophagoides pteronyssinus*, and mixed grasses and histamine; eosinophil count $>0{\cdot}4/mm^3$; and IgE >200 U/ml were compared in hyperresponders and non-responders. We conclude that bronchial hyperresponsiveness in the elderly is associated with low baseline FEV_1 and, in contrast to what has been found in other studies, is not associated with allergic features.

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Diagnostic labelling: its prediction and consequences in the management of patients with chronic respiratory symptoms

P LITTLEJOHNS *Department of Clinical Epidemiology and Social Medicine, St George's Hospital Medical School, London*
The relationship between chronic respiratory symptoms, their diagnosis and management was assessed in a postal survey of 1600 people aged 40–70 years. Eighty six per cent of people returned a self completed screening questionnaire, 35% of which reported respiratory symptoms and were followed up with detailed questionnaires, clinical interview and pulmonary function tests. Thirty four per cent had been given a diagnostic label (for example, asthma, acute bronchitis, chronic bronchitis). This labelling process was associated with the severity of reported wheezing, disability, frequency of consultation with a general practitioner (GP) and attendance at an outpatient department. The association between diagnostic labelling and frequency of consultation with a GP remained after controlling for severity and other associated factors (odds ratio 1·43, 95% confidence limit (CL) 1·11–1·82). Twelve per cent of people with symptoms were prescribed some form of "bronchodilator" therapy. The likelihood of treatment was increased by admission to hospital (odds ratio 1·8, 95%, CL 1·02–3·25) and the presence of a diagnostic label (odds ratio 1·78, 95% CL, 1·22–2·6) independently of severity. It is concluded that factors other than severity of symptoms and signs determine the giving of a diagnostic label, and that the presence of a label then determines treatment. Changes in labelling fashions will alter levels of treatment independently of changes in epidemiological factors.

Differential diagnosis of chronic respiratory symptoms in a general adult population

P LITTLEJOHNS *Department of Clinical Epidemiology and Social Medicine, St George's Hospital Medical School, London*
Difficulty in distinguishing between chronic bronchitis and asthma in adults has been suggested as contributing to recent trends in asthma treatment (Fleming and Crombie. *Br Med J* 1987;**294**:279–83). This was investigated as part of a study of the prevalence, diagnosis and treatment of respiratory disease in a general population. One thousand six hundred adults aged 40–70 years were sent a screening questionnaire enquiring about chronic respiratory symptoms. Eighty six per cent completed the questionnaire of whom 34% reported symptoms. They were followed up with detailed questionnaires, clinical interview and pulmonary function tests. In all 4·7% of men had received a label of asthma, and 3·9% a label of chronic bronchitis; the corresponding values for women were 3·3% and 2·1%. "Asthmatics" tended to be younger, report more severe shortness of breath and less frequent coughing than "chronic bronchitics." There was no statistical difference between the two diagnostic groups in terms of sex, social class, frequency of symptoms of wheeze or phlegm production, service utilisation (consultations with general practitioner (GP) or attendance at hospital) or pulmonary function (FEV_1 peak flow % reversibility). Thus there was close clinical similarity between patients labelled as asthmatic and chronic bronchitic. In a national study in 1961 the ratio of GP diagnosed chronic bronchitis to a standard definition was 2·1 in men and 2·6 in women. In 1985 using the same criteria we found the ratio to be 0·6 and 0·5. This shift away from the label of chronic bronchitis, and the apparent lack of criteria on which this diagnosis is distinguished from asthma, suggests that diagnostic transfer from chronic bronchitis to asthma in adults has contributed to recent trends in treatment.

Acute bronchitis: effects of ambient temperature and urbanisation

D BOLDY, B GILES, D FLEMING, JG AYRES *Department of Respiratory Medicine, East Birmingham Hospital; Department of Geography, Birmingham University; and Research Unit of the Royal College of General Practitioners, Birmingham*
The weekly returns (WR) of the Research Unit of the Royal College of General Practitioners show acute bronchitis (AB) to be common, particularly in the winter and in the North of England (Ruffles and Ayres. *Eur J Respir Dis* 1986;supp 146:A144). The data have been further analysed to assess the effects of ambient temperature and urbanisation of AB attack rates. Isothermal maps were constructed for each quarter of the year from established tables. From these maps three regions were defined: warm (W), intermediate (I), cool (C), containing similar numbers of WR practices. Mean weekly attack rates (per 10^5 population) for AB were calculated for 1983–6 for the three isothermal regions. AB rates averaged over the four years were: 54 (W); 80 (I); 142 (C). For each year these differences were highly significant (W *v* I, W *v* C, I *v* C all $p < 0{\cdot}0001$). Although the isothermal regions are geographically quite different from the North (N), Central (Cen), South (S) regions, the attack rates for the two classifications are very similar (that is, 145 (N) *v* 142 (C); 88 (Cen) *v* 80 (I); 50 (S) *v* 54 (W)). WR practices were classified as urban (U) or rural (R) and the average AB attack rates over the four years were 113 (U) and 61 (R); for each year the results were highly significant ($p < 0{\cdot}0001$). When considering U/R AB rates by geographical regions, the N/Cen/S gradient was maintained: 148 (NU), 89 (Cen U), 62 (SU) ($p < 0{\cdot}0001$ for all comparisons except CU *v* SU in 1986), and 88 (Cen R) 37 (SR) ($p < 0{\cdot}0001$ for each year; insufficient NR practices for analysis). Although there is an U/R difference in the S region ($p < 0{\cdot}0001$ for each year), AB rates in Cen U and Cen R are very similar. These results suggest that ambient temperature is more important than urbanisation in explaining regional differences in AB.

Seven year follow up of shipyard workers

DJ CHINN, JE COTES *Department of Occupational Health, Medical School, Newcastle upon Tyne*
In 1979 a cross sectional survey of 609 shipyard workers (mean age 45·4 y) revealed high prevalences of respiratory symptoms and respiratory impairment; these features were related to age, smoking history and previous exposure to fumes as a welder or burner (*Thorax* 1987;**42**:728). The subjects were followed up on average 7·2 years later. By then 53 men had died. Of the living, 18 could not be traced, 48 refused reassessment and two were too ill. Four hundred and eighty eight (88%)

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completed a respiratory and occupational questionnaire and performed spirometry. On some men information was obtained on atopic status, lung volumes, transfer factor and the physiological response to submaximal exercise. At follow up increased numbers of men reported chronic cough and phlegm, wheeze most days and breathlessness (≥grade 3). Significant associated factors included above average age, below average forced expiratory volume, continuing to smoke and, in the case of increased breathlessness, trade as a welder or caulker/burner. The annual change in forced expiratory volume (FEV_1) was significantly related to age and to smoking history. The prospects for continuing employment and life expectancy were affected adversely by respiratory symptoms and being a smoker in addition to being affected by age. The submaximal exercise ventilations at an oxygen uptake of 45 mmol min^{-1} ($\dot{V}E_{45}$) increased between the surveys (n = 92). The percentage change per annum was related to age and other factors, including recent smoking history. It was independent of shipyard trade. A reduced grade of breathlessness at follow up was associated with a below average $\Delta\dot{V}E_{45}$. The study, to which many colleagues contributed, provided longitudinal information on interdependence between age, smoking habits, respiratory symptoms, lung function, submaximal exercise ventilation and trade as a shipyard welder or caulker/burner. But large-scale redundancies during the period of follow up affected the estimates of recent fume exposure.

Can fitness of schoolboys be linked to the risk of coronary heart disease within a community?

W FREEMAN, DC WEIR, J WHITEHEAD, DI ROGER, S SAPIANO, C FLOYD, P KIRK, N FIELD, RM CAYTON, PS BURGE *East Birmingham and Solihull Hospitals, West Midlands* Poor physical fitness may be an important risk factor for coronary heart disease (CHD). In Solihull mortality statistics of people aged 50 and over identified a poorer socioeconomic area with more deaths from CHD (A: 2·8 per 100), than in the rest of the borough (B: 0·7 per 100) or the nation (0·5 per 100). This study compared the physical fitness and activity levels of boys aged 15–16 years (5th year) from a school in region A with a school in region B. Height, weight and % of body fat were measured, and a questionnaire documented activity levels and smoking history in 46 (94%) and 42 (93%) pupils from schools A and B respectively. A progressive "shuttle running" exercise test, completed by 35 (71%) (A) and 38 (84%) (B) pupils, allowed the prediction of maximum oxygen uptake ($\dot{V}O_2max$) (Leger and Lambert. *J Appl Physiol* 1982;**49**:1–12). Heart rate (HR) was obtained at rest, during exercise, and for 10 minutes in recovery. The time after exercise for the HR to fall by 50% of the increase observed from rest to maximum (HR t50%) was calculated. The pupils in school A were shorter (A mean 1·70 (SD 0·08) *v* B 1·73 (0·06) m; $p < 0.05$) and had a higher % body fat (A 13·7 (5·0) *v* B 11·5 (3·5); $p < 0.05$). In school A more were smokers (A 28% *v* B 17%); fewer were doing sufficient exercise to improve cardiorespiratory fitness (A 30% *v* 38%); and more watched over three hours of TV per night (A 46% *v* 29%), although these differences were not statistically significant. The $\dot{V}O_2max$ estimated from the exercise test (A 46·5 (5·0) *v* B 47·5 (5·6) ml/kg/min) and the HR t50% (A 1·48 (0·44) *v* B: 1·62 (0·55) min) were not different between the schools. There were no differences in the cardiorespiratory fitness between the school children, as defined by $\dot{V}O_2max$ and recovery HR. However, there was a trend towards a greater number of smokers, a higher % body fat and less active lifestyles in school A, suggesting an increase in these other risk factors for CHD.

Respiratory system adverse drug reaction reports received by the Committee on Safety of Medicines in 1987

GH BURTON *Medicines Division, DHSS, Market Towers, London* Of the 16431 reports of suspected adverse drug reactions (ADRs) reported to the Committee on Safety of Medicines (CSM) in 1987, only 714 (4·3%) related to the respiratory system. Twenty deaths were reported: 12 a result of bronchospasm or worsening asthma, three a result of pulmonary oedema, three a result of upper airway obstruction and two a result of fibrosing alveolitis. The most common agents reported as suspect drugs were angiotensin converting enzyme (ACE) inhibitors (244), non-steroidal anti-inflammatory drugs (NSAIDs) (100), beta blockers (45), inhaled therapy (65), anaesthetic agents (31), antibiotics (24) and intravenous contrast media (7). Two hundred and seventy four reports related to the development or exacerbation of asthma, 65 of which were associated with inhalation therapy. Thirteen (two deaths) of these reports involved nebuliser solutions. There were 31 reports of drug related parenchymal disorders, 12 of which were single reports linking various drugs to the development of pulmonary fibrosis. Other serious ADRs reported were dyspnoea (50) laryngeal disorders (19) and apnoea (11). There were 218 reports (30% of all reports) of cough—almost all in relation to ACE inhibitors. The data from 1987 show a low reporting rate of mainly predictable respiratory ADRs. Of interest are the reports of drug associated parenchymal diseases, inhalation therapy and bronchospasm and ACE inhibitors and asthma. The 1987 data, together with those from the previous 23 years of reports, may help to identify and document suspected respiratory ADRs and can provide physicians with a large data base from which information is available.

Synthesis of α_1 proteinase inhibitor by the promonocytic U937 cell line

SC AFFORD, C OWEN, RA STOCKLEY, D BURNETT *Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* $Alpha_1$ proteinase inhibitor (α_1PI) may protect the lung from destruction by proteinases. Macrophages synthesise α_1 but little is known about factors which control α_1PI synthesis by these cells. We have used the human U937 promonocytic cell line as a model to study the effects of bacterial endotoxin and cellular maturation on α_1PI synthesis by monocytic cells. U937 cells were cultured with or without 16 nM phorbol myristate acetate (PMA) for up to 72 hours (to induce differentiation into mature monocyte like cells). The effect of 1 μg/ml bacterial lipopolysaccharide (LPS) on α_1PI synthesis was investigated (n = 6, all experiments). $Alpha_1$PI in cell lysates and supernatants was assayed using a direct binding ELISA method. Untreated U937 cells demon-

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strated an increase ($p < 0.05$) in α_1PI from 11 ng/10^6 cells (SEM 3·0) to 27·0 ng/10^6 cells (3·1) in 24 hours, but no further increase thereafter. After 48 hours in culture the amount of α_1PI synthesised by LPS stimulated cells (99 ng/10^6 cells (20)) was greater ($p < 0.03$) than by the LPS free cells (28·1 ng/10^6 (3·6)). The cells matured with PMA also demonstrated α_1PI synthesis after 24 hours from 9·6 (0·2) ng/10^6 cells to 56 (7·5) ng/10^6cells. However, LPS failed to cause an increase in the α_1PI synthesis by the PMA matured cells. After 48 hours the matured cells synthesised more ($p < 0.03$) α_1PI (60 ng/10^6 cells ± 2·3) than the promonocytic U937 (28 ng/10^6 cells ± 3·6) but LPS had no effect on the matured cells. The U937 model suggests that α_1PI synthesis increases with cell maturity but upregulation in response to LPS is lost.

Antielastases inhibit human leucocyte elastase (HLE) bound to elastine by two distinct mechanisms

HM MORRISON, HG WELGUS, D BURNETT, RA STOCKLEY, EJ CAMPBELL *Jewish Hospital at Washington University Medical Center, St Louis, Missouri, USA, and General Hospital, Birmingham* Neutrophils adherent to extracellular matrix can exclude proteinase inhibitors from the subcellular space. Antielastases which inhibit HLE bound to elastin may thus be important in protecting lung connective tissue from proteolytic damage. We have studied the effect of naturally occurring inhibitors of HLE (α_1 antitrypsin (α_1AT), antileucoprotease (ALP) and eglin C (EgC)) and the synthetic antielastases MeO-Suc-(Ala)2-Pro-Val-CMK (CMK) and a modified cephalosporin (MC) on elastolysis of bovine elastin by HLE. α_1AT, ALP and EgC preincubated with HLE for 15 minutes inhibited the enzyme on approximately a 1:1 molar basis. CMK and MC incubated under these conditions inhibited the enzyme on a 30:1 and 20:1 molar basis respectively. When each inhibitor was added to HLE-elastin complexes, greater amounts of antielastase were required for inhibition equal to the preincubation experiments. Curvilinear inhibition profiles suggested competition between enzyme and inhibitor. ^{125}I HLE/elastin complexes incubated with a seven fold molar excess of α_1AT and EgC led to a 34% and 40% reduction of HLE activity over six hours respectively. This was due to the inhibitors dissociating HLE from the complexes. In contrast, a sevenfold excess of ALP, a 700 fold excess of CMK or a 700 fold excess of MC produced a 72%, 70% or 55% reduction in enzyme activity, while HLE remained bound to the enzyme-substrate complex. This study indicates that inhibitors of HLE are relatively less effective against enzyme bound to elastin. They may act either by promoting dissociation of HLE from elastin or by inhibiting the enzyme in situ.

Evidence of intravascular and intrapulmonary neutrophil elastase release in patients at risk of and with established adult respiratory distress syndrome (ARDS)

GM ROCKER, MS WISEMAN, D PEARSON, DJ SHALE *Respiratory Medicine Unit, City Hospital, Nottingham* Neutrophil elastase, in excess of antiproteinase capacity, may cause endothelial injury in ARDS. Elastolytic activity in bronchoalveolar lavage fluid (BALF) from ARDS patients has been reported (Lee *et al. N Engl J Med* 1981;**304**:192–6) but there is little evidence relating both intravascular and pulmonary elastase release with lung injury in man. Fifty patients were studied in an intensive care unit. Twenty eight never developed ARDS (group 1); nine progressed to and 13 met criteria for established ARDS (groups 2 and 3). Increased capillary permeability was assessed by the protein content of BALF (BALFprot), and by a double isotope assessment of transferrin accumulation (TA) in the lung (Rocker *et al. Thorax* 1987;**42**:620–3). Systemic and BAL elastase release was quantified by detection of an elastase α_1 antitrypsin complex by ELISA. Free elastase activity in BALF was determined spectrophotometrically. The latter was associated (rank correlation) with evidence of increased permeability (TA: $r = 0.43$, $p = 0.005$, $n = 36$ and BALFprot: $r = 0.41$, $p = 0.007$, $n = 36$). Complexed elastase was detected in all BALF samples, highest levels were found in the established ARDS group and it was associated with BALFprot ($r = 0.73$, $p < 0.001$, $n = 36$). Circulating levels of elastase complex were related to increasing respiratory failure ($r = -0.41$, $p = 0.001$, $n = 50$), and levels were intermediate for patients yet to develop ARDS (group 2) but were five fold greater than normal control values in group 1 and 10 fold greater in group 3. These results support a role for pulmonary and intravascular elastase release in subsequent capillary endothelial damage and lung injury in man.

Determination of the concentrations of cysteine (CYSH) and glutathione (GSH) in plasma and bronchoalveolar lavage fluid (BALF) after *N*-acetyl cysteine (NAC) ingestion

MME BRIDGEMAN, M MARSDEN, M BAIN, R SANKARAN, W MACNEE, DC FLENLEY, AP RYLE *Departments of Biochemistry, University of Edinburgh Medical School, and Respiratory Medicine, Rayne Laboratory, City Hospital, Edinburgh* GSH is a sulphydryl containing tripeptide which is an antioxidant in cells and body fluids. NAC, a thiol containing drug, which is deacetylated to CYSH, a precursor of GSH, may thus have a role in increasing the antioxidant capacity of plasma and BALF. NAC (600 mg/day, by mouth) was given for five days to four healthy non-smokers. Plasma CYSH concentration increased from 6·7 (SEM) 1·3 μM to a peak concentration of 16·4 (4·2 μM ($p < 0.005$) on day one and from 6·2 (1·0) μM to 17·7 (5·2) μM ($p < 0.01$) on day five between 0·5 and 2·0 hours after NAC. Plasma GSH increased in every subject at a variable time between 0·5 and eight hours after NAC from a mean of 2·1 μM to 6·4μM on day one and from 2·9 μM to 5·8 μM on day five. In the 12 patients undergoing diagnostic bronchoscopy (mean age 45 (SD 25) years; five ex-smokers, two non-smokers, and five smokers), who took NAC (600 mg/day) for five days, plasma CYSH and GSH were 5·3 (1·9) μM and 2·9 (2·9) μM respectively compared with plasma concentrations of 4·2 (1·7) μM and 0·8 (1·2) μM in control patients ($n = 28$) ($p > 0.05$, $p < 0.005$). The concentrations of CYSH and GSH in BALF in these 12 patients were 0·1 (0·1) μM and 3·0 (1·7) μM respectively compared with BALF concentrations of 0·1 (0·1) μM and 1·9 (1·1) μM in patients ($n = 6$) who had not taken NAC ($p > 0.05$). No NAC was detected in plasma or BALF. In conclusion, NAC significantly increased the concentrations of GSH in the

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plasma of normal subjects and patients, but did not significantly affect their BALF and GSH concentrations. (This study was financially supported by Zambon Pharmaceuticals.)

Enhanced H_2O_2 response of human alveolar macrophages to environmental hypoxia is time dependent

AP GREENING, MH BAIN, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, Edinburgh* Extracellular release of oxidants by macrophages and neutrophils is thought to contribute to acute and chronic lung injury. We have shown previously (*Thorax* 1987;42:750) that human alveolar macrophages (AM) cultured in vitro for 24 hours under conditions of relative hypoxia demonstrate an enhanced release of hydrogen peroxide (H_2O_2) when subsequently stimulated. We questioned what duration of environmental hypoxia was necessary to induce the enhanced H_2O_2 response in AM. AM were obtained from 16 patients by bronchoalveolar lavage, enriched by plastic adherence and cultured for different time periods (4, 12, 16, or 20 h) in sandwich boxes "gassed" to give O_2 concentrations of 21% or 2·5%. After the culture period, phorbol ester stimulated H_2O_2 release from the AM was assayed fluorometrically. Culture in hypoxic environments for 16 hours or more resulted in enhanced release of H_2O_2 by the AM.

Culture duration (h)	*(n)*	*Mean (SEM) H_2O_2 release (nmol/10⁶ cells/h)*		
		(21% O_2)	*(2·5% O_2)*	
4	6	8·9 (3·7)	9·4 (3·8)	NS
12	10	8·5 (2·5)	9·8 (2·2)	NS
16	11	8·9 (1·7)	12·1 (2·2)	$p < 0·001$
20	5	7·0 (2·7)	10·6 (3·1)	$p < 0·05$

We conclude that an hypoxic stimulus of 16 hours is capable of priming AM for an enhanced release of H_2O_2. This implies that relative localised pulmonary hypoxia in vivo may affect AM oxidative functions even if the hypoxia is relatively transient.

Bronchoalveolar lavage cells in patients with AIDS

VL KRISHNAN, DR BUCHANAN, FM MOSS, RJ SHAW, MR HELBERT, AJ PINCHING, DM MITCHELL *St Mary's Hospital Medical School, London* Bronchoalveolar lavage (BAL) cell populations obtained from AIDS patients were studied and compared with BAL cells from patients investigated for haemoptysis for which no cause was found. In eight of 11 AIDS patients with bronchoscopically (FOB) proved *Pneumocystis carinii* pneumonia (PCP), the BAL lymphocyte count was elevated ($p < 0·001$); the remaining three patients had elevated neutrophil counts. A further elevation in lymphocyte count was seen in five patients who on clinical grounds and treatment response had PCP but who had negative bronchoscopy results.

	Mean (SEM)		
	% macrophages	*%polymorphs*	*% lymphocytes*
Control	85·4 (7·4)	5·7 (4·9)	7·3 (4·2)
AIDS control	88·8 (6·9)	5·6 (4·0)	4·6 (3·5)
PCP + FOB	65·8 (16·3)	4·8 (3·1)	29·8 (6·7)
PCP − FOB	32·3 (7·8)	4·2 (3·8)	63·5 (5·8)

Analysis using monoclonal antibodies to cell surface antigens revealed that 80–90% of BAL lymphocytes from AIDS patients with pcp had suppressor/cytotoxic T cell phenotype (CD +ve). There was a significant increase in numbers of cells expressing markers associated with the monocyte phenotype in BAL from AIDS patients. DR expression on alveolar macrophages was not significantly altered from the control group in contrast to reduced levels of DR expression on peripheral blood monocytes, dendritic cells and Langerhans cells previously reported in patients with AIDS. The results of these findings will be discussed both in terms of diagnosis and immunopathology (W Heagy *et al* 1984), decreased expression of human class II antigens on monocytes from patients with acquired immune deficiency syndrome and increased expression with γinterferon *J Clin Invest* 74:2089–96).

Assessment of mixing between sequential aliquots during bronchoalveolar lavage (BAL)

M DUDDRIDGE, CA KELLY, J FENWICK, DJ HENDRICK, EH WALTERS *Departments of Medicine and Medical Physics, Newcastle General Hospital, University of Newcastle upon Tyne* We have investigated the degree of mixing between sequential aliquots of a standard 3 × 60 ml BAL in five subjects with normal pulmonary function undergoing diagnostic bronchoscopy. BAL was performed in a subsegment of the middle lobe (2) or lingula (3), and each aliquot aspirated immediately after instillation into a separate container. With 0·005% methylene blue in the first aliquot and 1MBq technetium-99m colloid in the second aliquot, the dilution volumes for the individual aliquots (that is, the volumes to which the aliquots were diluted within the lung subsegment) were calculated according to stoichiometric principles. Concentrations of methylene blue and technetium-99m were measured by ultraviolet spectrophotometry and gamma counter respectively. The median dilution volume for aliquot 1 was 84 ml (range 68–106 ml) and that for aliquot 2 83 ml (70–107 ml). From the calculated total dilution volume for technetium-99m colloid in aliquots 2 and 3 the net dilution volume for aliquot 3 was 73 ml (50–150 ml). The degree of mixing between the second and first aliquots was calculated from the methylene blue recovery in the second aspirate, with a median of 25% (range 11–44%) of the residual 1st aliquot mixing with the second. This represented 24% (8–28%) of the second aspirate being derived from the residual of the 1st aliquot. The degree of mixing between the third and second aliquots was determined from the technetium-99m recovery in the third aspirate. Twenty eight per cent (11–41%) of the residual second aliquot mixed with the third. There was also the equivalent of 24% mixing (10–45%) of the residual fluid from the first aliquot with the third aliquot to account for the

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methylene blue recovered. This represented 16% (5–21%) of the third aspirate being derived from the residual of the second aliquot, and the equivalent of 8% (5–24%) derived from that of the first. These studies offer further quantitative analysis of the complex fluid dynamics occurring during BAL, and suggest that a greater proportion of BAL aspirate may represent a central lavage than was previously thought.

Clinical value of local versus serum ACE and lysozyme in stage II and III pulmonary sarcoidosis

C PRIOR, RA BARBEE, PM EVANS, PJ TOWNSEND, ZS PRIMETT, F FYHRQUIST, C GRONHAGEN-RISKA, PL HASLAM *Cardiothoracic Institute, London: University of Arizona; Minerva Institute and University of Helsinki* This study has explored whether amounts of ACE and lysozyme produced within the lungs correlate more closely than serum levels with clinical activity in stage II and III pulmonary sarcoidosis. We have measured these enzymes in serum and lavage (considering only the proportion locally produced by reference to serum and lavage albumin) in 25 patients and compared them with chest radiograph profusion scores (ILO/UICC) and lung function measurements before and after treatment with steroids. Following treatment the group showed improvement in chest radiograph scores ($p < 0.01$), TLCO ($p < 0.01$) and FVC ($p < 0.02$). There were falls in serum lysozyme ($p < 0.02$), serum ACE ($p < 0.01$) and local ACE levels ($p < 0.05$). Before treatment chest radiograph scores correlated with serum lysozyme levels ($p < 0.025$) indicating a correlation of this marker with the extent of parenchymal disease; in addition lower TLCO values correlated with higher serum lysozyme ($p < 0.025$) and local ACE ($p < 0.01$). A prognostic value for pretreatment local ACE levels was indicated by a significant inverse correlation with the final TLCO values ($p < 0.025$). Moreover, when we compared patients ($n = 7$) whose chest radiograph had cleared completely after treatment with the remainder ($n = 18$) who had residual shadows, the latter had higher pretreatment numbers/ml and % lavage neutrophils ($p < 0.05$). We conclude that in stage II and III sarcoidosis (*a*) pretreatment serum lysozyme and local but not serum ACE correlate with clinical impairment; (*b*) pretreatment lavage neutrophils and local ACE respectively predict residual chest radiography or lung functional impairment following steroid therapy.

Prognostic significance of bronchoalveolar lavage cell counts in pulmonary sarcoidosis

NM FOLEY, AP CORAL, DG JAMES, N MCI JOHNSON *Middlesex and Royal Northern Hospitals, London* We have previously reported on the clinical value of repeated bronchoalveolar lavage (BAL) as an indicator of "activity" in pulmonary sarcoidosis. Here we report the results of a prospective study of outcome in 67 patients with biopsy proved sarcoidosis. Our aim was to assess whether initial high intensity alveolitis (HIA)—that is, BAL lymphocyte count >30%—is an indicator of poor prognosis with regard to pulmonary function, as previous studies have suggested. Our patients were recruited from a sarcoid clinic: 33 male, mixed racial origin; 24 black, 33 white, 10 Asian. Mean age at onset of study was 42 years, mean disease duration 61 months, with a range from newly diagnosed to 20 years. At the beginning of the study period, BAL, chest radiograph, pulmonary function tests (PFTs) and gallium-67 lung scan were performed. No patient was on corticosteroid therapy at the time of initial BAL. Thirty nine patients had HIA on initial lavage. Patients were subsequently followed up in the clinic with chest radiograph and PFTs, and therapeutic decisions were made without knowledge of BAL cell counts. Mean follow-up period was 25 months (range 13–37). All patients had repeat chest radiograph and PFTs at the end of this period. Twenty three patients required corticosteroid therapy over the follow-up period, 20 for extra-pulmonary or multisystem involvement, three for pulmonary disease alone. Patients with initial HIA showed a significant improvement in pulmonary function over the two year period (FVC $p < 0.001$, TLCO $p < 0.05$), while those with low-intensity alveolitis (LIA) did not. (Wilcoxon signed rank test.) Thirty of the 39 patients with HIA had chronic sarcoidosis (duration >2 years, mean 80 months). These patients showed a significant improvement in FVC ($p < 0.003$), but not in TLCO. Improvement in PFTs was seen both in treated and untreated patients in the HIA group. Neither treated nor untreated patients with initial LIA showed significant improvement. We found no significant correlation between BAL neutrophil count and change in PFTs or chest radiograph. Our results suggest that high lymphocyte count on BAL is a favourable prognostic factor for lung function in pulmonary sarcoidosis, even in patients with chronic disease, while LIA may indicate more stable disease with less margin for improvement.

Emergence of a "suppressor macrophage population" may contribute to the pathogenesis of pulmonary sarcoidosis

MA SPITERI, J TUCKLEY, SW CLARKE, LW POULTER *Royal Free Hospital and School of Medicine, Pond Street, London* Alveolar macrophages were obtained from 10 patients with active pulmonary sarcoidosis and 10 healthy volunteers. These phenotypically distinct macrophage subsets were identified using a panel of monoclonal antibodies, RFD1 and RFD7 (identify dendritic cells and mature macrophages respectively in normal tissue). Sarcoid lavage was found to have significantly higher proportions of RFD1+ macrophages (mean 48% compared to 14% in normals) and RFD7+ macrophages (31% compared to 22% in normals). A third distinct subpopulation expressing positivity to both surface markers (RFD1+D7+) was observed to emerge in sarcoid patients (26% compared to 6% to normal). This RFD1+D7+ subset has been observed to increase in proportion with disease severity (being maximum in stage 3 disease). The functional significance of these 3 phenotypically distinct subsets was investigated by setting up allogenic mixed lymphocyte reactions (MRL). First these subsets were isolated by using plastic plate adhesion, metrizamide density gradients and D1-conjugated magnetic beads. Each subset was then co-cultured with healthy peripheral blood lymphocytes (PBM). Both the RFD1+ and RFD7+ subsets stimulated the MLR of allogenic PBM (stimulation index SI 6·1 and 3·4 respectively) whilst the RFD1+D7+ subpopulation abolished allogenic lymphocyte reactivity (SI 0·8). These results suggest that the emergence of

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RFD1+D7+ macrophages in sarcoidosis may account for the suppressor reactivity previously observed in unfractionated sarcoid BAL (Spiteri *et al*, 1987). We postulate that this subset plays a central role in the pathogenesis of sarcoidosis. In support of this, we have observed that efficacious therapeutic regimens in a homogneous group of stage 3 patients significantly reduce the proportion of these "suppressor" macrophages in lavage (Spiteri *et al*, 1988).

Cell mediated immunity in pigeon breeder's lung: effect of removal from antigenic exposure

MA JOHNSON, SW CLARKE, A CONDEZ, LW POULTER *Departments of Thoracic Medicine and Immunology, Royal Free Hospital and Medical School, London* Eighteen patients with pigeon breeders lung disease (diagnosis based on symptoms, lung function tests, *x* ray changes and circulating precipitins) underwent bronchoalveolar lavage and cytospins were prepared. One cytospin was stained for cell morphology to facilitate differential cell count. Others were analysed using a panel of monoclonal antibodies to determine the phenotypic profile of the BAL populations. A subsequent study removed five patients from exposure to pigeons for three weeks and then repeated the immunoanalysis. All 18 patients had a lymphocytosis in BAL fluid (mean 47·6% of total BAL fluid): these lymphocytes were almost exclusively T cells. The mean ratio of $CD4^+$ T cells to $CD8^+$ was 0·95. A significantly higher than normal proportion of these cells expressed positivity to McAb UCHL1 indicating they were immunologically committed. There was also a significant increase in dendritic cells (RFD+1 mean 56% of macrophage like cells). Other phenotypic parameters tested were within the normal range. When a group of patients were re-lavaged after isolation from pigeons for three weeks the lymphocytosis dropped from 51·8% to 16·2% of total BAL fluid. The proportion of UCHL1 lymphocytes decreased from 71% to 37% and RFD1+ cells were reduced from 72% to 44%. Results using other McAb probes were equivocal. These data suggest that pigeon breeders lung is associated with a cell mediated immune response, which is down regulated by isolating patients from antigenic exposure.

The longitudinal course of avian related extrinsic allergic alveolitis

S BOURKE, SW BANHAM, R CARTER, P LYNCH, G BOYD *Departments of Respiratory Medicine, Royal Infirmary, Glasgow* Patients who are diagnosed as having pigeon breeders' disease (PBD) are usually advised to discontinue their hobby since it is assumed that continued antigenic exposure will result in progressive pulmonary damage. However, many fail to comply with this advice and avoid further contact with doctors so that little is known of the longitudinal course of this disease. We therefore undertook a follow-up study of patients with documented PBD to assess the evolution of their symptoms, physiological parameters and immunological responses. A cohort of 24 patients who were diagnosed in 1977 as meeting criteria for PBD (*Thorax* 1986;**41**:274) were restudied 10 years later. Twenty one (87%) attended for clinical assessment, chest *x* ray, and pulmonary function studies and had IgG antibody to pigeon gamma-globulin measured by ELISA. Only three (14·2%) had discontinued pigeon fancying (two because of symptoms). Eighteen (85%) had continued their hobby but had regulated their exposure, mainly by use of masks (77%). Their symptoms had diminished in severity and frequency over the 10 years and only five (23%) were still experiencing troublesome symptoms. Three (14·2%) had developed mild symptoms of chronic bronchitis. There was no evidence of immunological tolerance since persistently high levels of sensitisation to pigeon antigens were found. Three (14%) showed a mild reduction in lung function and three (14%) had abnormal chest radiographs. No patient had developed significant respiratory disability. A pattern of 'acute recurring' (non-progressive) disease appears to be the commonest form of PBD in which patients follow a stable course with no deterioration in clinical status over many years. Self regulation of antigenic exposure rather than immunological tolerance is the likely explanation for this phenomenon.

Cyclophosphamide and low dosage prednisolone compared with prednisolone alone (with an initial high dose phase) in the treatment of cryptogenic fibrosing alveolitis

MA JOHNSON, S KWAN, NJC SNELL, JH DARBYSHIRE, AJ NUNN, M TURNER-WARWICK *Cardiothoracic Institute, Brompton Hospital, London* Cyclophosphamide in combination with low dose prednisolone (CY series) has been compared with prednisolone alone with an initial high dose phase (HS series) in a randomised study in 43 patients with previously untreated fibrosing alveolitis, all followed up for a minimum of three years. Improvement on treatment (defined as improvement in breathlessness score, radiographic appearance and lung function) occurred at one or more assessments (out of a maximum of five) in seven (32%) of the 22 patients in the HS series and five (24%) of the 21 in the CY series. Only three (one CY, two HS) were classified as improved at three years or later, but an additional 10 (seven CY, three HS) were stable. Although there was a suggestion of longer survival in the patients in the CY series this was not significant ($p > 0·1$, logrank test). The data were also analysed considering outcome as either death or failure of first treatment regimen and there was a significant advantage ($p < 0·05$) to the CY regimen. The advantage was explained in part by better lung volumes in this series on admission and after allowance for total lung capacity (TLC) no other factor was predictive of outcome. Repeating the analysis for subgroups according to TLC on admission demonstrated that for both regimens patients with severe disease (TLC of less than 60% predicted on admission) did badly and those with mild disease (TLC of 80% or more predicted) did well. However, for the subgroup of patients with an initial TLC of 60–79%, those in the CY series did significantly better ($p < 0·05$). Side effects were reported in 13 (seven CY, six HS) patients and those due to CY resolved on stopping therapy. The results suggest that the CY regimen is an effective alternative to high dose steroids in this condition.

