Thorax 1984;**39**:216–240

Proceedings of the British Thoracic Society

The 1983 winter meeting of the British Thoracic Society was held on 8-9 December at the Metropole Hotel, Birmingham.

Comparative radiographic features of legionnaires' disease and other sporadic community acquired pneumonias

J.T. MACFARLANE, A.C. MILLER, A.H. MORRIS, D.H. ROSE, W.H.R. SMITH We have compared the chest radiographs (CXR) of 49 consecutive adults seen with sporadic community acquired Legionnaires' disease pneumonia (LD) with those of 147 adults with other forms of community acquired pneumonia. These included 91 with pneumococcal pneumonia (PNP), (31 with pneumococcal bacteraemia/antigenaemia (bacT/Ag) and 46 with mycoplasma pneumonia (MP).

On presentation, CXR shadowing was mainly homogeneous in 80% of LD cases and multilobe involvement was seen in 40% — a pattern similar to the other bacterial pneumonias. Radiographic deterioration after admission was commoner with LD (65%) and bact/Ag PNP (52%) than with non bact/Ag PNP (25%) and MP (25%). Spread to the opposite lung was a feature particularly of LD and bact/Ag PNP pneumonia.

Segmental or lobar collapse was seen with all types of pneumonia and occurred at some stage in 37% LD cases. Pulmonary cavitation occurred in 1 patient with LD and in 4 patients with PNP. Hilar lymphadenopathy was identified in MP (22%) cases only. Pleural fluid was detected on the radiographs of 12 LD cases.

Rate of radiographic resolution was examined for 161 survivors. Pulmonary shadows cleared particularly slowly following LD and bact/Ag PNP. Only 60% cases had cleared by 12 weeks and 12% LD radiographs were still not clear at 20 weeks. CXR clearance following MP was much faster. Non bact/Ag PNP improved at an intermediate rate. Subsequently, linear streaky opacities were still seen in 29% Ld and 26% bact/Ag PNP radiographs, suggesting that healing may be associated with fibrosis.

We conclude that there are no unique radiographic features of different forms of sporadic community acquired pneumonia.

Suppurative lung disease: a manageable complication of inflammatory bowel disease (IBD)

G.S. BASRAN, J.T. MACFARLANE, D. DAVIES Four cases of rapidly progressive suppurative lung disease (SLD) are described in patients with pre-existing IBD (Crohn's or ulcerative colitis (UC)). In 3 cases SLD followed colectomy. The cardinal features were cough productive of large volumes of purulent phlegm (normal respiratory flora on culture) which was resistant to repeated courses of antibiotics. This was accompanied by increasing dyspnoea and increased linear basal markings on CXR. Bronchoscopy on Case 1 showed inflamed bronchial mucosa and intraluminal pus and bronchial histology and showed chronic inflammation with apthous ulcers rather similar to the colonic biopsy.

	Case 1	Case 2	Case 3	Case 4
Sex	F	F	F	M
Bowel disease — type	Crohn's	UC	UC	Crohn's
— age of onset	60	36	69	55
— colectomy	Yes	No	Yes	Yes
SLD — age of onset	66	57	70	55
— **symptoms before prednisolone**				
days/month with cough	28	28	28	28
days/month with phlegm	28	28	28	28
— **symptoms on prednisolone**				
days/month with cough	0	4	0	28
days/month with phlegm	0	0	0	28

In the 3 post-menopausal women but not the man, SLD improved dramatically on prednisolone (25 mg. daily). The response was shown as a reduction in the symptom score (table) and improvement in lung function (FEV_1/FVC and daily PEFR). A maintenance dose of up to 5 mg. daily of prednisolone was titrated against the symptoms. This report should remind the physician of this subgroup of steroid-responsive SLD associated with active or inactive IBD.

Diffuse asbestos-related pleural thickening: disability and lung function abnormalities

C.R. McGAVIN, G. SHEERS A retrospecitve survey of records of men working in the Devonport Naval Dockyard has been carried out in order to assess disability arising from diffuse asbestos-related pleural thickening (DARPT). Thirty seven men were identified who had DARPT but no physiological evidence of airways obstruction and no definite radiographic evidence of asbestosis (profusion score for small irregular opacities $< 1/1$ by the ILO classification). Breathlessness grade, lung function data, dust-exposure rating and a simple X-ray score were compared.

Fifteen men were in M.R.C. breathlessness grades 3, 4 and 5. Men with higher (worse) X-ray scores had significantly lower vital capacities and were significantly more breathlessness than those with lower X-ray scores. Vital capacity was significantly lower in men with higher breathlessness grades. Transfer coefficient (K_{CO}) was significantly raised in men with higher X-ray scores. There was no correlation between dust exposure rating and either

X-ray score or breathlessness grade. The 8 men with unilateral disease were less disabled than those with bilateral disease.

The significant interrelationships between radiological findings, breathlessness and lung function abnormalities support the hypothesis that DARPT is a cause of disability in its own right.

Occupational asthma due to formaldehyde

P.S. BURGE, M.G. HARRIES, W.K. LAM, I.M. O'BRIEN, P.A. PATCHETT Bronchial provocation studies on 14 workers occupationally exposed to formaldehyde are described. Six developed immediate asthmatic reactions which were shorter in duration than seen after soluble allergen exposure and were closely related to histamine reactivity, suggesting that the formaldehyde was acting as a non-specific irritant. The breathing zone levels of formaldehyde required to illicit these irritant reactions (mean 4.8 mg/m^3) were higher than those encountered in buildings recently insulated with urea formaldehyde foam, but within levels sometimes found in industry. Two workers developed reproducible late asthmatic reactions that are likely to represent true hypersensitivity to formaldehyde.

Outcome of asthma induced by isocyanates

S. LOZEWICZ, B. ASSOUFI, R. HAWKINS, A.J. NEWMAN-TAYLOR Exposure to isocyanates is a well recognised cause of occupational asthma but there are few reports of the outcome in affected individuals after removal from exposure. We have studied fifty six patients with isocyanate induced asthma, all of whom had changed their jobs to avoid futher exposure. The diagnosis was made where there was both a history of exposure related symptoms, and an asthmatic reaction to bronchial challenge with toluene di-isocyange (TDI), diphenylmethane di-isocyanate (MDI), hexamethylene di-isocyanate (HDI), or naphthylene di-isocyanate (NDI).

At the time of follow-up, which in all cases was at least four years following removal from exposure, forty one patients (73%) continued to have asthma, and twelve of these had daily symptoms. Bronchial hyperreactivity was demonstrated in 12 (63%) of nineteen patients who underwent bronchial challenge by isocapnic hyperventilation of subfreezing air at the time of follow up. All 12 cases of isocyanate asthma in a factory using TDI were studied, and their characteristics did not differ from those of the population as a whole. Individuals with a poor outcome were more likely to have an immediate reaction to challenge with isocyanates ($p<0.10$) and bronchial hyperreactivity to histamine ($p<0.001$) at the time of diagnosis.

Lung function tests in chronic byssinosis: evidence that emphysema is not a feature of byssinosis but is due to smoking habits

D. HONEYBOURNE, C.A.C. PICKERING A group of female grade 3 byssinotic subjects were seen consecutively over a 3-year period in an occupational out-patient clinic. Detailed lung function tests were obtained and the results between smokers and non-smokers compared. A total of 178 subjects were seen and of these 118 were either life-time smokers or smoked $\geq$ 10 cigarettes per day. After correction for ages the mean FEV_1 was found to be significantly lower ($p<0.05$) in smokers compared to non-smokers.

In a sub-group of 89 subjects who were able to perform the carbon monoxide gas transfer test there was a significantly lower DLCO ($p<0.05$), DLCO% predicted ($p<0.001$) and KCO ($p<0.001$) in the smokers compared to the non-smokers despite the fact that the non-smokers had spent a longer period of years in the cotton mills ($p<0.02$). The mean DLCO was significantly lower than the mean DLCO predicted value in the smokers ($p<0.001$) but not in the non-smokers.

These results provide evidence additional to recent pathological studies that emphysema is probably due to concomitant cigarette smoking and is not itself a feature of byssinosis in females.

Maintenance chemotherapy for small cell lung cancer — a randomised controlled trial

M.H. CULLEN, D.A.L. MORGAN, M.A. RICHARDS, M. ROBINSON, M. WARD, D. COX, *for the Midlands (UK Small Cell Lung Cancer Group*. Since June 1980, 287 patients have entered a randomised prospective trial of maintenance chemotherapy (M) versus no maintenance (N). Induction chemotherapy consists of 6 courses of VAC (vincristine 1 mg/m^2, adriamycin 40 mg/m^2 and cyclophosphamide 1000 mg/m^2, IV) q 3 weeks. Limited stage patients also receive 30 Gy mediastinal irradiation between VAC1 and 2. Patients with no unequivocal residual disease are then randomised to no treatment or 8 further courses of VAC q 4 weeks (V-1 mg/m^2, A-30 mg/m^2, C-600 mg/m^2). Patients failing to achieve randomisation status receive palliative treatment only. Patients responding well to treatment receive elective whole brain irradiation. Overall figures for 287 patients show median survivals of 356 and 232 days for limited (LD) and extensive (ED) disease ($p<0.0001$). By 1st May 1983, 86 patients had been randomised (33 LD, 53 ED). For LD, median survivals are 324 days (M) and 549 days (N) ($p=0.053$ log-rank test). For ED the corresponding figures are 371 days (M) and 259 days (N) ($p=0.053$). Thus for LD there is no benefit from maintenance chemotherapy in patients achieving a good response to induction therapy. In ED there is a trend in favour of the maintenance arm with a shift of the survival curve to the right. Randomisation continues in this group.