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Bronchial reactivity in patients recovering from acute asthma

MKB WHYTE, NB CHOUDRY, PW IND *Departments of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Bronchial reactivity and airway narrowing are cardinal features of asthma. Measurement of airway calibre is often used to monitor recovery and treatment in acute asthma but bronchial reactivity has not been described. We have studied 14 patients, 10 female, aged 18–66 (mean 32) years, admitted to hospital with acute asthma. Written informed consent was obtained. Histamine reactivity was determined as the provocative dose causing a 20% fall in FEV_1 (PD_{20}) according to the method of Yan *et al* (*Thorax* 1983;**38**:760–5). Saline was administered as two puffs from a DeVilbiss 40 nebuliser, followed by increasing doses of histamine (0·04–2·56 μmol). Measurements were performed at least four hours after nebulised salbutamol. Other therapy included prednisolone, theophylline and nebulised ipratropium. Salbutamol 200 μg was inhaled after histamine challenge. At the time of hospital admission, mean heart rate was 116 (7 SEM) min^{-1}, respiratory rate was 30 (2) min^{-1} and systolic blood pressure 132 (4) mm Hg. Peak expiratory flow was markedly reduced at 155 (23) l min^{-1} or 31 (4)% predicted. PD_{20} was first measured 3–5 days (median 4) following admission and varied from 0·02 to 0·39 μmol (geometric mean 0·10 μmol). Mean prechallenge FEV_1 was 2·2 (range 1·0–3·3) l, representing 67% (44–93%) predicted. Mean FEV_1 postchallenge was 2·6 (range 1·2–3·6) l after salbutamol. Further histamine challenges were performed after discharge. At two weeks geometric mean PD_{20} was 0·14 μmol (range 0·02–0·95, n = 6), at four weeks 0·30 μmol (range 0·11–1·1, n = 6) and at 12 weeks 0·70 μmol (range 0·32–1·7, n = 6). The mean increase in PD_{20} over 12 weeks was 10·3 fold (range 1·2–34). Sensitivity to inhaled histamine is markedly increased in patients with acute asthma despite adequate conventional therapy. Moreover, dramatic improvement in reactivity continues for at least 12 weeks after the acute episode (even though reactivity is underestimated due to treatment). Measurement of bronchial reactivity is safe and may suggest a need for more aggressive treatment in patients recovering from acute asthma.

Rate of change in mean peak flow and in diurnal variation in peak flow in patients recovering from acute asthma

GE PACKE, AC ATKINSON, W FREEMAN, RM CAYTON *Department of Respiratory Physiology, East Birmingham Hospital, Birmingham, and Department of Statistics, Imperial College, London* In patients being treated for acute asthma there is usually a progressive rise in mean peak flow (PF) to a plateau. After the start of treatment, wide diurnal variations in PF are also seen, which tend to decline in amplitude to a stable level. The present study was designed to compare the rates of change in mean PF and in diurnal variation in PF in patients recovering from acute asthma. We studied 13 patients (five males, eight females) with a mean (SD) age of 24 (5) years. PF on admission was 28 (5)% predicted normal. All made an uncomplicated recovery in hospital after treatment with a nebulised beta agonist, hydrocortisone and prednisolone, and were discharged taking an inhaled beta-agonist and a topical corticosteroid. PF was measured six hourly for three weeks. Measurements were initially made in hospital; after discharge patients made their own recordings. PF variability was assessed by calculating amplitude % mean (highest—lowest/mean daily reading). Measurements of PF and of diurnal variation in PF for each patient were fitted to a single-component exponential model using the computer programme GLIM. The data for two patients did not fit the model and were excluded from analysis. The median (range) time taken for mean PF to reach 95% of its plateau value was 3·7 (0·4–19·5) days, and the mean time for diurnal variation in PF to reach 95% of its stable value was 11·2 (1·6–39·4) days ($p < 0·05$, Wilcoxon signed rank test). Since the extent of variation in PF reflects the level of bronchial reactivity (Ryan *et al. Thorax* 1982;**37**:423), these data suggest that in patients recovering from acute asthma increased bronchial reactivity persists for some days after mean PF has become stable.

Assessing the severity of childhood asthma in outpatients

S O'HALLORAN, DP HEAF *Respiratory Unit, Royal Liverpool Children's Hospital, Liverpool* Assessing severity of asthma in outpatients can be difficult. Histories are often unreliable and physical signs absent. Objective pulmonary function tests (PFT), other than PEF are rarely performed. To compare severity by history with objective tests we performed a questionnaire and PFTs in 225 asthmatic children aged 5–16 years attending the outpatient department. PFTs were FEV_1, FVC, FEV_1/FVC, PEFR, MMEF, exercise induced bronchoconstriction (EIB), bronchodilator response (BDR) and lability index (LT). There was significant correlation between frequency of attacks and emergency hospital visits and lower FEV_1 and MMEF ($p < 0·05$) were lower in those with severe attacks. Values of FEV_1, FEV_1/FVC and MMEF were lower ($p < 0·05$) in children whose parents smoked. Lability tests showed greater BDR and LI in those with frequent attacks ($p < 0·05$). There was no correlation between PEF and any historical index of severity. There was no association between PFT and school absence, or nocturnal coughing. The most useful tests to assess severity of asthma in the outpatient department are FEV_1 and FEV_1/FVC: EIB, LI and BDR give little extra information. Single PEFR measurements, although helpful in the acute attack, are of limited value in assessment of severity in outpatients.

Assessment of asthma severity

JCR PEREIRA, F CARSWELL *Respiratory Research Group, Department of Child Health, University of Bristol, and Royal Hospital for Sick Children, Bristol* There are no established techniques for measuring the severity of asthma in the community. Accordingly we have examined this in primary schoolchildren in Avon County. From 1671 children surveyed by questionnaire, 74 asthmatic and 74 age and sex-matched controls were obtained. These 148 subjects subsequently recorded their symptoms and peak expiratory flow rate (PEF) twice daily for 28 days. An asthmatics PEF was

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defined as impaired when it fell below the controls' 5th centile. The number of impaired PEF days (IP DAY) and the coefficient of variation of PEF (COV) were examined as potential measurements of asthma severity and divided the asthmatics into severe and not severe groups. More symptoms and greater treatment requirements were found in the severe group ($p < 0.05$, Mann-Whitney). Cutaneous prick test positivity or exercise-induced bronchial reactivity predicted the risk of severe asthma ($p < 0.05$); the more responses or the more the individual responses, the greater the risk. Both IP DAY and COV appear to be functional indicators of asthma severity in the community. Prick tests positivity or exercise induced bronchial reactivity can predict that severity.

Nocturnal cough and airway lability in asthma

AR FALCONER, C OLDMAN, PJ HELMS, CBS WOOD, J STROOBANT *Hospital for Sick Children, Queen Elizabeth Hospital, and Whipps Cross Hospital, London* Nocturnal asthma may be characterised by cough or wheeze or a combination of these symptoms. Our study was designed to test whether a relationship exists between nocturnal cough and peak expiratory flow (PEF). Diary assessment and taped measurement of nocturnal cough together with morning, afternoon and evening PEF were performed in 13 asthmatic children (age 5–12 years) covering a period of eight nights and % predicted morning PEF and a PEF variability index [(maximum PEF–minimum PEF)/maximum PEF] × 100 were calculated. As reported previously (Archer LNJ *et al. Arch Dis Child* 1985;**60**:473–5) diary scores did not accurately predict taped cough. The maximum hourly cough (the amount of cough in the worst affected hour of each night) showed considerable variation both between and within patients, varying from 0 to 178 (median 50) in the most severe patient to between 0 and 12 (median 6) in the least severe. Rank correlation coefficients (Kendall's method) were calculated for each individual and ranged from −0·65 to +0·58 for maximum hourly cough and % predicted morning PEF and between −0·32 to +0·58 for maximum hourly cough and PEF variability index. These data suggest that the cough reflex, which is thought to be sensitive to relatively short lived changes in bronchomotor tone, may not be linked to background motor tone.

Comparison of the effects of ipratropium and salbutamol on airway calibre and bronchial reactivity in patients with asthma and chronic bronchitis

RM POWELL, BG HIGGINS, SE COOPER, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We have previously shown that salbutamol and ipratropium bromide are equipotent as bronchodilators in a small group of asthmatic subjects (Britton *et al. Thorax* 1988;**43**:300–5). The purpose of the present study was to confirm this finding in a further nine subjects with asthma (mean FEV_1 2·8 l) and 10 subjects with chronic bronchitis (mean FEV_1 1·5 l), and to examine the relation between change in FEV_1 and bronchial reactivity in the two groups. The agents were administered double-blind in random order on separate days, doses of 100, 750, and 1000 μg being given at 20 minute intervals. FEV_1 was measured before and 20 minutes after each dose. The dose of histamine causing a 20% fall in FEV_1 (PD_{20}) was measured before and 25 minutes after the last dose of drug (Yan method). There was no difference in baseline airway calibre on the two study days for either group. Both salbutamol and ipratropium produced a greater change in FEV_1 in asthmatic subjects than in those with chronic bronchitis (max change 0·58 *v* 0·29 l, $p < 0.05$ with salbutamol, 0·57 *v* 0·32 l, $p < 0.05$ for ipratropium). Within groups the change in FEV_1 produced by salbutamol and ipratropium did not differ significantly. The increase in PD_{20} was greater after salbutamol than ipratropium in asthmatic subjects (2·28 *v* 0·84 doubling doses, $p < 0.05$) and bronchitic subjects (1·89 *v* 0·71 doubling doses, $p < 0.05$): the differences between the two groups were not significant with either agent. There was no correlation between change in FEV_1 and change in PD_{20}. Salbutamol and ipratropium appear to the equipotent bronchodilators in both asthmatic and bronchitic subjects. Salbutamol produces a greater change in PD_{20} for the same change in FEV_1, suggesting that the mechanisms underlying bronchodilatation and change in bronchial reactivity are not the same for all bronchodilators.

Recovery from pneumonia in the community

MA WOODHEAD, JT MACFARLANE, JS MCCRACKEN, DH ROSE, RG FINCH *Departments of Thoracic Medicine, Radiology, and Microbiology, City Hospital, and Department of General Practice, University Hospital, Nottingham* The period of recovery was assessed as part of a prospective study of 236 adults with pneumonia (defined as an acute lower respiratory tract infection with new localising chest signs on examination) in the community from 1 October 1984 to 30 September 1985. The majority (78%) of patients were managed entirely at home. Simple 10-day symptom charts, recording cough, phlegm, dyspnoea, chest pain, feeling unwell, appetite, twice daily temperature and days spent in bed, were completed by 162 (69%) patients. Patients were reviewed at two and six weeks after presentation. The six recorded symptoms improved at a similar rate, which tended to be slower in those aged >65 years and those with fresh radiographic shadowing. Only 46 (41%) of 113 patients managed at home had a temperature >37·5°C and of these 80% were afebrile by the second day. Sixty six (48%) of 137 were confined to bed, but only five (4%) were still in bed at one week. Only 67/184 (36%) were back to normal by two weeks and 116/151 (77%) by six weeks. No features were significantly related to the patient's assessment of normality at either two or six weeks. Ninety three patients were in full time employment at study entry. Eight remained at work during their illness, the median period of sick leave was 14 days and 45% were absent for more than two weeks, although 74% were considered fit for work at this time. Patients admitted to hospital were absent from work for longer than those managed at home ($p < 0.05$). These infections were not severe and were usually managed at home, but despite this the period of post-infection disability was prolonged, emphasising the morbidity associated with pneumonia in the community.

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Penicillin versus clindamycin in the treatment of anaerobic lung infections

F MANRESA, J BOADA, J DORCA, M CISNAL, G RUFI, F GUDIOL *Departments of Pneumonology and Microbiology and Infectious Diseases Unit, Hospital de Bellvitge, University of Barcelona, Spain* The objective of this study was to compare the efficacy of penicillin versus clindamcin in the treatment of anaerobic lung infections (ALI). Since January 1985 52 patients with clinical and radiological features suggesting ALI were studied as possible candidates to be included in a prospective and open randomized study. Among them, 15 were excluded owing to one or more of the following reasons: known allergy to penicillin or clindamycin, antibiotic treatment in the prior 72 hours, demonstration of lung diseases other than anaerobic infection, or loss in the follow up. Among the other 37 (27 abscesses and 10 necrotizing pneumonias), 17 received penicillin (2 million units/4 hours/IV) and 20 clindamycin (600 mg/6 hours/IV). The intravenous treatment was maintained for a minimum of eight days, and the total treatment for at least four weeks. Therapeutic failure was considered when there was not any improvement in clinical status in five days, or in the radiology in 10. Special effort was made in order to demonstrate the pathogenic organisms and their sensitivity: transthoracic needle aspiration was carried out in 29 cases, and a bronchoscopy with protected specimen brush in 19. Anaerobic cultures were positive in 26 cases (70·3%): in 17 only anaerobes grew, and in nine there was a mixture of aerobic and anaerobic bacteria. Among the penicillin group there were eight failures *Bacteroides melaninogenicus-asaccharolyticus*. In the clindamycin group there was only one failure (5%). Penicillin-resistant *Bacteroides* of the *melaninogenicus* group were recovered in three cases treated with clindamycin. No clindamycin-resistant anaerobes were found in any case. In our study clindamycin obtained better results than penicillin ($p = 0·0082$) in the treatment of ALI.

Protected specimen brush bronchoscopic catheter in the diagnosis of hospital acquired pneumonia

J DORCA, J BOADA, R BLAVIA, R VERDAGUER, F GUDIOL, F MANRESA *Departments of Pneumonology and Microbiology and Infectious Diseases Unit, Hospital de Bellvitge, University of Barcelona, Spain* The objective of this study was to analyse the diagnostic reliability and the real influence on therapy of the protected specimen brush (PSB). From September 1984 to April 1987 we carried out this procedure in 220 cases of suspected hospital acquired pneumonia (HAP) following the method described by Wimberley *et al* (*Chest* 1982;**81**:556–62). Cultures were considered positive when species grew in concentrations $\geq 10^3$ colony forming units per ml. All cases were further controlled, and other tests were performed if considered necessary, in order to confirm lung infection or disregard diseases other than pneumonia. Among the initial 220 cases, only 145 (65·9%) were retrospectively confirmed as HAP. In 54 cases (24·5%) HAP was disregarded and finally 21 (9·5%) remained undeterminate after the retrospective analysis. According to the results obtained, the diagnostic reliability of the PSB was: sensitivity 91·3%, specificity 84·9%, positive predictive value 89%, and negative predictive value 88%. Special effort was made to analyse the influence of PSB result on the empirical antibiotic treatment. The cases with positive PSB result also diagnosed by a classical diagnostic technique (for example, blood culture), and those which died before the PSB result, were disregarded. The PSB result had real influence on the treatment in 90 cases (40·9% of the initial 220), permitting us to stop an unnecessary antibiotic treatment in 16 (17·8%), simplify a previously effective treatment in 48 (53·3%), and change an ineffective treatment in 26 (28·9%). Our results confirm PSB as a reliable technique in the diagnosis of hospital acquired pneumonia, with a real influence on therapy, allowing us to reduce costs and probably leading to a decrease in the HAP mortality rate.

Optimal cardiorespiratory patterns: implications for positive end expiratory pressure (PEEP) therapy

SG BREAR, JD EDWARDS, P NIGHTINGALE *Intensive Care Unit, University Hospital of South Manchester* Cardiorespiratory patterns for optimal survival in the critically ill have been defined as an oxygen delivery (Do_2 > 600 ml/min/m^2 a cardiac index (CI) > 4·5 l/min/ms and an oxygen consumption ($\dot{V}o_2$) > 170 ml/min/m^2. The indications for PEEP in the adult respiratory distress syndrome (ARDS) are disputed, but include a fractional inspired oxygen (Fio_2) > 0·55 or a shunt fraction (Qs/Qt) > 20%. Application of PEEP in ARDS has been shown to reduce Do_2 and $\dot{V}o_2$ by an unpredictable amount in a variable number of patients. These studies have included patients with varying initial values of CI, Do_2, $\dot{V}o_2$ and systemic vascular resistance (SVR). We have have assessed the haemodynamic effects of PEEP in 24 patients with severe ARDS (mean Qs/ Qt = 36% +/−8%) in whom optimal cardiorespiratory patterns had been achieved and maintained (stage 1). The influence of

Table 1

	Cardiac index			
Stage	1 *v*	2 *v*	3 *v*	1
Mean	5·2	3·9	4·9	5·2
SD	0·9	0·9	0·8	0·9
p	> 0·001	< 0·001	< 0·05	
	SVR			
Stage	1 *v*	2 *v*	3 *v*	1
Mean	673	821	669	673
SD	154	237	166	154
p	< 0·001	< 0·005	NS	

Table 2

	Do_2	*$\dot{V}o_2$*	*Qs/Qt*
Stage	1 *v* 3	1 *v* 3	1 *v* 3
Mean	819 813	168 164	36 25
SD	179 147	34 38	8·0 7·0
p	NS	NS	< 0·0001

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PEEP in CI, SVR and mean arterial pressure (MAP) were studied. Optimal values of CI and Do_2 were maintained to the end of PEEP manoeuvres by adjustment of fluid (modified fluid gelatin) and inotropic therapy (dobutamine) (stage 3). All patients required an $Fio_2 > 0{\cdot}55$ to maintain a $Pao_2 > 8$ kPa and had a $Qs/Qt > 20\%$. PEEP caused highly significant falls in CI without significal fall in MAP levels of 5 or 10 cm H_2 (stage 2). At the end of PEEP manoeuvres all patients had significantly lower Qs/Qt, approaching 20%, and increases in Pao_2 such that Fio_2 could be reduced to $<0{\cdot}55$. Fifteen (62·5%) patients survived to leave hospital. Optimisation of CI and Do_2 resolves the controversy about indications and end points for PEEP therapy and may improve outcome in severe ARDS.

Lung function abnormalities and the role of physiological assessment in the management of patients after fire trauma

CJ CLARK, R CARTER, J KINSELLA, T POLLOK *Department of Respiratory Medicine and Anaesthesia, Royal Infirmary, Glasgow* Major incidents such as the Kings Cross disaster highlight the contribution of smoke inhalation to mortality following fire trauma. This hospital is conducting an extensive study of smoke inhalation injury, of which this report on the physiological sequelae forms a part. Over three years 73 fire trauma patients with suspected smoke inhalation, based on a clinical scoring system combined with carboxyhaemoglobin level (COHb) extrapolated back to time of injury (Clark CJ *et al Br Med J* 1986;**292**:1303–5) have undergone physiological assessment within one week of injury, consisting of flow-volume analysis, body plethysmography for lung volumes and specific conductance, and measurement of diffusing capacity for carbon monoxide. Twenty two had normal lung function, 39 had obstruction both by flow-volume criteria and reduced specific conductance ranging from 19 mild (1·1–0·8), 12 moderate (0·8–0·5), six moderately severe (0·5–0·25) and two severe ($<$ 0·25). Nine subjects had restrictive and three mixed defects. Diffusing capacity was reduced in seven subjects. There was a weak correlation between smoke exposure indicators and lung function abnormalities ($r = 0{\cdot}45$, $p < 0{\cdot}001$). For example, several patients with unequivocal severe exposure judged by COHb levels >40% had minimal lung function abnormalities whilst others with minor exposure had severe changes which could not be explained by pre-existing disease. This may reflect the heterogeneity of smoke constituents with a variable potential for direct respiratory tract injury. From the high incidence of defects in the study group, we conclude that lung function assessment should be performed on all suspected smoke inhalation patients followed by appropriate specialist referral where abnormalities are found.

Reproducibility of ciliary beat frequency measured by video photometry

D VEALE, AD RODGERS, CJ GRIFFITHS, T ASHCROFT, GJ GIBSON *Departments of Respiratory Medicine, Medical Physics and Histopathology, Freeman Hospital, Newcastle upon Tyne* We have investigated an inexpensive system of analysis of ciliary beat frequency (CBF) which allows storage of ciliary motion for repeated analysis (based on *Med Biol Eng Comput* 1986;**24**:193). Brushed samples of nasal mucosa were taken from nine healthy non-smoking subjects and placed in medium 199X under a sealed cover-slip, on a heated stage at 37°C. A video recording of ciliary motion was made using a X100 oil immersion objective and microscope video camera with the image displayed on a TV monitor. CBF was measured by placing a light sensitive diode against the TV screen over an area of beating cilia. The amplified and filtered output of the probe was fed to an oscilloscope monitor and CBF measured from the sinusoidal trace obtained. From each brush specimen 10 separate areas of ciliary beating were recorded; from each area the average of six consecutive readings was used. CBF from the ten areas within each subject showed appreciable variation. The differences between the highest and lowest values for each subject ranged from 4·4–9·9 Hz (average within-subject coefficient of variation 18%). The mean of the values for the 10 areas counted was the CBF for that individual and ranged from 9·4 to 12·8 Hz for the nine subjects. We conclude that the variation in CBF within subjects should be taken into account in the assessment of abnormalities or changes in CBF with treatment.

Chest pain in chronic sputum production: a neglected symptom

NC MUNRO, DC CURRIE, ND GARBETT, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* Chest pain in patients with chronic sputum production (not in acute exacerbation) is a neglected symptom. We have characterised this symptom and described its relation to other symptoms and signs, and site and severity of disease. One hundred and sixteen consecutive patients with daily sputum production were surveyed, 81 with radiologically proven bronchiectasis (Bx) and 35 with mucus hypersecretion (Mh) but no evidence of bronchiectasis. Twenty eight different chest pains were reported by 26 Bx (32%) and one pain by each of 6 Mh (17%). More Bx patients with chest pain produced purulent, as opposed to mucoid, sputum than those without pain (22/26 [85%] *v* 39/55 [71%]), they had a lower mean PEF (274 *v* 339 l/min) but were similar in mean daily sputum volume, number of lobes affected, and duration of disease. The chest pains were commonly described as "dull," "gnawing," or an "ache." In most cases the pain was described as of mild or moderate severity. Classification of the pain at time of interview as "respiratory," "origin unclear" or "non-respiratory" showed that in the Bx group it was "respiratory" in 18/28 (64%), "unclear" in 6/28 (21%), and "non-respiratory" in 4/28 (15%); in Mh "respiratory" in 3/6 (50%) and "unclear" in 3/6. In Bx 17/18 (94%) "respiratory" pains and 3/6 (50%) "unclear" pains were sited over a bronchiectatic lobe. We conclude that non-exacerbation chest pain is a frequent symptom, that in bronchiectatics it is likely to originate from the diseased lobe, and that in both groups is associated with purulent sputum production and possibly with more severe disease.

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Silent myocardial ischaemia during acute exacerbations of chronic airflow limitation

R LIM, MJ WALSHAW, S SALTISSI, CRK HIND *Department of Medicine, Royal Liverpool Hospital, University of Liverpool*
The mechanism of sudden death in patients with an acute exacerbation of their chronic airflow limitation (CAL) is assumed to be due to cardiac arrhythmias, induced by myocardial ischaemia secondary to the hypoxaemia. To determine how frequently such ischaemia occurs, ST segment analysis was performed on 24 hour ECG recordings in 12 patients (mean age 69 years, range 50–79) with an acute exacerbation of their CAL. Recordings were made with an Oxford Medilog 4000–II recorder both on the day of admission (acute record) and just prior to discharge (convalescent record). ST depression was regarded as significant if it was $\geq$ 1 mm in amplitude 0·08s from the J point, $\geq$ 30 s in duration, and planar or downgoing (*Eur Heart J* 1987;**8**:124–9). We found 40 episodes (33 asymptomatic) of significant ST depression in four patients' acute records, and six episodes (four asymptomatic) in two patients' convalescent records. None of these patients gave a past history to suggest ischaemic heart disease. The mean duration of ST depression was greater in the acute records (acute 280 s, range 31 s–39 min; convalescent 187s, range 56 s–14 min 8 s), as was the mean heart rate during the period of ST depression (acute 128 beats/min, range 108–171; convalescent records 94, range 91–96), though these differences did not reach significance because of the small number of patients. These results suggest that significant myocardial ischaemia does occur during acute exacerbations of CAL, and is usually asymptomatic. The clinical importance of these findings merits further study.

Small airways obstruction in rheumatoid arthritis

U PATEL, AP KIRK, PF JENKINS, BDW HARRISON *United Norwich Hospitals, Norwich*
Bronchiolitis obliterans is a recognised rare complication of rheumatoid arthritis (RA) but mild subclinical airways obstruction may be more common in RA. Thirty nine patients with classical or definite RA were studied to document the presence and incidence of airflow limitation using expiratory flow volume measurements. All patients were unaware of cough or dyspnoea within the limits of their exercise capacity and had normal chest radiographs. Small airways disease (MEF_{50} or MEF_{25}, < 50% of predicted normal with preserved lung volumes) was demonstrated in 23 patients ($p < 0·001$). These 23 patients were subgrouped into lifelong non-smokers (13/23), ex-smokers for more than five years (6/23) and current smokers (4/23), but the difference in incidence in these three subgroups was not significant ($p > 0·1$). Four patients with restrictive lung disease were also identified (vital capacity and total lung capacity <80% of predicted normal). The presence of small airways disease was not related to age, sex, duration of RA, rheumatoid latex positivity, erosive changes on hand, the presence of rheumatoid subcutaneous nodules or an abnormal Schirmer's test. Similarly RA disease activity (clinically and serologically) and current or previous therapy did not influence the presence of small airways obstruction. The incidence of airways disease in this study was high (58% in the overall group, 33% in the lifelong non-smokers) and suggests that mild subclinical airways obstruction may be the commonest pulmonary manifestation of RA.

Effect of histamine on the power spectrum of lung sounds

K ANDERSON, S AITKEN, R CARTER, J MCLEOD, F MORAN *Department of Respiratory Medicine, Glasgow Royal Infirmary, and University Department of Electrical Engineering, Glasgow*
Serial breath sound recordings during histamine challenge in five asthmatic subjects were obtained at the right lower posterior chest wall during deep tidal respiration by means of a hand held electret microphone with a tufnol diaphragm. The lung sound was quantified by calculating the frequency which divided the power spectrum into two halves (F_{50}) in the range 100–1500 Hz. The resulting alteration in breath sound frequencies were then correlated with the FEV_1 before and after cumulative doses of histamine. Despite the absence of wheeze the F_{50} increased significantly in each subject (baseline F_{50} range 211–318 Hz, post-challenge F_{50} range 337–440 Hz, $t = 8·57$, $p < 0·001$) and correlated with the change in FEV_1 (baseline FEV_1 range 2·39–3·86 l, post-challenge 1·99–2·91 l). These results suggest an inverse relationship between F_{50} and FEV_1 that is partially influenced by other variables, such as chest wall thickness or airway geometry, which are difficult to quantify. These observations utilise a method of inducing variation in airway calibre, thereby primarily altering lung sound generation without altering factors important in sound transmission, and support previous assumptions that lung sounds are generated in the large airways.

Abnormalities of lung function in patients with Anderson-Fabrey disease

PS THOMAS, SH MORGAN, JS MILLEDGE, RWE WATTS *Department of Respiratory Medicine and Division of Inherited Metabolic Diseases, Northwick Park Hospital, and MRC Clinical Research Centre, Harrow, Middlesex*
Anderson-Fabrey disease (AFD) is an X linked lysosmal storage disorder caused by α galactosidase A (α gal A) deficiency. There is a high morbidity and mortality in hemizygous males and some heterozygous females owing to the deposition of glycosphingolipids, predominately ceramide trihexoside, in the heart, kidney and cerebrovascular system. We present the results of lung function studies in seven patients; two were smokers, mean age was 31·3 years, and one was a heterozygote. AFD was confirmed by clinical examination and reduced leucocyte α gal A. All were assessed by spirometry (FEV_1), peak flow (PEF), lung volumes (helium dilution) and carbon monoxide transfer test (TLCO, KCO) and five had a flow-volume loop determined. One patient, a hemizygote, had normal values. Abnormalities were found in the non-smoking heterozygote carrier and five hemizygotes. With all the subjects taken together, there was a reduction in FEV_1 and PEF which was significantly lower than predicted ($p < 0·005$). Lung volumes showed no clear trend but both the TLCO and KCO were significantly reduced from predicted ($p < 0·02$). The flow-volume loops showed a lack of the

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normal peak early in expiration so that PEF was reduced disproportionately to FEV_1. The mean (SD) ratio of PEF to FEV_1 was 0·69 (0·15), predicted 2·32 (0·26). This suggests large airways obstruction, possibly owing to a lack of compliance in these major airways. The reduced gas transfer may be due to poor gas mixing and/or decreased perfusion due to deposition of ceramide trihexoside in the alveolar and capillary walls. This study underlines the partial manifestation of the disease shown by some carriers and goes some way to elucidating the aetiological basis of the unexpected obstructive airways disease that develops.

Patterns of asthma in general practice

FRG CROSBY, E WHYTE, S OGSTON, RA CLARK *Carnoustie Health Centre, Department of Community Medicine, Ninewells Hospital, Dundee, and Department of Respiratory Diseases, King's Cross Hospital Dundee* From a health centre six doctors serve the town and rural area surrounding Carnoustie (Population about 11 500). A search of all prescriptions issues over a two year, period identified 273 asthmatic patients aged 0–55 years, the diagnosis being confirmed by a review of their notes. From a questionnaire, two week diary card and pulmonary function tests their disease was classified into persistent daily symptoms 163 (59·7%), severe intermittent attacks 38 (13·9%) and mild intermittent episodes 72 (26·4%). The "age" breakdown of the 273 patients was 24 aged 0–4 years, 58, 5–9 years, 80, 10–19 years, and 111 20–54 years giving percentages of those with daily symptoms in each age group of 29·2% (7) aged 0–4 years, 43·1% (25) 5–9 years, 56·3% (45) 10–19 years and 77·4% (86) 20–54 years. In those under 10 s 26 of 82 (31·7%) had mild intermittent symptoms, 24 (29·3%) severe intermittent attacks and 32 (39%) daily symptoms. There was a discrepancy between the patients own assessment of their disease and the physicians classification (in brackets)—that is, persistent daily symptoms 80 (163), severe intermittent attacks 64 (38) and mild episodes 129 (72). Treatment was generally suboptimal: of 163 with daily symptoms, 86% had a bronchodilator inhaler and 53% prophylactic medication, of 38 with severe intermittent attacks only 34% had a bronchodilator and of 72 with mild symptoms 56% had a bronchodilator. After a year 254 of the 273 patients were reassessed in the same way. There was an increase in those, classified as having daily symptoms, with fewer in the severe intermittent attack and mild symptoms groups, possibly reflecting an increased awareness of the disease by the patients. An awareness of the pattern of disease influences management and education.

Hospital management of asthmatic patients compared with those given a diagnostic label of "chronic obstructive airways disease"

CE BUCKNALL, C ROBERTSON, F MORAN, RD STEVENSON *Department of Respiratory Medicine, Royal Infirmary, and Department of Mathematics, Strathclyde University, Glasgow* The management of 46 asthma cases in whom the hospital discharge diagnosis was chronic obstructive airways disease (COAD) was compared with 85 cases with a final diagnosis of uncomplicated asthma. The group labelled COAD were older ($p < 0·005$), more likely to be male ($p = 0·02$), smokers or ex-smokrs ($p < 0·005$) and less likely to have objective evidence of reversible airflow obstruction recorded in their case notes ($p = 0·03$). Nevertheless, more were taking inhaled and oral corticosteroids before admission to hospital. No differences in the use of oral corticosteroids, or antibiotics in hospital or in the use of inhaled corticosteroids after discharge were observed between those labelled COAD and asthma. Fewer COAD cases had peak flow recordings made in hospital ($p < 0·005$) or hospital review arranged ($p = 0·03$). At interview a fortnight after discharge from hospital similar proportions of "COAD" and asthma labelled cases reported symptoms of poorly controlled asthma, although more COAD cases described wheeze on climbing one flight of stairs ($p < 0·05$). These data suggest that asthma may be being underdiagnosed in older men with a smoking history by failing to evaluate their symptoms objectively or over time. Nevertheless, this group was not treated differently from those with a diagnosis of uncomplicated asthma.

Do chest doctors follow up too many patients?

AG LEITCH, S PARKER, A CURRIE, T KING, GJR MCHARDY We have examined the pattern of attendance of 750 randomly selected regular attenders at a chest outpatient clinic and sought the patients' views on the frequency of their follow up appointments and the possible consequences of discharge to the care of their general practitioner (GP). In addition the clinic doctors and the patients' GPs were asked about the appropriateness of the frequency of follow-up and whether the pattern of attendance should change or the patient be discharged. Patients were most commonly seen at three monthly intervals. Clinic doctors felt that 24% and GPs that 9% of patients attended too often while only 2% of patients felt that this was the case. Clinic doctors recommended discharge for 28% and GPs for 21% of patients. Sixty-nine per cent of patients felt that their condition would be unchanged or would improve if they were discharged to the care of their GPs. Our findings suggest that at least 20% of our patients should be discharged to the care of the GPs, and if the patients are correct in their interpretation of the consequencies of discharge, that as many as 70% could safely be discharged.

Prospective study of expected and actual jobs in thoracic medicine in Great Britain 1984–7

PDO DAVIES *South Liverpool Chest Clinic, Sefton General Hospital, Liverpool* Calculations of job opportunities within a given medical speciality are usually based on expected retirements. From 1979 to 1983 a relatively large number of consultant thoracic physicians were expected to retire. In the event, many of these posts were not reappointed. A prospective study comparing job vacancies with expected retirements, based on a survey of all consultant thoracic physicians in 1983, has been undertaken for the years 1984/7. In the four year period, 58 retirements were expected from the

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survey data. In fact, 69 appointments in thoracic medicine (an "expansion" of 19%) were actually made. Of these 69 appointments, only 21 were made within the same year as the relevant expected retirement. For 24 appointments it was unclear from the 1983 survey data whether or not they represented replacement of retiring physicians, but in that they were "unexpected;" some probably represented genuinely new posts. For nine appointments there was apparently a delay of over a year between retirement and appointment, and 15 were actually appointed over a year before expected, from the retirement date. Over the past eight years, calculation of job prospects based on expected retirements has been unreliable, initially overestimating and then, as indicated in this study, underestimating the need for trainee consultant thoracic physicians. Other methods, such as those based on national and regional mortality and morbidity data, should be considered.

Trends in respiratory care in Mersey Region from 1974 to 1985

PDO DAVIES, CC EVANS *South Liverpool Chest Clinic, Sefton General Hospital, and Royal Liverpool Hospital, Liverpool*
Mortality statistics for Mersey have been extracted from the relevant Office of Populations Censuses and Surveys Monitors for 1974–85 (Mortality Statistics, Area, DH5). Age specific death rates for certain respiratory diseases for the population aged 15–74 (those most likely to present to the chest services) have been calculated from annual population data. Over 12 years for which data have been extracted, the age specific death rate for ages 15–74 (all causes) fell from 943.6/100 000 to 792·5/100 000. Death rates for respiratory tuberculosis fell more than threefold from 2·4 to 0·73, for carcinoma of the larynx, trachea and bronchus from 87·2 to 80·9, and for chronic bronchitis and emphysema from 52·8 to 22·5; but rates for asthma rose nearly two fold from 1·9 to 3·2 per 100 000. However, over the same period there has been a 30% decline in the number of chest physicians in Mersey from 24 in 1974 to 16 in 1985. Considering deaths per chest physician, there has been an increase in deaths from the respiratory diseases, defined above, from 106 to 120 per year per chest physician. For the 15–74 age group there was a decline from 1·75 to 0·8 for respiratory tuberculosis, and from 38·8 to 25 for chronic bronchitis and emphysema but an increase from 64 to 90 for respiratory carcinoma, and from 1·4 to 3·6 for asthma. Though mortality from respiratory diseases has declined steadily in Mersey Region over the 12 year period, respiratory services—in terms of consultant staffing—appear to have declined much more rapidly. The result must be either a deterioration in the quality of service, or a much increased work load for the remaining chest physicians. The increase in death rates from asthma follows a national trend and gives cause for concern.

GP open access service: is spirometry with chest radiograph useful?

EC SMITH, D SMITH, AH KENDRICK, G LASZLO *Respiratory Department, Bristol Royal Infirmary, Bristol*
In a recent survey by the British Thoracic Society (1987) into the state of thoracic medicine in the UK it was found that 96% of health districts provided a GP open access chest radiography service. In the Bristol and Weston (BW) health district, we have been providing a combined service of spirometry with bronchodilator response and chest radiography (S + CR) since June, 1984. In addition, a modified MRC questionnaire was completed. The patient attended for about one hour. GPs were immediately notified if a major abnormality was detected; otherwise a report was sent out within one week. We have reviewed the first three years of the service to determine its usefulness. Of the 284 GPs in BW, 71 (25%) had used the service on one or more occasions and found it helpful. Of the remaining 213, 57 (27%) did not reply to our questionnaire, 34 (16%) referred patients directly to the outpatients, 37 (17%) regarded the Bristol Royal Infirmary too inconvenient for patients to attend and 85 (40%) were unaware of the service. There were 331 referrals for S + CR. A normal chest radiograph was found in 128 patients, of whom 59 (46%) had abnormal S. An abnormal CR was found in 203 patients, of whom 68 (33·5%) had normal S. Major abnormalities (? carcinoma) were detected in nine (3%) patients. Further tests and/or referrals to outpatients were suggested in 140 (42%) and a change in treatment in 71 (22%). A number of GPs used the service for steroid trials. We conclude that the information obtained from spirometry is a useful addition to the GP chest radiography open access service.