Carcino-embryonic antigen (CEA) in the diagnosis of malignant pleural effusion

C.J. GIBBS, I.I. COUTTS, R.J. WHITE, H.D. MITCHELL The routine investigation of pleural effusion commonly fails to identify a cause even when due to malignant disease. Elevated levels of carcino-embryonic antigen (CEA) have

been found in malignant pleural effusions and we have attempted to access its value in predicting malignancy. Pleural fluid CEA was measured by radio-immunoassay in 40 pleural effusions. Effusions were classified as benign when there was a definite non-malignant aetiology or resolution over a period of 3 months and malignant when there was histological or cytological confirmation. In 18 benign effusions the median CEA level was 5 μg/litre (range 2-38) and in 22 malignant effusions it was 27 μg/litre (range 2-2689). No relationship was found between CEA concentration and pleural fluid protein concentration in either benign or malignant effusions. Using a CEA level $\geqslant$ 20 μg/litre to distinguish between benign and malignant effusions resulted in the appropriate classification of 13 out of 22 malignant effusions and the misclassification of one out of 18 benign effusions, giving a sensitivity of 59% and a specificity of 94%. High levels of CEA in pleural fluid are of value in confirming malignant infiltration of the pleura.

Endobronchial metastasis from carcinoma of the breast: a common site for recurrence

A.J.R. MORRIS, J.P. O'SULLIVAN, F.J.C. MILLARD, A.M. HUMBERSTONE, J. HUNT, T.J. POWLES, R.C. COOMBES Nine out of 26 women (35%), with a past history of carcinoma of the breast who were bronchoscoped (fibreoptic) as part of the investigation of new respiratory symptoms or non-specific chest X-ray changes, were found to have endobronchial metastases from their breast carcinoma on bronchial biopsy. None had any macroscopic endobronchial tumour, but mucosal appearance showed various minor abnormalities which may easily have been overlooked (mucosal induration, whitish infiltrates or small mucosal nodules). In five women, endobronchial metastasis was the first manifestation of relapse. One had an entirely normal chest X-ray. With hormonal manipulation and/or chemotherapy four women remain alive and well one year to 2.5 years after diagnosis of endobronchial disease.

Recent onset of cough, dyspnoea or wheeze, with or without accompanying pulmonary shadowing in women with a past history or carcinoma of the breast, may indicate endobronchial metastasis. Any abnormal looking bronchial mucosa should be biopsied to make a histological diagnosis.

Oxygen as a driving gas for nebulisers: safe or dangerous?

K.A. GUNAWARDENA, B. PATEL, I.A. CAMPBELL, J.B. MACDONALD, A.P. SMITH Blood gas changes occuring when 100% oxygen or air was used as the driving gas for nebulised salbutamol are reported in three groups of patients with severe airways obstruction; 9 with chronic bronchitis and emphysema with carbon dioxide (CO_2) retention, 7 with emphysema and chronic bronchitis without CO_2 retention and 7 patients with severe asthma (no CO_2 retention). When oxygen was used as the driving gas, CO_2 retainers showed a mean rise of 1.03 KPa (7.73 mm.Hg.) in their PCO_2 after 15 mins. ($p<0.001$), but the PCO_2 returned to the base-line values within 20 mins. of stopping the nebuliser. The other two groups showed no rise in PCO_2 with oxygen. When air was used as the driving gas none of the groups became significantly more hypoxic. Whilst it is safe to use oxygen as the driving gas in patients with obstructive airways disease with normal PCO_2, caution should be exercised in those who already have CO_2 retention.

A comparison of recurrence rates of thromboembolic disease after 3 weeks or 6 weeks' anticoagulation

A. FENNERTY, J. DOLBEN, P. THOMAS, D.P. BENTLEY, I.A. CAMPBELL, P.A. ROUTLEDGE Treatment with anti-coagulants is effective in thrombo embolic disease, but the optimum duration of treatment is unknown. O'Sullivan[1] has shown that Warfarin for 6 weeks after heparin infusion is as effective in preventing recurrences as 6 months treatment. We are conducting a trial to determine whether 3 weeks treatment is as effective as 6 weeks in patients with deep vein thrombosis and/or pulmonary embolism. Warfarin is started on day 3 of a 5 day heparin infusion and continued to give a total of 3 or 6 weeks anti-coagulation. 83 patients have entered the study and randomly allocated to 3 weeks (40 patients) or 6 weeks (43 patients) treatment. All have been followed up for at least 3 months with a mean follow up of 9 months. There have been 9 recurrences (10.8%), 5 in the 3 week group (12.5%) and 4 in the 6 week group (9.3%); none were fatal and all but one occurred within 3 months or stopping treatment. Follow up for one year is planned, but on the results to date 3 weeks anti-coagulation appears as effective as 6.

Reference 1. E.F. O'Sullivan, 1972. Duration of anticoagulation therapy in venous thromboembolism. Med J. Aust. **2:** 1104.

Respiratory stimulation by almitrine in patients with chronic airways obstruction

N.N. STANLEY Almitrine is a new drug which stimulates peripheral chemoreceptors in animals. It improves the blood gas state in patients with chronic airways obstruction and yet some have attributed this to a favourable action on pulmonary gas exchange. Having previously reported that the drug augments respiratory chemosensitivity in healthy subjects (Stanley et al. Br. J. Dis. Chest 1983, 77, 136-46), a further double-blind placebo-controlled study was undertaken to assess the effects of the drug given orally in 100 mg doses to twelve patients with chronic bronchitis and emphysema. With almitrine their arterial O_2 tension rose by 1.1 kPa and CO_2 tension fell by 0.6 kPa ($p<0.01$) whilst ventilation rose by 11% ($p<0.01$). Two rebreathing tests causing either progressive hyperoxic hypercapnia or progressive asphyxia were used to assess drug effects on chemosensitivity. In hyperoxia the ventilatory response to hypercapnia rose by 35% after almitrine ($p<0.05$); but even greater was an increase by 80% ($p<0.05$) it caused in the response to hypoxia, quantified by disparity in ventilation between the two response curves at a given arterial O_2 saturation difference measured by ear oximetry. Thus almitrine enhanced chemosensitivity in these patients and the concomitant stimulation of ventilation must have

helped relieve their respiratory failure.

Alveolitis in adult coeliac disease — a new syndrome

A.J. WILLIAMS, P. ASQUITH, C. EDWARDS, D.E. STABLEFORTH Cryptogenic fibrosing alveolitis and extrinsic allergic alveolitis have been occasionally reported in association with coeliac disease but seldom substantiated by lung biopsy. To investigate the prevalence of alveolar pathology in patients with adult coeliac disease (ACD) we studied 73 subjects (49 female) mean age 41 years by clinical assessment, pulmonary function, X-ray, bronchoalveolar lavage and transbronchial lung biopsy.

Eighteen (25%) patients had a significant reduction of gas transfer coefficient (KCO<80% predicted) and 9 of these complained of exertional dyspnoea; only 1 patient's chest X-ray showed diffuse lung shadowing. Twelve patients with a low KCO have so far been further investigated. Their mean arterial oxygen tension was 10.9 kPa and 5 patients had resting hypoxaemia (<10.6 kPa).

Measurement of membrane diffusing capacity (DM) confirmed an alveolar disorder was predominant (mean DM 62% predicted) in the causation of this low KCO. Transbronchial lung biopsy showed interstitial and perivascular fibrosis in 10 of the 12, and in 8 there was an increased proportion of inflammatory cells in the lavage fluid.

Although the pathogenesis of the alveolitis remains unknown exposure to avian antigens and the presence of avian precipitins was not a feature in these patients. The finding of alveolitis in a significant number of patients with ACD has important clinical and therapeutic implications.

The value of percussion, vibratory-shaking and breathing exercises in chest physiotherapy

P.P. SUTTON, M.T. LOPEZ-VIDRIERO, D. PAVIA, S. NEWMAN, M.M. CLAY, B. WEBBER, R.A. PARKER, S.W. CLARKE Eight patients with stable chronic obstructive airways disease and copious tracheobronchial secretions (mean sputum weight 44 g per day) underwent a 20 minute period of chest physiotherapy on four separate occasions. The periods studied were: 1) control, 2) vibratory-shaking with breathing exercises 3) percussion with breathing exercises 4) percussion without breathing exercises. Each treatment and control period included postural drainage and voluntary coughing. Clearance of secretions — the principal aim of chest physiotherapy — was objectively assessed by the inhaled radioaerosol technique using 2μm diameter tc 99m labelled polystyrene microspheres.

We found that neither percussion, vibration or breathing exercises produced more tracheobronchial clearance and sputum mobilisation than postural drainage alone, contrary to previous clinical impression. The mean ($\pm$ SE) percentage clearance of radioaerosol after each treatment period was a) 40 $\pm$ 9, b) 43 $\pm$ 7, c) 38 $\pm$ 7, d) 44 $\pm$ 8. Previously using the same technique in similar patients we have demonstrated the value of postural drainage and the Forced Expiration Technique (FET) (Sutton et al, Eur. J. Dis., 1983, **64**, 62-68).

Chest physiotherapy should be rationalised using the objective evidence now available to include postural drainage and FET, both of which can be used in domiciliary physiotherapy and carried out unaided.

Spontaneous pneumothoraces are associated with mitral valve prolapse

S.G. BREAR, D. BETON, YVONNE M. SLAVEN, D. HONEYBOURNE Spontaneous pneumothorax has long been associated with a tall slim build, Ehler's Danlos and Marfan's syndromes. Mitral valve prolapse (MVP) is a common condition which has also been associated with Ehler's-Danlos and Marfan's syndromes, and with osteogenesis imperfecta, pseudoxanthoma elasticum and various skeletal abnormalities. A number of complications of M.V.P. have been described (D. Beton, S.G. Brear, J.D. Edwards, J.C. Leonard, 1983, Q.J.M. 52, **206**, pages 150-164).

We have undertaken a 12 month prospective study to find the prevalence of MVP in patients presenting with a spontaneous pneumothorax. These patients had no evidence of any underlying lung disease and, after resolution of the pneumothorax, were assessed by standard M-mode echocardiographic criteria.

A group of age and sex matched controls also underwent echocardiography and their tracings were mixed with those of the pneumothorax group and then read by an experienced cardiac radiologist who was unaware of which subjects were in the two groups. Of the 21 in the pneumothorax group 17 had MVP (80.9%) whereas only 5 of the 21 control subjects had MVP (23.8%), this difference is highly significant, $p<0.001$.

We believe that this evidence lends further weight to the view that MVP may be only one expression of a more generalised collagen disorder.

Postal survey of medical bronchoscopies in the United Kingdom — 1: deaths and complications

A.G. ARNOLD, P.W. BELFIELD, M.F. MUERS, N.J. COOKE Since the introduction of the fibreoptic bronchoscope chest physicians have increasingly performed diagnostic bronchoscopy themselves, rather than referring patients to thoracic surgeons. The use of this instrument with local anaesthesia, together with a generally accepted low complication and mortality rate, may have encouraged an increase in investigations. A postal survey carried out in the United States in 1974 reviewed 24,251 procedures (Credle et al. Am. Rev. Respir. Dis., **109**, 67-72). No comparable survey has been undertaken in the United Kingdom. Therefore we sent questionnaires to chest physicians likely to be involved with bronchoscopy (90% response rate), and analysed 193 completed forms describing the practice of 231 physicians. The respondents had performed approximately 40,000 bronchoscopies in the preceding year, with 87% of these being fibreoptic procedures performed with topical anaesthesia. Transbronchial biopsies, carried out by 85% of respondents, totalled 3,400 procedures in the same year. The mortality rates from fibreoptic bronchoscopy with and without transbronchial biopsy were found to be 0.12 and 0.04% respectively.

Major complications were twenty times more likely with transbronchial biopsy (2.7%) than without (0.12%; $p<0.0001$) and followed a different pattern. Details of the deaths, major complications and associated risk factors will be presented in this first report of the results of the survey.

Mediastinoscopy in Asians with thoracic lymphadenopathy

P.R. FARROW, D.A. JONES, P.J. STANLEY, J.S. BAILEY, J.B. COOKSON, J.M. WALES Thoracic gland enlargement in Asian patients is often treated presumptively as tuberculosis. Forty-one consecutive Asians with thoracic lymphadenopathy underwent diagnostic mediastinoscopy. Thoracic gland biopsy was possible in 39, tuberculosis was diagnosed in 24 (histology alone 9, histology and culture 11, and culture alone 4). All positive cultures grew Mycobacterium tuberculosis var hominis fully sensitive to standard chemotherapy. Sarcoid histology was found in 7 but 6 were treated for tuberculosis because of positive Heaf tests, 4 with apparent response. Other diagnoses included lymphoma (1), thymoma (1), and vascular anomaly (1). In 7 patients mediastinoscopy yielded no diagnosis but 6 responded to a trial of antituberculous therapy. There was one false negative Heaf test and 2/4 were falsely positive. Morbidity included one serious haemorrhage and two wound sinuses which healed slowly on treatment. Average admission was 4.5 days. 20% required analgesia for over 24 hours. Biopsy in Asians with superficial lymph node enlargement leads to a diagnosis other than tuberculosis in 22% and is thus a useful procedure (Stanley et al. Thorax 1981, 36, 9, 711). Mediastinoscopy, however, has a higher morbidity, is unlikely to lead to a change in therapy and should be reserved for cases in which there is addditional clinical doubt.

Can electron microscopy help to celltype lung tumours seen at fibreoptic bronchoscopy?

C.E. JOHNSON, C. GRAY, K. EGLETON, S.R. APPARICHIO, M.F. MUERS In lung cancer, histological and cytological examination of material sampled at bronchoscopy together yield high diagnostic rates. Problems arise however in ascribing a cell of origin to some tumours. This is now important as treatment options may be determined on this knowledge.

In other fields electron microscopy has proved useful in cell typing tumours. We therefore set out to study, prespectively, the value of this investigation in patients with lung cancer.

In 26 patients, bronchial biopsies and catheter aspirates were taken from suspected tumours during fibreoptic bronchoscopy. Each aspirate was examined by both cell cytology and electron microscopy.

Malignancy was diagnosed by at least one of these methods in 24 patients. In 7 cases, conventional histology and/or cytology were unable to ascribe or agree a cell of origin. Electron microscopy provided a tumour cell type in 5 of these cases. In 2 cases, subsequently, pneumonectomies were performed. In these, electron microscopy predicted the correct cell type whereas histology and cytology were either unable to type the tumour or reported it incorrectly.

Histology and immunofluorescence of oesophageal smooth muscle in achalasia

J.A.A. THORPE, C. EDWARDS, R. THOMSON, H.R. MATTHEWS In achalasia there is chronic inflammation of the nerves and ganglion cells of the oesophageal myenteric plexus. It has been postulated that either an infective process or an immunological disorder is responsible (1, 2, 3).

Biopsy material taken from within 4-6 cms. of the oesophagogastric junction, has been examined by light and immunofluorescent microscopy in 14 patients undergoing oesophageal myotomy for achalasia and in 6 control patients undergoing thoracotomy for other conditions. One half of each specimen was sent for conventional histological examination and the other half examined for direct immunofluorescence to demonstrate IgA, IgG, IgM and C3 antibody.

In 8 patients with achalasia ganglia were present and showed varying degrees of chronic inflammation; in the remaining 6 patients nerve trunks were seen but no ganglia were identified; there was no obvious abnormality of the smooth muscle. In biopsy material from the control patients there was no evidence of neural inflammation. IgG deposition was demonstrated in 10 patients with achalasia, IgA in 9, IgM in 7 and C3 in one. Fluorescent material was deposited predominently in the walls of vessels, connective tissue and the plasma membrane of muscle. Two of the control specimens showed weak IgG staining but the remainder were negative.

There is therefore evidence of immunoglobulin deposition in patients with achalasia, but its significance remains uncertain. An automatic process may be responsible but it is also possible that the changes are the result of local tissue damage.

1. A.F. Hurst, G.W. Rake. Achalasia of the cardia. Q. J. Med. 491-507, **23**, 1930.
2. J.J. Misiewicz, S.L. Waller, P.P. Anthony, J.W.P. Gummer, Achalasia of the cardia: Pharmacology and histopathology of isolated cardiac sphincteric muscle from patients with and without achalasia. Q. J. Med. 17-30, **38**, 1969.
3. B. Smith, The neurological lesion in achalasia of the cardia. Gut. 388-391, **11**, 1970.

Irrigation in the management of empyema

J. HUTTER, D. HARARI, M.V. BRAIMBRIDGE A technique of irrigation for the management of empyema and post-pneumonectomy space infections was described by Rosenfeldt[1] in 1981. Modifications have been made to this technique and the results in a further 14 patients presented. Thoracoscopy under general anaesthetic enabled full debridement and division of loculi within the empyema cavity under direct vision. Irrigation with two tubes was then instituted until 3 consecutive cultures of irrigation fluid became sterile when the chest drains were removed.

Using this method, irrigation was required for an average of 18 days and chest drains were removed after an average of 23 days. Patients remained in hospital for an average of 5.6 weeks.