Assessment of smoking habits in a "no smoking hospital"

KG RAJAN, PDO DAVIES *Department of Thoracic Medicine, Llandough Hospital, Penarth, South Glamorgan*
To understand the impact of no smoking policy of South Glamorgan Health Authority, the smoking habits and attitudes of staff and patients in a recently declared "no smoking hospital" were assessed. Nine hundred and forty nine paid employees and five hundred and fifty patients were given a questionnaire to complete on voluntary basis. Questions were designed to know their age, sex, occupation and smoking habit. Opinion about having a total no smoking hospital or if any specific area(s) should be declared as smoking or non smoking, knowledge about passive smoking and whether any help is needed to give up smoking were assessed. Six hundred and sixty three (70%) of staff returned the questionnaire with maximum response from administrative (80%), nursing (75%), and medical (72%) staff and poor response from catering (28%) and domestic (47%) departments. The highest proportions of smokers were identified among catering (35%), portering (44%) and domestic (57%) staff and they were generally less concerned about the new no smoking policy. Three hundred and forty six (63%) of both in and out patients were responded, of whom 76 (22%) were current smokers and 136 (39%) gave up smoking in the recent past. More smokers were found among unemployed patients and fewer among self employed group. A majority in both groups (70%) were in favour of having a total no smoking hospital but a separate smoking rest room was requested for staff by both groups. Ignorance about passive smoking was about 3% among staff and 7% among patients and at least one third of smokers in each group requested some help from the hospital to give up smoking. We feel that a great swing in smoking habits and attitudes is needed among staff to implement a no smoking policy successfully.

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Airways selectivity of atenolol

BJ LIPWORTH, RA BROWN, DG McDEVITT *Department of Clinical Pharmacology, Ninewells Hospital, and Department of Mathematical Sciences, University of Dundee* Atenolol, despite being a highly cardioselective beta blocker, may cause bronchoconstriction in asthma. We therefore performed a dose-ranging study to assess the beta adrenoceptor selectivity of atenolol on airways (sGaw), tremor (Tr) and chronotropic (HR) responses. Five non-atopic, non-smoking, normal subjects were given oral doses of atenolol 50 mg, 100 mg, 200 mg (A50, A100, A200), propranolol 40 mg (P40) or matching placebo (Pl) in a randomised single-blind crossover design. Three hours after drug ingestion, cumulative dose-response curves (DRC) were constructed with metered-dose salbutamol aerosol (200, 700, 1700, 3200, 6200 μg). The DRC for all three variables was displaced to the right with increasing doses of atenolol, the greatest with propranolol. Multiple ANOVA showed significant differences between doses of beta-blocker. Comparison of 95% confidence intervals for mean % Δ sGaw at 3200 mcg showed a difference between Pl: 393 (267–519) and all doses of beta-blocker—P40: 61 (21–101), A200: 122 (11–231), A100: 173 (76–270), A50: 208 (143–272). Similar differences were observed between P40 and A50 (at 3200 μg), and P40 from A100 (at 6200 μg). For % Δ Tr the following were different (at 3200 μg): P40 from A100, A50, Pl; and A200 from A50. For Δ HR (bpm) at 3200 μg: placebo from all doses of beta-blocker, P40 from all doses of atenolol, and A200 from A50. In conclusion, increasing doses of atenolol are associated with a loss of beta adrenoceptor selectivity in airways, tremor and chronotropic responses in normal subjects. This may be of clinical relevance in asthmatic airways where there is a higher resting adrenergic tone.

Effect of enalapril and atenolol on lung function in hypertensive patients

KE BERKIN, GD MURRAY *Western Infirmary, Glasgow* Patients with hypertension are usually asymptomatic so drug side effects are relatively more important. Beta-blockers and angiotensin converting enzyme (ACE) inhibitors are effective but can cause wheeze and cough respectively. The effects of chronic treatment with these drugs on airway calibre were assessed. One hundred and sixty two hypertensive patients with no history of asthma were randomised to receive atenolol 50–100 mg (n = 76, mean age 53 years) or enalapril 20–40 mg (n = 86, mean age 49 years). In 118 patients FEV_1 and flow rate at 25% of vital capacity ($\dot{V}_{25}$) were measured during placebo and after 8 weeks' treatment with atenolol (n = 54) or enalapril (n = 64). Three patients on atenolol were withdrawn for side effects (non-respiratory). One of five patients withdrawn from enalapril developed an exacerbation of his previously unrecognised asthma coincident with enalapril treatment. Cough, not severe enough to withdraw treatment, was reported by four patients on enalapril and two on atenolol. Results (mean (SEM)) of lung function tests are shown below. The 95% CI for the difference on active drug between atenolol and enalapril was −0·21, +0·03 for FEV_1 and −0·04, +0·18 for V_{25}. Drug compliance as assessed by tablet counts and plasma renin measurements was good, and both drugs reduced blood pressure. Thus in non-asthmatic hypertensive patients neither the beta-blocker nor the ACE inhibitor caused important changes in FEV_1 and V_{25} during a two month period.

	Atenolol		*Enalapril*	
	Placebo	*Change*	*Placebo*	*Change*
FEV_1 (l)	2·77 (0·08)	−0·12 (0·05)	2·97 (0·11)	−0·03 (0·03)
$\dot{V}_{25}$ (l/s)	1·11 (0·06)	0·0 (0·04)	1·55 (0·11)	−0·07 (0·04)

Effects of captopril on pulmonary and renal function in patients with chronic airflow obstruction

AJ PEACOCK, D WALLER, RM OLIVER *Wessex Right Heart Group and Department of Nuclear Medicine, Southampton General Hospital, Southampton* We have reported in an open study that patients with chronic airflow obstruction have high serum angiotensin II levels and that blockade of angiotensin converting enzyme with captopril improves FVC and TLCO but not FEV_1 (Peacock AJ. *Thorax* 1986;**41**:225). We suggested that captopril may have redistributed lung water or enhanced its renal elimination. We have now carried out a double blind study of captopril (25 mg bd) *v* placebo in nine similar patients with airflow obstruction (mean FEV_1 0·9 l), hypoxemia (mean Pao_2 7·8 kPa) and a history of fluid retention. Each patient received captopril or placebo for 28 days and then switched over to the other drug for a further 28 days. Measurements of body weight, arterial blood gases, spirometry and TLCO were made at baseline, 28 and 56 days. Simultaneously, we measured glomerular filtration rate (GFR) using ^{99m}Tc DTPA and effective renal plasma flow (ERPF) using 1131 Hippuran. During treatment with Captopril FVC rose by 7·5% ($p < 0·05$) but there was no change in FEV_1, TLCO or Pao_2. Captopril caused a rise in ERPF of 18% ($p < 0·01$) and a fall in filtration fraction of 14% ($p < 0·05$) but no change in GFR or body weight. Captopril therefore resulted in a small improvement in vital capacity associated with a potentially favourable change in renal haemodynamics, which may favour natriuresis.

Dose-duration effect of nebulised nedocromil sodium in exercise induced asthma

MK ALBAZZAZ, MG NEALE, KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow, and Fisons PLC, Loughborough* Nedocromil sodium has recently been approved for the treatment of reversible airways disease and is marketed as a pressurised aerosol (Tilade). We have previously shown that nebulised nedocromil sodium is effective in inhibiting exercise induced asthma (Albazzaz *et al. Thorax* 1988;**43**:252P). In this study we have compared the dose-duration effect of three concentrations of nedocromil sodium (0·05%, 0·25% and 1%) with that of placebo in 10 patients (7M), mean (SEM) age 30·1 (3·5) y and predicted FEV_1 102% in double blind randomised manner. One millilitre of each solution was nebulised via a Wright

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nebuliser. Effects were assessed from the mean maximal percentage fall in FEV_1 after 6–8 min treadmill exercise 15, 145 and 265 min after each treatment. The mean baseline FEV_1 values before and after treatments were comparable on four days of testing. Nedocromil sodium inhibited exercise induced fall in FEV_1 at all concentrations ($p < 0.001$) and the inhibitory effect was still present at 265 min. There were no differences observed between active treatments.

Mean maximum (SEM)% fall in FEV_1 in three tests with placebo and nedocromil sodium

		Nedocromil sodium		
	Placebo	*0·05%*	*0·25%*	*1%*
1st	30·1 (2·1)	12·1 2·8	9·5 (1·7)	8·6 (1·9)
2nd	33·1 (3·1)	18·4 (3·9)	10·8 (2·3)	13·9 (3·0)
3rd	36·0 (2·9)	20·1 (3·3)	15·2 (3·3)	20·9 (3·5)

Is aspiration of saliva the cause of nocturnal asthma?

A JAVAID, AP SYKES, JON G AYRES *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham* The cause of nocturnal asthma is not known, despite many attempts to identify specific triggers. Aspiration of gastric acid has long been considered as a possible cause of nocturnal asthma but studies have produced conflicting results. In order to investigate whether aspiration of saliva during sleep might cause nocturnal asthma we studied 3 age and sex matched groups: five normal subjects, five patients with a history of nocturnal asthma and five patients with asthma but no nocturnal symptoms. The study was randomised and double blind comparing inhalation of 2 ml of the subjects own saliva diluted in 1 ml of saline with 3 ml of saline delivered by nebuliser. Subjects were studied on separate days. No subject was taking oral steroids. FEV_1 and PEF were measured before and at regular intervals up to one hour after the nebulised solution. PD_{20} histamine was measured on separate days. There was no significant difference between the baseline FEV_1 within each group between study days. Baseline FEV_1 was significantly lower in the nocturnal group (mean (SD)) (l) 2·31 (1.31)) compared with the normal group (3·63 (0·53); $p < 0.005$) but was similar to that of non-nocturnal asthmatics (2·97 (1·47)). The maximum % fall in FEV_1 after saliva was −26·6% (nocturnal), −6·5% (non-nocturnal and −4·1% (normals). After saline the values were −19·3%, −5·9% and −2·2% respectively. The difference in response both to saliva and to saline was significant for nocturnal *v* non-nocturnal asthmatics ($p < 0.02$) and for nocturnal asthmatics *v* normal subjects ($p < 0.01$). Mean PD_{20} histamine was > −8 μmol (normals), 1·5 μmol (nocturnal) and 3·7 μmol (non-nocturnal). We suggest that saliva can cause airway narrowing in patients with nocturnal asthma possibly by triggering of hyperreactive airways. Saliva contains both an elastase and an amylase but the time course suggests an irritant rather than an enzymatic mechanism.

The supine posture does not cause sustained bronchoconstriction

KF WHYTE, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh*

Double blind controlled trial of chemoprophylaxis against tuberculosis in patients with silicosis in Hong Kong

AJ NUNN *(for the Hong Kong Chest Service, Tuberculosis Research Centre, Madras, and the British Medical Research Council) and* MRC CARDIOTHORACIC EPIDEMIOLOGY GROUP *Brompton Hospital, London* During 1981–7 641 Chinese male patients in Hong Kong with silicosis, and with no history of previous antituberculosis chemotherapy and no evidence of active tuberculosis were admitted and have been studied for between six months and five years. They were randomised to four series: isoniazid (H) for 24 weeks, rifampicin (R) for 12 weeks, isoniazid and rifampicin (HR) for 12 weeks, or placebo (P). All received isoniazid tablets and/or rifampicin capsules and matching placebo tablets and/or capsules daily for 24 weeks as required to achieve the double-blind design. Breakdown to active pulmonary tuberculosis was more frequent during the five years in the P than in the other three series ($p < 0.01$, log rank test). Of 349 patients who received their tablets and capsules as allocated and who were assessed at three years, 11% of the 80 H, 5% of the 92 R, and 7% of the 76 HR compared with 20% of the 101 P patients developed active disease. Of the 39 breakdowns, 11 occurred in the first years, 15 in the second and 13 in the third. The alanine aminotransferase (ALT) concentrations during chemoprophylaxis were higher in the H than in the R series ($p < 0.001$); there was no difference between the R and P series, suggesting that rifampicin on its own is not hepatotoxic. At three months 27% of the H and 13% of the HR compared with 4% of the R and 5% of the P patients had a raised ALT. Only eight patients (3 H, 3 HR, 2 P) among the 641 had hepatic toxicity, only one (H) having symptoms. Other types of reaction were mostly trivial. In conclusion, the breakdown rate was high in the untreated series and was only moderately reduced by the chemoprophylaxis regimens.

Assessment of eight hourly changes in urine colour and urine drug concentration during daily rifampicin treatment

LN BIRRELL, WJM KINNEAR, JT MACFARLANE, L MORGAN *City Hospital, Nottingham* Compliance with anti-tuberculosis (TB) therapy is often assessed in a chest clinic by looking for pink discolouration of urine from patients having rifampicin. To analyse the usefulness of this technique, six adults being treated for TB with a drug regimen including rifampicin 600 mg daily collected urine samples at eight hourly intervals after taking their TB drugs. On two days the rifampicin was taken in the morning and on two days in the evening. On one other occasion a gap of 32 hours was left between dosage. All urine specimens were assessed visually in a random order by six observers to reduce individual observer bias (four TB health visitors and two chest clinic doctors). In addition, the

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presence of rifampicin and its metabolites were assessed spectrophotometrically in the laboratory after extraction in N-butanol. The lower limit of detection for this method is 5 μg/ml. Eight hours after taking rifampicin, 92% of 144 observations on 24 urine specimens were recorded as positive by visual assessment compared with 35% at 16 hours, 11% at 24 hours and none at 32 hours. There was no difference if the rifampicin was taken in the morning or in the evening. The results obtained by laboratory analysis were very similar. After eight hours all 24 urine samples were positive for rifampicin (range 35–255 μg/ml) compared with 58% at 16 hours, 8% at 24 hours and 0% at 32 hours. Nine per cent of visual assessments said to be positive were found to be negative after laboratory urine analysis, the figure for the false negative rate for visual assessment being 12%. We conclude that monitoring of rifampicin compliance by visual assessment of the urine or by laboratory testing produces similar results, but both are reliable for only eight hours after taking the tablets. Approximately one in 10 visual assessments will be incorrect.

Tuberculosis contact tracing in Edinburgh

CD SELBY, MB ALLEN, AG LEITCH *Royal Victoria Dispensary, Edinburgh* This unit provides a centralised service for the documentation and implementation of contact tracing procedures for tuberculosis (TB) in the Lothian area (population 0·6 million). Heaf positive contacts undergo radiological follow up at 0 and 3 months, 1 year and 2 years. Non-attenders are encouraged by letter or visit to comply. From February 1984 to March 1986 inclusive 806 contacts were eligible for such follow up. Records show that 800 attended the initial appointment, 643 (79·8%) attended at 3 months, 481 (59·7%) completed one year and 294 (36·5%) completed two years. Nine cases of pulmonary TB were identified radiologically, an overall rate of $11/10^3$ contacts. All were identified by three months. Seven cases were in non-BCG vaccinated individuals (2·5% of all definite non-BCG vaccinated contacts), five aged 24 years or less. Only two cases developed in BCG vaccinated individuals representing 0·5% of all contacts who were known to have definitely received vaccination. One case occurred in a non-indigenous contact. No cases to date have been identified in those contacts who defaulted from follow up. With such a high default rate during follow up and since all the cases were identified by the three month examination, does radiological follow up of contacts need to extend beyond six months? These findings also lend support to continuing BCG vaccination, at least in South East Scotland.

Value of the tuberculosis contact clinic in Harrow

PS THOMAS, MG HARRIES *Department of Respiratory Medicine, Northwick Park Hospital, and Clinical Research Centre, Harrow, Middlesex* Contact tracing has been reviewed recently and a low case-finding rate noted in South East Kent (*Lancet* 1983;i:232–3). We reviewed the yield from the contacts of two hundred and twenty patients who were notified as having tuberculosis in Harrow from 1984 to 1986 inclusive. Household contacts of these patients totalling 907 people were seen at the chest clinic, each having a chest radiograph and tuberculin skin test (Heaf). A total of 16 (1·8%) of these were notified as having tuberculosis themselves. Comparing site of disease in the original patients with the rate of disease in their contacts, we found that those with tuberculous lymphadenopathy had a contact infection rate of 1·0% ie 1 per 100 contacts seen. Those with pulmonary or miliary disease had contact infection rates of 2·9% and 3·7% respectively. Of those contacts who were given chemoprophylaxis on the basis of a grade III or IV skin test result, the rates were 1·6% in association with lymphadenopathy, 2·6% with pulmonary disease and 1·9% with miliary disease. Harrow is an urban area of high immigration: here 10·7% of the population are from the New Commonwealth. This is reflected in the large number of immigrants, who comprise 154 (70%) of those notified with tuberculosis. While the many of the contacts seen may have brought their disease into the country with them, it would appear that those contacts of pulmonary and miliary disease remain at greater risk than those in proximity to lymph node disease. With a case finding rate of nearly two per 100 contacts examined, we conclude that in this community the contact clinic remains a useful public health measure.

Tuberculin reactivity in new employees in a London health district

A COCKCROFT, S CHAPMAN, C INSALL, P SOPER, Y KENNARD, C HOLLIS *Occupational Health Unit, Royal Free Hospital, London* Tuberculin testing is carried out on new employees by most NHS occupational health (OH) services, although details of who and how to test vary. We currently perform Mantoux tests (starting at 1:10000 and end at 1:100) on new staff unless they have a definite BCG scar within 10 years or evidence of a positive skin test within 5 years. We undertook the present study in order to decide in what circumstances Mantoux testing was necessary. Three hundred and twenty consecutive new employees and students (mean age 25 y) were included. The OH nurses recorded the presence of a BCG scar only if this was unequivocal. Two hundred and sixty five had a definite history of BCG and 240 of these had a definite scar. The results of Mantoux tests are summarised in the table. Only one person with a definite BCG scar and two without scars who had a definite history of BCG were Mantoux negative. There were significantly more Mantoux negatives among those without a BCG scar ($p < 0·005$). Thus in this type of population tuberculin reactivity seems to persist for many years (our longest interval was 34 years). In future, we will not Mantoux test anyone with a definite BCG scar, whatever its age.

	Mantoux test results					
	N	*Neg*	*Pos 1:100*	*Pos 1:1000*	*Pos 1:10000*	*Not done**
+BCG + scar						
< 10 y	145	0	2	1	4	138
10–19 y	50	1	11	19	10	9
> 19 y/? date	45	0	6	18	20	1
+BCG − scar						
< 10 y	15	1	6	5	1	2
≥ 10 y	10	1	2	3	4	0
−BCG − scar	55	8	13	20	12	2

*Policy not to test with BCG scar < 10 y or +ve skin test < 5 y.

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Constriction of isolated human airways to hypertonic Krebs buffer: pharmacological characterisation of the response

RC JONGEJAN, JC DE JONGGSTE, HC RAATGEEP, IL BONTA, KF KERREBIJN *Departments of Paediatric Pulmonology and Pharmacology, Erasmus University Rotterdam, The Netherlands* In asthma exercise and hyperventilation of dry cold air induce bronchoconstriction, which may be triggered by an increased osmolarity of the airway lining fluid (SD Anderson *Chest* 1985;**87**:191S). We measured the effects of hypertonic Krebs buffer on responses to methacholine of isolated human bronchioles in vitro at 37°C and at 27°C. Peripheral airways were dissected from human lung tissue obtained at thoracotomies, and cut into segments. These were studied isotonically in organ baths containing aerated Krebs-Henseleit buffer (317 mmol) at 37°C. Osmolarities were changed by adding NaCl. Hyperosmolar buffer constricted the bronchioles by (mean (SEM)) 32·1 (6·6)% at 450 mmol, 74·6 (12·7)% at 600 mmol and 37°C and 61·9 (14·5)% at 600 mmol and 27°C (n = 5, expressed as % of the maximal response after 10^{-5}M methacholine). To determine the mechanisms of hypertonicity-induced airway contraction, we examined the effects of the H_1 receptor antagonist mepyramine ($2{\cdot}8 \times 10^{-6}$M), the inhibitor of mast-cell degranulation disodiumcromoglycate (10^{-4}M), the cyclooxygenase inhibitor indomethacin ($6{\cdot}0 \times 10^{-6}$M), the βB_2 receptor agonist isoprenaline (10^{-5}M), the leukotriene receptor antagonist FPL 55712 ($11{\cdot}5 \times 10^{-6}$M) and of calcium-free buffer containing EGTA (0·5 mM). The bronchoconstriction was significantly inhibited, by isoprenaline and calcium-free buffer at 450 mmol, 600 mmol (37°C) and 600 mmol (27°C). None of the other drugs changed the response of the airways to hyperosmolar buffer at 37°C or at 27°C. We conclude that hyperosmolar buffer contracts human airways in vitro by a mechanism that is partly dependent on extracellular calcium, and does not seem to be due to the release of prostaglandins, leukotrienes or histamine in the preparation.

Amiloride inhibits histamine induced constriction in bovine tracheal smooth muscle

AJ KNOX, P KEMP, JR BRITTON, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* To determine whether the sodium-hydrogen exchange mechanism is involved in contractile responses in airway smooth muscle, we have studied the effect of amiloride, an inhibitor of Na/H exchange on the response to histamine in bovine trachealis. Tissue was obtained immediately after death and bathed in Krebs-Henseleit solution. Four strips of tracheal smooth muscle were dissected out from each of eight animals and suspended under a resting tension of 2 g in organ baths containing Krebs maintained at 37° C and aerated with 95% O_2 and 5% CO_2. Changes in tension were recorded on a Grass FTO3 force displacement transducer attached to two CR600 two channel flat bed recorders. After letting the tissue settle for one hour, histamine dose response curves were measured, the tissue washed and allowed to settle again. One strip then served as a control whilst the other three strips were exposed to 10^{-5}M, 10^{-4}M and 10^{-3}M amiloride, 10 minutes before a repeat of the histamine dose-response curves. Amiloride did not affect resting tone but caused a dose related increase in log histamine EC_{50}(ANOVA $p < 0{\cdot}001$) and reduction in maximum tension generated by histamine (ANOVA $p < 0{\cdot}001$). Mean change in EC_{50} was 1·5 fold in the control strip, and 2·6, 7·7 and 34·7 fold after 10^{-5}M, 10^{-4}M and 10^{-3}M amiloride respectively. Mean change in maximum tension generated was +13% in the control strip and −6%, −28% and −41% after 10^{-5}M, 10^{-4}M and 10^{-3}M amiloride respectively. Receptor operated stimulation of airway smooth muscle is thought to lead to formation of diacylglycerol, which stimulates protein kinase C and sodium-hydrogen exchange. Sodium-hydrogen exchange has been shown to be a prerequisite for calcium mobilisation in platelets (Siffert W *Nature* 1987;**325**:456). Our results suggest that a similar system may operate in bronchial smooth muscle contraction.

Beta$_2$ adrenoceptor stimulation inhibits histamine induced hydrolysis of inositol phospholipids in bovine airway smooth muscle

IP HALL, SJ HILL *Department of Physiology and Pharmacology, Queen's Medical Centre, Nottingham* Contraction of airway smooth muscle (ASM) in response to stimulation with Histamine (HA) is thought to involve the hydrolysis of inositol containing membrane phospholipids with the consequent production of the intracellular second messengers inositol 1, 4, 5 tris-phosphate and diacylglycerol. Beta$_2$ adrenoceptor agonists relax ASM precontracted with HA. We report here that Beta$_2$ agonists inhibit the inositol phosphate response to HA in bovine ASM. Slices of bovine trachealis muscle (300 μm) were incubated for 75 min at 37°C in Krebs-Henseleit (KH) solution containing [^{3}H]-myo-inositol (0·4 μM) and then aliquoted into insert vials containing KH, LiCl (5 mM) and, where appropriate, antagonists for 30 min. Agonists were then added in a minimum volume of medium and incubations then terminated after 45 min with 10% (w/v) perchloric acid. [^{3}H]-inositol phosphates ([^{3}H]-IP were then separated by anion exchange chromatography. HA produced concentration related [^{3}H]-IP formation (mean (SEM) EC_{50} 34 (7) μM, n = 13) in slices of bovine ASM, and this response was inhibited competitively by mepyramine (50 nM) indicating the involvement of H_1 receptors. Noradrenaline (IC_{50} 0·8 ± 0·6 μM, n = 3), isoprenaline (IC_{50} 0·08 (0·04) μM, n = 5) and salbutamol (Sal) (IC_{50} 0·29 (0·12) μM, n = 15) all produced inhibition of the [^{3}H]-IP response to 100 μM HA, maximum inhibitions being 55 (5)%, 68 (5)% and 66 (3)% respectively. The inhibition of HA induced [^{3}H]-IP formation by Sal was competitively inhibited by the selective beta$_2$ adrenoceptor antagonist ICI 118551 (1 μM) (*J Cardiovasc Pharmacol* 1983;**5**:430), indicating the involvement of beta$_2$ adrenoceptors in this response.

Airway responsiveness to adenosine-5-monophosphate after hypertonic saline challenge in asthmatic subjects

SP O'HICKEY, PJ REES, TH LEE *Guy's Hospital, London* Hypertonic saline induced bronchoconstriction is characterised by the development of a refractory period during which a second identical challenge will elicit significantly less bronchoconstriction. It has been suggested that this is due to mast

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cell mediator depletion and represents the time necessary for mediator replenishment. Adenosine-5-monophosphate (AMP) causes bronchoconstriction via the release of preformed mast cell mediators. We have therefore studied the airway responsiveness to AMP following hypertonic saline. Three male and four female subjects aged 21–34 (mean 26 years) attended the laboratory on three occasions. On day 1 a hypertonic saline challenge was performed followed one hour later by a second hypertonic challenge. On day 2 an AMP challenge was performed. On day 3 a hypertonic saline challenge was performed, followed one hour later by an AMP challenge. All challenges were performed in a dose dependent manner and airway responsiveness was determined by changes in PD_{35} sGaw. Airway responsiveness to an initial hypertonic saline challenge ranged from 24 to 315 litres of aerosol (mean 82·4 l). Airway responsiveness to a second hypertonic saline challenge ranged from 52 to 800 litres (mean 148 l; $p = 0{\cdot}001$, $n = 9$). Airway responsiveness to AMP ranged from 0·66 to 14·0 μmol (mean 2·4 μmol) at baseline and ranged from 0·37 to 7·9 (mean 1·6) μmol ($p = 0{\cdot}4$) after hypertonic saline challenge. Thus there was no significant change in AMP responsiveness during the refractory period to hypertonic saline challenge. Our results suggest that the refractory period to hypertonic saline is not due to mediator depletion.

L648,051, a specific leukotriene antagonist active by the inhaled route of administration in man

JM EVANS, NC BARNES, JT ZAKRZEWSKI, PJ PIPER, JF COSTELLO *Department of Thoracic Medicine, Kings College Hospital, and Department of Pharmacology, Royal College of Surgeons, London* Leukotriene (LT) antagonists can be active by the oral route in man. The inhaled route may have advantages in terms of safety and efficacy. L648,051 (Jones *et al. Can J Physiol Pharmacol* 1986;**64**:1532–42) is a cysteinyl-LT antagonist active when inhaled in various animal models. We have investigated the ability of inhaled L648,051 (6 and 12 mg) to inhibit LTD_4 induced bronchoconstriction and of 12 mg to block histamine-induced bronchospasm. Six normal male subjects (mean age 30·8 years) participated. Baseline lung function consisting of FEV_1, specific airways conductance (sGaw) and flow at 30% of vital capacity above residual volume ($\dot{V}max_{30}$) was measured. Subjects then inhaled either placebo L648,051 6 mg or 12 mg according to a double blind, random order design. Lung function tests were repeated and then LTD_4 was inhaled at a concentration previously shown to cause a 50% fall in sGaw. Following this sGaw and $\dot{V}max_{30}$ were measured frequently until sGaw returned to baseline. In a second part of the study the same procedure was followed except that placebo or L648,051 12 mg was inhaled prior to inhaling a concentration of histamine known to cause a 50% fall in sGaw. Both 6 and 12 mg L648,051 protected against LTD_4 induced bronchoconstriction in a manner compatible with competitive antagonism. The mean (SEM) maximum percentage fall in sGaw was: placebo 49 (7)%; L648,051 6 mg 31 (5)%; L648,051 12 mg, 21 (6)%. The recovery time for bronchoconstriction was placebo 41 (5) min; 6 mg 30 (6) min; 12 mg 19 (7) min. L648,051 had no effect on baseline lung function or histamine-induced bronchoconstriction. L648,051 was well tolerated with no side effects. We conclude that L648,051 is a cysteinyl-LT antagonist active by the inhaled route with no evidence of partial antagonist activity. As L648,051 is well tolerated it may be a useful drug for evaluating the role of LTs in asthma.

Human airway reflexes: effects of inhaled nicotine

L HANSSON, JA KARLSSON, N CHOUDRY, R FULLER *Department of Lung Medicine, University Hospital, Lund, Sweden, AB Draco, Lund, and Department of Clinical Pharmacology, Hammersmith Hospital, London* Inhaled cigarette smoke may cause cough and a reflex bronchoconstriction in man that resembles the effects of inhaled capsacian. However animal studies have suggested that nicotine (N) and capsacian (C) may induce cough through separate neural pathways. We have therefore compared the effects of inhaled N and C in 15 healthy non-smoking subjects, seven female, who inhaled single breaths of nebulised N (0·1–7·9 μmol), C (0·4–50 nmol) or vehicle. A cough dose response (D/R) was performed for each agent. Total respiratory resistance (Rrs) was measured after inhalation of a single dose causing less than two coughs using a forced oscillation technique. The geometric mean dose of C and N causing four coughs (D_4) was calculated. Two subjects did not cough at any dose of N but did cough after C. Both N and C produced a dose dependent cough with C being approximately 200 times more potent than N, geometric mean (95% CI) D_4 was 1·6 (0·9–3·0 μmol) for N and 9·1 (5·0 to 16·6) nmol) for C. The D/R to N was reproducible when tested on three separate days (1·6 (0·9–3·0), 2·3–(1·2–2·4) and 1·6 (1·0–2·6)); but when measurements were repeated on the same day there was a significant loss of response (1·6 (1·0–2·6), 3·7 (2·2–6·2), 3·7 (2·3–5·9) and 3·5 (2·5–4·9)) at 0, 10, 30 and 60 minutes respectively. However, the response to C was not altered 10 minutes after N. N and C increased Rrs by 30·7 (7·7)% and 28·7 (5·5)% respectively. Rrs was maximal 6s and increased for 3·6 (1·1) min and 1·6 (0·5) minute by N and C. Both N and C caused rapid onset of cough and bronchoconstriction. N caused a more persistent bronchoconstriction than C. Partial loss of the cough response to N occurred on repeated challenge but the response to C was maintained. These experiments suggest that bronchoconstriction and cough response may be served by different receptors and nervous pathways.

Enhancement of capsaicin induced cough by inhaled prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)

GM NICHOL, A NIX, PJ BARNES, KF CHUNG *Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* Inhaled $PGF_{2\alpha}$, which causes bronchoconstriction in some normal and most asthmatic subjects, stimulates airway cough and irritant receptors. We studied the effect of inhaled $PGF_{2\alpha}$ on cough induced by the C fibre stimulant capsaicin (C) in seven healthy non-smoking male volunteers. The subjects were aware of the nature but not the purpose of the study. The number of coughs and the intensity of the irritant stimulus indicated on a 10 cm visual analogue scale

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(VAS) were determined three times at each of four doses of C (0·3, 0·6, 1·2 and 2·4 nmol) inhaled in random order at one minute intervals, before and after inhaling $PGF_{2\alpha}$ (7 μl of the 5 mg/ml solution). Five subjects completed a control protocol in which normal saline (NS) was substituted for $PGF_{2\alpha}$. Total respiratory resistance (Rrs) was measured before and after each series of inhalations by the technique of forced oscillation. C led to a dose-dependent increase in cough (0·9 (0·3), 1·5 (0·4), 2·8 (0·5) and 3·7 (0·4)) and VAS (1·1 (0·2), 1·5 (0·4), 3·2 (0·6) and 5·3 (0·7) cm) at 0·3, 0·6, 1·2 and 2·4 nmol respectively. Rrs increased by 17·5 (3·8)% ($p < 0·05$) after $PGF_{2\alpha}$ but was unchanged after NS. All subjects reported an increase in the sensation of C-induced irritation after $PGF_{2\alpha}$. $PGF_{2\alpha}$ significantly enhanced cough at inhaled doses of 0·3 nmol (1·2 (0·4) to 2·2 (0·5); $p < 0·001$) 0·6 nmol (1·3 (0·5) to 2·4 (0·7); $p < 0·01$) and 2·4 nmol (3·6 (0·5) to 4·5 (0·6); $p < 0·02$) of C. The enhancement at 1·2 nmol (2·6 (0·7) to 3·5 (1·0)) was not significant. Cough enhancement did not correlate with the degree of bronchoconstriction. Similar enhancement was observed in VAS. There was no change in C-induced cough or VAS following NS at any dose of C. Thus $PGF_{2\alpha}$ enhances the response of laryngeal and/or airway C-sensitive cough receptors, and the irritant sensation associated with C. Endogenous prostaglandins may play a part in states of increased cough.

Association between diabetes mellitus and meconium ileus equivalent in cystic fibrosis

GE PACKE, ME HODSON *Department of Cystic Fibrosis, Brompton Hospital, London* Diabetes mellitus (DM) is a recognised complication of cystic fibrosis (CF) and occurs as a result of damage to pancreatic islet cells (impaired endocrine function). Patients with CF also have impaired pancreatic exocrine function, which results in hyposecretion of digestive enzymes, steatorrhoea, and in some patients, episodes of small bowel obstruction-meconium ileus equivalent (MIE). Pancreatic damage occurs in the majority of patients with CF, but it is possible to speculate that those with DM, also suffering from MIE, are the patients who respectively have more severe pancreatic endocrine or exocrine dysfunction. We therefore conducted the present study to see if there is an association between the occurrence of DM and MIE in patients with CF, and, by implication, to see if there was any relation between the extent of pancreatic endocrine and exocrine dysfunction. The computerised records of 383 patients seen in an adult CF unit were examined to find the prevalence of DM and the number of patients with one or more documented episodes of MIE.

	DM	*Non-DM*	*Total*
MIE	13	51	64
No MIE	34	285	319
Total	47	336	383

$p < 0·05$ (χ^2 test).

In the 13 patients who had DM and one or more episodes of MIE there was a correlation between the age that DM was diagnosed, and the age of the first episode of MIE ($r = 0·66$, $p < 0·02$). These results show that in CF there is an association between the presence of DM and the occurrence of MIE, and between the age of onset of DM and the age of an initial episode of MIE. The results moreover suggest that there is a relationship between the degree of impairment of pancreatic endocrine and exocrine function in CF, and that pancreatic endocrine and exocrine function may decline in parallel.

Sweat testing after 9α-fluorohydrocortisone as an aid to the diagnosis of cystic fibrosis

AH HAMILTON, F CARSWELL *Respiratory Research Group, Department of Child Health, University of Bristol* Sweat tests were performed after treatment with two daily doses of 3 mg/m^2 9 α-fluorohydrocortisone (fludrocortisone) (Lobeck *et al. J Pediatr* 1963;**62**:393–8) in 23 out of approximately 500 patients attending the Bristol Cystic Fibrosis (CF) clinic during 1980–7 for diagnostic sweat testing. In these 23 patients there was real diagnostic doubt, because of either equivocal sweat tests or results out of keeping with the clinical picture. The diagnosis has since become clear with clinical change, pancreatic function and other diagnostic tests; eight patients have proved to have CF and 15 to be normal. The fludrocortisone sweat test results, which did not influence the diagnostic classification have been reviewed. The phenomenon of higher chloride (Cl) than sodium (Na) values in true CF (Green *et al. Ann Clin Biochem* 1984;**22**:171–6) is confirmed in the pre-suppression tests, but there is an overlap of ratios between normal and CF limiting clinical usefulness. In the post-fludrocortisone tests, however, complete segregation of the two populations is achieved above and below a ratio of 1. Thus all 15 CF patients' sweat had a ratio $(Cl-/Na+) > 1$ and all eight normals < 1. Sweat tests after 9 α-fluorohydrocortisone may be useful in the clarification of the difficult diagnosis.