The method, in combination with jejunostomy, was used

successfully in the management of a patient with a ruptured oesophagus and, combined with surgery, in the management of post-pneumonectomy space infection with broncho-pleural fistula. Tuberculous empyema was not found to be a contraindication to the irrigation technique.

1. F.L. Rosenfeldt, D. McGibney, M.V. Braimbridge, D.A. Watson. Comparison between irrigation and conventional treatment for empyema and pneumonectomy space infection. Thorax 134, **34**, 1979.

The role of rectal indomethacin and cryoanalgesia in the control of early pain following thoracotomy

D.J. KEENAN, K. CAVE, L. LANGDON, R. LEA Following thoracotomy, each of four groups of 15 patients was allocated on a randomised, double-blind basis to one of the following analgesia regimes: indomethacin suppositories, 100mgs. administered eight-hourly, cryoanalgesia, rectal indomethacin and cryoanalgesia, or neither. All patients had free access to intramuscular papaveratum, the dose and number of injections administered during the first 24 hours being recorded. Pain scores were registered by the patient, on a 100mms visual analogue scale both at rest and during physiotherapy, and our chief physiotherapist who supervised the measurements, recorded her impression of overall comfort and measured the pre- and post-operative peak flow.

Statistical analysis of the data showed a significant reduction in pain scores with both cryoanalgesia ($p<0.01$) and rectal indomethacin ($p<0.001$) and that the effects, when combined, were additive, although there was no interaction. There was, as expected, an increase in pain on movement and indomethacin was significantly effective in reducing this increase ($p<0.01$) whereas cryoanalgesia was not. The subjective impressions of the physiotherapist were in accordance with these findings.

Groups receiving either indomethacin alone or the combination treatment, required significantly less opiate and exhibited improved peak flow measurements ($p<0.0001$).

We conclude that rectal indomethacin can provide good, safe, easily administered, analgesia.

Is there a role for prophylactic antibiotics in pulmonary surgery?

P.M.B. WHITE, K.H. HAN, D.C.T. WATSON, J.D. FARRELL This trial was designed to assess the efficacy of perioperative cefamandole (a broad spectrum antibiotic with high activity against *Haemophilus influenzae*) in preventing infections after pulmonary surgery.

111 patients entered the trial and were randomly allocated to receive either 1g cefamandole intramuscularly after induction of anaesthesia (group C) or nothing (group N). Patients were assessed daily for signs of pulmonary or wound infection.

No infections occurred in the 26 patients who underwent thoracotomy only and they are not included in further discussion. 85 patients underwent pneumonectomy, lobectomy or wedge resection. 14 of the 47 patients (29.8%) in group N developed an infection. 8 of these (17%) had a wound infection or empyema and 8 (17%) developed a chest infection. 8 of the 38 patients (21%) in group C developed an infection. 2 (5.3%) had a wound infection or empyema and 6 (15.8%) a chest infection.

Applying the χ^2 test Yates' correction for small numbers to these results ($p>0.5$) indicates that there is no significant difference between the two groups. We would suggest that the common practice of using routine perioperative antibiotics in pulmonary surgery is not justified and that infective complications should be treated if they arise.

Gated ventilation scanning: a new approach to regional pulmonary function

A.L. MUIR, W.J. HANNAN, D. BELL, C.J. ADIE, P.K. WRAITH, H.M. BRASH The role of ^{133}Xe ventilation scanning is uncertain. This may result from poor resolution of the images due partly to the low energy of ^{133}Xe (80 KeV) and also as static images are produced of the dynamic process of breathing. We have developed a novel gated respiratory scan which, in a manner analogous to cardiac gated blood pool imaging, accumulates counts from patients rebreathing ^{127}Xe (with a more suitable energy of 203 KeV). The accumulated counts are framed in a computer into iso-volume images and these are subsequently displayed in movie form for inspection. As the lung changes shape during respiration corrections for changes in geometry are obtained by simultaneous collection of ^{99m}Tc counts from the gated macro-aggregate perfusion scan. From the corrected counts, regional tidal volumes, residual volumes and total capacity are computed and any inhomogeneity in ventilation demonstrated. When 10 patients were asked to breath at 2 different tidal volumes the change in the sum of regional ventilation detected by the gamma camera corresponded to the change in tidal volume. In 8 patients with known localised lung disease regional defects were clearly demonstrated even when static ventilation images and regional wash outs were unhelpful. This novel gated lung imaging technique should improve ventilation scanning.

Aerosol ventilation scanning in obstructive lung disease

H.W. CLAGUE, S. VINITSKI, M.J. CHAMBERLAIN, W.K.C. MORGAN A simple, rapid and reliable method for pulmonary ventilation scanning is required for those departments which do not have ready access to the relatively expensive short lived radioactive gases such as ^{133}Xe and ^{81m}Kr. We have studied the regional deposition pattern of an inhaled submicron sized ^{99m}Tc sulphur colloid aerosol in 8 patients with obstructive lung disease to determine whether aerosol ventilation scanning is a practical alternative.

Aerosol ventilation studies were evaluated by comparison with studies obtained by a ^{133}Xe gas rebreathing technique. Aerosol scintiscans were performed immediately and again at 24 hours to allow for mucociliary clearance of aerosol from the conducting airways. Immediate imaging gave valuable information on aerosol penetration and by inference the topographical distribution of airway disease.

The delayed aerosol image gave an index of alveolar retention and, therefore, alveolar ventilation. The value of this index as a measure of regional ventilation was confirmed by the highly significant correlation ($p<.001$) obtained when compared with the results obtained by xenon wash-in. In 2 subjects large areas of delayed xenon wash-out corresponded closely with areas of reduced aerosol penetration confirming the value of the aerosol technique as a measure of ventilatory impairment.

In conclusion, aerosol ventilation scanning can give an accurate reflection of regional ventilatory impairment and the combination of immediate and delayed imaging may give additional topographical information on the localisation of airway disease.

Effects of inhaled salbutamol on the regional distribution of alveolar ventilation in asthma, studied with positron emission tomography

S. VALIND, C.G. RHODES, P.J. BARNES, J.M.B. HUGHES Whole lung scanning with radioactive gases (e.g. ^{133}Xe, ^{81m}Kr) shows patchy distribution of ventilation in asthmatics at segmental and even lobar level. Using positron emission tomography much greater precision and spatial resolution of regional ventilation is possible. The effect of salbutamol on the regional distribution of specific alveolar ventilation ($\dot{V}A/VA$, alveolar ventilation per alveolar volume) has been studied in five asthmatics.

The regional distribution of $\dot{V}A/VA$ (l/min/l) was obtained using steady-state continuous inhalation of the short-lived positron emitting isotope neon-19. Measurements were made in the supine position in a single transaxial tomographic slice (spatial resolution 1.7 cm), before and after nebulised salbutamol (2.5mg).

After salbutamol there was a mean increase in FEV_1 and VC of 26% and 8% respectively. Specific ventilation in the tomographic slice, prior to medication, was low (mean 1.2 l/min/l, range 0.5-1.9) compared to normal subjects previously determined (mean 2.5, range 1.8-3.5). Furthermore, the distribution of specific ventilation showed large regional abnormalities. With bronchodilatation mean $\dot{V}A/VA$ in the slice increased to 1.8 l/min/l (mean of the five subjects, range 1.0-2.6). However, this increase was not uniform in the slice, as the largest increases were seen in the regions with least ventilation, although some of these regions remained unaffected by bronchodilator.

Positron emission tomography allows quantitative measurements of regional alveolar ventilation with a high spatial resolution. Using this technique we have demonstrated that the increase in regional alveolar ventilation after bronchodilation is highly non-uniform, suggesting varying reversibility of the airway obstruction.

A role for digital subtraction angiography in the diagnosis of pulmonary embolism

K.C. FLINT, P. DAWSON, A. MANNHIRE, S. GEORGE, P.J. ELL, N.McI. JOHNSON We have developed a method of digital subtraction angiography which provides consistently good images of the pulmonary arterial tree and have compared this with radionuclide ventilation perfusion scanning in 17 patients with suspected pulmonary embolic disease. Both investigations were reported independently without knowlege of clinical details but in the presence of a chest radiograph. In 8 patients both digital subtraction angiogram (DSA) and ventilation-perfusion scan (V/Q) were reported as negative. Both investigations were considered positive in 5 patients. The DSA was reported as positive in the presence of a negative V/Q scan in 3 patients. In one, in whom all the available information strongly suggested pulmonary embolism, there was obstruction of the right lower lobe artery. In the other 2, pulmonary embolism was felt to be unlikely and the less specific picture of diminished perfusion as shown by the capillary filling phase was seen on DSA. In one patient the V/Q scan was reported as abnormal and the DSA as normal. The subsequent clinical course in this 79-year-old woman with mild airways obstruction did not suggest pulmonary embolic disease. The specific finding of central or peripheral arterial obstruction was found in 4 of 8 DSA reported as positive. The less specific abnormality in perfusion image occurred in the remaining 4, 2 of whom probably did not have pulmonary emboli.

Monitoring lung vascular permeability in health and ARDS in man

G.S. BASRAN, A.J. BYRNE, J.E. HARDY Increased vascular permeability with resulting increased plasma protein extravasation and accumulation (PPA) in the lung forms the cardinal pathological feature of adult respiratory distress syndrome (ARDS). We have developed a non-invasive technique for monitoring PPA in man. This involves the radiolabelling of the protein transferrin with indium-113m, and measuring the radioactivity over the lung field and cardiac blood pool using a portable scintillation probe. To compensate for any changes in circulating protein levels (in response to therapy) the blood distribution was monitored over the same sites using erythrocytes radiolabelled with technetium-99m. An index of protein accumulation was calculated using the equation:

$$\text{PPA index} = \frac{\text{In lung counts}}{\text{In heart counts}} \Big/ \frac{\text{Tc lung counts}}{\text{Tc heart counts}} \times 10^3$$

The rate of protein accumulation (the slope of the PPA index-time plot) provides an index of lung vascular permeability (Pi min^{-1}).

Five healthy volunteers and six ventilated patients (5 with ARDS, and 1 with severe pneumonia) were studied. In healthy subjects the Pi was low (<0.5) and equilibrium was established within 1 hour. This contrasted with the ARDS patients all of whom had Pi values of >1.0. Three patients received a test dose of methylprednisolone (3 mg/kg iv) during the study. Patient 1 showed no change in Pi and died within 24 hours; patient 2 exhibited a moderate fall and survived 5 days; and in patient 3, Pi returned to normal and she made a full recovery.

This technique clearly demonstrates increased lung vascular permeability in patients with ARDS, and provides a means of monitoring the response to therapy.

The diagnosis of pulmonary emphysema in life

M.D. HAYHURST, W. MACNEE, D.H. WRIGHT, A. MACLEAN, P.M. WARREN, J.J.K. BEST, A.S.W. WIGHTMAN, E.W.J. CAMERON, D. LAMB, D.C. FLENLEY The diagnosis of emphysema is difficult in life. We have used computerised axial tomography (CAT) of the thorax as a densitometer to quantify, pre-operatively, the amount and distribution of emphysema in 11 patients (10 M; 1 F, age 46-70 years) who had resections for pulmonary tumours. We compared the emphysema, quantified by the CAT scanner with the pathological extent of emphysema in the resected specimens.

The frequency distributions of EMI number from two upper lobe CAT scan slices from each of the normal lungs ($n=20$ $FEV_{1.0}$ 87%, FVC 80%, TCO 94% of predicted values) were different from comparible slices of lungs which had emphysema ($n=24$, $FEV_{1.0}$ 84%, FVC 97%, TCO 59%) confirmed pathologically. In an analysis of the frequency distributions of EMI numbers in the range -460 to -500 the relative frequency of occurrence of pixel values in this range in emphysematous lungs (2.68 $\pm$ SD 4.3%) were significantly different ($p<0.01$) from those from normal lungs (0.54 $\pm$ 0.76%).

Those areas with EMI numbers in the range -460 to -500 could then be highlighted and matched with pathologically proven emphysema in the respected specimens. From these results CAT scanning may prove useful in diagnosing and quantifying the extent of emphysema in life.

Gastrointestinal tuberculosis: a retrospective review of 97 cases, 1970-1982

L.P. ORMEROD, O.E. KLIMACH In the Blackburn District Health Authority (population 279,000), there were 1,837 cases of tuberculosis notified during 1970-1982. A retrospective survey showed 97 patients with gastrointestinal tuberculosis, 86% in immigrants of Asian origin; 6 cases were found at post-mortem. Only 29% had evidence of pulmonary disease. Abdominal pain, weight loss, fever and vomiting were the commonest symptoms. Barium contrast studies showed abnormalities in 52% which could not be differentiated from the changes of other chronic inflammatory bowel disease. Drug treatment was used in 91 cases, combined with biopsy in 32, and resection in 33. Results of treatment were good with low morbidity and mortality. There have been few long term problems and no relapses have occurred. Surgical resection would seem best reserved for mechanical complications, as the results of medical treatment alone are very good. Further details of investigations and treatment will be presented.

Changes in tuberculosis notification rates in ethnic groups in England between 1971 and 1978/9

V.H. SPRINGETT, I. SUTHERLAND, A.J. NUNN Annual rates of decline in tuberculosis notification rates between national surveys conducted in 1971 and 1978/79 have been estimated for the four main ethnic groups resident in England, namely the white ethnic group born in the United Kingdom, and three ethnic groups born outside the UK, the Indian, the Pakistani/Bangladeshi and the West Indian.

The most rapid falls in rate of about 10% per year were shown for West Indians of each sex and for Pakistani/Bangladeshi males. For Pakistani/Bangladeshi females the rate fell by 6.5% per year. For Whites of each sex the rate fell by 5.1% per year. Indian immigrants showed only small changes.

For all groups combined the annual rate of decline was 3.8% in males and 2.0% in females. These rates of decline were considerably retarded by continued immigration from high incidence areas during the period under study; when standardised for an unchanged composition of ethnic groups the annual rates of decline become 4.3% for males and 3.7% for females.

Pulmonary infection with Mycobacterium xenopi — a review of treatment and response

J. BANKS, A.M. HUNTER, I.A. CAMPBELL, A.P. SMITH, P.A. JENKINS Forty-seven patients (82% male) with pulmonary infection caused by *Mycobacterium xenopi* have been reviewed to assess response to treatment and long term prognosis. In 21 patients the disease was sub-acute developing over a period of 2-4 months, whilst another 20 patients had longer histories and slowly progressive changes on chest radiographs. Response to treatment was poor and unpredictable, and did not correlate with either results of in vitro sensitivity tests, pre-existing lung disease nor mode of onset of symptoms. Only three patients (6%) were **completely cured** with chemotherapy and a further 8 (17%) had **bacteriological cure** i.e. showed satisfactory clinical and bacteriological response with radiographic improvement, but failed to close cavities. In patients with favourable outcome the best regimen appeared to be rifampicin and isoniazid combined with either streptomycin or ethambutol. Another 12 (25.5%) showed initial favourable responses to drug treatment, but eventually relapsed. Three patients had progressive disease while receiving prolonged courses of chemotherapy. Surgical resection was performed in 5 patients with resultant cure in 4.

Since the prognosis following drug treatment alone is so unpredictable it is suggested that resection might be part of first line treatment, and should usually be performed if patients fail to respond to initial chemotherapy or relapse.

Antituberculous chemoprophylaxis with isoniazid-rifampicin

MARTIN W. McNICOL, H. THOMSON, J.F. RIORDAN, E. FORDE, C.J. ALLEN At the Willesden Chest Clinic chemoprophylaxis is routinely given to immigrants from India/East Africa/Asia without evidence of active tuberculosis but with strong positive tuberculin reactions, to child contacts of sputum positive cases and children with positive tuberculin tests who have not had B.C.G.

From 1979 to 1981 a three month course of isoniazid-rifampicin was given to 505 patients (age range 0-77 years, mean 31 years). 334 (67%) were of Asian origin. 218 (44%) were female. Outcome assessed in August 1983 by questionnaire to general practitioners is known for 296

(59%). Shortest follow-up was 18 months and longest 42 months, mean 28 months.

Compliance was generally good, and side effects few. Cessation or change of treatment was required in only 9 patients (2%). No major toxic effects were ecountered.

Three patients relapsed; they were sisters with mediastinal nodes. One also had a lymph node abscess from which sensitive organisms were recovered. They had not been fully compliant.

This preliminary assessment suggests that 3 months' treatment with isoniazid-rifampicin is a safe and effective form of chemoprophylaxis.

The prognosis of sarcoid heart disease in the United Kingdom

HUGH A. FLEMING, SHELIA M. BAILEY For 12 years we have been collecting and following up cases of sarcoid heart disease in the United Kingdom. (1) The series now numbers 251 cases of whom 110 have died and 75 have had a necropsy with confirmation. Sudden death has occurred in 65 and has been the mode of presentation in 27.

However, the prognosis of survivors with this diagnosis is not always bad even in cases with severe cardiac involvement. The criteria for inclusion in this study have been extremely strict and some cases included in our earlier reports have now been eliminated.

We present an analysis of survival. Of 141 living patients, 5 have survived for more than 20 years from diagnosis, 20 for more than 10 years and 48 for more than 5 years. Of those who had died from their disease, 21 had survived for over 5 years, the longest being 22 years from the time of diagnosis.

Details of type of clinical cardiac involvement and treatment used are analysed. The very variable natural history makes the assessment and the effects of steriods in particular, very difficult.

1. H.A. Fleming, S.M. Bailey. Sarcoid Heart Disease: report of 197 United Kingdom cases with necropsy confirmation in 62. J. Roy. Coll. Phycns. Lond. 245-53, **15**, 1981.