Changes in numbers of *Pseudomonas aeruginosa* during treatment in cystic fibrosis

CD SHELDON, TL PITT, ME HODSON *Department of Cystic Fibrosis, Brompton Hospital, and Central Public Health Laboratory, London* *Pseudomonas aeruginosa* (PA) in cystic fibrosis (CF) is seldom eradicated by antibiotics. We followed the changes in PA numbers during treatment with a Beta lactam and aminoglycoside antibiotic in 11 adult CF patients. Accurate quantitation of antibiotic sensitive and resistant strains was made by plating serial logarathmic dilutions of sputum onto control plates and plates containing Azlocillin (64 μg/ml), Ceftazidime (16 μg/ml), Ciprofloxacin (2·0 μg/ml) and Gentamicin (8 μg/ml). At the start of treatment eight patients had no detectable strains of PA resistant to one of the antibiotics they received. Despite predominantly sensitive organisms, the mean decrease in total $\log_{10}$ PA count for all patients was less than 1 $\log_{10}$ CFU/ml (range −1·43 to −0·22). All patients showed clinical improvement. The mean and (range) of changes in lung function were: PEF +114 l/min (5–210), FEV_1 524 ml (−30–+1700), FVC 870 ml (50–1900). Sputum production decreased by a mean of 30·8 g/24 h (−75–+53). There was no correlation bet-

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ween the reduction in bacterial numbers expectorated per 24 h and degree of spirometric improvement. These findings suggest that bacterial elimination is only partially responsible for clinical improvement. In vitro studies of three selected strains of PA showed decreased protease production in the presence of sublethal antibiotic concentrations. Inhibition of the synthesis of extracellular products by antibiotics may contribute to clinical improvement.

Infective respiratory exacerbations of young adults with cystic fibrosis: role of viruses and atypical microorganisms

ELC ONG, ME ELLIS, AK WEBB, KR NEAL, M DODDS, EO CAULL, S WELSHMAN *Department of Infectious Diseases and Respiratory Medicine, Monsall Hospital, Manchester and Public Health Laboratory Service, Bristol* Thirty-six young patients with Cystic Fibrosis (18 male, 18 female) with a mean age of 23·6 years (range 17–32) were studied for evidence of infection with a variety of respiratory viruses and some atypical microorganisms over a course of one year. Two groups of patients were investigated: a "deteriorated" group of 19 patients in whom an increase in purulent sputum production, cough or breathlessness accompanied by worsening FEV_1 and a "stable" group of 17 patients who were clinically stable and had steady lung function values, and were seen routinely at three monthly intervals in outpatient clinic. Serological evidence of viral (influenza B, cytomegalovirus, human rhinovirus 2) and mycoplasma infections ("non-bacterial") was documented in 21·1% of cystic fibrosis (CF) patients with acute exacerbations of their respiratory disease. There was no significant difference in "non-bacterial" infections between infective respiratory exacerbations of CF patients who deteriorated clinically and that of the "stable" group. There was no association between serological conversion of viral infections and the number and type of bacteria isolated from sputum cultures in both "stable" and "deteriorated" group. Human rhinovirus 2 infection did not cause significant clinical deterioration on CF patients we studied.

Short and long term effects of exercise on sputum output in patients with cystic fibrosis

B SALH, M DODDS, AK WEBB *Monsall Hospital, Manchester* We report two studies of the effect of exercise on sputum expectoration. The short term study examined 10 patients (aged 17–33 y) who were hospitalised for a respiratory exacerbation of their cystic fibrosis. They received conventional chest physiotherapy (postural drainage plus forced expiration technique) or were asked to exercise for 15 min at 50% of their peak work capacity (PWC) on an exercise cycle. The sputum expectorated during the next two hours (including the 15 minute study period) was collected and weighed. The order was reversed in the next (consecutive) two hour study period, the total period being four hours. The long term study examined 19 patients (aged 16–32). After their daily basal sputum outputs had been determined, they were asked to train at 50% of their PWC for 15 minutes each day for two months. Assessments of daily sputum output and PWC were then repeated. Results from the short term study indicated that exercise contributed to between 10–39% of the total sputum expectorated over the four hour period. The findings from the long term study were that six patients increased their sputum output by an average of 98%, two patients decreased their sputum output, four patients produced less than 5 g per day on both occasions, five patients were in respiratory exacerbation at the time of reassessment, accounting for their increased sputum outputs, and the two remaining patients failed to comply with the study requirements. Collectively the results indicate an additive effect of exercise with physiotherapy in promoting sputum expectoration. The short term study may provide a means of determining which patients are likely to gain most benefit from the prescription of an exercise programme, from the point of view of enhancing sputum output.

Improving prognosis for cystic fibrosis in the UK, 1977–1985

DM GEDDES, JA DODGE *(for British Paediatric Association working party on cystic fibrosis) Brompton Hospital, and Department of Child Health, Queen's University, Belfast* This study attempted to identify all CF patients alive in the UK at any time between 1977 and September 1985. A total of 6220 subjects were entered into the database. Age-specific mortality rates were calculated for the two periods 1977–9 and 1980–5. Considerable improvement in prognosis has occurred during the period under study, particularly in the under five years age group. Comparative data also showed that survival is better in patients managed in large CF centres than in small local clinics. Regardless of any future improvements in treatment, numbers of adult CF patients will inevitably increase in the UK during the next decade, highlighting the need for appropriate medical services.

Current survival: large v small clinics

	Males		*Females*	
Survival to age (y)	*Large (%)*	*Small (%)*	*Large (%)*	*Small (%)*
1	97·2	96·1	94·8	95·3
5	94·7	92·0	91·8	89·9
10	87·2	85·5	83·5	79·6
15	77·5	70·8	69·0	65·8
20	64·5	60·0	49·7	48·2
80%	14 y	11 y	12 y	10 y
50%	25 y	20 y	23 y	20 y
Age standardised mortality/1000/year	19·9	29·4	23·1	32·4

Heart-lung transplantation for cystic fibrosis

JP SCOTT, JA HUTTER, TW HIGENBOTTAM, ME HODSON, S STEWART, J WALLWORK *Papworth Hospital, Cambridge* We report our experience of heart-lung transplantation for the terminal pulmonary complications of cystic fibrosis (CF). Although as many as 80% of CF sufferers now survive to have complications in early adulthood (*Thorax* 1987;**42**:526–32), with 80–90 CF patients of a transplantable age dying each year in

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England and Wales. Twenty-six patients mean age 24·2 years (range 9–44) have been referred as potential candidates for heart-lung transplantation, of whom 13 patients, mean age 25·7 years (range 11–44) have been accepted for surgery. Five patients, mean age 25·4 years (range 20–37), have successfully undergone heart-lung transplantation. All five patients are alive with normal lung function and exercise tolerance two to 27 months after operation and two have returned to work. Only one patient had persistent sputum infection after surgery and one had a brief episode of meconium ileus equivalent, otherwise postoperative complications have been limited to one episode of rejection per patient. All patients required high oral doses of cyclosporine (CS), mean dose 1040 mg daily. Six patients have died within six months of referral and of those accepted for surgery, a third died without surgery, within three months of acceptance. We suggest that heart-lung transplantation is an appropriate treatment for the management of terminal pulmonary cystic fibrosis.

Controlled trial of palliative radiotherapy given in only two fractions or conventionally fractionated in the treatment of inoperable non-small cell lung cancer

NM BLEEHEN, PM FAYERS, DJ GIRLING, RJ STEPHENS *(for the MRC Lung Cancer Working Party) MRC Cardiothoracic Epidemiology Group, Brompton Hospital, London* A total of 374 patients with inoperable non-small cell lung cancer were admitted to the study from March 1985 to February 1988. All had their main symptoms related to tumour in the chest, even if metastases were present, and had disease too advanced for radical radiotherapy. They were randomised on admission to receive either high-dose (HD) radiotherapy (17 Gy in two fractions of 8·5 Gy one week apart) or conventional dose (CD) radiotherapy (30 Gy in 10 fractions in two weeks, or 27 Gy in six fractions in two weeks). The nature and severity of symptoms were recorded monthly by the clinicians. Nausea, vomiting, dysphagia, level of physical activity, mood and overall condition were recorded daily by patients using a diary card. The two regimens achieved similar palliation of symptoms, and both caused a temporary and similar increase in dysphagia. There was no difference between the two series in survival from admission ($p = 0.16$, log rank test), the median survival periods being HD 28 weeks and CD 31 weeks. The two fraction regimen (HD) is therefore recommended.

	% of patients at month: 0		1		3	
Symptom	*HD*	*CD*	*HD*	*CD*	*HD*	*CD*
Cough	93	91	84	82	70	82
Haemoptysis	47	47	21	16	17	8
Chest pain	55	59	31	34	41	37
Dysphagia	11	12	33	38	16	13
No of patients	158	153	61	45	37	38

Oesophageal function studies before and after lung resection

J OLAK, K JEYASINGHAM, HR PAYNE, C FORRESTER-WOOD *Department of Thoracic Surgery, Frenchay Hospital, Bristol* The high incidence of oesophageal dysfunction in patients being evaluated for surgery of bronchogenic carcinoma has been stressed in an earlier presentation (*Thorax* 1988;**43**:222P). Several anecdotal reports exist of patients developing oesophageal motility disorders after lung resection. Thirty eight patients with a male/female ratio of 29 to nine and undergoing lung resection for bronchogenic carcinoma were prospectively subjected to oesophageal function studies before and after lung resection. Their ages ranged from 40 years to 79 years with a mean of 65·6. Preoperative and postoperative oesophageal function studies included symptomatology, endoscopy, manometry and prolonged pH recordings. The same studies were conducted 12–24 months after surgery with a mean interval of 16 months. Fifteen patients (39·5%) developed de novo symptoms, or had exacerbation of symptoms of gastro oesophageal reflux postoperatively. This correlated with manometry and/or prolonged pH evidence of reflux in every case. Thirteen patients (34·2%) who had no postoperative symptoms, nonetheless had manometric and/or prolonged pH evidence of gastro oesophageal reflux postoperatively. Seven patients had no change in symptomatology, manometry or pH studies on postoperative testing. In the remaining three patients (7·9%) postoperative assessment was incomplete due to technical problems. Of nine patients whose lower oesophageal sphincter tone on preoperative assessment was considered to be above the normal for our laboratory the postoperative sphincter pressure was significantly lowered in seven patients. In the remaining two patients the sphincter pressure showed very little change. It is concluded that oesophageal dysfunction in the early years after lung resection is almost entirely related to lowered lower oesophageal sphincter pressure and gastro oesophageal reflux, 73·7% of postoperative patients showing these features.

Assessment of placental alkaline phosphatase as a tumour marker in pleural fluid

RJ FERGUSSON, FG HAY, J FISKEN, MA MCINTYRE, JE ROULSTON, RCF LEONARD *Departments of Clinical Oncology and Pathology, Western General Hospital, and Department of Clinical Chemistry, Royal Infirmary, Edinburgh* Human placental alkaline phosphatase (PLAP) has been shown to be produced on the surface of many malignant cells and seems to have potential as a tumour marker in gynaecological cancers. Since it is found in normal lung and was first described in a patient with a bronchial carcinoma (Fishman WH *et al. Cancer Res* 1968;**28**:150–4) we have assessed its potential as a diagnostic marker in the pleural fluid of 60 patients with 'benign' and malignant pleural effusion. PLAP was measured by an enzyme-linked immunosorbent assay (ELISA) using the two monoclonal antibodies H317 and H17E2. Of the 60 patients, 12 had a primary lung tumour, 23 had an effusion associated with secondary tumour (seven ovary, seven breast, three lymphoma, three adenocarcinoma, three others) and 25 had a 'benign' effusion (10 cardiac failure, five related to infection, two rheumatoid, one tuberculosis, one thrombo-

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embolism disease and six unknown). 'Benign' cases were followed for up to one year to exclude an occult malignancy. Mean (SD) pleural PLAP levels in patients with primary lung cancer were not elevated when compared with the 'benign' group (0·48 (0·47) IU/l v 0·54 (0·86) IU/l). Patients with secondary tumours appeared to have raised PLAP levels (0·88 (2·02) IU/l) but this may be explained by the high levels seen in the small subgroup of patients with ovarian cancer (2·16 (3·5) IU/l). PLAP was not influenced by smoking habits. Apart from perhaps identifying a small group of patients with metastatic ovarian cancer the measurement of pleural PLAP levels is unhelpful as a diagnostic aid in patients with 'benign' and malignant pleural effusions.

Bombesin (GRP) gene products in human pulmonary endocrine cells and tumours

DR SPRINGALL, JM POLAK, MA GHATEI, Q HAMID, S SQOMRO, M BHATNAGAR, NBN IBRAHIM, ER SPINDEL, F CUTTITTA, SR BLOOM *Departments of Histochemistry and Medicine, Royal Postgraduate Medical School, London; Department of Histopathology, Frenchay Hospital, Bristol; Harvard Medical School, Boston; and National Cancer Institute, Bethesda, USA* Gastrin-releasing peptide (GRP), the mammalian analogue of bombesin, is produced as a precursor containing a signal peptide, GRP itself and a C-terminal flanking peptide. The flanking peptide occurs in three forms, the N-terminus of which is conserved and the C-terminus variable. GRP is known to be a growth factor in pulmonary endocrine tumours and possibly a normal lung, and is produced by both. We have therefore examined the synthesis, degree of storage and the molecular forms of peptides produced by the gene translation both in tumours (small cell carcinoma—SCCL, and carcinoids) and normal lung endocrine cells. Carcinoid tumours (n = 40) had both GRP and flanking peptide-like immunoreactivity, whereas SCCL (n < 250) had much less GRP immunoreactivity but much more flanking peptide like immunoreactivity. In the normal lung, many endocrine cells showed colocalisation of the two immunoreactivities, but some only demonstrated flanking peptide. This was confirmed in normal lung and tumours by radioimmunoassay and chromatography, which demonstrated higher molar ratios of flanking peptide than GRP. This technique also revealed that some of the GRP was cleaved to produce GRP 18–27 (formerly called neuromedian C). These results suggest that GRP and flanking peptide may be differentially secreted and that GRP 18–27 is also produced in pulmonary endocrine cells. The differential secretions suggest that flanking peptide may have a function, possibly also growth-promoting like GRP, that remains to be established.

Tru-cut biopsy needle: an alternative to the Abram's needle for routine pleural biopsy

DT MCLEOD, I TERNOUTH, N NKANZA *Department of Medicine, University of Zimbabwe, Harare* Pleural effusion is a manifestation of many common diseases which can be diagnosed by pleural biopsy. The Abram's pleural biopsy punch is the instrument most commonly used in Britain (*Br Med J* 1980;i:693–5). The Tru-cut needle is much thinner and is used primarily for biopsying solid lesions or organs. By suitably angling of the Tru-cut pleura may be biopsied without encroaching on the lung. In a prospective study of 36 patients (27 males) mean age 48·5 years, range 10–70, both needles were used on each patient and the pleural biopsies were read by one pathologist who had no knowledge of which biopsy needle had been used. In one patient the biopsy was repeated (n = 37). There were no serious complications. In 23 patients both biopsy needles produced adequate diagnostic material. In eight patients the Tru-cut alone yielded diagnostic material, and in six the Abram's only yielded the diagnosis. Overall, the Tru-cut needle was deemed to have produced better pleural samples than the Abram's in 25 of 37 (67·6%) patients. If the Abram's alone had been used 29 of 37 (78%) biopsies would have yielded diagnostically adequate material; with the Tru-cut the figure was higher, 31 of 37 (83·8%). Diagnoses made included carcinoma (12), tuberculosis (11), chronic inflammation (9), pleural fibrosis (3), mesothelioma (1) and normal (1). It is concluded that the Tru-cut biopsy needle is a useful alternative to the Abram's particularly in the presence of thickened pleura; patients preferred it and the doctors found the Tru-cut easier to use. Combined use of the two needles guaranteed procurement of adequate pleural material.

Thoracoscopy: a review of 121 consecutive procedures

RD PAGE, RR JEFFREY, RJ DONNELLY *Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Liverpool* One hundred and twenty one patients presented for thoracoscopy to one surgeon (RJD) over a 10 year period. Indications were pleural effusion (86%), pleural thickening (7·5%), and a solid mass on the chest radiograph (15%). Pleural aspiration or biopsy had been performed previously in 67% of patients but was negative in 90% and inconclusive in 10%. There was a failure rate of 5% because of inability to enter the pleural space. Subsequent thoracotomy was undertaken in 16% of the 121 patients. Results of biopsies taken at thoracoscopy were as follows: undifferentiated carcinoma 19%, adenocarcinoma 14%, mesothelioma 17%, inflammatory 19%, and non-specific 21%. No biopsy sample was taken in 3% of cases (excluding failed procedures). An operative assessment of whether malignancy was present or not was accurate in 86% of patients. There was one death. This occurred seven hours postoperatively and was due to myocardial infarction. Complications included respiratory infection (2·5%), bleeding from the biopsy site (0·8%), and broncho-pleural fistula (0·8%). Tumour seeding at the chest wall incision occurred in 1·7% of patients. Thoracoscopy is a well tolerated procedure and is of value in the investigation of undiagnosed pleural disease.

Pleural abrasion, a simple and effective method of pleurodesis

SC GRIFFIN, ER TOWNSEND, SW FOUNTAIN *Harefield Hospital, Uxbridge* Pleurectomy with bleb ligation as a treatment for recurrent or persistent pneumothorax can be complicated by

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excessive bleeding, haemothorax, fibrothorax and Horner's syndrome. Tube pleurodesis is effective only when the underlying lung is demonstrated to be capable of full expansion and the long term consequences of talc insufflation are uncertain. A series of 33 patients with a mean age of 34 years were treated with bleb ligation and pleural abrasion alone. This was achieved via a small lateral thoracotomy. The air leaks are sealed and the parietal pleura abraded using a domestic scouring pad. The group had suffered a mean 1·84 pneumothoraces prior to operation. Twenty two had intercostal tubes in situ at the time of surgery. Mean blood loss was 274 ml. Mean time spent with an intercostal tube in-situ post operatively was three days. All lungs were fully expanded at the time of extubation. Mean post operative stay was 5·8 days. No patients returned to theatre or had haemothorax, there were no postoperative wound dehiscences or infections. Three patients had persistent air leaks for more than seven days, all were sealed by 14 days. One man suffered from retention of urine but there were no other complications. Patients were reviewed at six weeks. The wounds were all soundly healed and none complained of post-thoracotomy pain. There have been no recurrent pneumothoraces. We suggest that pleural abrasion is a safe, simple and effective treatment for this common condition.

Controlled trial of 12 versus six courses of chemotherapy in the treatment of small cell lung cancer

NM BLEEHEN, PM FAYERS, DJ GIRLING, RJ STEPHENS *(for the MRC Lung Cancer Working Party) MRC Cardiothoracic Epidemiology Group, Brompton Hospital, London* A total of 497 patients with confirmed small cell lung cancer and good performance status were all prescribed an initial six courses of chemotherapy at three week intervals. Etoposide 120 mg/m^2, cyclophosphamide 1 g/m^2, methotrexate 35 mg/m^2, and vincristine 1·3 mg/m^2 (max 2 mg) were given IV on day 1, and etoposide 120 mg/m^2 IV or 240 mg/m^2 orally on days two and three. Patients with limited disease (74% of the total) received radiotherapy to the primary site between courses two and three. The response rates were complete 11% and partial 74%. All patients have been studied for three years or longer. For the total 497 the median survival period from the date of start of chemotherapy was 39 weeks; 31% were alive at one year, 6% at two years, and 3% at three years. At the end of six courses 265 patients still showing complete or partial response were randomised to six more courses of the same drugs or no further chemotherapy until relapse. There was no overall survival advantage to either series ($p = 0·27$, log rank test), but in a subgroup of 99 patients with a complete response at the time of randomisation there was a suggestion that survival was longer with the policy of 12 courses of chemotherapy ($p < 0·05$, log rank test), the median survival periods from date of randomisation being 42 weeks for 12 courses and 30 for six courses. In patients who received 12 courses, there was, however, more toxicity and a poorer quality of life as assessed intermittently by clinicians and daily by patients. It is concluded that no worthwhile clinical advantage was achieved by a policy of giving 12 rather than six courses of chemotherapy.

Quality of life in small cell carcinoma of the lung: a comparison of two chemotherapy regimens using daily diary cards

DM GEDDES, KS LAW, SG SPIRO, RL SOUHAMI, PF HARPER, JS TOBIAS *Brompton Hospital, Middlesex Hospital, Guy's Hospital, and University College Hospital, London* Quality of life was assessed by daily diary (DD) cards in 80 out of 220 patients with small cell carcinoma of the lung during a randomised trial of chemotherapy. Patients were randomised to receive a maximum of eight courses of cyclophosphamide, etoposide, and vincristine—either regularly, at three weekly intervals (group I), or on an "as required" basis (group II) (treatment being given if the patient had symptoms or was showing disease progression). Patients scored diary cards daily, on a four point scale according to severity, for sickness, vomiting, appetite, pain, sleep, mood, general well being and activity. Four hundred (three weekly) DD have been returned, 62 patients being evaluable (i.e. have returned at least one card). Groups were matched for all DD questions at presentation. In the categories of sickness, appetite, pain, sleep, mood and general well being, group II consistently scored themselves as having more severe symptoms ($p < 0·001$). We conclude from this preliminary analysis that quality of life appears no better with a policy of as required CT and may even be worse.

Chemotherapy for cerebral metastases in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)

C TWELVES, R SOUHAMI, P HARPER, J TOBIAS, S SPIRO, D GEDDES, C ASH, J DRAKE *Clinical Oncology Unit, Guy's Hospital; Department of Oncology, University College Hospital; Brompton Hospital; London Chest Hospital, London* Cerebral metastases are conventionally treated by cranial irradiation in the belief that although such metastases may be chemosensitive, they are protected by the blood-brain barrier (BBB). We have assessed response to chemotherapy in NSCLC and SCLC patients with CT-proved cerebral metastases at presentation, witholding cranial irradiation. In 25 SCLC patients treatment was cyclophosphamide 1 g/m^2 IV day 1, vincristine 2 mg IV day 1 and etoposide either 100 mg orally tds days 1–3 or 120 mg IV day 1 and 100 mg orally bd days 2 and 3 on a 21 day cycle. On repeat brain scan 10 of 17 patients responded; of eight patients assessed clinically alone, three responded. All cranial responders improved on the chest radiograph. Overall SCLC cranial response rate was 13/52 (52%). For six NSCLC patients treatment was mitomycin C 6 mg/m^2 IV, ifosfamide 3 g/m^2 IV and cisplatin 50 mg/m^2 IV day 1, repeated every 21 days. On repeat scan, two of five patients responded (one adenocarcinoma, one large cell carcinoma); the final patient died suddenly at home. Both cranial responders also responded in the chest. Overall NSCLC cranial response rate was 2/6 (33%). SCLC and NSCLC cerebral metastases respond to chemotherapy which suggests they do not have a BBB. Indeed, the "blood-tumour barrier" may be the same in the brain as other sites of metastatic disease. Chemotherapy has the advantage of treating both cerebral metastases and extracranial tumour.

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Detection of small cell lung carcinoma (SCLC) cells in bone marrow using monoclonal antibodies (moabs)

F MOSS, LG BOBROW, RL SOUHAMI, PC BEVERLEY *Department of Chest Medicine, St Mary's Hospital, and Human Tumour Immunology Group, Imperial Cancer Research Fund, London*
Moabs, which recognise epitopes expressed by carcinoma cells but not expressed by cells of haemopoietic lineage, are potential reagents for detecting micrometastases of tumour cells in bone marrow at levels of infiltration not detected cytologically. In SCLC detection of micrometastases may effect staging and would have important implications for treatment protocols which include autologous bone marrow transplantation. We used immunoalkaline phosphatase and separated nucleated bone marrow cells by gravitational sedimentation. Four moabs (UJ13A, AUA1, HMFG2, 5·2) and four mixtures of these were tested on: (1) Marrow from eight people with no known carcinoma. A small population of single stained cells was seen with each reagent. (2) On marrow from eight SCLC patients whose marrow was "cytologically positive" for SCLC infiltration. SCLC cells, recognisable as stained clumps, were seen in each. Variation of antigen expression was also seen. In particular UJ13A, the most consistent marker of SCLC in solid tumours, was unreliable as a single reagent. (3) On marrow from 20 SCLC patients whose marrow was "cytologically negative" for SCLC infiltration. In four (20%) clumps of stained cells, interpreted as SCLC, were seen. Moabs, although somewhat limited by staining of haemopoietic cells and variation in antigen expression by SCLC, improve detection of marrow metastases from 8/28 (29%) to 12/28 (43%). The clinical implications of this have yet to be established.

Perioperative morbidity and mortality associated with total lung resection for lung cancer in elderly patients

J MANEKSHA, C FORRESTER-WOOD, K JEYASINGHAM *Department of Thoracic Surgery, Frenchay Hospital, Bristol*
Pneumonectomy is well tolerated by young patients but less so by patients over the age of 70 years. Fifty consecutive patients in the age range of 70–78 years undergoing total pneumonectomy with a left to right ratio of 28:22 were studied prospectively during the perioperative hospital stay and for a 30 day period after surgery. No attempt was made to predict the multifactorial index of cardiac risk. Two patients required assisted ventilation for respiratory inadequacy. Ischaemic cardiac events occurred in two patients on the 4th and 14th day respectively. Cardiac arrhythmias were noted in 14 patients. One patient developed pulmonary embolism on the 6th day, while a second developed deep venous thrombosis on the 13th day. Both were anticoagulated to therapeutic levels. Two patients sustained cerebral vascular accidents on the 2nd and 10th day respectively. Pneumonitis was noted in two patients, whilst one other was treated for acute gastric dilatation. The mean postoperative stay in hospital was 12 days with a range of 8–31, the vast majority returning home between the 10th and 14th days. The perioperative mortality was 6%, each of three patients succumbing to a cerebral vascular accident, oesophageal fistula and myocardial infarction respectively. Despite the age, elderly patients tolerate pneumonectomy well, but they do have disturbances of the cardiovascular and cerebrovascular systems to a high degree. These complications can be minimised by preoperative preparation and high dependency care during the postoperative period.

Local excision-evaporation of pulmonary nodular lesions with the use of non-contact YAG laser

K MOGHISSI, E NEVILLE *Humberside Cardiothoracic Surgical Centre, Castle Hill Hospital, Hull*
We present a new method for local excision of pulmonary nodular (coin lesions) using the non-contact mode of YAG laser. Fifteen patients, six male and nine female age 47–77 years (mean 64·6) with a radiological diagnosis of single or multiple nodular (coin lesions) of the lung were treated. Standard thoracotomy using conventional technique was first employed to explore the lesion, then the laser was used to excise the nodule (when larger than 0·5 cm) or evaporate it (when less than 0·5 cm). Eleven of the patients had primary (n = 7) or secondary (n = 4) tumours and four had inflammatory granulomas. There was no hospital mortality in this series. The hospitalisation was short and the blood and air leaks were less than expected. On account of this experience we intend to use this method in preference to wedge, segmental or lobectomy in these cases.

Spinal cord compression in small cell lung cancer (SCLC)

JM GOLDMAN, CM ASH, RL SOUHAMI, SG SPIRO, PG HARPER, DM GEDDES *Brompton Hospital; Department of Oncology, University College and Middlesex Hospital School of Medicine; and Guy's Hospital, London*
In a randomised trial of 610 patients with SCLC there were 24 (4%) cases of spinal cord compression (CC). Five hundred patients had isotope bone scans at presentation. In 131 (26%) there was abnormal isotope uptake in the spinal column, only 7% of these patients developed CC. However, of the 25 patients who presented with back pain and had a positive bone scan affecting the spine, 36% developed CC. The incidence of cerebral metastases in the trial was 19·5% and in patients with CC 45%. The combination of cerebral metastases and a positive bone scan gave a 25% chance of developing CC. There were two clinical presentations. Six patients (group A) presented with CC, all had back pain and positive bone scans, five out of six had sphincter disturbance. Median survival from CC was 30 weeks. Eighteen patients (group B) developed CC while on treatment, 28% had positive bone scans, 44% back pain and 61% sphincter disturbance; median survival from CC was four weeks. Overall median survival was 30 weeks in group A, 34 weeks in group B and 37 weeks in the multicentre trial. The study shows that it is possible to select patients at high risk of CC who should receive radiotherapy as prophylaxis against this complication.

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Single dose and steady state pharmacokinetics of 4 mg and 8 mg oral controlled release salbutamol in asthma

BJ LIPWORTH, M CHARTER, J PALMER, DG MCDEVITT *Department of Clinical Pharmacology, Ninewells Hospital, Dundee, and Glaxo Group Research, Greenford, Middlesex* Oral salbutamol is an alternative to the inhaled route in asthmatic patients where compliance or coordination is a problem. Controlled release salbutamol ("Volmax," Duncan Flockhart and Co Ltd) is a novel formulation using an oral osmotic drug delivery system. Fifteen patients (mean (SEM) age 36 (4) years) with asthma were given controlled release salbutamol 4 or 8 mg twice daily for seven days, in a double blind, double dummy, two way crossover study (with a seven day washout between treatment periods). Plasma salbutamol levels were measured after the first and fifteenth doses: at 1, 1·5, 2, 2·5, 3 hours and then at hourly intervals up to 12 hours after drug ingestion. After single doses, the geometric mean value of C_{max} was 4·6 ng/ml (with 95% confidence limits from 4·1 to 5·1 ng/ml) for the 4 mg formulation, and 9·5 ng/ml (8·5 to 10·7 ng/ml) for the 8 mg formulation. The median values of t_{max} were 300 min and 360 min respectively. At steady state the geometric mean C_{max} values were 8·2 ng/ml (7·4 to 9·1 ng/ml) and 16·1 ng/ml (14·5 to 17·9 ng/ml); median t_{max} values were 300 and 240 minutes. Geometric mean C_{min} values were 4·5 ng/ml (4·0 to 5·0 ng/ml) and 8·7 ng/ml (7·8 to 9·7 ng/ml). The geometric mean areas under the curve from 0 to 12 hours after steady state dosing (AUC_{0-12}) were 4507 ng min/ml (4094 to 4962 ng min/ml) and 8980 ng min/ml (8157 to 9885 ng min/ml). The peak to trough fluctuation ratios (PTF) were 0·577 (0·520 to 0·641) and 0·572 (0·516 to 0·636). There were no statistically significant differences between any of the parameters measured, after the appropriate corrections for dose. These results show that 4 and 8 mg oral formulations of controlled release salbutamol provide predictable smooth plasma profiles at steady state with a twice daily dosing regimen.

Beta adrenoceptor responsiveness to inhaled salbutamol in normal and asthmatic subjects

BJ LIPWORTH, RA CLARK, DP DHILLON, RA BROWN, DG MCDEVITT *Department of Clinical Pharmacology, Ninewells Hospital, Department of Thoracic Medicine, Kings Cross Hospital, Department of Mathematical Sciences, Dundee* The purpose of the study was to compare beta-adrenoceptor responsiveness in seven asthmatics (group A: FEV_1 66 (SD 9)% predicted) to a control group of age and sex matched normal subjects (group N: FEV_1 103 (4)% predicted). Salbutamol was given by metered-dose inhaler in cumulative doubling doses from 100 mcg to 4000 mcg. Airways (sGaw), tremor (Tr), chronotropic (HR) and metabolic responses (plasma K, Mg, Glu, cAMP) were measured at each dose increment (every 20 minutes). Baseline values (95% CI for mean) were similar for both groups apart from: sGaw ($s^{-1}kPa^{-1}$) 0·54 (0·12, 0·96) group A, 2·8 (1·48, 4·12) group N; K(mmol/l) 3·48 (3·28, 3·68) group A, 3·77 (3·61, 3·93) group N. There were linear log dose-responses for all parameters in both groups. Inverse regression analysis of the fitted straight line was used to calculate the mean (95% CI) dose of salbutamol (μg) required for a given change in each parameter over baseline ($s\Delta$). There were differences between groups in ΔsGaw, ΔHR and ΔK. For ΔsGaw:s $\Delta 3(s^{-1}kPa^{-1})$ 134 μg (37,493) in group A and 1441 μg (573,3605) in group N, $p < 0{\cdot}01$. For ΔHR: $s\Delta 8$ (b.p.m.) 1393 μg (812,3295) in group A and 562 μg (440,773) in group N; $p < 0{\cdot}01$. For ΔK: $s\Delta 0{\cdot}2$ (mmol/l) 1202 μg (602,4023) in group A and 475 μg (365,580) in group N; $p < 0{\cdot}01$. Maximum Δ K(mmol/l) within our dose range was $-0{\cdot}4$ ($-0{\cdot}64$, $-0{\cdot}16$) in group A and $-0{\cdot}96$ ($-1{\cdot}1$, $-0{\cdot}82$) in group N ($p < 0{\cdot}001$). In conclusion, there were dose dependent beta adrenoceptor responses to inhaled salbutamol in both normal and asthmatic subjects. There was marked subsensitivity in chronotropic and hypokalaemic responses in the asthmatic group, which may reflect beta-adrenoceptor down regulation from long term salbutamol therapy.

Comparison of the haemodynamic effects of inhaled isoprenaline, fenoterol, salbutamol, and placebo

J CRANE, C BURGESS, R BEASLEY *Department of Medicine, Wellington School of Medicine, Wellington, New Zealand* In this double-blind study, the haemodynamic effects of equal doses of inhaled fenoterol, isoprenaline, salbutamol and placebo were compared in eight healthy male volunteers. Increasing doses of 400, 600 and 800 μg were given from metered dose inhalers at 15 minute intervals. Measurements of heart rate (HR), systolic blood pressure (SBP), and total electromechanical systole (QS_2I) were made five minutes following each inhalation. After both the 600 μg and 800 μg doses, fenoterol caused a significantly greater increase in HR and SBP and reduction in QS_2I than salbutamol. When compared with isoprenaline at the same time points, fenoterol caused equivalent changes in SBP and QS_2I, and significantly greater increases in HR. The mean (SEM) change in HR, SBP and QS_2I five minutes after 800 μg fenoterol were 16·9 (2·7) bpm, 16·7 (4·4) mm Hg, $-30{\cdot}0$ (5·8) ms, compared with 4·1 (1·7) bpm ($p < 0{\cdot}0001$), 8·8 (2·2) mm Hg ($p < 0{\cdot}0007$), $-13{\cdot}2$ (4·8) ms ($p < 0{\cdot}0001$) respectively for salbutamol; and 6·9 (2·7) bpm ($p < 0{\cdot}0001$), 14·0 (3·6) mm Hg ($p = 0{\cdot}94$), $-31{\cdot}4$ (6·1) ms ($p = 0{\cdot}32$) respectively for isoprenaline. We conclude that repeated inhalation of fenoterol causes cardiac beta adrenergic inotropic effects equivalent to those of isoprenaline, and greater than those of salbutamol.

Comparison of the hypokalaemic and electrocardiographic effects of inhaled isoprenaline, salbutamol and fenoterol

C BURGESS, J CRANE, R BEASLEY *Department of Medicine, Wellington School of Medicine, Wellington, New Zealand* The hypokalaemic and electrocardiographic effects of equal doses of inhaled fenoterol, isoprenaline, salbutamol and placebo were compared in eight healthy male volunteers in this double-blind study. On four separate days, increasing doses of 400, 600 and 800 μg were given from metered dose inhalers at 15 minute intervals. Measurements of QTc, T wave amplitude (ΔT% and plasma potassium (K^+) were made 15 minutes after each inhalation. Compared with placebo, fenoterol significantly increased QTc interval after all doses, whereas salbutamol and isoprenaline were sig-

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nificantly different after the final dose. The mean (SEM) maximum increase following fenoterol (50·4 (7·4) ms) was significantly greater than both salbutamol (28·6 (7·2) ms; $p < 0.001$) and isoprenaline (14·1 (6·1); $p < 0.001$). Fenoterol also significantly decreased T wave amplitude after all doses, whereas salbutamol and isoprenaline demonstrated significant decreases after the last two doses. The maximum change after fenoterol (−55·8 (4·7)%) was significantly greater than both salbutamol (−38·2 (4·8)%; $p < 0.0001$) and isoprenaline (−21·9 (3·0)%; $p < 0.0001$). Only fenoterol and salbutamol significantly decreased plasma K^+. The maximum decrease following fenoterol (−0·81 mmol/l) was significantly greater than that of salbutamol (−0·33 mm/l; $p < 0.0001$). Repeated inhalation of fenoterol causes significantly greater decreases in plasma K^+ and greater electrocardiographic effects than salbutamol or isoprenaline.

Prospective measurement of peak expiratory flow rate used to assess the speed of onset and domiciliary treatment of asthmatic attacks

MJ WARD, SR REYNOLDS, B CHEONG *Department of Tuberculosis and Chest Diseases, Llandough Hospital, Penarth*
Patients admitted with a severe acute asthmatic attack were at the time of discharge from hospital asked to partake in the study. They recorded their peak expiratory flow (PEF) twice daily, and also noted any change in treatment or symptoms using a simple scoring system. The patients and doctors were not given any guidance concerning changes in treatment and PEF; it was the sole intention to use the charts to study the progression of attacks as they might occur. Twenty five patients did not suffer an attack. A further 19 had 44 attacks, 14 of which were severe (a fall in PEF to <25% of the usual best value) and 28 were moderate (a fall in PEF to 25–50% of the usual best value). Only 25% of all attacks occurred within 24 hours of onset, the remainder showed deterioration in PFR for a mean of six days (range 2 to 40) before either seeking medical help or increasing self treatment. Although some may not perceive a fall in PEF all the patients after a day or two experienced severe symptoms for a further number of days (mean 4) before doing anything about the attack. The general practitioner (GP) was usually called late. In only two instances did the GP admit a patient to hospital.