A new profile of the sarcoid granuloma

D. GERAINT JAMES, B.B. MISHRA, L. POULTER, G. JANOSSY The sacoid granuloma consists of lymphocytes, macrophages and epithelioid cells. Monoclonal antibodies distinguish subsets of lymphocytes, and histochemical stains identify macrophage subpopulations. This analysis in tissue sections has added to our knowledge of spatial inter-relationships of the different cell types in the granuloma. The present study applies these techniques to punch biopsies of skin sarcoid lesions and sites of Kveim tests. The sarcoid granuloma has a central core and a peripheral mantle. The centre is populated by strongly HLA-DR+, macrophage like cells, which exhibit reactivity with the specific monoclonal antibody RFD-2 as well as strong lysosomal activity; these are the conventional epithelioid cells also in the centre are T4+ helper lymphocytes. The peripheral mantle contains macrophage-like cells which are distinguished by their reactivity with monoclonal antibody RFD-1; they are antigen-presenting cells. Also in the peripheral rim are T8+ suppressor cells, admixed with T4+ cells. T8+ cells are not found in the centre. This interesting architectural arrangement of different macrophages associated with T4+ lymphocytes in the centre and with T8+ cells in the periphery is a feature of the natural sarcoid skin lesion. This is the first occasion on which it has been shown that the Kveim granuloma shares the same pattern.

Prediction of glucocorticoid resistance in chronic asthma by culture of blood mononuclear cells

J.G. DOUGLAS, M. POZNANSKY, A.C.H. GORDON, A.H. WYLLIE, I.W.B. GRANT Patients with chronic asthma usually respond to treatment with glucocorticoids, but some are resistant even to large doses. Recent studies have shown that complement receptors on blood monocytes are reduced when exposed to prednisolone in vitro in patients with glucocorticoid sensitive asthma but not in those with resistant asthma.[1] This suggests that glucocorticoid resistance might be demonstrated in peripheral blood leucocytes by in vitro tests.

Peripheral blood mononuclear cells from asthmatic patients and normal controls were cultured in soft agar. The cells harvested from 15 patients with glucocorticoid sensitive asthma were similar to those from 15 resistant patients with respect to their subsets and to colonies generated in the presence of phytohaemagglutinin. Low concentrations of methylprednisolone (10^{-8}M) inhibited colony growth of cells from glucocorticoid sensitive patients and normal controls but had little effect in those with resistant asthma. In a prospective study of 11 newly-diagnosed asthmatics, the cellular response to glucocorticoid, as determined by colony inhibition by methylprednisolone in vitro, was found to correlate with the increase in FEV_1 during a therapeutic trial with oral prednisolone.

Thus in vitro assessment of glucocorticoid sensitivity may have applications in predicting which patients may be spared ineffective and potentially harmful corticosteroid therapy.

1. J. Carmichael et al. Br. Med. J. 1419-22, **282**, 1981.

Inhaled therapy can abolish morning dips in asthma

C.R. HORN, T.J.H. CLARK, G.M. COCHRANE Morning dips in peak expiratory flow rate (PEFR) are associated with an increased risk of death in asthmatic patients. Inhaled therapy is sometimes thought to have an insufficient length of action to be of benefit and long acting oral beta agonists or methylxanthines are often used despite the high incidence of side effects. Fourteen patients monitored their PEFR at home before starting regular inhaled salbutamol (800 μg q.d.s.). After one or two weeks, inhaled beclomethasone dipropionate (BDP) (400 mcgs q.d.s.) was added for a further two weeks. 13 patients improved significantly, mean daily PEFR rising by 8% with salbutamol and a further 5% with the addition of BDP. Mean early morning PEFR rose with combined treatment

from 290 litres a minute to 350 litres a minute. In 8 subjects the size of the morning dips was reduced to half of those in the pre-treatment period on salbutamol ($p<0.01$) and to one third on combined therapy ($p<0.0025$). Dips were abolished in three subjects when taking both therapies. No subject reported side effects. Inhaled beta agonist alone or in combination with inhaled steroid can therefore reduce the overnight fall in lung function found in asthmatic patients.

Ipratropium dose-response curves in childhood asthma, assessed by hyperventilation challenge

NICOLA WILSON, CAROLINE DIXON, MICHAEL SILVERMAN The effect of multiple doses of inhaled ipratropium bromide (IB) on hyperventilation dose response curves, was studied in 11 children with asthma of varying severity. Isocapnic hyperventilation (HV) was performed using dry air at 20°C. Minute ventilation ($\dot{V}$) was increased in 10 1/min steps every 5 minutes until a 25% fall in FEV_1 occurred or the maximum $\dot{V}$ had been reached. The $\dot{V}$ which caused a 20% fall in FEV_1 (PD_{20}) was calculated from the dose-response curve. On the first two study days, after a control HV test, the effect of either placebo or IB 200 μg (double-blind) on PD_{20} was measured. On the third day lower doses of IB were given to those children completely protected by IB 200 μg, and higher to those in whom there was still a response. The PD_{20} was reproducible before and after placebo (coefficient of variation 7.5%). 9/11 children were completely protected by IB 200 μg and in 6 of these 40 μg was sufficient to abolish response. Of the remaining two children, one required the highest dose used, 1500 μg for complete protection, while the other remained unprotected by this dose. The dose of IB required to protect against the stimulus of hyperventilation was dependent on the size of the stimulus and the overall severity of asthma. The recommended dose would have been inappropriate for about half of the children, at levels of $\dot{V}$ commonly achieved during exercise.

Airway responsiveness to histamine in man: in vivo and in vitro measurements

J.A. ROBERTS, D. RAEBURN, I.W. RODGERS, N.C. THOMSON The relative importance of the different factors influencing airway responsiveness in man is unclear. We have previously demonstrated that in vivo airway responsiveness to methacholine is not related to in vitro smooth muscle sensitivity to this agent (Roberts *et al.* Thorax 705-6, **38, 1983**). We have now examined the relationship between in vivo and in vitro responsiveness to another agonist, histamine. We studied 11 patients (age range 51-72 years) undergoing thoracic surgery, one of whom had been asthmatic since childhood. In vivo responsiveness was expressed as the provocation concentration (PC) of histamine causing a decrease in FEV_1 of 20% ($PC_{20}FEV_1$) and in sGaw of 35% (PC_{35}sGaw). Bronchial tissue obtained at thoracotomy was used to measure in vitro smooth muscle sensitivity to histamine. Log dose-response curves were constructed and the concentration causing a 50% maximum contraction (EC_{50}) derived. $PC_{20}FEV_1$ ranged from 0.6 to 64 mg/ml and PC_{35}sGaw from 0.2 to 11.3 mg/ml. The EC_{50} ranged from 1.5×10^{-6}M to 9.5×10^{-6}M. The asthmatic patient showed the most marked in vivo response to histamine but in vitro smooth muscle sensitivity was not increased ($EC_{50}2.3\times10^{-6}$M). These results indicate that histamine airway responsiveness in man is not determined solely by smooth muscle sensitivity to this drug. Furthermore, the findings in one patient with asthma suggest that airway hyperresponsiveness to histamine is unlikely to be due to increased sensitivity to histamine at the receptor level.

Pharmacological modulation of airway and plasma histamine responses to inhaled antigen in asthma

P.H. HOWARTH, G.J.-K. PAO, S.T. HOLGATE Both sodium cromoglycate (SCG) and salbutamol (S) may have several modes of action in asthma. This study investigated their ability to inhibit mast cell degranulation in vivo.

Eight grass pollen-sensitive asthmatic subjects whose mean FEV_1 was 109% predicted and mean methacholine PC_{20} was 4.0 mg/ml participated in the study. Antigen bronchial provocation was carried out to define a concentration producing a 25% fall in FEV_1 from baseline. On a separate day each subject had a single antigen challenge (control) which was repeated on 3 subsequent occasions, 30 minutes after pre-treatment with inhaled SCG 20mg, S 0.2mg and saline placebo. Before and at regular intervals up to 30 minutes after challenge FEV_1 was measured and blood taken for plasma histamine measurements[1]

Both control and placebo challenges produced maximal falls in FEV_1 of 26% which were preceded by increases in plasma histamine from a mean baseline of 0.18 to 0.44 ng/ml and 0.16 to 0.45 ng/ml respectively. SCG had no effect on baseline FEV_1 but significantly inhibited the airway response to challenge by 71% and plasma histamine rise by 65%. S, while only increasing the mean FEV_1 by 4%, significantly reduced the airway and plasma histamine response by 95% and 84% respectively.

Thus antigen inhalation in asthma is associated with reproducible airway and plasma histamine changes which are both inhibited by sodium cromoglycate and salbutamol.

Prostaglandin D_2—a mast cell mediator with potent bronchoconstrictor properties in man

C. HARDY, C. ROBINSON, A.E. TATTERSFIELD, S.T. HOLGATE Although PGD_2 is the most abundant prostanoid released from human lung mast cells with IgE-dependent activiation (Lewis *et al,* J. Immunol. 1627-1631, **129,** 1982), its effect on human airways has not been studied. We have therefore investigated the effects of inhaled PGD_2 on the airways of 7 normal and 7 mildly asthmatic subjects (geometric mean PC_{35} histamine, 0.18 mg/ml) and compared the findings with those of inhaled $PGF_{2\alpha}$. Cumulative dose response curves in normal subjects showed a reduction in sGaw of 22% with PGD_2, though only after the highest concentration (0.5 mg/ml, $p<0.025$). The same doses of $PGF_{2\alpha}$ had no effect. In contrast, both PGD_2 and $PGF_{2\alpha}$ caused marked dose

related falls in sGaw in the asthmatic subjects. Geometric mean PC_{35} values for PGD_2 and $PGF_{2\alpha}$ were 0.008 and 0.028 mg/ml respectively.