Systemic salbutamol plasma concentrations in acute severe asthma: are they excessive?

LD LEWIS, M MACLEAN, E ESSEX, GM COCHRANE *Department of Thoracic Medicine, Guy's Hospital, London*
Evidence demonstrating an increase in asthma mortality in the UK has yielded the idea that present therapeutic regimens for the management of asthmatics may be dangerous. We studied plasma salbutamol concentrations in a group of 11 asthmatics (eight female), median age 40 (range 21–74) years who presented acutely with a respiratory rate of >28/min; pulse rate of >100/min; pulsus paradoxus of >10 mm Hg and a PEFR of <120 l/min. Venous blood was taken immediately on presentation and one hour after the administration of 5 mg of nebulised salbutamol. Plasma was separated and stored at −20°C until analysed for salbutamol concentrations using a thin layer chromatography method (Colthup PV *et al. J Chromatogr* 1985;**345**:111). The plasma salbutamol concentrations are shown below. Five of the 11 asthmatics did not have measurable systemic plasma salbutamol levels post nebuliser therapy. Those patients exhibiting high concentrations of salbutamol were either on oral therapy or probably had taken high doses of inhaled therapy prior to presentation. None of the group developed clinical toxicity from the salbutamol treatment. These data suggest that nebulised salbutamol in acute severe asthma does not produce toxic systemic concentrations of the drug.

	Plasma salbutamol conc (μg/l)	
Patient No	*Pretreatment*	*1 h post-treatment*
1	ND	ND
2	23·4	33·6
3	4·8	7·4
4	ND	ND
5	ND	36·0
6	ND	ND
7	6·2	11·6
8	34·6	56·0
9	ND	13·0
10	ND	ND
11	ND	ND
Median	ND	7·4†

ND = none detected; † = non-significant (Wilcoxon's test).

Should nebulised salbutamol be given alone or with ipratropium bromide in acute airflow obstruction?

BRC O'DRISCOLL, HS AULAKH, RJ TAYLOR, M HORSLEY, D CHAMBERS, A BERNSTEIN *Department of Thoracic Medicine, Hope Hospital, Salford*
Most British doctors use a nebulised beta agonist in the treatment of acute airflow obstruction and many add a nebulised anticholinergic agent. It is not known whether the second drug confers any extra benefit and previous studies have come to differing conclusions but most have involved small numbers of patients. We have studied 103 patients with acute severe asthma (53 cases) or chronic bronchitis with airflow obstruction (50 cases). They were randomly assigned to receive either salbutamol 10 mg (S) or salbutamol 10 mg mixed with ipratropium bromide 0·5 mg (S + IB) in a double blind manner. Both groups had a mean peak expiratory flow rate (PEF) of 128 l/min before treatment. The mean PEF of the patients given salbutamol rose to 163 l/min one hour after treatment, whereas the mean PEF of the S + IB group rose to 184 l/min. This difference was not significant (Mann-Whitney U test, $p = 0.12$). The 95% confidence intervals for the mean percent PEF rises were 17·4% to 38·2% for the salbutamol group and 34·2% to 70·6% for the S + IB group. Of seven patients in the S + IB group whose PEF was 60 or less before treatment, five were able to record a PEF above 60 after treatment. Four patients in the S group had a starting PEF of 60 or less but none could record a greater PEF measurement at one hour. We conclude that the routine addition of ipratropium to salbutamol is unnecessary but the combined treatment may benefit some patients with extremely severe airflow obstruction.

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Rapid theophylline analysis at the chest clinic using a portable high performance chromatograph (HPLC)

DR BALDWIN, JD BERG, BM BUCKLEY, AD MACKAY *Departments of Thoracic Medicine and Clinical Biochemistry, Sandwell District General Hospital, West Bromwich* The value of therapeutic drug monitoring of theophylline is usually diminished by the delay in obtaining results. Some immunoassay based analyses are suitable for clinic use, but are expensive and have other disadvantages. We have developed a rapid, and simple HPLC allowing theophylline and metabolites including caffeine to be measured in situ at the chest clinic. Here we present the clinical use of this development. We compared 40 outpatients managed on the basis of our in situ HPLC assay (group A) with 40 outpatients managed with conventional laboratory based theophylline analysis (group B). Only 12 patients (30%) in group A had levels in the therapeutic range at the first study visit. After a period of six weeks a further 20 (50%) were in the therapeutic range. The remaining eight (20%) were either non-compliant (2) or complained of side effects (6). In group B it took 11 weeks to get such a 50% increase in the number of patients within the therapeutic range. The HPLC system was readily accepted by staff and patients. Results were available for action by the clinician in less than six minutes. Stabilisation was achieved in patients monitored in situ in half the time taken for those conventionally monitored. Overall, the cost of near patient analysis was comparable with conventional procedures and improved clinical efficiency considerably.

Is theophylline or inhaled steroid the next choice in asthmatics not controlled with salbutamol?

AS VATHENEN, P EBDEN, JB COOKSON *Department of Medicine, Glenfield General Hospital, Leicester* We have compared the effects of inhaled beclomethasone dipropionate (BDP), oral slow release theophylline (Nuelin SA), and the combination of both drugs when used as additional treatment in patients with asthma whose symptoms were inadequately controlled by regular inhaled salbutamol (S). The study consisted of a placebo controlled two week selection phase (phase S) and three four week phases, all of which included daily doses of S 200 μg qds, BDP 100 μg qds or placebo, and theophylline (T) 350 mg bd or placebo: Phase S (S only), Phase SB (S/BDP), Phase ST (S/T) and Phase SBT (S/BDP/T). Subjects recorded daily PEF at 07 h and at 22 h, symptom scores for sleep, wheeze, activity and cough, and additional puffs of salbutamol inhaler used. Of 25 subjects entered single blind into phase S, 16 (age 21–66) whose S usage exceeded 800 μg a day on three or more days were entered in double blind random order into phases SB, ST and SBT. Two subjects withdrew because of theophylline side effects. The last two weeks of each phase were analysed for the 14 subjects who completed the study. Mean trough theophylline levels at the end of phases AT and ABT were 9·8 and 8·7 μg/ml respectively. Mean PEFR values in the morning for phase SB (471 l/min) and phase SBT (481 l/min) were both significantly ($p < 0·001$) higher than for phase S (415 l/min) and phase ST (423 l/min). The differences in PEF between SB and SBT and between S and ST were not significant. Diurnal variation between the morning and evening PEF values was lowest for SB (31 l/min) and SBT (35 l/min) and significantly higher ($p < 0·02$) for S (41 l/min) and ST (47 l/min). Scores for sleep and wheeze were significantly lower (better) for SB (sleep $p < 0·001$, wheeze $p < 0·05$) and SBT (sleep $p < 0·001$, wheeze $p < 0·01$) than for ST. Daily extra S use was significantly lower for SB (1·0 puffs, $p < 0·001$) and SBT (1·3 puffs, $p < 0·05$) compared to ST (2·0 puffs). Thus the addition of BDP to regular inhaled S resulted in greater improvement in asthma control than the addition of T in this group of patients and the addition of T to BDP and S did not provide any further improvement.

Controlled trial of budesonide via the Nebuhaler in preschool asthma

JGA GLEESON, JF PRICE *Departments of Child Health and Thoracic Medicine, King's College Hospital, London* Preschool asthma is often more severe and less responsive to treatment than asthma in older children. We have shown that the Nebuhaler can be used to administer bronchodilator drugs effectively from two years of age (Pool JB *et al. Arch Dis Child* 1988;**63**:288–91). Our aim was to investigate the efficacy of an inhaled steroid, budesonide via the Nebuhaler in young asthmatics with frequency wheezing. Twenty eight children aged 2–6 years with perennial asthma completed a double blind placebo controlled crossover trial of budesonide 200 μg twice daily via the Nebuhaler. Two six week treatment periods were preceded by a two week run in and separated by a three week washout. Five children were withdrawn because of acute severe asthma, four on placebo. During the last three weeks of treatment with budesonide peak expiratory flow rates recorded at home were considerably higher, in the mornings (mean difference 11·8%, 95% CI, 6·3–17·3%; $p = 0·0001$) and in the evenings (mean difference 14·1%, 95% CI, 7·2–21%; $p = 0·0004$), and the need for concomitant bronchodilator therapy was less ($p = 0·0221$) than with placebo. Symptom scores also favoured budesonide. No adverse effects were observed and early morning plasma cortisol levels were similar at the end of each treatment period. We conclude that budesonide via the Nebuhaler is an effective treatment for preschool children with frequent asthma.

Do steroid aerosols cause cataracts in asthmatic patients?

MB ALLEN, S RAY, B DHILLON, R CULLEN, AG LEITCH *Chest Unit, City Hospital, and Princess Alexandra Eye Pavilion, Edinburgh* The association between posterior subcapsular cataract (PSCC) and oral steroid therapy is well recognised. This type of cataract is rarely seen unless patients have been taking over 10 mg of prednisolone daily for a year or more, the risk increasing with dose and duration of therapy. We have now seen three asthmatic patients aged 40–47 years presenting with visual problems due to unexplained PSCC. They had been treated with steroid aerosols (beclomethasone dipropionate, BDP) for 2–12 years and had only received intermittent short courses of oral prednisolone, with a total lifetime intake of 0·5–1·5 g. Two of the patients required cataract extraction. PSCC has been reported in a nine year old child taking inhaled BDP for two years and 0·2 g of oral

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prednisolone (*Austr Paed J* 1980;16:117). Our patients are the first reported adult asthmatics to develop PSCC while taking standard doses of inhaled BDP supplemented with only small doses of oral prednisolone.

Effect of nebulised salbutamol on the maximum exercise performance of asthmatics

W FREEMAN, A JAVAID, GE PACKE, RM CAYTON *Department of Respiratory Physiology, East Birmingham Hospital, Birmingham* The effect of antiasthmatic drugs on sports performance is unknown. This study evaluated the effect of 5 mg nebulised salbutamol on the maximum exercise capacity in eight asthmatic men (mean age 30 (SD 10) y). Each asthmatic underwent two progressive exercise tests on a cycle ergometer after either placebo (P) or salbutamol (S) administered according to a randomised double-blind protocol. Exercise started from a work load of 50W and increased by 20 w/min until exhaustion. Expired ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and heart rate (HR) were monitored continuously. FEV_1 was recorded at rest (pre and post nebuliser), and for 30 minutes post exercise. FEV_1 was significantly higher following nebulised salbutamol, both pre-exercise (S: 3·92 (0·94) l *v* P: 3·38 (1·02) l; $p < 0·05$) and post-exercise (S: 3·60 (1·13) l *v* P: 2·85 (0·80) l; $p < 0·05$). Maximum exercise values are tabulated (*$p < 0·05$). The pre-test administration of salbutamol resulted in a higher FEV_1 and a significantly higher maximal tidal volume. Despite the improved FEV_1 with salbutamol, the $\dot{V}O_2$max, test duration and maximum workload were unchanged. This study suggests that nebulised salbutamol does not influence the maximum exercise capacity in asthmatics.

	Mean (SD)			
	Salbutamol		*Placebo*	
Exercise test (min)	11·60	3·17	10·94	2·73
Work rate (W)	275	64	263	54
$\dot{V}O_2$ max (l/min)	3·20	0·77	3·12	0·68
HR max (beats/min)	190	17	186	18
$\dot{V}E$ max (l/min)	109	23	101	22
RER ($\dot{V}CO_2/\dot{V}O_2$)	1·14	0·05	1·15	0·09
Tidal volume (l)	2·60	0·26	2·41	0·30*
Respiration rate (breath/min)	41·8	6·9	41·8	7·9

Analysis of factors improving cardiovascular fitness in asthmatics following an exercise rehabilitation programme

LM COCHRANE, CJ CLARK *Department of Respiratory Medicine, Hairmyres Hospital, East Kilbride, Glasgow* EXRE has been recommended in the management of COAD (Hudson LD, Pearson DJ. *Med Clin North Am.* 1981;65:629–44). Despite the inter and intrapatient variability in asthma providing a potentially wider therapeutic window for such a programme, there has been no systematic evaluation of the likely benefits for this group of patients. This study analyses the factors influencing the physiological improvements obtained from a hospital based exercise rehabilitation programme. Thirty six asthmatics were randomly allocated into trainers and controls. Work intensity during training sessions was individualised using heart rate monitors with a target heart rate of 75% predicted maximum in 3 × 30 minute sessions per week. There was a highly significant improvement in $\dot{V}O_2$max (ml/kg/min) in the trainers from 23·00 (4·7) to 28·41 (6·0) at three months ($p < 0·001$) with no significant change in the controls. However, there was a considerable individual variability with a range of improvement from 1·5% to 53·6%. Multiple regression analysis revealed that the magnitude of improvement was dependent on the variability of asthma through its influence on continuity of exercise sessions and subject motivation, which was independent of the severity of asthma measured by serial lung function plus diurnal peak flow measurements and initial level of fitness. These results contrast with the frequent failure of exercise rehabilitation programmes to significantly improve cardiovascular fitness in COAD. To minimise the adverse effect of asthma variability on achievement of training goals, medical supervision is essential for specialised exercise prescription. Even asthmatics who show good compliance have to face a more difficult motivational challenge than normal subjects through enforced periods of reduced activity with consequent detraining. This therefore requires alternative training strategies during exacerbations to optimise improvements in fitness. The success of the programme depends on recognition of the dynamic nature of the underlying condition in individuals.

Pulmonary diseases in AIDS patients in central Africa

DT MCLEOD, A LATIF, P NEILL, VJ ROBERTSON, S LUCAS *Department of Medicine, University of Zimbabwe, Harare Wolfson Tropical Pathology Unit, London School of Hygiene* During the 11 month period November 1986 to September 1987, 37 patients (26 males, 11 females; mean age 27 years) who were HIV positive were studied prospectively on 40 occasions to determine the causes of pulmonary disease. HIV was heterosexually transmitted. Predominant symptoms were cough (89%), fever (89%), weight loss (83%), and dyspnoea (60%). Transnasal fibreoptic bronchoscopy, with bronchoalveolar lavage, bronchial brushings and transbronchial biopsy was performed on 35 patients; on two separate occasions in three patients. Trucut lung biopsies were obtained in two patients who died just prior to bronchoscopy. Pulmonary tuberculosis was the commonest disease, being found in almost one third of patients (12 of 37). Cavitation was present in three patients. *M tuberculosis* was cultured in four; the remaining culture plates were contaminated. *P carinii* was present in eight patients; as the sole pathogen in two, with *S pneumoniae* in four and *Staph aureus* in two. Endobronchial Kaposi's sarcoma was seen in six of seven patients with widespread skin nodules. Bacterial pathogens isolated from eight patients included *Staph aureus* (6), *S pneumoniae* (4), *K pneumoniae* (2), *H influenzae* (2), *H parainfluenzae* (1), *P aeruginosa* (1). Invading *Aspergillus fumigatus* was diagnosed on lung biopsy of one patient. There was considerable overlap of disease, with the majority of patients having more than one pathology. No diagnosis was reached in eight patients. Viral studies were not available. It is concluded that in Central Africa pulmonary complications in AIDS patients are similar to those in

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Europe and North America, though the incidence of different pathogens is dependent on the prevalence of pathogens in the local community. *M tuberculosis* is probably the commonest mycobacterium. This is the first bronchoscopic study to confirm that *P carinii* does cause pneumonia in AIDS patients in Africa. Pulmonary Kaposi's sarcoma should be excluded in patients with skin nodules and pulmonary infiltrates.

Isotopic quantitation of lung tissue mass in *Pneumocystis carinii* pneumonia

DJ SEDDON, BA BRIGGS, PD SNASHALL *Departments of Medicine and Nuclear Medicine, Charing Cross Hospital, London* Transmission emission scanning of the thorax using a flood source of ^{99m}Tc, autologous ^{99m}Tc-labelled red blood cells, and Tc labelled diethyltriaminepentaacetic acid (^{99m}Tc-DTPA) allows measurement of total thoracic tissue thickness, blood and interstitial fluid volume per pixel of the gamma camera image. Volume of blood and interstitium per pixel divided by pixel area gives the thoracic tissue thickness for these compartments. We have studied five patients with *Pneumocystis carinii* pneumonia (PCP). At presentation, all patients had characteristic history and examination findings and an abnormal chest radiograph. All cases were seropositive for the human immune deficiency virus. In three cases diagnosis of PCP was established following examination of lavage fluid obtained at bronchoscopy. In the remaining two patients a prompt clinical and radiological response to antibiotic therapy was taken as indicative of infection with *Pneumocystis carinii*. Patients were rescanned one to three months following treatment with either co-trimoxazole or pentamidine. The results were compared with those of a group of seven healthy male controls. We measured total thoracic thickness (Tt), blood thickness (Tbl) and interstitial fluid thickness (Tin) at base of the right lung. Chest wall thickness (Tcw) measured on a lateral chest radiograph when subtracted from Tt gives lung tissue thickness. Tin was increased in all five patients and decreased following treatment in all five patients. We assume that the increase in Tin is due to an expansion of the extravascular extracellular space in the alveolar septum, and an increase in permeability of alveolar epithelium allowing ^{99m}Tc DTPA access to inflammatory exudate present in the alveolar lumen. We believe that this technique may be of use in the diagnosis and monitoring of pneumonia due to *Pneumocystis carinii*.

	Ti	*Tcw*	*Tl*	*Tbl*	*Tin*
Normal	9·0 (0·87)	5·0 (1)	4·0 (0·9)	0·8 (0·5)	(0·2)
PCP (at presentation)	11·5 (2·1)	3·3 (0·3)	8·3 (2·5)	1·8 (0·5)	2·3 (0·8)
PCP (at follow up)	9·3 (1·1)	3·3 (0·3)	6·0 (1·3)	2·2 (0·6)	1·3 (0·3)

All values in cm (means and SDs)

Complications of fibreoptic bronchoscopy in HIV-1 antibody positive patients undergoing investigations for pulmonary disease

RF MILLER, AB MILLAR, SJG SEMPLE *Department of Medicine, University College and Middlesex School of Medicine, London* Fibreoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) are routine procedures for investigating HIV-1 antibody positive patients presenting with clinical features and radiological evidence of lower respiratory tract (LRT) disease. We have studied the complications of FOB in 75 consecutive HIV-1 antibody positive patients undergoing investigation for LRT disease. All were male homosexuals, aged 21–57 years (mean 39·6) years and they underwent a total of 93 FOB procedures. At FOB all had BAL and 74 also had TBB. Clotting studies and platelet counts were normal. TBB was performed obtaining four biopsy samples, usually from the lateral segment of the right lower lobe, without fluoroscopic control. The overall complication rate (including death, pneumothorax, haemorrhage and significant oozing) was 20%, including a 16% pneumothorax rate. The single death, from massive haemorrhage, occurred in the group who underwent TBB (74 patients). In this group 15 developed a pneumothorax (20%), of whom eight required an intercostal drain. Two bled profusely. Of 52 undergoing TBB who were subsequently found to have *Pneumocystis carinii* pneumonia (PCP), 14 patients developed a pneumothorax (27%), whereas of 22 patients having TBB in whom other pathologies were established, only one (4·5%) developed a pneumothorax. In the group of 19 patients who had BAL but not TBB, the only complication was marked oozing in two cases, both were receiving nebulized pentamidine therapy for PCP. FOB in HIV-1 antibody positive patients had a high complication rate. The risk of complications is markedly increased when TBB is performed, particularly if the lungs are infested with PCP.

Transbronchial biopsy and bronchoalveolar lavage in the diagnosis of pulmonary disease in HIV infection

RF MILLER, AB MILLAR, MH GRIFFITHS, G KOCJAN, SJG SEMPLE *Departments of Medicine and Pathology, University College and Middlesex School of Medicine, London* Transbronchial biopsy (TBB) is responsible for haemorrhage and pneumothorax, the major complications of fibreoptic bronchoscopy (FOB). We have assessed the value of TBB in the diagnosis of HIV-1 antibody positive patients presenting with clinical and radiological evidence of lower respiratory tract (LRT) disease. Sixty four consecutive patients, 63 male homosexuals and one female intravenous drug abuser, underwent 80 FOB (some patients had repeated episodes of LRT disease and underwent repeat FOB). The histology of 74 TBB and the cytology of 66 bronchoalveolar lavage (BAL) specimens were examined; 60 paired TBB/BAL obtained at the same FOB were available for comparison. A specific pathological diagnosis was made on 50 occasions, from a total of 84 TBB and BAL specimens (60%). *Pneumocystis carinii* pneumonia (PCP) was the commonest diagnosis on 43 occasions (86%); cytomegalovirus (CMV) was diagnosed on three occasions, mycobacteria twice, actinomycosis and

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Kaposi's sarcoma (KS) once each. In 60 cases of paired TBB/BAL PCP was diagnosed 33 times; BAL positive in 32 cases (97%) but TBB was positive in only 22 cases (67%). In only one case was PCP diagnosed on TBB when the corresponding BAL cytology was negative. CMV was diagnosed on three BAL, but only one TBB. No concurrent infection with PCP was seen. Mycobacteria were seen on one TBB, the corresponding BAL was negative, the second case was diagnosed on open lung biopsy (OLB) after negative TBB and BAL. The case of KS was also diagnosed on OLB after negative FOB investigation. TBB contributes little to the diagnosis of LRT disease in HIV-1 antibody positive patients, whereas the less traumatic BAL provides accurate diagnostic information.

Nebulised pentamidine is not an effective therapy for *Pneumocystis carinii* pneumonia

RF MILLER, AB MILLAR, P GODFREY-FAUSSETT, SJG SEMPLE *Department of Medicine, University College and Middlesex School of Medicine, London* Conventional treatment of *Pneumocystis carinii* pneumonia (PCP) is either with intravenous sulphamethoxazole-trimethoprim (co-trimoxazole) or pentamidine. We have assessed the efficacy of nebulized pentamidine in treating PCP. We studied 13 HIV antibody positive homosexual men with PCP, confirmed at fibreoptic bronchoscopy (FOB) in 12 patients, and on induced sputum in one patient. Pentamidine isethionate was given once daily via an Acorn nebuliser (system 22 medic Aid) driven with air at 8 litres/min. Patients 1–6 received 4 mg/kg pentamidine, 7–13 8 mg/kg. Mass median diameter of particles measured by a Malvern 2400 laser diffraction sizer was 1·3 μm and 90% of particles were less than 6·1 μm diameter. Response to treatment was determined by symptomatic improvement, defervescence of fever, rising Pao_2 and clearing of chest radiograph. Two patients responded; treatment was discontinued in the remainder. The reasons for stopping treatment were persistent/worsening fever in seven patients, hypoxaemia/worsening Pao_2 in four patients, static/worsening in four patients, symptomatically worse in three patients, severe cough in two patients (one of whom bled profusely at FOB). Another patient died of massive haemorrhage at FOB, having received two doses of nebulised pentamidine. Treatment with nebulised pentamidine cannot be recommended as effective therapy for PCP with delivery systems available in the UK at present.

Cytomegalovirus: respiratory pathogen or passenger in AIDS?

AB MILLAR, RF MILLER, G PATOU, JE GRUNDY, IVD WELLER, SJG SEMPLE *Departments of Medicine, Virology, and Genitourinary Medicine, University College and Middlesex School of Medicine, and Department of Virology, Royal Free Hospital, London* Cytomegalovirus (CMV) is recognised as a cause of disease in many immunosuppressed patients producing retinitis, colitis and pneumonitis. In the acquired immune deficiency syndrome (AIDS) the role of CMV as a cause of pneumonitis has been questioned. We have studied 107 such patients presenting with respiratory symptoms, to determine the prevalence of CMV as a pathogen in the lung. Each patient was to undergo fibreoptic bronchoscopy (FOB) and bronchoalveolar lavage (BAL). BAL, urine, saliva and blood samples were then tested for the presence of CMV using the detection of early antigen by fluorescent foci (DEAFF) technique, which employs monoclonal antibodies to detect proteins released by cells infected with CMV. BAL was positive for CMV in only 12 patients; among these, urine and saliva were also positive in three, urine was positive in three, and in six cases urine, blood and saliva were negative. Seven of these cases had coexistent *Pneumocystis carinii* pneumoniae (PCP), six made full recoveries treated with co-trimoxazole, and one died. Two had Kaposi's sarcoma and recovered from their respiratory illness. Two other patients had bacterial pneumonias and recovered on appropriate antibiotic therapy. A final patient was already undergoing treatment for tuberculosis and no additional pathogen was found. In the remaining 95 patients saliva was positive in 12 cases, urine positive in seven and blood was positive in one case. From these data we conclude that CMV is rarely a pathogen in the lung in patients with AIDS.

Natural history of *Pneumocystis carinii* pneumonia in AIDS patients in London

DS ROBINSON, MR HELBERT, CS STONEHAM, S FOSTER, RJ SHAW, DR BUCHANAN, FM MOSS, AJ PINCHING, DM MITCHELL *St Mary's Hospital, London* Clinical features of 113 episodes of *Pneumocystis carinii* pneumonia (PCP) were analysed. All patients were homosexual or bisexual men (mean age 37·6 y, range 25–60). Of these, 75 (66%) were known to be HIV antibody positive (mean 13·8 months before PCP) at diagnosis; the remainder were positive on subsequent testing. Cough was present in 84% of the patients; breathlessness, 86%; sweats, 50%; malaise, 45%; sputum, 35%; and chest pain in 21%. Thirty nine per cent were smokers, 42% had crackles, 33% had Kaposi sarcoma (KS), 33% had oral candidiasis and 12% had fundal cottonwool spots. Mean Pao_2 on air was 67·5 mm Hg (9 kPa), $PaCO_2$ 33·3 mm Hg (4·4 kPa), transfer factor 48% of predicted, and mean alveolar arterial oxygen gradient 41 mm Hg (5·5 kPa). Bronchoscopic diagnosis of PCP was achieved in 79 patients (70%); 12 (11%) had negative bronchoscopy and 22 (19%) were too ill for bronchoscopy. Patients who did not have bronchoscopic confirmation of PCP had typical clinical features or postmortem confirmation. Endobronchial KS was seen in 11 (12%) of patients bronchoscoped. Seventy four (67%) patients were treated for PCP alone but 37 (23%) also required treatment for second concurrent pulmonary infections which were usually diagnosed at bronchoscopy. Seventy nine (71%) patients were treated for PCP with high dose co-trimoxazole alone, but the remainder were switched to other agents because of side effects. Thirty four (30%) patients died from PCP. The mean duration in hospital of the 79 who were discharged was 14 days. Of the 79 survivors, 20 (25%) had subsequent episodes of PCP. These findings have implications for the diagnosis, treatment and prophylaxis of PCP.

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Respiratory physicians: attitudes to HIV positive and AIDS patients

SE CHURCH, S OWEN, BC LEAHY, S KALRA, A WOODCOCK *Manchester Royal Infirmary and Wythenshawe Hospital, Manchester* A questionnaire on HIV and AIDS was sent to respiratory physicians throughout the UK. The response rate in consultants was 56% (224/398) and in senior registrars was 63% (41/65). Thirty eight per cent had never seen an HIV positive or an AIDS patient and only 4% had seen more than 20. Twenty four per cent of respondents were the nominated District AIDS Physician. *Confidentiality* Sixty per cent of respondents would enquire directly as to sexual orientation if clinically suspicious, whereas only 4% would directly enquire of all patients. Seventy three per cent always obtain written consent prior to HIV antibody testing, 22% usually, 4% rarely and one subject never. With a positive result and with the patient's consent, 95% of respondents would inform both hospital based and primary health care workers and spouse. Without consent 75% of respondents would still inform hospital based and 60% primary health care workers, but only 25% would inform the spouse. *Notifiable disease* Seventy per cent thought that HIV positivity and 84% that AIDS should be notifiable. *Patient management* When a patient who is HIV positive develops respiratory symptoms with pulmonary shadowing, 64% would treat empirically and bronchoscope if there was no subsequent improvement. Thirty one per cent would bronchoscope immediately and only treat an isolated pathogen. Five per cent would treat without bronchoscopy. If the patient subsequently developed respiratory failure, 47% would ventilate. Fifty six per cent of respondents thought that AIDS patients should be cared for in isolation cubicles on the general ward, 30% in a designated AIDS unit and only 14% would accept them onto an open ward. Forty three per cent thought that terminal care of the AIDS patient should take place solely at home, 25% in a hospice, 13% using both facilities and 19% favouring home and hospital based care. We have analysed the above data according to age and found no significant differences in attitudes between physicians aged >40 and those $\leqslant 40$ years.

Respiratory physicians: attitudes to invasive procedures in high risk, HIV positive, and AIDS patients

SE CHURCH, S OWEN, BC LEAHY, S KALRA, A WOODCOCK *Manchester Royal Infirmary and Wythenshawe Hospital, Manchester* A questionnaire on attitudes to invasive procedures in HIV positive (HIV+) and AIDS patients was sent to respiratory physicians throughout the UK. In matters of unit policy one reply was considered per hospital from the most senior respondent. *Bronchoscopy:* One hundred and fifty nine of one hundred and ninety (83%) have at least one fully immersible bronchoscope. Thirty nine of one hundred and ninety one (20%) have a dedicated bronchoscope for high risk (HR) or HIV+ patients. Only 34/189 (18%) have an automatic washer, although 74/188 (39%) have an ultrasonic forceps cleaner. During bronchoscopies 142/207 (71%) wear gloves routinely increasing to 189/199 (95%) for HR patients. Seventy nine of two hundred and seven (39%) routinely wear a gown increasing to 154/195 (79%) for HR and to 173/194 (89%) for known HIV+ patients. Only 12/200 (6%) wear eye protection routinely increasing to 133/193 (69%) for HR and to 165/192 (86%) for HIV+ patients. Glutaraldehyde is used universally but many bronchoscopists (42/211 (20%)) seemed ignorant of sterilisation times and those reported varied enormously. *Pulmonary function:* Fifteen of two hundred and five (7%) of physicians have a separate spirometer for HR patients. One hundred and fifty six of one hundred and eighty five (85%) refuse to allow such patients to use their rebreathing equipment. *Physiotherapy:* Precautions taken by physiotherapists in dealing with routine, HR, HIV+ or AIDS patients were as follows: gown (4:50:66:68%), gloves (5:49:71:75%) and goggles (0:17:30:32%) respectively. *Intensive care:* Precautions taken by personnel when performing a procedure as a routine or on HR, HIV+ or AIDS patients include: gloves (64:93:97:97%), gown (31:75:90:90%), goggles (1:34:55:59%) and overshoes (5:18:28:31%) respectively. We conclude that there seems little uniformity in infection control measures taken by respiratory physicians. More data for adequacy of sterilisation are urgently needed.

Mycobacterial infection in human immunodeficiency virus infected patients

MR HELBERT, DS ROBINSON, DR BUCHANAN, I BROWN , K CANN, AJ PINCHING, DM MITCHELL *St Mary's Hospital, London* Clinical details of 206 AIDS patients were reviewed. A further 11 patients with AIDS related complex (ARC) and mycobacterial infection (eight with *M. tuberculosis*, three with atypical organisms) were identified. In 49 cases specimens were positive for acid fast bacilli (AFB) on microscopy and of these 39 were positive on culture. *Mycobacterium avium intracellulare* (MAI) and *M tuberculosis* (MTB) were distributed as shown in the table. Pattern of disease differed between MTB and MAI. MAI in AIDS patients was never the presenting major opportunist infection (OI), the mean number of preceding OIs in this group being 1·8. MTB was seen in ARC and AIDS. In AIDS patients the mean number of preceding OIs was 0·5. Mean survival for MTB in both ARC and AIDS was 10·7 months yet only one patient died of MTB (declined treatment). Mycobacterial infection may accelerate HIV disease by T lymphocyte activation. Mean survival for patients with MAI was 7·5 months. Two patients with MAI had positive blood cultures and two had infection with two different strains of MAI concurrently. All patients with stool isolates of MAI had diarrhoea and abdominal pain. Isolates of MTB were all sensitive to first line drugs, whereas MAI isolates were resistant but showed varied sensitivities to second line drugs. Three patients with MAI improved on amikacin. Other mycobacteria isolated were *M fortuitum* (3), *M flavescens* (2), *M xenopi* (2), *M kansasii* (1). No close contacts of any of the AIDS or ARC patients are known to have become infected.

	No of patients	*Pulmonary only*	*Stool only*	*Disseminated*
MTB (ARC)	8	6	1	1
MTB (AIDS)	5	2	1	2
MAI (AIDS)	18	2	7	9

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Mycobacterial resistance to disinfection in AIDS: whither infection control policies now?

PJV HANSON, MV CHADWICK, G NICHOLSON, H GAYA, JV COLLINS *Brompton Hospital, London* *Mycobacterium avium intracellulare* (MAI) infects over half of patients with the acquired immunodeficiency syndrome (AIDS); *Mycobacterium tuberculosis* infection occurs in 2–10% of AIDS patients, the diagnosis usually preceding that of AIDS. The implications for infection control policies in bronchoscopy units are considerable. Inadequate disinfection of bronchoscopic equipment has caused mycobacterial contamination of diagnostic specimens and transmission of non-tuberculous and tuberculous mycobacteria between patients. Previous studies on disinfectants and mycobacteria have used non-pathogenic, attenuated organisms with scant regard to ambient temperature, the presence of protein and inactivation of residual disinfectant, all of which influence mycobactericidal activity. On the basis of such studies recommended disinfection times vary from five minutes to one hour. We examined the effect of 2% glutaraldehyde on three strains of mycobacteria: two, *MAI* and *M tuberculosis*, were from AIDS patients; the third was a laboratory strain, H37RV. Disinfectant was added to 10^8 organisms/ml held in protein suspension at 23°C. Samples were taken in triplicate at intervals up to one hour. Residual disinfectant was removed by dilution and colonies counted after 28 days culture in Middlebrook 7H10 agar. Inactivation of *M tuberculosis* occurred at a rate of 1·0 log10 colony forming units (cfu) per 6·6 minutes; sterility was achieved in 35 minutes. *MAI* proved very resistant to disinfection with a reduction of 1·0 log10 cfu per 72 minutes; the estimated time to achieve sterility was six hours. Tests on two other disinfectants confirmed the relative resistance of *MAI* to chemical inactivation. These results suggest that current recommended disinfection times for bronchoscopic equipment are inadequate to prevent the transmission of mycobacteria between patients.

Exercise hypoxaemia in fibrosing alveolitis: $\dot{V}/\dot{Q}$ mismatch or diffusion defect?

DNJ LOCKWOOD, RJ CLARK, HA JONES, JMB HUGHES *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Five patients with cryptogenic fibrosing alveolitis exercised for five minutes at a workload equal to 60% of their own maxima. Oxygen saturation (oximetry), O_2 consumption, ventilation and cardiac frequency were monitored. At rest and after five minutes' exercise they rebreathed rapidly for 12 seconds from a bag containing 0·8–1·0 l of 10% each of helium, sulphur hexafluoride and freon-22, 30% oxygen in argon and <1 ppm ^{11}C labelled carbon monoxide. Pulmonary capillary blood flow ($\dot{Q}c$) (freon-22) and transfer factor (TLCO) (^{11}CO) were measured from flow-weighted breath-by-breath concentrations after correction for gas mixing delays. Alveolar PO_2 (ideal) and mixed venous O_2 saturation and content were calculated (Fick) and Pao_2 and P v O_2 derived from standard dissociation curves. TLCO was taken as TLCO × 1·24 (Meyer *et al. J Appl Physiol* 1981;**51**:1643). Using the Bohr Integral $(TL)\beta\dot{Q})$ the alveolar-end capillary Po_2 gradient was calculated and compared with the measured PA-Pa gradient. On exercise Sao_2 fell by 3–15% to 86% (71–92%) (mean and range); $\dot{Q}c$ and $\dot{V}o_2$ averaged 10·5 and 1·08 l/min. TLCO was low at rest (20–44% pred) and increased on exercise to 20–58% pred normal. $TL/\beta\dot{Q}$ fell from 1·54 (rest) to 0·37 on exercise (normal $>1·5$ for this work). The calculated alveolar-end capillary Po_2 gradient was 69 (49–84) mm Hg and the actual $(PA\text{-}Pa)o_2$ difference was 66 (49–84) mm Hg, the difference between them being 3 (-1 to $+9$) mm Hg. The helium and SF_6 washin indicated good ventilation distribution. These data suggest that the desaturation and PA-Pa oxygen gradient that the desaturation and PA-Pa oxygen gradient on exercise can be explained by diffusion-perfusion imbalance rather than $\dot{V}/\dot{Q}$ heterogeneity and shunt.