The greater potency of PGD_2 was confirmed in a separate time course study of a single inhalation of 0.25 mg/ml of each prostanoid in the asthmatic subjects. There was a 75% reduction in sGaw with PGD_2 and a 33% reduction with $PGF_{2\alpha}$. The maximum response with both prostanoids occurred at 3 min. Recovery was slower for PGD_2 (>45 min), whilst sGaw had returned to baseline by 20 min with $PGF_{2\alpha}$. Thus PGD_2 is not only the predominant prostanoid released from mast cells but it is the most potent prostaglandin bronchoconstrictor so far studied.

Choice of walking tests to assess respiratory disability and breathlessness

P.A.W. EDGAR, L.W.E. VAN HEURN, A.D. MORGAN, G.J.R. McHARDY The 12 minute walking test (12MD) and shorter tests have been proposed as measures of every-day disability. We have examined the relation between distances walked in 12 minutes or less and estimates of percieved exertion (PE) and breathlessness made by 22 male bronchitic patients (mean age 63 ± SD 5 y, FEV_1 1.5 ± 0.97 l, VC 3.23 ± 0.85 l). Ventilatory capacity (FEV_1 and FVC), single-breath CO transfer factor (Tco), the distance walked in 12, 6 (6MD) or 2 (2MD) minutes, and the times taken to walk 50m on the level or on a 6% gradient were measured. Walks were performed in random order; following each, the patient estimated PE and breathlessness, using a modified Borg scale (PB) and a visual analogue scale (VAS). Distances walked and velocity of walking correlated significantly with FEV_1, VC and Tco, but the better correlations were with 6MD or 12MD. Perceived breathlessness was most strongly correlated with 6MD ($r = -0.72$, $p<0.001$), less with 2MD ($r = -0.43$) and not significantly with the 50m level walk. All correlations with PB were higher than comparable correlations with VAS. Walks of at least 6 minutes' duration are of greater value in assessing disability and breathlessness and the scale of perceived breathlessness is superior to VAS in these circumstances.

How long is exercise training required to produce and maintain maximum improvement in patients with chronic airways obstruction?

DIANA TYDEMAN, ANN CHANDLER, ANNA CULOT, BERYL GRAVELING, BRIAN HARRISON 24 patients aged between 56 and 69 years with an average FEV_1 of 0.68 litres were studied over 2½ years. They were trained to their peak performance attending weekly exercise classes and were then randomised into one of two groups. Group 1 continued weekly attendance and exercised at home; Group 2 exercised only at home. Assessments were made at the beginning of the trial, after one month, and then at two monthly intervals.

8 patients withdrew from the programme for various reasons. The time to peak performance in the remainder ranged from 26 to 51 weeks. There was a significant increase in 12 minute walking distance from 552 to 782 metres. By the end of training all but one patient could walk 1600 metres in their own time without resting compared with an average distance of 734 metres before training began.

Following randomisation patients were followed for a further 6 months. There were no significant differences between the entry characteristics of patients in either group. Patients in both groups maintained their improvement.

Exercise training produces greater improvement in performance than any drug therapy in this group of patients. The time to peak performance was between 6 and 12 months. Weekly follow up once peak performance is reached is unnecessary.

Responses to prednisolone in chronic airflow limitation (CAL)

D.M. MITCHELL, P. GILDEH, M. REHAHN, A.H. DIMOND, J.V. COLLINS Evidence is conflicting regarding steroid responsiveness in CAL. Few studies have been randomised, controlled or double blind and in those that have only one or two variables for response have been measured. We report a randomised, controlled, double blind, crossover study of the acute effect of Prednisolone 40 mg/day on 43 patients (mean age 60.3 years) with CAL (mean FEV_1 = 1.02 FEV_1/FVC ratio 43.7%), measuring changes in several subjective factors and a number of indices of lung function and exercise performance. There was a striking improvement in some measurements following placebo treatment (breathlessness score $p<.01$; oxygen cost diagram $p<.05$; PEFR $p<.001$; FVC $p<.05$; 12 minute walking distance $p<.001$). There was further improvement in some measurements following Prednisolone when compared to placebo (PEFR $p<.01$; FEV_1 $p<.01$; 12 minute walking distance $p<.01$). Further analysis showed that placebo effects were not due to carry over effect in those (20 patients) who received Prednisolone first. Over and above the placebo response, 17 patients showed significant response (>20% improvement) to Prednisolone but not to placebo in two or more of 10 variables in which change was measured. A response in one index was often not accompanied by improvement in other indices. This study shows (1) a marked placebo effect occurring in patients with CAL who receive a trial of steroids (2) the necessity of measuring several variables to identify genuine steroid response over and above placebo effects in CAL.

Does aminophylline improve exercise tolerance in chronic obstructive pulmonary disease?

A.C. DAVIDSON, C.B. COOPER, I.R. CAMERON, Respiratory muscle fatigue may limit exercise in chronic obstructive pulmonary disease (Grassino et al, Bull. Eur. Physiopathol. Respir. 105-11, **15**, 1979). Aminophylline is reported to prevent fatigue (Aubier et al, N. Eng. J. Med. 249-52, **305**, 1981); although this is disputed (Moxham et al, Thorax. 232, **38**, 1983). We have studied patients with severe irreversible airways obstruction to assess the effect of aminophylline on exercise ability and respiratory muscle function.

Patients were familiarised with the methods and studied in double-blind fashion before, and four hours after, oral aminophylline or placebo. Theophyllines were discontinued before the study and other bronchodilator therapy was omitted on study days. We recorded spirometry, lung volumes, 6 minute walking distance and progressive cycle ergometry with visual analogue scales, maximal static inspiratory and expiratory pressures and CO_2 rebreathing responses measured as minute ventilation and occlusion pressures.

Ten patients have been studied (age 58 ± 2.3 years; FEV_1 0.86 ± 0.1 l; mean ± SEM). Therapeutic aminophylline levels were achieved 13.8 ± 1.0 mg/l. No significant change in FEV_1 or PEFR occurred. Subjects walked further ($p<0.05$) but breathlessness scores were increased ($p<0.05$). There were no significant changes in maximal inspiratory and expiratory pressures nor in maximal ventilation and oxygen uptake during exercise. Responses to rebreathing CO_2 were increased in terms of both minute ventilation and occlusion pressures ($p<0.05$). We conclude that after acute administration of aminophylline patients walked further but felt more breathless.

Effects of oral and inhaled salbutamol and oral pirbuterol on right and left ventricular function in chronic bronchitis

R.J.D. WINTER, J.A. LANGFORD, R.M. RUDD In many patients with chronic bronchitis and emphysema right and left ventricular ejection fractions (RVEF and LVEF) are reduced (MacNee et al. Thorax. 594, **38**, 1983). We used multiple gated equilibrium radionuclide ventriculography to compare the effects of oral salbutamol 4 mg and pirbuterol 15 mg, which have equal peak bronchodilator effects, on cardiac function in 12 patients with chronic bronchitis (FEV_1 858, SD 412 ml, Pao_2 8.2, SD 1.9 kPa). We also compared nebulized salbutamol 0.5 mg and 5 mg in 9 of the patients. A randomized double-blind crossover design was used. The initial mean RVEF was 0.31 (SD 0.10); the initial mean LVEF was 0.53 (SD 0.12). Both oral salbutamol and pirbuterol produced significant increases in RVEF and LVEF at 60 and 90 minutes after drug ingestion ($p<0.01$ in each case). The increases in RVEF after 60 and 90 minutes were respectively 0.07 (SD 0.04) and 0.04 (SD 0.04) for salbutamol, not significantly different from 0.06 (SD 0.04) and 0.05 (SD 0.03) for pirbuterol. The increases in LVEF after 60 and 90 minutes were respectively 0.07 (SD 0.04) and 0.06 (SD 0.05) for salbutamol, not significantly different from 0.08 (SD 0.04) and 0.07 (SD 0.06) for pirbuterol. Inhaled salbutamol 0.5 mg and 5 mg had no significant effect on RVEF or LVEF after 20 and 60 minutes. Oral β_2 agonists improve right and left ventricular function in patients with chronic bronchitis.

What is the optimum haematocrit in hypoxic lung disease?