Diurnal variation, exercise, and posture and the single breath carbon monoxide transfer factor, membrane diffusing capacity, and volume of blood in pulmonary capillaries in normal subjects

JP JAMISON, JHM LANGLANDS *Respiratory Investigation Centre, Belfast City Hospital, Belfast* The repeatability of transfer tests on patients with interstitial lung disease is important in following spontaneous variations in the disease or in its response to treatment or alveolar challenge. Single breath carbon monoxide transfer factor (TLCO) was measured twice after room air breathing and after breathing 100% oxygen for five minutes in eight normal subjects aged 18–25 (four males and four females). These measurements were taken at 8.30–9.00 am and again at 8.30–9.00 pm. Mean TLCO, membrane diffusing capacity (DM) and volume of blood in the pulmonary capillaries (Vcap) (% predicted) were 91%, 89% and 90% respectively at 9.00 am and 90%, 89% and 86% at 9.00 pm—no significant change ($p > 0·4$) compared with an expected 20% decrease (Cinkotai and Thomson. *J Appl Physiol* 1986;**21**:539–42). In six subjects lying supine for five minutes significantly increased the mean TLCO from 92% to 105% ($p < 0·01$), owing to about equal increase in DM and Vcap. Exercise at 60 watts in these subjects increased the mean TLCO to 129% ($p < 0·001$), two thirds of this increase being due to increase in Vcap and one third to increase in DM. It is considered that, contrary to the previous report, the time of day has no significant effect on transfer factor. Significant changes were found in transfer factor and its components with change of posture and exercise.

Measurement of the transfer factor by the single breath method with a shorter breath holding time

N AL-JARAD, C WEST, DW EMPEY, JA WEDZICHA *Respiratory Function Department, London Chest Hospital, London* The purpose of the study was to determine whether the values of the transfer factor for the lung for carbon monoxide (TLCO), the transfer coefficient (KVO), and the alveolar volume (VA) are significantly affected by reducing the breath-holding time (BHT) during the single breath technique to half of the standard time of 9–10 seconds. We studied 12 normal subjects (seven female, five male; age range 19–38 years), and 22 patients (six female, 16 male; age range 22–76 years). Sixteen of the patients had moderate or severe airflow

obstruction (mean FEV_1 1·7 l (SD 0·85)) and the remainder had restrictive lung disease. Transfer factor was measured in each subject on four occasions on the same day using the method described by Oglivie *et al* (*J Clin Invest* 1956;**36**:1–17). During two of the estimations the subject held his breath twice for the short technique (mean BHT 4·56 (0·52) s), and twice for the standard method (mean BHT 10·3 (0·37) s). There were no significant differences in the measurements of the transfer factor in all subjects and patients, whether performed using short or standard time techniques. The estimations obtained by both methods were closely related in all the groups of subjects studied—for T_{LCO} ($r = 0·97$; $p < 0·01$), for K_{CO} ($r = 0·96$; $p < 0·002$) and for V_A ($r = 0·97$; $p < 0·01$). This suggests that reduction of the standard time for breath-holding does not significantly affect the transfer factor estimations. This shorter BHT technique will be advantageous to breathless patients who are unable to breath-hold for the standard time.

Validation of a two phase bicycle exercise test

CK CONNOLLY, G POWER *Memorial Hospital, Darlington, Co Durham* Protocols for exercise tests, often originally designed for normal subjects, prolong exercise so that untrained or poorly motivated subjects stop for non-specific reasons before their physiological maximum performance is achieved. A two phase test was described with 760 subjects (*Respiration* 1985;**47**:114–9). The first stage, a rapid logarithmic increase in workload from 25 watts to failure at 10 second intervals, is followed by constant exercise at two-thirds of the work achieved in the first stage. The aim is to achieve exercise for six minutes, raising the pulse to 130 beats/min to enable physiological measurement during and after submaximal exercise. The test was validated in the next 533 subjects with all forms of airway obstruction (mean (SD) FVC (l): men 3·65 (0·72), women 2·89 (0·90)). Multiple regressions were obtained. Men: work done = $-74·4 + 28·9$ FVC $- 1·068$ age $+ 1·4$ height ($R = 0·76$); women: work done = $-42·6 + 27·3$ FVC $- 0·0609$ age $+ 1·09$ height ($R = 0·64$). Simple regression equations of work done on FVC in men are compared with 1985 in the table. Sixty five per cent of males (1985 69%) and 68% of females (1985 71%) succeeded in the second task, achieving a pulse of 130. Thirty one per cent stopped early and 11% did not reach the pulse rate. Exhaustion of the legs caused most failures, but breathlessness became more important with poorer pulmonary function. The test was validated, the first phase giving a correlation between pulmonary function and exercise performance that compared favourably with other protocols, and the second phase giving a suitable workload for physiological testing in two-thirds of subjects.

Age	*n(1985)*	*r(1985)*	*Slope(1985)*	*Intercept (1985)*
39	72 (185)	0·55 (0·70)	35·1 (35·4)	156·1 (116·5)
40–59	90 (193)	0·54 (0·52)	31·3 (31·2)	117·0 (130·9)
60	59 (103)	0·57 (0·59)	46·1 (50·4)	53·5 (52·3)

Long term suppression of REM sleep in the treatment of sleep disordered breathing

AK SIMONDS, N CARROLL, R SHINER, MA BRANTHWAITE, R JAMES, C IDZIKOWSKI *Brompton Hospital, London, and Janssen Pharmaceutical Limited* Suppression of REM sleep-associated apnoeic and hypopnoeic episodes is beneficial in sleep-disordered breathing (SDB). Tricyclic antidepressant agents reduce the percentage of REM sleep, but the duration of this effect is unclear. The long term action of protriptyline (5–20 mg nocte) on REM time in seven subjects (six female; mean age 48·4 years) with SDB was investigated by polysomnography before treatment (study 1), and after 4–6 weeks (study 2) and 12–36 months (mean 29·1 months) on the drug (study 3). The mean proportion of REM sleep fell from 19·1% (range 7–31%) in study 1 to 12·5% (range 0·23%) in study 2 ($p < 0·05$). This reduction was maintained in study 3 (mean 12·6%, range 0·73–20·5%). Two of the seven subjects showed an increase in percentage REM time and this was associated with a deterioration in clinical status. In the five who demonstrated persistent reduction in percentage REM time, an initial significant improvement in diurnal oxygen tension was maintained (pretreatment mean Pao_2 7·91 kPa, range 7·2–8·86 kPa; mean Pao_2 at time of study 3 8·8 kPa, range 8·4–9·33 kPa) ($p < 0·05$). Protriptyline has a sustained effect on REM sleep duration in some individuals with SDB and this may be associated with prolonged clinical benefit.

Peripheral oedema in the sleep apnoea-hypopnoea syndrome

KF WHYTE, MB ALLAN, AA JEFFREY, NJ DOUGLAS *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* Some patients with the sleep apnoea/hypopnoea syndrome (SA/HS) develop cor pulmonale. On the basis of a study incorporating six such patients, it has been proposed that cor pulmonale is most common in patients who have both SA/HS and airways obstruction (Bradley *et al. Am Rev Respir Dis* 1985;**131**:835). However, in that study the patients with cor pulmonale were significantly more obese than the remainder. To clarify the roles of airways obstruction and obesity, we have investigated 65 patients with the SA/HS, defined as more than 15 A + H/h of sleep plus symptoms. Patients with ischaemic heart disease or other known cause for peripheral oedema were excluded, leaving 51 patients (of whom 16 had had peripheral oedema (PO) on average of 13 months), aged 38–69 years. The PO patients were more obese (164 (SD 41), 135 (31)% ideal body weight; $p < 0·01$). The groups had equally severe SA/HS (49 (29), 52 (20), A + H/h) but the PO patients had lower oxygenation both awake and asleep (lowest 46 (17), 71 (19)% sat; $p < 0·01$). PO patients had lower FEV_1 as % predicted (58 (19), 86 (18); $p < 0·01$) and lower FEV_1/VC (66 (10), 77 (10)%; $p < 0·01$). Ninety-four per cent of the PO patients were current smokers or ex-smokers compared with 57% of non-PO ($p < 0·01$). To exclude the effects of obesity, patients with PO and body weight 135–236% ideal were each weight matched with a patient without PO (168 (28), 169 (28)% IBW). These patients with PO still had impaired lung function (FEV_1/VC 75 (10), 64 (11)%; $p < 0·05$; and FEV_1% pred (75 (15), 62 (19); $0·1 > p > 0·05$). Thus peri-

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pheral oedema in patients with the sleep apnoea/hypopnoea syndrome is associated with airways obstruction independent of any effect of weight.

Comparison of two different mouthpieces for the measurement of PImax and PEmax

N KOULOURIS, DA MULVEY, CM LAROCHE, M GREEN, J MOXHAM
King's College and Brompton Hospitals, London We investigated the hypothesis that differences reported for normal range of static mouth pressures (Black and Hyatt. *Am Rev Respir Dis* 1969;**99**:696; Leech *et al. Am Rev Respir Dis* 1983;**128**:17) may reflect the use of different mouthpieces. We measured PEmax at TLC and PImax at RV in 21 normal subjects (six highly trained—HT; 15 naive—NN), and in 40 patients referred for respiratory muscle testing, 20 with low static inspiratory mouth pressure (LP), and 20 normal (NP) as judged by the data of Black and Hyatt. We compared two mouthpieces, a rigid plastic flanged type fitting inside the lips (flange), and a rubber tube of 4 cm internal diameter held against the lips as described by Black and Hyatt (tube). The subjects were seated and wore a nose clip and pressures were sustained for at least one second. After a period of learning measurements were made until three consistent readings were obtained. Six patients were unable to use the tube owing to neuromuscular disease, hand deformity or quadriplegia and their data are not included above. We conclude that (1) for subjects able to use the tube pressures may be higher; (2) the flange is more widely applicable; (3) the choice of mouthpiece does contribute to the variability in the reported normal ranges for PEmax and PImax; (4) the differences are unlikely to be important clinically, provided that the appropriate normal ranges are used.

	Mean (SEM) PI_{max} (cm H_2O)		Mean (SEM) PE_{max} (cm H_2O)	
Mouthpiece	*Flange*	*Tube*	*Flange*	*Tube*
HT (n = 6)	119·9 (15)	125·5 (19·9)	140·3 (23·1)	178·6 (25·5)*
NN (n = 15)	99·1 (8·1)	106·9 (10·2)	143·0 (9·9)	165·1 (10·3)**
NP (n = 20)	84·4 (7·1)	93·1 (7·2)**	117·6 (9·6)	142·5 (10·5)**
LP (n = 20)	40·7 (3·1)	43·6 (3·3)	84·1 (8·1)	94·7 (8·5)*

*p < 0·05, **p < 0·02 (paired *t* test).

The shrinking lung syndrome of systemic lupus erythematosus not caused by diaphragm weakness

CM LAROCHE, D MULVEY, P HAWKINS, M WALPORT, J MOXHAM, M GREEN *Brompton and Hammersmith Hospitals, London* Diaphragmatic myopathy has previously been postulated as causing the reduction in vital capacity which can occur in systemic lupus erythematosus (SLE). However, previous studies have used only a limited range of tests to assess respiratory muscle strength, many of which are dependent on patient motivation and technique. We studied 12 patients with a reduction in lung volume associated with confirmed SLE, none of whom had polymyositis or other peripheral neuromuscular abnormalities. Vital capacity was 54 (11)% predicted, total lung capacity 59 (14)% pred, residual volume 76 (30)% pred, TLCO 48 (11)% pred, and KCO 104 (19)% pred. Chest radiography and fine cut (3 mm) computed tomography of the chest showed no evidence of interstitial or pleural disease. Maximum static expiratory mouth pressure was normal in 8/12 patients and maximum static inspiratory mouth pressure normal in 9/12. Sniff oesophageal pressure was normal in 11/12 patients. Transdiaphragmatic pressure (Pdi) was normal in 8/12 patients when measured during a maximum static inspiration and 9/12 during a maximum sniff. The four patients with low Pdi during voluntary manoeuvres had normal bilateral twitch Pdi generated by phrenic nerve stimulation. This pattern is consistent with an upper motor neurone lesion affecting control of the respiratory muscles. These results do not support the hypothesis that the restrictive defect seen in patients with SLE without polymyositis is due to diaphragmatic myopathy.

Simple method for the assessment of inspiratory muscle weakness

N KOULOURIS, DA MULVEY, CM LAROCHE, M GREEN, J MOXHAM
King's College and Brompton Hospitals, London Respiratory physicians may need to diagnose and quantitate weakness of the inspiratory muscles. Measurement of static inspiratory mouth pressure is commonly used, but the normal ranges are wide and some patients have difficulty with the manoeuvre. Oesophageal pressure measured during a sniff from FRC without a nose clip can be more discriminating (Miller *et al. Clin Sci* 1985;**69**:91–6), but its usefulness may be offset by the need to pass an oesophageal balloon. We have investigated whether nasopharyngeal pressure (Pnp) or pressure within the mouth (Pmo) reflect oesophageal pressure (Poes) during a maximum sniff. We measured Poes, Pnp and Pmo simultaneously in 10 normal subjects and 12 patients with inspiratory muscle weakness of various aetiologies. The oesophageal balloon (10 cm long, 0·5 ml air) was positioned in mid oesophagus, the nasal balloon (5 cm long, 0·7 ml air) 10 cm from the anterior nares, while the mouth balloon (5 cm long, 0·7 ml air) was held in the oral cavity with the lips closed. In normal subjects the mean ratio Pnp/Poes was 0·92 (0·006) (mean (SE)) and Pmo/Poes was 0·95 (0·006). Correlation coefficients were for Pnp and Poes: $r = 0·995$, $p < 0·001$; Pmo and Poes: $= 0·994$, $p < 0·001$. Regression analysis showed Poes = 4·57 + 1·05 Pnp and Poes = 0·74 + 1·05 Pmo. In the patients the mean ratio Pnp/Poes was 0·9 (0·02) and Pmo/Poes was 0·87 (0·03). Correlation coefficients were for Pnp and Poes: $r = 0·949$, $p < 0·001$; Pmo and Poes: $r = 0·936$, $p < 0·001$. Regression analysis showed Poes = 5·12 + 1·0 Pnp and Poes = 11·2 + 0·882 Pmo. We conclude that Poes can be predicted from both Pnp and Pmo in both normal subjects and patients. Measurements of Sniff Pnp and Pmo are simple and well tolerated by all subjects, and provide a useful method for the quantification of inspiratory muscle weakness.

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Static versus dynamic assessment of inspiratory muscle strength

J PERTUZE, A WATSON, J THOMPSON, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Despite the considerable flow ($\dot{V}$) and volume changes during nasal (Na) sniffs, maximum transdiaphragmatic (Pdi) and oesophageal (Poes) pressures are surprisingly similar to those measured during maximum static inspiratory efforts from FRC (Mips). To investigate how such large intrathoracic pressures can be developed when breathing through the unobstructed nose, we studied Poes-$\dot{V}$ relations in five young normal subjects. We found that near plateaux of $\dot{V}$ (range: 0·9–2 ls^{-1}) developed in all subjects at inspiratory Poes in the range of 10–30 cm H_2O; no further increases in $\dot{V}$ developed as Poes reached maxima in the range of 58–130 cm H_2O, indicating the development of a Starling resistor (SR) mechanism. We investigated whether the advantages of the sniff manoeuvre could be combined with measuring only mouth pressure (Pmo) (so avoiding oesophageal or pharyngeal intubation) by comparing pressures generated during brief inspiratory efforts via the mouth against a SR (Mo sniff + SR) with those during Na sniffs and Mips in nine normal subjects (six male). Mean values and 95% confidence limits for max inspiratory Poes (cm H_2O) were: Mo sniff + SR 121 (111–132); Mip: 111 (100–121); Na sniff: 108 (97–118). In 5/9 subjects we compared Poes with Pmo simultaneously recorded via a lateral port in the mouthpiece. The mean difference between Poes and Pmo during Na sniffs was 30·8 (SD 20·4) s cm H_2O; in Mo sniff + SR: 5·6 (3·8) cm H_2O. Therefore brief inspiratory efforts via the mouth against an SR result in excellent intrathoracic pressure generation, which is transmitted to the mouth. Measuring Pmo alone during this manoeuvre may provide an alternative non-invasive method for the assessment of inspiratory muscle strength in subjects who experience difficulties during standard static inspiratory efforts.

Cardiac and plasma atrial natriuretic peptide levels in rats during chronic hypoxia and recovery

RJD WINTER, L MELEAGROS, SR BLOOM *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Plasma atrial natriuretic peptide (ANP) in rats is increased after 21 days exposure to chronic hypoxia (*Proc Soc Exp Biol Med* 1986;**181**:459). We have examined the effect of shorter exposure and recovery on cardiac and plasma ANP levels. Male Wistar rats (weight range 300–400 g) were placed in an environmental chamber with FiO2 maintained at 10%. Animals were removed after seven days hypoxia (n = 10) and compared with normoxic controls (n = 10). A further group maintained in hypoxia were allowed to recover breathing air for 24 hours (n = 10). The ratio of right to left ventricular weights (RVW/LVW) in the three groups was: 0·224 ± (SEM) 0·012 normoxic control (NC), 0·320 (0·012) hypoxic (H), 0·316 (0·015) hypoxic with recovery (HR), $p < 0·001$ both hypoxic groups compared with NC. The ratio of right atrial weight to left ventricular weight was not significantly changed in hypoxia (NC 0·075 (0·006), H 0·089 (0·008), HR 0·096 (0·08)). Plasma ANP, measured by radioimmunoassay (*Clin Sci* 1986;**71**:151), was increased after seven days (H 43 (5), NC 27 (2) pmol/l; $p < 0·01$), but had returned to normal in the hypoxic recovery group (HR 30 (2) pmol/l; NS compared with NC). Cardiac ANP levels (per g wet wt) are given in the table (n = 10, all groups). We concluded that (1) plasma ANP is increased after seven days exposed to hypoxia, when no depletion of cardiac stores is evident; (2) ANP release in hypoxia is independent of associated cardiac hypertrophy; (3) the right ventricular hypertrophy seen in hypoxia is associated with selectively increased right ventricular ANP immunoreactivity. The relevance of this latter observation is being further investigated using quantitative in situ hybridisation techniques.

	ATRIA (nmol/g)		*VENTRICLES (pmol/g)*	
	Right	*Left*	*Right*	*Left*
NC	130 (11)	75 (6)	6 (1)	9 (2)
H	138 (18)	66 (9)	30 (5)*	15 (4)
HR	120 (14)	86 (8)	27 (4)*	10 (2)

*$p < 0·001$ compared with NC.

Effect of gradated hypoxia on pulmonary artery pressure measured by Doppler echocardiography in normal subjects

AJ PEACOCK, V CHALLENOR *Wessex Right Heart Group, Southampton General Hospital, Southampton* Research on the effects of hypoxia on the pulmonary circulation is limited by the need for cardiac catheterisation to obtain haemodynamic measurements. Continuous wave Doppler assessment of blood flow characteristics across the tricuspid valve offers a simple repeatable non-invasive method for measuring peak systolic pulmonary artery pressure (PAP) in those subjects who have tricuspid regurgitation (TR). In patients with chronic hypoxic lung disease there is a high correlation between pressures measured in this way and those obtained at catheterisation (Peacock A *et al.* SEPCR meeting, Paris, 1986). Furthermore "physiological" TR is present in a high percentage of normal subjects (Upward J *et al. Br Heart J* 1985;**54**:618). We assessed the effects of gradated hypoxia and hyperoxia on PAP in five normal subjects with physiological TR. The velocites of TR were measured at differing percentages of inspired oxygen (Fio_2). Sao_2 was measured continuously by ear oximetry (Hewlett Packard). We found a linear relationship between Fio_2 and calculated peak PAP ($r = 0·5$, $p < 0·001$) using hypoxic mixtures but hyperoxia produced no further decrease from room air (20·9%). Mean calculated peak PAP in mm Hg for the five subjects were 31 at 10%, 28 at 12·5%, 22 at 15%, 17 at 20·9% and 18 at 30%. We conclude that Doppler echocardiography provides a non-invasive method for measuring pulmonary artery pressure in normal people subjected to hypoxia.

Relation between rapid growth and pulmonary hypertension in fast growing broiler chickens

AJ PEACOCK, JT REEVES *Cardiovascular Pulmonary Research Laboratory, Denver, USA* It is well known that pulmonary hypertension (PH) develops rapidly in a setting where there is also rapid systemic growth such as children with neonatal

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PH. We have studied the fast growing chicken which is reported to have a high incidence of right heart failure from PH at 4–6 weeks of age. First we measured body weight in 53 fast (FG) and slower growing (SG) chickens, 4–14 weeks of age and compared this with right ventricular/left ventricular weight (RV/LV). The peak fractional differences in body weight occurred at 6–8 weeks and that was the time when RV/LV was high in VFG but not in SG chickens (48 (SE) 5% *v* 27 (4)%; $p < 0.001$). We therefore compared pulmonary haemodynamics in seven normal and 15 FG chickens of mean age 8 weeks. The resting pulmonary artery pressure (PAP) was similar in normal and FG chickens (16 *v* 18 mm Hg) but, on challenge with hypoxia ($Pao_2 < 8$ kPa) the PAP in the VFG chickens but not the normals rose to 23 (2) mm Hg ($p = 0.05$). This rise was accompanied by a fall in cardiac output so that total pulmonary resistance (TPR) rose in the VFG chickens from 80–175 units ($p < 0.05$). No change in TPR was seen in the normal chickens until Pao_2 fell below 6·5 kPa. Finally, in order to determine whether restricting growth prevented the rise in PAP we placed eight normal and eight FG chickens in a hypobaric chamber at "10 000 ft" for two weeks. Four of each group were fed ad lib and four were fed a restricted diet. The FG but not the normal chickens developed marked RVH in response to the hypoxia when fed ad lib but this could be prevented by growth restriction (RV/LV < 48 (2)% unrestricted growth *v* 36 (2)% restricted growth; $p < 0.05$). We conclude that FG chickens develop PH at the times of most rapid growth which can be prevented by growth restriction. This PH may be due in part to an increased sensitivity of their circulation to hypoxia. The fast growing chicken may be a useful model with which to study the relationship between growth and pulmonary hypertension.

BCG immunisation of infants by percutaneous multiple puncture

DB CUNDALL, D ASHELFORD, SB PEARSON *Department of Paediatrics and Child Health, St James's University Hospital, and Chest Clinic, Leeds* BCG immunisation by the intradermal route is technically difficult in infants. We describe a prospective study of the percutaneous multiple puncture technique using a modified Heaf gun. Infants aged four to ten weeks were allocated alternately to receive BCG immunisation by either the percutaneous or the intradermal route. Both techniques were used by three doctors. Infants were Heaf tested and reassessed four months after immunisation. There were 100 infants in each group. Sixty eight of the percutaneous group and 73 of the intradermal group had Heaf tests of grade one or more. Sixty three of the percutaneous group and 95 of the intradermal group had visible BCG scars. None of the percutaneous scars and five of the intradermal scars had ulcerated. The proportion of positive Heaf tests was similar for each immuniser using the percutaneous method but differed significantly when the intradermal route was used as shown below in the table. The percutaneous multiple puncture method of infant BCG immunisation was less susceptible to immuniser error and was free from complications.

Number of grade 1–2 Heaf tests/total immunisations by immuuniser and method of immunisation

	Immuniser			
	A	*B*	*C*	*All*
Percutaneous	26/36	27/42	15/22	68/100
Intradermal*	26/41	28/40	19/19	73/100

*$\chi^2 = 9.02$, df = 2, $p < 0.02$.

Diagnosis of pulmonary tuberculosis by sputum smear and culture

M REZA, WJM KINNEAR, JT MACFARLANE *City Hospital, Nottingham* It is traditional teaching that three sputum specimens should be obtained from patients with suspected pulmonary tuberculosis (PTB). In a retrospective analysis we have investigated the value of this rule in 94 adults with bacteriologically proven PTB in the setting of a respiratory unit in Nottingham. The laboratory employs an auramine stain to screen sputa for acid fast bacilli (AFB). Sixty seven patients (71% of total) were smear positive. Sixty one (91%) of these were positive on the first smear, an extra four (6%) on the second smear and two (3%) on the third smear. Eighty nine patients (94% of total) were positive on culture of the first sputum specimen, an extra five (6%) on second sputum culture and no further positive cultures were seen for the third specimen. Sixty nine per cent (131/191) of sputum specimens that were graded mucopurulent/purulent by the laboratory were smear positive compared with 52% (28/49) for mucoid sputa ($p > 0.5$). The comparative figures for positive culture were 96% and 97% respectively. Pulmonary cavitation was present on the chest radiograph in 45% of those who were smear positive compared with 18% who were smear negative ($p < 0.02$). There was no difference in rate of smear or culture positivity as regards unilateral or bilateral disease. A Heaf test had been recorded in only 21 cases; 17 were grade 3/4 and four were grade 2 or less. In summary, we found that 94% of patients studied were diagnosed with one sputum smear and culture and further samples contributed only marginally to a positive bacteriological diagnosis. This is in agreement with studies performed in the past in countries outside West Europe where tuberculosis is much commoner. The macroscopic appearance of the sputum did not significantly affect the smear or culture result. The Heaf test did not feature prominently as a diagnostic tool in the cases studied.

Results at 24 months of a controlled trial of complete surgical drainage and of prednisolone in the treatment of tuberculous pericardial effusion

JIG STRANG, HHS KAKAZA, DG GIBSON, BW ALLEN, DA MITCHISON, DJ EVANS, DJ GIRLING, AJ NUNN, W FOX *Umtata Hospital Transkei; Brompton Hospital, Royal Postgraduate Medical School; and British Medical Research Council, London* In Transkei, 240 patients with tuberculous pericardial effusion all received streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 14 weeks followed by isoniazid

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and rifampicin daily up to six months; 198 are assessable 24 months after admission. The 101 willing were randomised to open pericardial biopsy and complete drainage of pericardial fluid on admission (48 patients), or to simple percutaneous pericardiocentesis as required. All 198 were randomised to receive prednisolone or matching placebo double-blind for the first 11 weeks. By 24 months, apart from 16 patients who died from pericarditis, all but three had a favourable status on all or all except one of eight clinical, radiographic and ECG criteria. Complete open drainage on admission abolished the need for repeat pericardiocentesis which was needed in 23% of patients who did not have this done ($p < 0.01$), but did not influence the need for pericardiectomy for subsequent constriction, the risk of death, or the status at 24 months. It is therefore not recommended as a routine. Among the 150 patients who did not have open drainage on admission, 3% of 76 given prednisolone compared with 14% of 74 placebo died from pericarditis, 9% and 23% respectively required repeat pericardiocentesis, and 96% and 84% had a favourable status at 24 months ($p < 0.05$ for each comparison); 8% and 12% required pericardiectomy, and 3% and 9% open surgical drainage because of the rapid reaccumulation of pericardial fluid. In the absence of a contraindication, antituberculosis chemotherapy should be supplemented by corticosteroids initially in the treatment of this disease.

Deaths in patients with pulmonary tuberculosis in England and Wales, 1983

P CULLINAN, SK MCDONALD, SP BYFIELD, JH DARBYSHIRE, AJ NUNN, KM CITRON, W FOX *MRC Cardiothoracic Epidemiology Group, Department of Clinical Epidemiology, Brompton Hospital, London* In a survey of all new notifications of tuberculosis in England and Wales during the first six months of 1983, 1115 adults, of white or Indian subcontinent origin, with disease confined to the lungs, for whom bacteriological and radiographic information was available, were identified. Two years after notification details of their outcome were sought. Before completing treatment 139 (13%) patients died. This fatality rate is the same as that in a similar survey in 1978–9 (Humphries *et al. Br J Dis Chest* 1984;**78**:149–58). One hundred and thirty two (95%) deaths were in white patients, who made up 77% of the survey group. Men accounted for 112 (81%) deaths but only 65% of the patients studied. When standardised for age and sex the mortality rate in the survey group was over five times that of the general population. Nineteen (14%) of the deaths occurred before treatment started. Analysis of the death certificates showed that in 11 of these, death was attributed primarily to tuberculosis, as it was in 35 (61%) of the 57 deaths within a month of starting treatment. There was an association between death and the radiographic extent of disease: 42 (25%) of 167 patients with the equivalent of three or more lung zones affected died, compared with only 24 (6%) of 318 patients with disease of less than one zone. Treatment details were obtained for 1067 (97%) of the patients who started chemotherapy. Of 108 patients who died 14 only ever received two antituberculosis drugs compared with 36 of 959 survivors ($p < 0.001$). Logistic regression analysis indicated that the risk of death from pulmonary tuberculosis was independently related to age, extent of disease, number of drugs used and ethnic origin.

Tuberculosis and HIV infection: surveillance in England and Wales

JM WATSON, ON GILL *PHLS Communicable Disease Surveillance Centre (CDSC), London* The number of reports of tuberculosis in the United States of America (USA) in 1986 rose by 2·6% over the 1985 total, having declined by an average of 5·9% per annum from 1963 to 1985 (CDC. *MMWR* 1988;**36**:817–20). This reversal in the trend has been attributed to the epidemic of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) because the areas with the largest increase in tuberculosis were those with the highest number of people with AIDS (CDC. *MMWR* 1987;**36**: 254–5). CDSC maintains confidential reporting systems for clinical cases of AIDS, and laboratory reports of HIV infection, in the United Kingdom. Notifications of tuberculosis in England and Wales have been studied to determine if an effect similar to that seen in the USA, as a result of the HIV epidemic, is evident in this country. Total notifications of tuberculosis in England and Wales increased slightly in 1986 but the downward trend was resumed in 1987. Notifications in persons aged 25–44 years resident in the south-east of England, also rose slightly in 1986, but no difference is apparent in the trend between males and females. Tuberculosis notifications in health districts in Greater London between 1982 and 1987 have been obtained from the Office of Population Censuses and Surveys (OPCS) and matched with numbers of reports of cases of AIDS resident in those districts (CDSC) data. No correlation is seen between recent changes in the trends of tuberculosis notifications and AIDS cases reported to date in these districts. The implications of these findings, and the approach to future surveillance, are discussed.

Altered vitamin D homeostasis in tuberculosis

PDO DAVIES, HA CHURCH, A CHARUMILIND, S BYRACHINDRA, S BOVONRKITT *South Liverpool Chest Clinic, Sefton General Hospital, Liverpool; Department of Medical Biochemistry, University Hospital of Wales, Cardiff; Department of Medicine, Siriraj Hospital, Bangkok* Altered vitamin D homeostasis in sarcoidosis, sometimes causing raised serum calcium concentration, is well established. There have also been reports of raised serum calcium in tuberculosis. The mechanism for this is thought to be by the production of a 1-alpha hydroxylase enzyme in the granulomata. This results in increased formation of $1,25(OH)_2O_3$ at the expense of $25(OH)_D$. Elevated serum formation of $1,25(OH)_2D_3$ may then cause a rise in serum calcium by increasing intestinal absorption and bone resorption of calcium. A study to investigate altered vitamin D and calcium homeostasis in tuberculosis has been undertaken in 51 smear positive patients and matched healthy controls in Bangkok, Thailand. Patients had lower serum $25(OH)D_3$ concentrations than controls (mean 27·8 (9·8) ng/ml compared with 38·2 (11·7) ng/ml; $p < 0.001$); higher $1,25(OH)_2D_3$, (median 33·6, range 11·9–71·1 pg/ml compared with 20·5, range 10·0–42·3 pg/ml; $p < 0.01$); lower PTH (mean 1·75 (1·2) ng/ml, compared with 2·8 (1·2) ng/ml; $p < 0.001$); but were normocalcaemic (mean 2·34 (0·1) mmol/l compared with

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2·38 (0·1); p > 0·5). Extrarenal 1α-hydroxylation in the tuberculoid granulomata may be responsible for raising $1,25(OH)_2D_3$ in the patient group at the expense of $25(OH)D_3$. Normocalcaemia may therefore be maintained by a reduction of serum PTH. It is possible that the hypercalcaemia of tuberculosis found in some individuals is caused by inappropriately high serum PTH concentrations in the presence of raised $1,25(OH)_2D_3$.

Long term home nebuliser therapy: peak flow, heart rhythm, steroid therapy, hospital admission, and death in 391 patients with chronic obstructive airways disease

RG TAYLOR, PA WEBB *Chest Clinic, Hull Royal Infirmary, Hull* We studied retrospectively the three years before and after nebuliser issue. At the time of issue, the 118 patients who later died (non-survivors) were older than 273 survivors (68 *v* 66 y), fewer had peak flow or reversibility measured, and more had been admitted once or more to hospital (74% *v* 62%, p < 0·05), despite shorter pre-issue follow up (0·6 *v* 1 y). Fewer non-survivors took inhaled $beta_2$ agonist drugs (60% *v* 84%, p < 0·0005) or inhaled steroids (18% *v* 30%, p < 0·005), but similar numbers took systemic steroids (31% *v* 36%), theophylline or ipratropium. Non-survivors' pre-issue peak flow was similar to survivors' (mean 142 *v* 146 l/min), but their post-issue rise in peak flow was not significant, and smaller (6 *v* 14 l/min, p < 0·001), despite their using the nebuliser more (>4 times/day: 84% *v* 67%, p < 0·005), with a higher daily salbutamol dose (>10 mg/day: 50% *v* 29%, p < 0·0005). After nebuliser issue, more non-survivors than survivors took systemic steroids (58% *v* 42%, p < 0·005); systemic steroid use increased in non-survivors (p < 0·0005) and inhaled use fell (p > 0·05), but neither changed significantly in survivors. Post-issue hospital admission rate fell in survivors (45%, p < 0·0005) despite longer follow-up (2·4 y), and did not rise in non-survivors (81%, p > 0·1) despite longer follow-up (1·4 y to death). Cardiac arrhythmia was commoner in non-survivors than in survivors (pre-issue 11% *v* 4·8%, p < 0·01; post-issue 11% *v* 5·4%, p > 0·05), but heart rhythm was often not recorded (pre-issue 20% *v* 16%; post-issue 24% *v* 31%), especially in clinic. Of non-survivors, 42% died of respiratory failure, 8% of lung cancer, 17% of non-respiratory causes and 33% of causes not reported to the clinic; 59% died in hospital. Home nebuliser treatment may reduce hospital admission and improve peak flow in chronic obstructive airways disease, but some patients of similar age and initial peak flow respond less well and die soon after nebuliser issue, more of them having been treated with systemic and fewer with inhaled steroids. Hospital admission is more common both before and after nebuliser issue in this group than in those who survive.

Oxitropium bromide in chronic bronchitis

A EYRE-BROOK, D WILLIAMS, M RUDOLF *Ealing Hospital, Southall, Middlesex, and Boehringer Ingelheim Limited, Bracknell, Berkshire* This double blind, randomised, placebo controlled, crossover study was set up to investigate the efficacy and duration of effect of oxitropium bromide, a new anticholinergic bronchodilator, in the treatment of patients with chronic bronchitis. Following a two week "run in" period, oxitropium bromide or placebo was given in a dose of two puffs (200 μg) twice daily for four weeks. The trial treatments were then crossed over. Double-blind, dose-time course studies were carried out prior to each treatment period, and twice daily peak expiratory flow rate (PEF) measurements, symptom scores and the need for "rescue" bronchodilators were recorded. Thirty patients (all of whom had at least 10% airway reversibility to inhaled ipratropium bromide 80 μg were studied). Statistically significant improvements were shown in the mean morning PEF (mean improvement 7·6%, p < 0·001) and in the mean evening PEF (mean improvement 7·7%, p < 0·01) in favour of oxitropium bromide compared with placebo. Significant overall treatment differences were seen in all assessments of daytime symptoms (p < 0·05), and in the need for "rescue" medication during the night (p < 0·05), on active medication. The duration of effect studies showed a statistically significant difference in favour of the active drug. Fifty five per cent of patients on oxitropium bromide, compared with 14% on placebo, recorded PEFs greater than their baseline at 12 hours post inhalation. Life table estimates were also made for the percentage of patients whose pulmonary function remained at least 5% and 10% above their baseline at 12 hours. On oxitropium bromide these were 31% and 21% respectively; on placebo no patients remained above these levels. These results show that oxitropium bromide is an effective long-acting bronchodilator, providing both night and daytime benefit to patients with chronic bronchitis when administered twice daily.

Trial of steroids in airflow obstruction: a reassessment

K PEARCE, JA ROBERTS, ST HOLGATE *Medicine 1, Southampton General Hospital, Southampton* Patients with airflow obstruction often have a trial of prednisolone to assess whether there is a reversible component to their obstruction. Some report symptomatic improvement without objective change in lung function. This is thought to be due to CNS effects of steroids. We investigated whether symptomatic improvement without change of spirometry could be due to a reduction in airway responsiveness. Twenty two patients with airflow obstruction which appeared to be irreversible on pulmonary function testing were recruited. Their ages ranged from 25 to 80 years. Resting FEV_1 (% predicted) ranged from 37 to 76. On first attendance patients answered a respiratory questionnaire and baseline FEV_1, FVC and PEF were recorded. Airway responsiveness to methacholine was measured and a provocation concentration producing a 20% fall in FEV_1 ($PC_{20}FEV_1$) derived. Patients then took eight placebo tablets per day for 14 days followed by eight prednisolone tablets (5 mg) for 14 days in a single blind manner. After each treatment period pulmonary function was measured, change in symptoms recorded by means of visual analogue scales and airway responsiveness assessed. Patients fell into three groups: 1—subjective and objective response (n = 7); 2—no subjective nor objective response (n = 4); and 3—a subjective but no objective response (n = 11). An objective response was defined as a >20%

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increase in FEV_1 or FVC. Pre and post steroid $PC_{20}FEV_1$ (mg/ml) for the three groups were as follows: objective responders 1·23–>2·35, p = 0·11, NS; for non-responders 3·1–>4·2; and for subjective only responders 1·6–>2·67, p = 0·02. Within the latter group there were four subjects with a >2 log unit change in responsiveness. These results suggest that in patients who feel better after a trial of steroids without objective improvement in spirometry the improvement in symptoms may be associated with a reduction of airway responsiveness. Thus a subgroup of steroid "non-responders" may benefit from steroid therapy although their basic pulmonary function does not improve.

Non-asthmatic chronic airflow obstruction: can inhaled corticosteroids slow down disease progression?

DC WEIR, AS ROBERTSON, RI GOVE, P SHERWOOD BURGE *East Birmingham Hospital* We have studied 121 patients who completed a therapeutic trial of oral and inhaled corticosteroids 12–44 (mean 26·3) months previously in order to document changes in lung function and relate them to intended treatment with inhaled beclomethasone dipropionate (BDP) 750 mg bd. All patients completing the trial were advised to take inhaled BDP irrespective of acute response, and the drug was not stopped in the clinic because of lack of response. Seven patients had died since the original trial and seven were not available for follow-up. Of the remaining 107 patients, 58 had shown an acute response to treatment during the original trial. The height adjusted decline in FEV_1 was calculated from the follow-up value and the level achieved during the BDP treatment phase of the original trial. The rate of decline in FEV_1 was similar between responders (R) and non-responders (NR) in the original trial (mean (SD), ml/m^3/y: R 18·5 (29·1), NR 16·1 (26·8)). Only 25% of patients had received treatment as intended for the entire follow-up period. A significant correlation was seen between decline in FEV_1 and the period of follow-up for which inhaled corticosteroids were taken (r = −0·22, p < 0·05). We therefore compared decline in 50 patients who had received BDP for >50% of the follow-up period (GpA) to that in all other patients (GpB). Decline in FEV_1 was significantly lower in GpA (mean (SD), ml/m^3/y: 10·6 (30·5), GpB 23·0 (23·9); p < 0·02). This was despite significantly more patients continuing to smoke cigarettes (GpA 20/50, GpB 8/57; p < 0·02). These results suggest that inhaled BDP 750 mg bd may have a retarding effect on disease progression in patients with non-asthmatic chronic airflow obstruction.

Exercise tolerance, breathlessness, and bronchodilator reversibility after oxitropium bromide in chronic obstructive lung disease

J HAY, P STONE, S OWEN, S CHURCH, J CARTER, C WALLIS, A LAWTON, A EYRE-BROOK, P CALVERLEY, A WOODCOCK *Fazakerley Hospital, Liverpool; Manchester Royal Infirmary, Manchester; Boehringer Ingelheim UK Ltd* Patients with chronic obstructive lung disease often report subjective improvement after apparently insignificant changes in spirometry. We have studied the effects of a new anticholinergic bronchodilator, oxitropium bromide, in 32 patients (15 male) with chronic obstructive lung disease (mean age 66 years range 40–78; mean FEV_1 0·69, range 0·28–1·40 litres) with range of bronchodilator response to inhaled salbutamol 200 μg (mean 32·4%, range 7–150%) and ipratropium bromide 80 μg (mean 24·3%, range 0–50%). Patients attended on four days. On the first two days bronchodilator responses and practice six minute walks (6MD) were performed with breathlessness scores (Borg scale) before and at the end of each walk. On days three and four, spirometry and corridor walks were repeated immediately before ("pre") and 45 minutes after ("post") either 200 μg oxitropium bromide or placebo in a randomised, double blind crossover study (table). Oxitropium bromide is an effective bronchodilator and produces useful improvement in both exercise tolerance and breathlessness. However, spirometric improvement did not predict improvement in walking distance (R = −0·171; p = 0·35) or breathlessness (R = −0·016; p = 0·91).

			Oxitropium (O)	*Placebo (P)*	*p(O v P)*
FEV_1	Pre		0·70	0·72	
	Post		0·88	0·73	<0·001
6MD	Pre		393	394	
	Post		420	397	<0·01
BORG	Pre	Rest	1·81	1·65	
		Exercise	4·30	4·28	
	Post	Rest	1·23	2·01	<0·001
		Exercise	3·21	4·09	<0·01

Should bronchodilators be combined in chronic airflow obstruction (CAO)?

S OWEN, P STONE, A WOODCOCK *Wythenshawe Hospital, Manchester* What are the benefits and costs of combining bronchodilators in CAO? We have studied 50 patients with CAO (mean FEV_1 1·09, range 0·44–2·71 l; mean age 58, range 38–75 y; 16 male). Patients were entered into a randomised double-blind crossover study comparing: (1) SA (salbutamol (Ventolin) 200 μg qds); (2) SA + IB (ipratropium bromide (Atrovent) 80 μg qds); (3) SA + TH (theophylline (Uniphyllin) 600 mg nocte; >60 kg 800 mg nocte); (4) SA + IB + TH. A double dummy technique was used and each treatment period was two weeks. Domiciliary PEF, symptoms and side effects were monitored with diary cards. Spirometry and theophylline levels were measured at each clinic visit. Results are given for the second week of each

		SA	*SA/IR*	*SA/TH*	*SA/IB/TH*
FEV_1	Post inhalers	1·25	1·30	1·23	1·35*
	Pre inhalers	227	231	243	248**
am	Post inhalers	263	277	278	294***
	Increment	36	46	35	46
PEF	Pre inhalers	248	258	254	268***
pm	Post inhalers	272	294	280	299****
	Increment	24	36	26	31

*SA/TH/IB > SA/IB = SA/TH = SA, p = 0·03;
**SA/TH/IB = SA/TH > SA/IB = SA, p < 0·001;
***SA/TH/IB > SA/TH = SA/IB > SA, p< 0·001;
****SA/TH/IB > SA/IB > SA/TH = SA, p< 0·001.

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treatment. Thirty four patients completed; all of 13 who dropped out because of side effects were on theophylline-containing regimens. Ipratropium regimens produced an excessively dry mouth but no other anticholinergic side effects. Combination therapy (SA/IB/TH) produced clinically useful additional bronchodilation compared to beta agonist alone, but this must be balanced against side effects in individual patients.

Anxiety, depression, walking speed and spirometry in chronic airways obstruction

PW JONES, CM BAVEYSTOCK, P LITTLEJOHNS *Departments of Medicine I and Clinical Epidemiology, St George's Hospital Medical School, London* Submaximal tests such as the six minute walking distance (6MWD) are frequently used in studies on patients with chronic airways obstruction (COAD). Morgan *et al* (*Br Med J* 1983;**286**:171) reported that walking distance was unrelated to psychological morbidity, while Guyatt *et al* (*Br J Dis Chest* 1987;**81**:45) showed low spirometric values to be weakly correlated with anxiety and depression. To examine these relationships more closely, we have studied 106 patients (68 male) with COAD, mean age 63 (SD 8) years. After 200 μg inhaled salbutamol, their FEV_1 was 52 (24)% predicted; FVC was 80 (20)%; 6MWD was 372 (103) m and arterial oxygen saturation (Sao_2) at the end of paced stepping was 92 (4)%. They completed the Hospital Anxiety and Depression Scale on a separate occasion. The correlations between 6MWD and post-bronchodilator FEV_1 and FVC were $r^2 = 0{\cdot}12$ and 0·23 respectively ($p < 0{\cdot}001$). Sao_2 did not correlate with 6MWD. Correlations between mood state scores and physiological measures are tabulated as r^2 values in the table. Correlations between mood scores and 6MWD were clearly higher than between mood and spirometry. Stepwise regression on the anxiety and depression scores showed that variance in 6MWD accounted for all the effects attributable to spirometry, but Sao_2 had a significant effect on anxiety ($p < 0{\cdot}006$) after removal of the variance due to 6MWD. Conversely, stepwise regressions on 6MWD revealed significant ($p < 0{\cdot}0003$) effects on anxiety and depression that were smaller than, but independent of, the effects of spirometry. In conclusion, mood state was the major determinant of the 6MWD. However, exercise tolerance (as measured) appears to be at the centre of a complex interaction involving both mood and lung function.

	FEV_1	*FVC*	*Sao_2*	*6MWD*
Anxiety	0·01 NS	0·05*	0·04 NS	0·18***
Depression	0·05*	0·11***	0·01 NS	0·20***

NS, $p > 0{\cdot}05$; *$p < 0{\cdot}05$; ***$p < 0{\cdot}001$.

Functional and morphological characteristics of peripheral neuropathy in chronic hypoxic lung disease

S CHURCH, EA MASSON, AJM BOULTON, A WOODCOCK *Manchester Royal Infirmary and Wythenshawe Hospital, Manchester* Peripheral neuropathy is associated with chronic hypoxia and the incidence and nature of this are controversial. We present data on 47 patients, mean age 64 years (range 31–75) with hypoxaemia (mean Pao_2 51, range 30–60 mm Hg) secondary to chronic lung disease. We have measured motor conduction velocities, sensory action potential amplitudes and objective sensory perception thresholds to assess small and large fibre function. Fifty four per cent of patients had peripheral neuropathy (>2 abnormal nerves and absent reflexes or impaired vibration perception), although only 13% reported symptoms. Motor nerve conduction velocities and sensory nerve amplitudes were reduced and vibration perception threshold increased by comparison with age matched controls ($p < 0{\cdot}01$). Six patients had sural nerve biopsies. These showed reduced myelinated fibre density, extensive demyelination and remyelination with axonal degeneration of small and large fibre populations with evidence of regeneration. Endoneural capillary endothelial cells showed proliferation and thickening. Peripheral neuropathy in hypoxic lung disease (1) is common, (2) affects all fibre types, (3) is usually asymptomatic and (4) has electrophysiological and morphometric characteristics in common with those of diabetic neuropathy. We hypothesise that diabetic neuropathy may be secondary to local tissue hypoxia.

Effects of acute ischaemia on peripheral nerve function

S CHURCH, EA MASSON, AJM BOULTON, A WOODCOCK *Manchester Royal Infirmary, Wythenshawe Hospital, Manchester* We have demonstrated that chronic hypoxia is associated with a peripheral neuropathy which is similar to diabetic neuropathy. Normal peripheral nerves show a rapid decline in function as they become ischaemic, whereas in diabetic neuropathy peripheral nerves show an abnormal resistance to ischaemia which can be measured by persistence of vibration perception during lower limb compression (resistance to ischaemic conduction block: RICB). We have studied age matched groups of (a) hypoxic patients with chronic lung disease (Pao_2 <60 mm Hg) (n = 24), (b) diabetic patients (n = 17), and (c) matched normal controls (n = 23). Patients with clinical evidence of peripheral vascular disease were excluded. Vibration perception threshold (VPT) was assessed at the great toe at five minute intervals during 30 minutes of ischaemia. The degree of RICB is expressed as the ratio of VPT at 30 minutes over VPT at baseline. There was no significant difference in the RICB between hypoxic (mean 1·64) and diabetic (mean 1·33) patients and both were significantly different from normal controls (mean 3·25; $p < 0{\cdot}01$). There was a significant inverse correlation between RICB and Pao_2 ($R = 0{\cdot}53$, $p < 0{\cdot}02$). We studied seven additional patients with acute exacerbations of chronic airways obstruction and profound hypoxia (Pao_2 range 38–51 mm Hg). There was extreme RICB on admission, which gradually improved with treatment over one week as Pao_2 improved. RICB is common to diabetic and hypoxic nerves. We speculate that chronic hypoxia produces a state of resistance to further hypoxic stimuli, possibly by induction of an alternative anaerobic energy pathway.

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Oxygen concentrators: which patients are being treated and are the DHSS guidelines being followed?

J MCCALLION, SJ PEARCE *Dryburn Hospital, Durham* For many years long-term oxygen therapy (LTOT) has been used for treating hypoxaemia due to chronic respiratory disease. Recently it has clearly been shown that oxygen administration for 15 hours daily prolongs life in those patients whose cor pulmonale is secondary to chronic bronchitis and emphysema (Medical Research Council. *Lancet* 1981;i: 681–5), and an oxygen concentrator is the most economical way of providing the oxygen (Evans TW *et al. Br Med J* 1983;**287**:459–61). In 1985 the DHSS issued clear guidelines on which patients should be treated in this way and how they should be assessed (Drug Tariff, DHSS 1985). The present study reports on the extent to which the guidelines are being followed in one regional health authority. The 16 district ethical committees in the region were individually approached and approved the study. The 345 patients who had been started on LTOT by oxygen concentrator during the first 20 months of their general availability were identified. One hundred and eleven had died, nearly half during the first three months of treatment. Six machines had been removed because of non-compliance with therapy. Of the remaining patients, 83% responded to a postal questionnaire. Case notes were obtained where possible, and the diagnosis and condition of the patients were reviewed. Most were elderly and very severely disabled. General practitioners appeared to have followed the DHSS guidelines in referring patients to chest physicians before LTOT, but most patients had not been assessed as fully as recommended. Patients' compliance appeared fairly good but 10% admitted to continued smoking. They appreciated LTOT but most probably started this too late to derive the intended benefit.

Prescription of oxygen concentrators for long term oxygen therapy in the Liverpool district: are the patients eligible?

MJ WALSHAW, R LIM, CC EVANS, CRK HIND *Department of Medicine, Royal Liverpool Hospital, University of Liverpool* When oxygen concentrators became available on form FP10 in December 1985, the DHSS issued clear guidelines for their prescription for long term oxygen therapy (LTOT). We have reassessed the eligibility of the 91 patients in this district who were prescribed a concentrator between December 1985 and August 1987. Of these, 20 patients had died and a further six concentrators were removed for underuse (<8 hours daily use). Sixty one of the remaining 65 patients consented to reassessment (spirometry, and arterial blood gas analysis on breathing air). Thirty four (56%) of the 61 concentrators had been prescribed on the advice of a respiratory physician ("resp" group), 10 (16%) on the advice of a non-respiratory physician ("non-resp" group), and 17 (28%) by the general practitioner alone ("GP alone" group). We found that only 33 (54%) had a Pao_2 below the DHSS required minimum (7·30 kPa). The resp group were significantly more hypoxic (mean Pao_2 6·86, range 4·60–9·40 kPa) than either the non-resp group (mean 8·19, range 5·10–11·30 kPa) ($p < 0·025$), or the GP alone group (mean 8·08, range 5·30–9·80 kPa) ($p < 0·005$). Fifty eight patients (95%) had spirometry which fulfilled the DHSS minimum requirements (FEV_1 <1·5 litres, FVC <2·0 litres). Overall, only 32 of the 61 patients reassessed (51%) fulfilled all the minimum DHSS criteria, comprising 24 of 34 (71%) in the resp group, four of 10 (40%) in the non-resp group, and four of 17 (24%) in the GP alone group. These results suggest that there is room for improvement in the initial assessment of patients for LTOT.

Prescription of oxygen concentrators for long term oxygen therapy in the Liverpool district: are the patients complying with their therapy?

MJ WALSHAW, R LIM, CC EVANS, CRK HIND *Department of Medicine, Royal Liverpool Hospital, University of Liverpool* Clinical studies have suggested that to obtain maximum benefit from long term oxygen therapy (LTOT) requires a minimum of 15 hours' daily use and that the patient stops smoking. We have assessed patient cooperation with treatment in 61 of the 65 patients in this district still undergoing LTOT who had had a concentrator prescribed between December 1985 and August 1987. We found that only 28 patients (48%) ran their concentrators for the recommended minimum of 15 hours per day, comprising 21 of the 34 (62%) undergoing LTOT on the advice of a respiratory physician ("resp" group), one of 10 (10%) on the advice of a non-respiratory physician ("non-resp" group), and six of 17 (35%) prescribed by the GP alone ("GP alone" group). However, there was no difference between the number of hours of oxygen prescribed (mean 13·3 hours, range 8–24) and the actual concentrator running time as assessed by meter reading (mean 14·7, range 2–24), suggesting that underuse was due not to poor compliance but to poor instruction by the prescribing doctor. Unfortunately, patients did significantly overestimate their oxygen usage (patients' estimate 16·2 hours, range 8–24) ($p < 0·001$), making clinical assessment of their compliance difficult. As regards smoking habits, 12 of the 54 who had smoked continued to do so after being prescribed an oxygen concentrator. Overall, only 23 of the 61 patients (38%) cooperated fully with their treatment by not smoking and by using oxygen for at least 15 hours each day, comprising 19 of 23 (56%) in the resp group, one of 10 (10%) in the non-resp group, and three of 17 (18%) in the GP alone group. These results suggest a need for better education of both doctor and patient in oxygen concentrator use.

A two year review of oxygen concentrators

JP DILWORTH, RJ WHITE, AR TANSER, CMB HIGGS, PA JONES *Department of Medicine, Frenchay Hospital, Bristol, and Royal United Hospital, Bath* Oxygen concentrators have been available on prescription in the UK since December 1985. We have reviewed, retrospectively, all prescriptions for concentrators in two health districts (pop 623 000) up to the end of 1987. We have particularly assessed whether the DHSS guidelines are being met. Eighty four prescriptions were issued, 58 male and 26 female. There were two children, who are excluded from the analysis; mean age for adults 72

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(range 42–86). Thirty five patients died, with a mean time from prescription of 5·8 months (range three days to 24 months); 11 patients died within one month of prescription. There were 49 chest consultant recommendations, four general physician, and 29 GP. Among the chest consultant recommendations, 41 patients (85%) satisfied the DHSS guidelines in the following categories, chronic obstructive airways disease with hypoxaemia, hypercapnia, oedema (23), chronic obstructive airways disease with hypoxaemia alone (7), pulmonary fibrosis with hypoxaemia (7), replacement of cylinders for >8 hours/day (5). Of those that did not fulfil the criteria two were not investigated and six were not assessed in the stable state. Of the four general physician referrals, three fell short of the criteria. Of the GP recommendations, no information was obtainable on two while the reason for prescription in the others was given as treatment of hypoxaemia in eight, replacement of oxygen cylinders in 10, and other reasons in nine. Five were removed because of insufficient use. In conclusion DHSS guidelines for hypoxaemia were met in 46% and in a further 18% the prescription was for replacement of cylinders. Thirty six per cent received a concentrator without strictly fulfilling either criterion. We believe that this result underlines the importance of referral to a chest physician of patients being considered for oxygen concentrators.

Is the packed cell volume a useful guide to therapy in patients undergoing long term oxygen therapy?

MJ WALSHAW, R LIM, CC EVANS, CRK HIND *Department of Medicine, Royal Liverpool Hospital, University of Liverpool*

Patients undergoing long-term oxygen therapy (LTOT) for hypoxaemic chronic obstructive lung disease show significant falls in their packed cell volumes (PCV) (NOTT group, *Ann Intern Med* 1980;**93**:391–8). This finding suggests that the PCV may provide a useful simple clinical monitor of therapy in such patients. To study this possibility further, the PCV was measured in 60 of the 65 patients still undergoing LTOT in the Liverpool district, having been prescribed an oxygen concentrator between December 1985 and August 1987. We found that the PCV was not significantly higher in those patients who still smoked, and did not correlate with actual concentrator running time as assessed by meter reading. However, the PCV was significantly greater in those patients whose hypoxaemia (Pa_{O_2} <7·30 kPa) was not corrected (>8·00 kPa) when given supplementary oxygen (19 patients whose hypoxaemia did not correct: mean PCV 48·5%, range 41·0–67·8%; 14 patients whose hypoxaemia did correct: mean PCV 44·0%, range 36·7–53·8%; $p < 0·05$). These results suggest that the finding of a high PCV should alert the clinician to the possibility that LTOT is not optimal, but that the PCV is not a useful guide to patient compliance in terms of oxygen consumption.

Does long term oxygen therapy (LTOT) improve pulmonary gas exchange?

SV BAUDOUIN, T·TAHTAMOUNI, JA SMITH, J BAXTER, JC WATERHOUSE, P HOWARD *Department of Medicine, Royal Hallamshire Hospital, Sheffield*

The natural history of chronic bronchitis and emphysema with hypoxaemia is characterised by a gradual deterioration of arterial blood gases and airway function. LTOT has improved survival in such patients but its effect on gas exchange is unknown. Seventy four patients were receiving LTOT in Sheffield in early 1987. Sixty four of these were visited at home and reassessed with either arterial blood gas or O_2 saturation analyses measured both on O_2 and air. Their indications for LTOT were compared with DHSS guidelines in 52 patients where sufficient information was available. Only 35 (67%) patients fulfilled the criteria (Pa_{O_2} <7·3 kPa, FEV_1 <1·5 l while stable). Some of the remainder were started on LTOT following a hospital admission because of the difficulty of sending severely hypoxaemic patients home. There was significant improvement in Pa_{O_2} on air following therapy (pre LTOT 6·7 (SD 2·0) kPa, post LTOT 7·6 (1·4) kPa; median length of treatment 16 months). There was no significant change in Pa_{CO_2} where this was measured on air (pre LTOT 6·8 (1·0) kPa; post LTOT 6·9 (1·2) kPa; n = 19) suggesting that the change in Pa_{O_2} was not a result of changing alveolar ventilation. Only 21 (33%) patients had a Pa_{O_2} on air of less than 7·3 kPa at reassessment. Many patients had stopped smoking as judged by CoHb levels (2·6 (1·9)%) and this might explain the improvement in gas exchange. Many patients on LTOT apparently improve and should be reassessed at six months to determine the need for longer term therapy.

Controlled trial of natamycin in treatment of allergic bronchopulmonary aspergillosis

DC CURRIE, C HARVEY, JL LONGBOTTOM, JH DARBYSHIRE, AJ NUNN, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, and Department of Allergy and Clinical Immunology, and MRC Cardiothoracic Epidemiology Group, Cardiothoracic Institute, Brompton Hospital, London*

Allergic bronchopulmonary aspergillosis (ABPA) often requires oral corticosteroids to control the host response to *Aspergillus fumigatus*. Natamycin, an antifungal agent might reduce the fungal load and therefore the requirement for corticosteroids. In a double blind study, 25 patients with ABPA on maintenance oral corticosteroids were randomly allocated to receive 5 mg natamycin (N) or placebo (P) bd for one year. The aim was to reduce corticosteroid dosage, using a standard schedule to the minimum required to control symptoms. Dose alterations were considered every five weeks during the study and high dose corticosteroids were prescribed when clinically indicated. Five patients (3N, 2P) were withdrawn, all in the first four months (two (1N, 1P) died, two (1N, 1P) suspected drug reactions and 1N for non-compliance). In the 20 patients (10N, 10P) who completed the study the pretreatment characteristics in the two groups were similar, medians and ranges for the whole group being age 53 (29–74) years, duration of disease 19 (1–35) years, number of chest exacerbations in the previous year 3 (0–12) and maintenance prednisolone dose on entry 7·5 (2–15) mg. Evidence of recent disease activity seen in 17 (9N, 8P). At the end of the study prednisolone dose had been reduced by a median of 2·5 mg in each group. Transient shadowing on the chest radiograph, blood eosinophilia and/or increases in specific and total IgE or specific IgG were observed in similar numbers of patients in each group (6N, 7P) during the study

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year. Also the groups were similar with respect to numbers of exacerbations (both medians 5/year), days unwell, courses of antibiotic and courses of high dose prednisolone. Natamycin conferred no benefit to these ABPA patients despite recent disease activity.

Immune response of patients with bronchiectasis to outer membrane antigens of non-typable *Haemophilus influenzae*

I MACIVER, SL HILL, T O'REILLY, D BURNETT, RA STOCKLEY, MRW BROWN *Department of Pharmaceutical Sciences, Aston University, and Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* Patients with bronchiectasis are chronically colonised with bacteria suggesting a failure of clearance by the immune system. The patients often have raised plasma immunoglobulins although it has been suggested that specific IgG to bacterial antigens may be deficient (*Clin Exp Immunol* 1986;**65**:427). Since *Haemophilus influenzae* (HI) is a common colonising organism in these patients we have used an ELISA to measure the specific antibody titres in serum and sputum to HI outer membrane proteins (OMP). HI was isolated from 11 patients with bronchiectasis. All were non typable strains and were of varied OMP profile as determined by SDS-PAGE. Serum from one of the patients confirmed cross reactivity with OMPs for all strains of HI on immunoblot. In eight patients who continually expectorated purulent secretions the mean serum titres to OMP were: IgG 163 700 (SEM 37 000); IgA 2100 (293); IgM 6375 (1079). Specific sputum IgG was measured in six of them and was lower than serum in every case (mean 1000 (434); $p < 0.03$) whereas specific sputum IgA was higher than serum (mean 4333 (938); $p < 0.03$). Three patients who usually expectorated mucoid secretions had serum titres below the lowest observed values for the purulent patients (mean IgG 15 300 (2900); IgA 300 (100); IgM 2000 (500)). The results suggest that these patients have high specific OMP antibodies to *Haemophilus influenzae*, particularly when the sputum is purulent. Sputum titres of specific IgA were higher than serum titres, indicating significant involvement of the local immune response.

Penetration of bronchial mucosa by erythromycin

D HONEYBOURNE, JM ANDREWS, JP ASHBY, A HUGGINS, I ISLIM, R WISE *Departments of Thoracic Medicine, and Medical Microbiology, Dudley Road Hospital, Birmingham* There is evidence that the ability of antibiotics to penetrate into bronchial mucosal tissue varies considerably between different antibiotic groups (Honeybourne *et al. Thorax* 1988;**43**:221). We have investigated the penetration of the macrolide erythromycin by using a technique of obtaining samples of mucosa at bronchoscopy. Ten subjects (mean aged 61, range 17–74 years; six female) who were undergoing bronchoscopy for diagnostic purposes were given 500 mg qds of oral erythromycin for four days prior to bronchoscopy. Venous blood was taken at the same time as mucosal biopsies. The biopsy specimens were treated by ultrasonification in a chilled phosphate buffer and then a microbiological plate diffusion technique was used to assay the erythromycin levels in serum and tissue with *Sarcia lutea* as the indicator organism. Controls and standard solutions were also assayed at the same time. The mean time of collection of samples after the last dose of erythromycin was 4 h 28 min (SD 1 h 16 min). The mean serum level of erythromycin was 3·9 (SD 2·8) mg/l and the mean tissue level 6·7 (SD 4·4) mg/kg. The percentage penetration into bronchial tissue was calculated for each subject as (bronchial tissue level ÷ serum level) × 100, and was found to be 183% (SD 70%). These results suggest that there is mucosal concentration of the macrolide erythromycin in the lungs.

The immunopathology of experimental bronchiectasis in rats reflects human disease

JRL SILVA, D GUERREIRO, B NOBLE, LW POULTER, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, and Department of Immunology, Royal Free Hospital School of Medicine, London* An experimental model of bronchiectasis (BX) has been developed in the Wistar rat by partial ligation of the apical lobe bronchus and injection of *Pseudomonas aeruginosa* (Ps). The immunohistological study analysed the composition and distribution of mononuclear cell (MNC) infiltrates arising in the lungs of two surgically treated groups of rats: one ($N = 13$) with partial ligation of the apical lobe and injection of Ps (Lig Ps), the other ($N = 11$) injection of Ps without ligation (Non-lig Ps). Five normal, age-matched rats were used as controls. All animals were killed 2–3 months after surgery. Frozen sections of the lung tissue were stained with a panel of monoclonal antibodies against determinants present in lymphocytes and macrophages. None of the apical lobes of Non-lig Ps rats exhibited bronchiectatic changes and MNC were not significantly different in number from those in the normal controls. In contrast, all 13 rats Lig Ps developed histologically definable BX. Intense MNC infiltration was also seen in all areas of the lung, sometimes in follicular aggregates. T lymphocytes, mainly of suppressor/cytotoxic phenotype, predominated and replaced the usual B cell areas in bronchus associated lymphoid tissue. Macrophages and dendritic cells, many of them acid phosphatase positive, were seen in the lymphocyte infiltrates. The majority of T cells and macrophages were Ia positive in the most severe cases. These results suggest that a cell-mediated immune response parallels the emergence of bronchiectatic changes in this experimental model and mirrors phenomena described in human BX (Silva J *et al. Thorax* 1987;**42**:709). This animal model of human bronchiectasis will therefore allow detailed analysis of the pathogenesis of Bx.

Interaction between *Haemophilus influenzae* and human polymorphonuclear leucocytes (PMNL) studied by measurement of luminol enhanced chemiluminescence (CL)

GDW CROOK, R WILSON, JS KROLL, H TODD, ER MOXON, PJ COLE *Host Defence Unit, Cardiothoracic Institute, Brompton Hospital, London, and Infectious Diseases Unit, John Radcliffe Hospital, Oxford* *Haemophilus influenzae* (Hi) commonly infects man. We have used CL elicited from PMNL perturbed by variously opsonised Hi to study its

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opsonin requirements (*Immunology* 1980;**41**:903). Bacterial cultures were centrifuged (8000 *g*), resuspended in PBS (1×10^9 organisms ml) and opsonised with either 10% pooled normal human serum (PNHS), hypogammaglobulinaemic serum (HGS), or heat treated PNHS (50°C for 20 min or 56°C for 30 min). Opsonisation of all Hi strains by PNHS stimulated more CL than opsonised Hi. Opsonisation with HGS reduced CL by about half and this was reduced further by prior heating of HGS to 56°C for 30 min. Heating PNHS to 50°C for 20 min, inactivating the alternative pathway of complement, did not affect CL, but heating it to 56°C for 30 mins reduced CL by 35–50%. CL from PMNL was also used to assess opsonisation of genetically modified Hi strains with different surface properties. In an isogenic series uniquely varying in capsule alone, acquisition of capsule (a, b, c, e or f but not d) stimulated less CL but there was no difference in CL evoked by these five capsular types. Closely genetically related capsulated and uncapsulated strains with different lipopolysaccharide (LPS) composition (*Microb Pathog* 1986;1:465) differed in their stimulation of CL. During broth culture of Hi capsule is released into the broth. Addition of similar concs of type b capsule (Praxis Biologics, Rochester) to the Hi suspension prior to opsonisation with PNHS did not stimulate less CL unless in high concentration (100 μg/ml). Similarly, Hi did not differ in ability to stimulate CL after repeated washings to remove loosely attached capsular material. We conclude that serum opsonisation of Hi is mediated by immunoglobulins and a heat labile factor(s), that possession of a capsule reduces stimulation of CL, but that all types of capsule except d are equally opsonised. Change in LPS can alter the ability of *Haemophilus influenzae* to stimulate CL independently of the possession of a capsule.

Immunoglobulin and subclass levels in patients with bronchiectasis

D VEALE, AG BIRD, PA CORRIS, GJ GIBSON *Department of Respiratory Medicine, Freeman Hospital, and Regional Department of Immunology, Newcastle General Hospital, Newcastle upon Tyne* Deficiency of immunoglobulin subclasses IgG_2 and IgG_4, in the presence of normal total IgG levels is said to be well correlated with chronic respiratory infection and bronchiectasis (*N Engl J Med* 1981;**304**:1476). The patients studied were, however, from selected populations with various diseases and they also had deficiency of IgA. We have measured serum immunoglobulin levels, including IgG subclasses, together with secretory IgA in saliva in 45 patients with bronchiectasis. The subjects represented an otherwise unselected population of patients with bronchiectasis attending respiratory clinics. Two had deficiency of all immunoglobulin classes and evidence of common, variable immunodeficiency (*Am J Med* 1976; **61**:221). One patient had an isolated reduction of IgG_2. No other deficiency of IgA or IgG subclasses was found. As expected, elevation of one or more immunoglobulin class or subclasses was found in 35 patients, the commonest being IgG_3 (17 patients) and IgA (25 patients). We conclude that deficiency of individual IgG subclasses is rare in patients with bronchiectasis who have no evidence of susceptibility to non-respiratory infections. Screening for subclass deficiency in such patients has a low yield, unless levels of total immunoglobulin are inappropriately low for chronic infection.

The bacterial flora of bronchiectatic secretions

P DRAGICEVIC, SL HILL, D BURNETT, RA STOCKLEY *Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* Previous studies have shown that routine bacteriological assessment of sputum is a poor predictor of the subsequent response to antibiotic therapy in bronchiectasis (*Thorax* 1984;**39**:414). For this reason we have performed more detailed bacteriological investigation of sputum, including anaerobic culture, from eight patients. Twenty six organisms were isolated from the eight samples. Of these, six were obligate anaerobes and in total seven were β lactamase (βL) producing organisms. The minimum inhibitory concentration (MIC) of all organisms isolated was determined for both amoxil and Augmentin (2:1 amoxil: clavulanic acid). There was no difference in MIC of the 19 βL negative organisms to amoxil or Augmentin (median 0·5 range 0·06–32 μg/ml). However, the MIC of the seven βL positive organisms was higher for amoxil (median 126, range 64–512) than Augmentin (2·0, 0·5–4·0; $p < 0·01$). In view of this observation the patients were treated with Augmentin (500 mg Amoxil/250 mg Clavulanic acid, thrice daily) for two weeks. At the end of therapy six patients had shown a change in sputum from purulent to mucoid. Bacteriology of the sputum showed no change in the overall number of organisms isolated (26), the proportion of anaerobics (23%) or the number of βL producing organisms (7), despite sputum amoxil levels exceeding the MIC of most of the organisms (mean = 0·88 (SD 0·31) μg). No consistent loss of any organisms were seen to account for the clinical response. The results suggest that detailed bacteriology is no better than routine bacteriology at predicting the response to β lactam antibiotics.

Beta lactamase and efficacy of cefaclor in bronchiectasis

SL HILL, P DRAGICEVIC, D BURNETT, RA STOCKLEY *Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham* Cefaclor is a β lactam antibiotic that is particularly active against *Haemophilus influenzae* and relatively resistant to β lactamase (βL) producing strains. Most sputum samples from patients with bronchiectasis contain β lactamase. In view of this cefaclor should be effective in the treatment of patients with bronchiectasis, especially when they are allergic to penicillins. An initial study in six patients treated with cefaclor 500 mg tds for 14 days reduced sputum elastase (measured by an elastin fluorescein assay) from a mean value of 13 (SEM 4·9) to 8·3 (4·8) μg/ml ($p < 0·05$) together with inflammation as indicated by a fall in the mean sputum to serum albumin ratios from 4·55 (SEM 1·9) to $3·04\ (1) \times 10^2$ ($p < 0·025$). However, the secretions remained purulent suggesting either insufficient penetration or some local inactivation by βL. We have therefore treated a further but similar group of eight patients with 1 g cefaclor tds. βL activity (measured using a nitrocefin assay) was

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present in all secretions prior to therapy ranging, from 25 to 77 (median 35·2) mU/ml. Five of the patients responded to therapy, their sputum becoming mucoid. In these subjects the mean sputum elastase fell from 3·7 (SEM 1·4) to 2 (1·4) μg/ml ($p < 0·05$) and the sputum to serum albumin ratios from 2·95 (SEM 0·6) to 1·1 (0·13) × 10^2 ($p < 0·05$), indicating a reduction in lung inflammation. βL activity fell in the eight patients to median 12, range 5–52·4 mU/ml ($p < 0·05$). In conclusion, cefaclor can be effective in treating patients with bronchiectasis, particularly when βL is present. However, the study demonstrates that dosage is critical in achieving this effect.

Beta lactamase activity and bronchiectasis: evidence for indirect pathogenicity

P DRAGICEVIC, SL HILL, D BURNETT, D MERRIKIN, RA STOCKLEY *Lung Immunobiochemical Research Laboratory, General Hospital, Birmingham, and Beechams UK* Antibiotics in conventional dosage are often ineffective at clearing sensitive pathogens from bronchiectatic patients and higher doses are often required (*Thorax* 1986;**41**:559–65), suggesting inactivation by β lactamases. We have measured β lactamase activity (βL) in sputum and saliva collected before and during sputum expectoration (seven patients), using the chromogenic substrate nitrocefin. Low levels of βL were present in saliva before and during sputum collection (median 6·2, range 2·2–50·4 mU/ml, and 9·2, range 5·2–27·2 mU/ml). However, sputum βL (median 23·2, range 15·6–65·2) was significantly higher than the two saliva values ($p < 0·025$). Beta lactamase activity in sputum from 28 stable patients with bronchiectasis was present in 5/7 mucoid (median 18·2, range 0–32·4), 8/10 mucopurulent (median 16·4; range 0–52), and 10/11 purulent samples (median 46·8, range 0–78), βL was higher in purulent compared than in mucoid or mucopurulent samples ($p < 0·01$). A further eight samples (seven βL positive) were studied to identify organisms present. *H influenzae* was identified in six, (two βL positive). However, several other βL positive organisms were isolated: *Staph aureus** (3), *Proteus spp** (1), *E coli** (1), *Bacteroides spp* (3)*. Fractionation of the sputum showed several peaks of βL activity (sizes 28 000–300 000 Da), which usually eluted in the same fractions as those from the positive organisms. The source is often bacteria considered to be non-pathogenic.

Immunoassay for the measurement of amoxycillin in lung secretions

SL HILL, RA STOCKLEY, P DRAGICEVIC, D LEE, D YOUNGS, D BURNETT *Clinical Teaching Block, General Hospital, Birmingham, and Beechams UK* Failure of β lactam antibiotics in the treatment of purulent bronchiectasis may be due to inadequate penetration or inactivation by β lactamases (βL). We have developed an immunoassay to measure total amoxycillin in lung secretions and compared the results with bioassay to assess local inactivation. βL activity of the lung secretions was measured using a nitrocefin assay. An antibody was raised in rabbits to an amoxycillin BSA conjugate and used in a competitive binding ELISA (sensitivity 5 ng/ml, precision (CV) = 9%). Accuracy was verified by adding known quantities of amoxycillin to both serum and sputum. Concentrations were similar in both whole sonicated sputum and sol phase obtained by ultracentrifugation following single 3 g (4·6 μg/ml sonicated, 4·7 μg/ml sol phase) and 250 mg (0·23 μg/ml both preparations oral dosing. Eight patients with bronchiectasis received 500 mg tds amoxycillin. On the second day of therapy mean concentrations of amoxycillin in sputum four hours after the morning dose were 0·88 (SD 0·31) μg/ml by ELISA and 0·40 (SD 0·13) μg/ml by bioassay, suggesting local inactivation by βL. This was supported by a significant inverse correlation between βL levels (median 17·5, range 0–70·2 mU/ml) and the underestimation by the bioassay ($r = -0·693$, $p < 0·05$). A pharmocokinetic study (day 3) revealed peak levels in secretions by 2–4 hours post dosing: mean 1·36 (0·75) μg/ml. By day 14 lung inflammation was reduced (decreased serum derived albumin in sputum) and this was reflected in lower concentrations of total (mean 0·48 (0·25) μg/ml) and active (mean 0·21 (0·18) μg/ml) amoxycillin penetrating the secretions from the blood.

Inhibition of non-opsonised *Streptococcus pneumoniae* by human alveolar macrophages

JR CATTERALL, CG WATHEN, DC FLENLEY, F MCCAFFERTY *Rayne Laboratory, Department of Respiratory Medicine, City Hospital, Edinburgh* Although there is evidence that alveolar macrophages (AM) play an important part in the host's defence against pulmonary infection, the interactions of *Streptococcus pneumoniae* and AM are poorly understood, and the mechanisms by which AM kill bacteria are unclear. We have studied the inhibition of non-opsonised encapsulated and unencapsulated *S pneumoniae* type I by human AM in vitro. The AM were obtained by bronchoalveolar lavage from patients who did not have clinical evidence of pulmonary infection and the unencapsulated variant of *S pneumoniae* was obtained by repeated subculture of the encapsulated strain. AM from eight of 10 patients inhibited multiplication of unencapsulated *S pneumoniae* (mean increase in number of viable bacteria over 90 min: without AM 13 fold; with AM 10 fold; $p < 0·05$) and AM from four of five patients inhibited multiplication of encapsulated *S pneumoniae* (without AM 4·1 fold; with AM 2·4 fold; NS). AM from all of six patients produced more H_2O_2 when incubated with unencapsulated *S pneumoniae* (mean 22 nmol/h/10^6 AM) than when incubated with encapsulated *S pneumoniae* (mean 10 nmol/h/10^6 AM; $p < 0·05$), but there was no significant difference between AM inhibition of unencapsulated pneumonococci (mean 19% inhibition, $n = 10$) and AM inhibition of encapsulated pneumococci (mean 36%, $n = 5$). Scavengers of reactive oxygen species (catalase and superoxide dismutase, SOD) had no effect on the inhibition of pneumococci by AM (mean inhibition by AM alone 41%; by AM incubated with catalase plus SOD 48%; NS, $n = 6$). Thus human AM are able to inhibit the multiplication of non-opsonised *S pneumoniae* to a modest extent. The mechanism of inhibition remains unclear but these results suggest that both oxidative and non-oxidative antimicrobial mechanisms play a part.

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Pseudomonas aeruginosa proteases stimulate mucus secretion in vivo

M SOMERVILLE, PS RICHARDSON, R WILSON, PJ COLE *Department of Physiology, St George's Hospital Medical School, and Host Defence Unit, Department of Thoracic Medicine, Cardiothoracic Institute, London* *Pseudomonas aeruginosa* proteases have been implicated in stimulating mucus secretion from tracheal explants in vitro (Adler *et al. Am J Pathol* 1986;**125**:501; Klinger *et al. J Clin Invest* 1984;**74**:1669). We have tested purified *P aeruginosa* alkaline protease and elastase for an effect on mucus secretion from the cat trachea in vivo, using ^{3}H glucose and ^{35}Sulphate to label secretory glycoconjugates biosynthetically. Alkaline protease stimulated the output of radiolabelled glycoconjugates in a dose-dependent manner between the concentrations of 50 and 150 μm/ml ($\Delta^{3}H$ 57 (SEM 17)%, $\Delta^{35}S$ 9 (7)% (n = 4) at 50 μg/ml; $\Delta^{3}H$ 287 (864)%; $\Delta^{35}S$ 92 (167)% (n = 2) at 150 μg/ml). *P aeruginosa* elastase also stimulated the output of radiolabelled glycoconjugates, but this effect was dose-dependent over the concentration range 1–10 μg/ml ($\Delta^{3}H$ 9 (164)%, $\Delta^{35}S$ 114 (7)% (n = 2) at 1 μg/ml; $\Delta^{3}H$ 208 (32)%; $\Delta^{35}S$ 130 (13)% (n = 4) at 10 μg/ml). From these data we provisionally conclude that both *P aeruginosa* alkaline protease and elastase stimulate mucus secretion in vivo, but to differing extents.

Cultured human bronchial epithelial cells: characterisation and use in the study of compounds affecting intercellular junctional complexes

JL DEVALIA, RJ SAPSFORD, C WELLS, RJ DAVIES *St Bartholomew's Hospital, London* Recently Farley and co workers (1986) have demonstrated that *Haemophilus influenzae*, a common respiratory tract pathogen, is capable of selectively attaching to and damaging non-ciliated nasopharyngeal epithelial cells in vitro. In view of our own findings that *H influenzae* and several other respiratory tract bacterial pathogens produce large amounts of histamine (H) in vitro, we set out to elucidate whether H could cause epithelial damage. Epithelial cells were cultured in vitro and the identity of these cells was studied by several techniques. Established cultures were treated with H, in doses ranging from 0·5 to 20 μmol/l for 15 minutes, and then processed for electron microscopic observation of the intercellular junctional complexes. This was compared with the treatment with house dust mite extract (HDM), in doses ranging from 0·002% to 0·2% (w/v). Identity of these cultures was confirmed by phase contrast and electron microscopy and also by indirect immunoperoxidase (IP) techniques with the use of monoclonal antibodies directed towards specific markers. IP confirmed the presence of cytokeratin and ciliated columnar epithelial cells. Although treatment with neither H nor HDM was found to cause any significant disruption of the desmosomes at any dose studied, the results suggest that the intermediate junctions may be separated.

Polymorphonuclear leucocyte kinetics in chronic obstructive pulmonary disease (COPD)

C SELBY, SM LANNAN, EM DROST, PK WRAITH, W MACNEE *Department of Respiratory Medicine, Rayne Laboratory, City Hospital, Edinburgh* Using a gamma camera-computer system we have measured the kinetics of indium-111 labelled neutrophils (PMN) and technetium-99m labelled erythrocytes (RBC) as they pass through the pulmonary vascular bed. We have previously shown that in healthy subjects during cigarette smoking there is a delay in the washout of PMNs from the lungs, which may be important in the pathogenesis of emphysema (MacNee *et al. Thorax* 1987;**42**:751). To determine how the presence of COPD affects PMN kinetics in the lungs, we compared PMN kinetics in five healthy non-smoking males with those in 10 patients (8M, 2F) who were recovering from an acute exacerbation of COPD (FEV_1 0·8 (SEM 0·3) l, FEV_1/FVC 36 (10)%, Pao_2 8·1 (1·9) kPa, $Paco_2$ 6·0 (1·0) kPa). Six of these patients were restudied at least six weeks later when clinically stable, but at a time when ventilatory capacity and blood gas values were similar. PMN retention on the first passage throught the lungs was greater in patients (10·1 (4·6)%) than in normal subjects (6·5 (2·0)%; $p = 0.05$), despite similar RBC transit times (5·2 (2·0) s *v* 4·7 (1·0) s; $p > 0.05$). In contrast to normal subjects, there was no correlation between RBC transit time and 10 minute retention in the patients with COPD. However, despite similar transit times, 10 minute retention was greater in patients with COPD. PMN first pass retention was similar in patients studied when recoverings from an exacerbation of COPD and those studied when stable (10·2 (4·3)%, 10·0 (3·3)%, $p > 0.05$); Neither was there a significant difference between the parameters of the PMN washout curves in the different groups. Thus the presence of COPD produces a greater retention of radiolabelled PMNs in the lungs. However, PMN kinetics measured during the recovery phase of an acute exacerbation of COPD were similar to the kinetics at a time of clinical stability. The reasons for this require further study.

Bradykinin induced bronchoconstriction: inhibition by terfenadine

R POLOSA, ST HOLGATE *Department of Immunopharmacology, Southampton General Hospital, Southampton* Bradykinin is a chemical mediator released during inflammatory (Marceau F. *Gen Pharmacol* 1983;**14**:209) as well as allergic reactions (Proud D. *J Clin Invest* 1983;**72**:1678), which may contribute to bronchoconstriction in asthma. It has been suggested that bradykinin induced bronchoconstriction may be due in part to histamine release from mast cells and to a cholinergic reflex activated by stimulating C fibre nerve endings. The aim of this study was to elucidate the contribution of histamine release to bradykinin induced bronchoconstriction. Bradykinin was administered as a nebulised solution and diluted in 10% ethanol in normal saline in order to produce a concentration range of 0·03–8 mg/ml. Airway response was measured as FEV_1. We

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compared pretreatment with terfenadine (180 mg) and matched placebo on bronchoconstriction induced either by histamine or bradykinin in a double blind, randomised study of 10 atropic asthmatic subjects. Each test was performed at the same time of day on five different visits. Bradykinin-induced bronchoconstriction was maximal 3–5 minutes after inhalation and lasted for 30–60 minutes. Seven out of 10 subjects reported cough and retrosternal discomfort, which was greatest during the first inhalation. Inhibition study showed that terfenadine taken three hours before reduced the sensitivity of the subjects to bradykinin (PC_{20} increasing from 0·26 to 0·45 mg/ml), but this change was not significant. On the other hand terfenadine reduced significantly ($p < 0·01$) the sensitivity to histamine (PC_{20} increasing from 0·86 to 25·33 mg/ml). In asthmatic subjects inhaled bradykinin is a potent bronchoconstrictor agent acting in part through cholinergic reflex. Its action as a proinflammatory agent through release of other mediators and neuropeptides requires further study.

Role of histamine and prostaglandins in the bronchial response to inhaled hypertonic saline

C WILMOT, JP FINNERTY, ST HOLGATE *Immunopharmacology Group, Southampton General Hospital, UK* Hypertonic saline (HS) bronchial challenge causes bronchoconstriction in many asthmatics, and may act via the same pathway as exercise-induced bronchoconstriction. We investigated the effect of the preadministration of placebo, terfenadine (T) 180 mg, a potent histamine H_1 receptor antagonist; flurbiprofen (F) 100 mg, a potent cyclooxygenase inhibitor; and T and F in combination on the dose-response to HS challenge in eight asthmatic patients in a double-blind randomised study. HS was administered as a 3·6% solution from a deVilbiss 65 ultrasonic nebuliser and the dose administered was measured as the volume of air in litres inhaled from the nebuliser. The test was continued until either a 25% fall in FEV_1 had occurred or 310 litres had been inhaled. PC_{25} of HS was calculated from linear interpolation of the plot of volume inhaled expressed logarithmically against %fall in FEV_1. The arithmetic mean PC_{25} following placebo was 45·1 litres and following F it was 104·8 litres. The geometric mean ratio of PC_{25} F:PC_{25} placebo was 2·30. After T a 25% fall in FEV_1 was not achieved in five of the eight subjects after the inhalation of 310 litres and so an overall PC_{25} T:PC_{25} placebo ratio could not be obtained. The results were similar after T and F had been administered in combination. Both T and F protected against HS challenge ($p < 0·01$), and T offered greater protection than F ($p < 0·01$). We conclude that HS bronchoconstriction is secondary to the release of histamine and to a lesser extent prostaglandin generation, implicating mast cell activation as a possible mechanism.

Effect of terfenadine on the bronchoconstrictor response to hypertonic saline and exercise in asthmatic subjects

SP O'HICKEY, N BELCHER, PJ REES, TH LEE *Guy's Hospital, London* Ten asthmatic subjects underwent hypertonic saline challenge after premedication with placebo or terfenadine (120 mg/ 12 and two hours before bronchial challenge. Eight subjects subsequently underwent exercise challenge after premedication in a similar fashion. Hypertrophic saline was administered in a dose dependent manner and response was determined by changes in the dose of hypertonic saline inducing a 20% fall in FEV_1 (the $PD_{20}FEV_1$). Exercise challenge was performed on a braked static cycle ergometer for six minutes to achieve 80% of maximal predicted pulse rate. Response to exercise was determined by changes in the area under the curve (AUC) of the plot of % changes in FEV_1 after exercise against time. Terfenadine induced a mean 11% increase in FEV_1 ($p = 0·005$) by comparison with placebo prior to hypertonic saline and a mean 14% increase in FEV_1 prior to exercise ($p = 0·05$). Airways responsiveness to hypertonic saline was significantly attenuated following premedication with terfenadine (PD_{20} placebo 22 l, PD_{20} terfenadine 56 l ($p = 0·011$, $n = 10$). Airway responsiveness to exercise was significantly reduced following terfenadine premedication with a mean 25% reduction in AUC following exercise ($p = 0·04$, $n = 8$). Our results demonstrate that both hypertonic saline induced bronchoconstriction and exercise induced asthma are inhibited by a specific H_1 antagonist, suggesting that histamine release has a significant role in both these challenges.

Airway responsiveness to inhaled sodium metabisulphite: reproducibility and relation to methacholine

GM NICHOL, A NIX, KF CHUNG, PJ BARNES *Department of Thoracic Medicine, Cardiothoracic Institute, Brompton Hospital, London* Sodium metabisulphite (MBS) induces bronchoconstriction in asthmatic and atopic subjects, although its mechanism of action is not clear. Part of this response could be due to release of sulphur dioxide causing cholinergic and non-cholinergic bronchoconstriction. We determined the relationship between airway responsiveness to inhaled MBS and the inhaled cholinergic agonist methacholine (M) in 12 atopic subjects, including nine asthmatics with mild to moderate symptoms and three subjects with allergic rhinitis (4M/8F, 32 (SD 3) years, FEV_1 85·8 (5·6)% predicted). Subjects were studied on three separate days within a 10 day period, inhaling doubling concentrations of MBS (0·3–100 mg/ml) twice and M (0·06–64 mg/ml) once. Aerosols were delivered from a nebuliser attached to a dosimeter, and FEV_1 was measured five minutes after each inhalation. From each response PC_{20}, the concentration needed to cause a 20% fall in post-saline FEV_1, was obtained. One non-asthmatic subject did not respond to the highest concentration of MBS or M. There was no significant difference in baseline FEV_1 on the three study days. Nine subjects showed a within two fold variation in PC_{20} to MBS, and the two others four and 10 fold variations. Mean PC_{20} to MBS (geometric mean 1·4 (geometric standard error 1·4) μmol/l) was six fold greater than for M (0·24 (1·6) μmol/l; $p < 0·001$). There was a weak positive linear relationship between mean PC_{20} MBS and PC_{20} M ($r = 0·66$; $p < 0·05$). These results show that short-term reproducibility of airway response to MBS is good in most subjects, supporting the use of MBS inhalation challenge to study the mechanisms underlying sulphur dioxide response in asthmatics.

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Refractoriness following histamine provoked bronchoconstriction: a controversy revisited

MJ CONNOLLY, SC STENTON, AJ AVERY, EH WALTERS, DJ HENDRICK *Newcastle General Hospital, University of Newcastle upon Tyne* Since we presented to the British Thoracic Society our preliminary report on refractoriness to further histamine challenge following histamine-provoked bronchoconstriction (*Thorax* 1985;**40**:216), there have been several conflicting communications on the subject. We now report the results of our completed study of 20 asthmatic subjects, aged 19–50 years. Histamine tests 1 and 2 were carried out on the same day 45–60 minutes apart, once the FEV_1 following test 1 had returned spontaneously to within 90% of baseline. A further ("control") test was carried out on a different day at the same time as test 1 ($\pm$ 2 h). Test results (conventional measurements of bronchial responsiveness) were recorded as the provoking dose of histamine (μg) needed to produce a 20% fall in FEV_1 (PD_{20}). The distribution of the logarithms of the ratios PD_{20} test 2/PD_{20} test 1 was skewed, and the median value of this ratio (the "refractory index") was 2·20. This was significantly greater than 1 ($p = 0·003$, sign test; 96% confidence interval 1·43–3·40), indicating refractoriness at the time of the second test. By contrast, the median ratio PD_{20} control/PD_{20} test 1 was 1·03 and not significantly different from 1. This refractoriness could not be accounted for by failure to regain the initial baseline FEV_1, though this may have exaggerated the effect. An increase in PD_{20} with the second test was uniformly observed with moderate or high initial PD_{20} values but there was no consistent pattern with low values, suggesting a possible threshold of the order of 25–100 μg histamine. Mediator depletion could not account for this phenomenon, which may be due to refractoriness in airway smooth muscle itself. Its practical importance lies with the possibility that it could exert a confounding effect in investigations with repeated histamine tests over short intervals.

Statistical aids in the identification of late asthmatic reactions (LARs)

SC STENTON, AJ AVERY, EH WALTERS, DJ HENDRICK *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne* During the investigation of SINOS, a newly recognised inducer of occupational asthma, we performed 225 inhalation challenge tests in three exposed asthmatic workers, three unexposed non-asthmatic controls and three unexposed asthmatic controls. We used nebulised solutions of SINOS, LAS (chemically similar but not to induce asthma) and saline; and administered individual challenges on different days in a blinded fasion at 1000 h. Serial chemical challenges were administered in $\sqrt{10}$ fold dose increments over the range 0·01–100 μg or until a clinically unequivocal LAR occurred. For three days prior to the challenge protocol, FEV_1 was monitored to determine the usual diurnal pattern. SINOS but not LAS nor saline resulted in unequivocal LARs in all workers but not in control subjects. They were quantified from hourly FEV_1 measurements 2–12 and 2–24 hours following challenge by calculating the area between a plot of FEV_1 measurements and a line extrapolated from baseline (area decrement, AD). There was an increase in magnitude of AD with increase in SINOS dose, which linear regression analysis showed to be significant for all three workers ($p < 0·001$). This dose-response method of statistical analysis will not often be practical, however, because steep regression slopes will limit the number of "safe" doses. We consequently sought analytical methods for individual challenge tests. The upper one-sided 95% confidence limit for AD for the three prechallenge days was calculated, and was exceeded following the higher dose SINOS challenge in the asthmatic workers. By contrast, this limit was not exceeded following 102 of an overall total of 108 LAS and associated saline challenges, or following 53 of 54 SINOS challenges in the controls. Finally, we used pooled variances of the FEV_1 measurements on the three prechallenge days to derive a joint lower one-sided 95% confidence limit for individual hourly measurements following challenge. When expressed graphically, this model also identified LARs and allowed the time of onset and duration to be determined.

Comparison of exercise induced bronchoconstriction and methacholine responsiveness in atopic 7, 8, and 9 year old children

S HUTCHISON, JB CLOUGH, ST HOLGATE *Department of Immunopharmacology, Southampton General Hospital, Southampton* Many children suffer from exercise induced bronchospasm (EIB) and a considerable proportion receive no treatment for this unpleasant and restricting symptom. In a study aimed at identifying a simple exercise test for use in seven, eight, and nine year old children, the relationship between EIB and methacholine responsiveness was examined. Thirty children identified as being atopic by skinprick testing with three common allergens and a positive and negative control underwent methacholine bronchial challenge and exercise testing. Each test was performed at the same time of day on two consecutive days, the sequence for each subject being randomly selected. Methacholine challenge was performed with the Yan method (*Thorax* 1983;**38**:70) and exercise testing employed treadmill exercise for six minutes, ensuring that heart rate reached 90% of the age predicted maximum. FEV_1 was measured before and three, five and 10 minutes after exercise. The dose of inhaled methacholine which caused a 20% fall in FEV_1 (PD_{20}meth) and the maximum drop in FEV_1 after exercise for each subject were compared by simple regression analysis. No significant correlation between the two tests was found ($R = 0·280$, $P = 0·114$). Our findings are in agreement with other studies performed in adults (*Am Rev Respir Dis* 1982;**126**:235), which have failed to show a correlation between the results of exercise testing and methacholine responsiveness.

Prediction of bronchial hyperresponsiveness in young adults by prick skin test polymorphisms

WOCM COOKSON, AW MUSK *Osler Chest Unit, Churchill Hospital, Oxford, and Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia* Prick skin tests with common antigens and bronchial re-

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sponsiveness to methacholine were measured in 143 young adults (126 male; mean age 23·4 (SD 7·4) years) seeking holiday employment. The distribution of non-specific bronchial responsiveness was shown to be bimodal with a maximum cumulative dose of 102 μmol methacholine (by the method of Yan *et al*). Seventy three (50%) of the subjects were atopic, and 50 of these (68·5%) had a PD_{20} < 102 μmol methacholine (χ^2 18·8). Forty eight (33·6%) subjects reacted to house dust mite (HDM), 20 (14·0%) to moulds, 33 (23·1%) to epithelia, and 57 (39·9%) to grasses. Bronchial hyperresponsiveness (PD_{20} ≤8 μmol) was significantly associated with positive skin test reaction to HDM (33% hyperresponsive, p = 0·0036) and moulds (45% hyperresponsive, p = 0·0036), but not with positive reactions to animal danders or to grass pollens. A logistic regression fitted to the data showed that reactivity to house dust mite increased the risk of hyperresponsiveness by a factor of 1·89 (p < 0·01) and that positive skin test reaction to moulds similarly increased the risk by 1·89 (p < 0·01). Reactivity to grass pollens alone carried no risk: however, reactivity to grass and to HDM concomitantly carried a risk of 2·7 (p < 0·001). The results indicate the presence or absence of bronchial hyperresponsiveness in an atopic individual may depend on the type of antigen to which he is capable of mounting an IgE response, and may explain why some atopic individuals are asthmatic and others not.

Comparison of $PD_{20}FEV_1$ and $PD_{40}\dot{V}_{30}p$ as measurements of response to inhaled methacholine

H COLEMAN, AJ KNOX, JR BRITTON, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Measurement of bronchial reactivity is being used increasingly in studies of asthma prevalence, most studies using $PD_{20}FEV_1$ as an index of response. However, FEV_1 is a relatively insensitive index of bronchoconstriction, only a minority of the general population having a measurable PD_{20} value. Measurement of bronchial reactivity using partial expiratory flow measurements may be more sensitive (Dehaut *et al. Thorax* 1983;**38**:516) but little is known about the repeatability of these measurements with the methods most suited to epidemiological practice. We have compared the sensitivity and repeatability of $PD_{20}FEV_1$ with $PD_{40}\dot{V}_{30}p$ (provocative dose of methacholine causing a 40% reduction in flow at 30% of vital capacity) in 20 subjects with mild, stable asthma. Subjects performed four methacholine challenge tests (Yan method) on separate days. On two occasions response was measured as $PD_{20}FEV_1$ on a Vitalograph and on two occasions as $PD_{40}\dot{V}_{30}p$ on an Ohio spirometer, each pair of tests being performed within an interval of seven days. Log transformed PD values were used in all analyses. Baseline FEV_1 did not differ significantly over the four days. $\dot{V}_{30}p$ was the more sensitive index of bronchoconstriction by a factor of 1·48 doubling doses of methacholine. The 95% range for a single measurement of both $PD_{20}FEV_1$ and $PD_{40}\dot{V}_{30}p$ was identical at 2·0 doubling doses, but the intraclass correlation coefficient was higher for $PD_{20}FEV_1$ (0·79) than for $PD_{40}\dot{V}_{30}p$ (0·69). Thus measurement of $PD_{40}\dot{V}_{30}p$ offers a more sensitive measure of bronchial reactivity, which for a given methacholine dose will produce a greater proportion of PD values. The increased sensitivity is achieved without loss of repeatability but with some loss of discrimination of between subject differences.

Relation between membrane fatty acids and leucocyte ionised calcium in asthma

IK TAYLOR, GC BOOTH, P EBDEN, JB COOKSON, RF BING *Medical Unit, Glenfield General Hospital, Leicester* Cell function can be modulated by receptor activated mechanisms involving increases in intracellular ionised calcium $[Ca]_i$. Alteration of the lipid composition of cell membranes may influence transmembrane signalling, $[Ca]_i$ and subsequent cellular expression. As $[CA]_i$ regulates smooth muscle contraction and inflammatory cell activation, the relation between cell membrane lipids and $[Ca]_i$ is of particular interest in asthma. Leucocyte $[Ca]_i$ was measured in 15 atopic asthmatics in remission (12 M; aged 18–42, mean age 28 years) and age and sex matched non-atopic, non-asthmatic controls (aged 18–42 mean 28). Leucocytes were prepared by differential sedimentation and loaded with the fluorescent indicator quin 2, which binds to $[Ca]_i$ in a stoichiometric 1:1 relationship. From the same venous blood sample fatty acids were extracted from erythrocyte membranes and quantified by gas liquid chromatography. The ratio of the saturated fatty acid palmitic acid to the unsaturated fatty acid linoleic acid (P:L) was used as an index of disturbed membrane fatty acid composition. Results (mean (SEM)) are shown below in the table. The membrane P:L ratio was positively correlated with leucocyte $[Ca]_i$ (r = 0·4, p = 0·014) when all data were used. In the asthmatic patients (r = 0·37, p = 0·08) and the controls (r = 0·36, p = 0·09) separately the correlation did not reach significance, although the regression lines were similar. These results show that membrane fatty acid profiles are significantly altered in those with atopic asthma. The relation between membrane fatty acid composition and $[Ca]_i$ is similar and continuous in control and asthmatic groups. This suggests that it is perturbations in cell membrane composition that result in abnormalities of intracellular activation in asthma.

	Control	*Asthma*	*p*
P:L	1·049 (0·060)	1·294 (0·083)	<0·02
$[Ca]_i$ (nmol/l)	235·1 (10·59)	254·1 (18·62)	NS

Role of felodipine, a calcium antagonist, in adenosine induced bronchoconstriction

S GHOSH, P RAFFERTY, I MCILROY, KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow* Inhaled adenosine monophosphate (AMP) provokes bronchoconstriction in asthmatics. It has been suggested that this may be secondary to mediator release since in vitro adenosine has been shown to enhance the release of performed mast cell mediators. Allergen induced mast cell mediator release is thought to occur via a calcium dependent mechanism. We have now investigated the effort of felodipine, a calcium

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antagonist, on AMP induced bronchoconstriction. Nine mild atopic asthmatics (4M, mean (SEM) age 33·9 (3·6) y, mean FEV_1 96·9 (4·7)% of predicted value) attended the laboratory on two separate days at least one week apart. After baseline FEV_1 had been recorded patients received either felodipine 10 mg oral solution or matched placebo in a double blind random fashion. Thirty minutes after drug administration FEV_1 was again recorded and patients then underwent a standardised inhalation test with 0·9% saline followed by doubling concentrations of AMP (0·2 mg–256 mg/ml) administered via a Mefar dosimeter. FEV_1 was recorded at 90 and 180 seconds after nebulisation of each concentration and increasing concentrations of AMP were administered until the FEV_1 had fallen by 20% from the post saline value. There was no significant difference between the FEV_1 values recorded before or 30 minutes after treatment nor after inhalation of nebulised saline on each treatment day. AMP inhalation provoked dose related bronchoconstriction in all patients. There was a significant difference in the concentration required to produce 20% fall in FEV_1 (PD_{20}) after the felodipine, with geometric mean PD_{20} values of 24·6 mg/ml and 36·8 mg/ml following placebo and felodipine respectively ($p < 0·05$). Since felodipine significantly inhibited AMP induced bronchoconstriction we conclude that the mechanism is likely to be calcium dependent.

Airways responses to inhaled ouabain and the effect of Na/K ATPase inhibition on histamine responsiveness in asthmatic patients

G HULKS, KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow* Increased Na/K adenosine triphosphatase (ATPase) activity has been reported in patients with asthma and this has been postulated as the cause of airways hyperresponsiveness. In contrast, inhibition of ATPase activity with inhaled ouabain has been shown to cause bronchoconstriction in hyperreactive guinea pigs and to make these animals hyperresponsive to histamine (Agrawal KP, Hyatt RE. *J Appl Physiol* 1986;**60**:2089–93). ATPase activity has therefore been suggested as a homeostatic mechanism to prevent Na^+ and Ca^{2+} loading of airway cells. We have examined the effect of inhaled ouabain (50, 250, 500 and 1000 μg/ml) on the bronchomotor tone and histamine responsiveness in nine patients (2F) of mean (SD) age 37·8 (11·5) years with allergic asthma in a double blind placebo controlled study. After the baseline FEV_1 had been recorded each subject inhaled 1 ml of ouabain solution of different concentrations or a placebo through a Wright nebuliser (flow rate 8 l/min, 50 lb/in^2). FEV_1 was recorded at one, three, five, seven, 10, 20 and 30 minutes, after which a histamine inhalation challenge was performed on Cockcroft's method and the results were expressed as the concentration of histamine/ml causing a 20% fall in FEV_1. Inhaled ouabain and placebo had no significant effect on the FEV_1 nor did ouabain alter histamine responsiveness. Our results, unlike those of guinea pig experiments, suggest that the inhibition of Na/K ATPase with ouabain has little effect on bronchial smooth muscle contractility and histamine responsiveness in man.

	n	*Baseline FEV_1*	*Max fall (%)*	*PC_{20} H(mg/ml)*
Placebo	9	3·10 (1·50)	4·4 (4·5)	0·27 (0·66)
Ouabain (μg)				
50	9	3·00 (1·04)	6·1 (2·9)	0·34 (0·73)
250	9	3·00 (1·04)	4·5 (2·9)	0·46 (0·53)
500	9	3·02 (0·97)	4·0 (5·0)	0·21 (0·54)
1000	9	3·03 (1·02)	4·6 (4·0)	0·16 (0·49)

PC_{20} values are geometric means; Max fall %—maximum fall in FEV_1 after placebo or ouabain inhalation.

Are alterations in circulating vasopressin responsible for the increase in bronchial reactivity with a high salt diet?

AJ KNOX, JR BRITTON, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* Two recent studies have shown an increase in bronchial reactivity when dietary salt intake is increased (Burney *et al. Thorax* 1988;**43**:259P; Javaid *et al. Thorax* 1988;**43**:259P). Circulating vasopressin levels are increased on a high salt diet and vasopressin is known to constrict vascular and intestinal smooth muscle. The effect of vasopressin on bronchial smooth muscle is unknown. To determine whether alterations in circulating vasopressin are responsible for the increase in bronchial reactivity on a high salt diet, we studied the effect of an infusion of vasopressin on histamine reactivity in six normal and eight asthmatic men aged 18–45. Subjects were studied at the same time on day on two non-consecutive days in the same week. After baseline measurement of airflow ($\dot{V}_{30}p$ in normal subjects, FEV_1 in asthmatic subjects), subjects received a control saline solution or an infusion of 2 IU vasopressin in 60 ml saline for one hour, followed by 4 IU/hour for a second hour (2 IU/hour has been shown to produce levels at the upper end of the physiological range (Grant *et al. Clin Sci* 1985;**69**:471)). Airflow measurements were repeated at 15 minute intervals with measurement of histamine reactivity (Yan method) at one and two hours. Vasopressin did not affect airflow in either group of subjects. There was no significant difference in histamine reactivity between placebo and Vasopressin at one or two hours, geometric mean $PD_{40}\dot{V}_{30}p$ with placebo and vasopressin being 10·8 and 11·9 μmol at one hour ($p = 0·8$) and 19·3 and 24·5 μmol at two hours ($p = 0·4$) in normal subjects, and geometric mean $PD_{20}FEV_1$ with placebo and vasopressin being 0·57 and 0·48 at one hour ($p = 0·5$) and 0·56 and 0·61 at two hours ($p = 0·6$) in asthmatic subjects. Our results suggest that alterations in circulating vasopressin are not responsible for the increase in bronchial reactivity when dietary salt intake is increased.

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volumes but with the rapid growth of interest in oesophageal disorders the time is now ripe for an oesophageal A to Z. Professor Jamieson has succeeded in his declared aim of producing an encyclopaedia of oesophageal surgery. This is a textbook of great breadth, detail, and authority with over 100 contributing authors. It starts with a chapter on the development of oesophageal surgery, and the following 105 chapters cover the whole range of oesophageal investigative techniques, basic science, questions of management, and details of operative techniques. Each chapter concludes with an extensive list of references. The list of authors reads like a Who's Who of oesophageal surgery and Professor Jamieson has done a skillful editing job in collating their contributions. There are, however, a few criticisms. The layout in terms of sections and chapters is a little puzzling. Chapters on operative techniques are sometimes included in the relevant section—for example, reflux disease—whereas elsewhere operative details are in a separate section—motility disorders. The chapter on oesophageal webs would be better included under the section dealing with miscellaneous conditions and I found this chapter a little confusing in its discussion of webs, sideropenia, and dysphagia. The illustrations are all of a high standard, although figure 44–3, purporting to show a hydropneumothorax, appears to have been sawn off above the fluid level (a minor criticism). Now for a few sins of omission. Little or no mention is made of the place of drug treatment as a causative factor in benign strictures. Practical radiotherapy is not represented and in particular no mention is made of alternative techniques in radiotherapy, such as brachytherapy. This is not to detract from the existing chapter on radiotherapy in oesophageal carcinoma, which is an authoritative review of the subject. Lastly, as a thoracic surgeon, I must demur at some of the comments in chapter 94 about rigid oesophagoscopy. Both rigid and fibreoptic instruments have their uses and the modern oesophageal surgeon should be experienced with both. There are circumstances in which the rigid instrument is superior and we are in danger of losing the benefits of a very useful instrument through lack of training. Enough of criticism and personal prejudice. This is an excellent and comprehensive textbook on surgery of the oesophagus and will undoubtedly become the standard reference work on the subject. It is a "must" for any clinician with a serious interest in oesophageal disease, whether surgeon, physician, or research worker. This book weighs nearly 3 kg and costs £135, so before purchasing check on the solidity of your bookshelf and the liquidity of your bank account.—WEM

Notice

Course in lung pathology

A course of lectures, hands on microscopy sessions, and a slide seminar on lung pathology will be held at the National Heart and Lung Institute, Brompton Hospital, London, on 12–15 June 1989. The lecturers will include B J Addis, P J Cole, B Corrin, P da Costa, B Fox, A R Gills, M Griffiths, P K Jeffery, M N Sheppard, S Stewart, and C A Wagenvoort. The programme and application form may be obtained from the Postgraduate Centre, National Heart and Lung Institute, London SW3 6LY (01 351 8172).

Correction

British Thoracic Society proceedings

In the proceedings of the summer 1988 meeting (October 1988, vol 43) the author of the last abstract on page 815P should be S Lawford Hill.