J.A. WEDZICHA, F.E. COTTER, A.C. NEWLAND, D.W. EMPEY Although reduction of an elevated packed cell volume in polycythaemia secondary to hypoxic lung disease improves exercise tolerance, the optimum haematocrit is unknown. Using our technique of isovolaemic haemodilution by erythrapheresis, we randomised 24 hypoxic polycythaemic patients into two equal groups aiming to reduce the PCV to around 0.43 in group A and 0.51 in group B. In group A (mean Pao_2 7.4kPa; FEV_1 0.961), a mean volume of 544ml of red cells was removed in a double-blind manner, the PCV falling from 0.56 ± 0.05 to 0.43 ± 0.03 (range 0.40-0.46). In group B (mean Pao_2 6.8kPa; FEV_1 0.721) after removing a mean volume of 521ml of red cells, the PCV decreased from 0.59 ± 0.03 to a significantly higher post treatment value ($p<0.001$) of 0.51 ± 0.02 (range 0.49-0.53). There were significant reductions in blood viscosity for both groups ($p<0.01$).

In group B the six minute walking distance improved from 354m to 426, ($p<0.01$) after erythrapheresis, which was significantly greater than the change in walking distance in group A ($p<0.02$) and for 8 polycythaemic patients who received a placebo erythrapheresis ($p<0.01$). Group B also showed significant improvement on visual analogue symptom scores for shortness of breath ($p<0.02$).

In polycythaemia secondary to hypoxic lung disease the PCV should be reduced to around 0.51, which is higher than the accepted optimum haematocrit in normal subjects.

Responses to the sequential administration of salbutamol and ipratropium bromide during recovery from acute severe asthma

D.V. McGIVERN, P.H. FENTEM, J.T. MacFARLANE, D. DAVIES The sequential administration of salbutamol (S) and ipratropium bromide (IPB) has proved effective in the treatment of acute severe asthma (ASA). By contrast, most patients with mild stable asthma achieve maximum bronchodilation with S alone and only a few will obtain further improvement with IPB. To see if the benefit obtained from IPB occurs only during the initial treatment of the acute attack, we have observed the response to sequential treatment with S and IPB for 4 days following admission.

Twenty-eight patients with ASA (PEFR<25% predicted, Pao_2<9.3 kPa) were randomly allocated to one of two treatment groups. Group A received nebulized S 10 mg on admission (day 1), followed by 50 μg IPB after 2 hours. Group B received these drugs in reverse order. PEFR was measured on admission and at hourly intervals for 4 hours. The same study was repeated on days 2 and 4 beginning at 9.00 a.m. In between studies patients received 10 mg S 6 hourly.

PEFR increased significantly after each nebulization, except when IPB was given as the second drug on day 2 (Table).

	Group A		
	Baseline PEFT (l/min ± SE)	% increase after S	% increase after IPB
Day 1	90 ± 7	56**	28*
Day 2	167 ± 15	33**	3 (NS)
Day 4	171 ± 23	29**	22**

	Group B		
	Baseline PEFR (l/min ± SE)	% increase after IPB	% increase after S
Day 1	119 ± 9	15*	18**
Day 2	155 ± 11	13**	24**
Day 4	229 ± 27	35**	9**

**p<0.01 *p<0.05

'Non-response' was defined as an increase in PEFR<15% 2 hours after nebulization. This occurred 24 times with S and 40 times with IPB.

It appears that the sequential administration of a beta-agonist and IPB is beneficial both on admission and during recovery from ASA. The data suggests that the beta-agonist should be given first in the sequence.

Monitoring theophylline therapy using dried blood spot samples

T.R. GAMLEN, E.J. COOMBES, G.F. BATSTONE, M.J. CUSHLEY, S.T. HOLGATE Theophylline and aminophylline preparations are being increasingly used for the maintenance treatment of asthma. We have found close concordance between plasma levels of theophylline measured by a standard HPLC method and by a simpler fluorimetric immunoassay (James et al, Ann. Clin. Biochem. 251-253, **204**, 1983). The high sensitivity of this fluorimetric assay, which requires very small samples, led us to adapt it for the assay of theophylline in dried blood spots. Forty-three patients on theophylline had simultaneous capillary and venous blood samples taken. The capillary blood was collected onto filter paper cards to fill 1.0 cm circles and allowed to dry. A 6 mm disc was punched from the centre of each spot from which theophylline was eluted.

There was a close correlation between capillary spot and plasma theophylline levels ($y = 0.79x + 0.33$, $r = 0.985$, $\sigma^2 = 0{\cdot}68$). The minimum 95% confidence interval was 1.71, the bias 1.67 and the precision 1.48 μg/ml. Theophylline was stable in dried spots for at least 1 month and levels were unaffected by the hematocrit (range 29-67%). The ease with which dried blood spots may be collected and posted to the laboratory, together with the simplicity, precision and accuracy of the assay offers advantages for the monitoring of theophylline treatment in domiciliary and out-patient practice.

Saliva theophylline concentrations as a guide to total (and free) plasma concentrations

P. EBDEN, D. LEOPOLD, D. BUSS, A.P. SMITH, P.A. ROUTLEDGE Although several studies have examined the relationship between saliva and total plasma theophylline concentration in adults with chronic airflow obstruction who are receiving long term theophylline therapy, their conclusions concerning the closeness of the relationship have differed markedly. In addition, no study has examined the relationship between saliva and free (unbound) plasma theophylline concentration.

We therefore measured total plasma, mixed stimulated saliva theophylline concentration (by high performance liquid chromatography) and free plasma theophylline concentration (by equilibrium dialysis) in simultaneous samples from 32 outpatients receiving chronic oral theophylline therapy and who had received the drug at least two hours before sample collection.

There was a close relationship between total saliva and total plasma theophylline concentration ($r = 0.943$, $n = 32$, $p<0.001$) and total saliva and free plasma theophylline concentration ($r = 0.949$, $n = 32$, $p<0.001$; saliva concentration = 1.07 × plasma free concentration + 0.23), mean difference between paired saliva and free plasma concentration being 0.65 (SE 0.17).

We conclude that 2 hours or more after dosage, stimulated mixed saliva provides a simple and non-invasive method of assessing total (and free) plasma theophylline concentration during chronic oral therapy. The therapeutic range for saliva (and free plasma) theophylline concentration corresponding to the generally accepted total plasma concentration range (10 to 20 μg/ml) is approximately 6 to 12 μg/ml.

Acute chest syndrome in sickle cell disease

P.J. LUCE, S.C. DAVIES, M. BROZOVIC, J.F. RIORDAN The combination of chest pain, fever, leucocytosis and new shadows on chest X-ray is frequently encountered in acutely ill patients with sickle cell disease. We surveyed 25 consecutive episodes which occurred in 13 patients (6 male, 7 female; age range 11 to 45 years, mean 22.9 years) admitted to the adult wards under the care of the haematology service at Central Middlesex Hospital between 1978 and 1982, representing 14% of all sickle related admissions.

Chest symptoms were almost invariably present on admission (23 episodes) whereas abnormal chest signs (11 episodes) and radiological findings (14 episodes) were less common on admission but developed later in virtually all patients. Radiological abnormalities were nearly always basal and included patchy or segmental consolidation, linear atelectasis and small pleural effusions. The X-ray findings were wholly or predominantly unilateral in 16 episodes and bilateral in 9 episodes. The bilateral episodes were associated with higher pulse rates, a longer duration of fever and larger falls in haemoglobin and platelet count than the unilateral episodes. Arterial hypoxaemia was common but data were insufficient to allow correlation with radiological findings. Routine blood and sputum cultures, routine tests for pneumococcal antigen, and paired serology for respiratory pathogens showed evidence of infection in only 3 episodes, (*Ecoli* septicaemia, raised mycoplasma titres, and raised influenza A titres). All episodes were treated with a regime of vigorous rehydration, antibiotics and analgesia. In 11 episodes clinical deterioration occurred and exchange transfusion was performed. This was commoner in bilateral disease which also required more exchanges to achieve a satisfactory result. Marked clinical and radiological improvement was apparent in 10 of 11 cases within 48 hours of the final exchange. Death occurred in 2 patients with bilateral disease, 1 with cerebral sickling and the other following a fit and inhalation of vomit.

It is concluded that the acute chest syndrome in adolescent and adult sicklers is rarely due to infection. A more detailed prospective study is required to elucidate the pathogenesis.

Malignant lymphoma of lung in two patients with Sjögren's syndrome

A. HERBERT, A.M. ANSCOMBE Two cases of diffusely infiltrating malignant lymphoma of lung are described. One case was a woman with a long history of Sjögren's syndrome and the other was a man who had bilateral parotid enlargement, also for many years, which was shown at autopsy to be malignant lymphoma.

Both patients became breathless and developed a restrictive pattern of lung disease. Chest radiographs showed diffuse bilateral shadowing simulating pulmonary fibrosis. After six and five years respectively, lung function deteriorated and both patients died of respiratory failure. Malignant lymphoma was suspected on transbronchial lung biopsy and was supported by the demonstration of Bence-Jones proteinuria. Immuno-peroxidase staining of sections of an open lung biopsy (DR female) and at autopsy (DS male) confirmed malignant lymphoma. In the latter, this was of the same light chain type in lung and parotid.

These are examples of B cell malignant lymphoma arising in mucosa associated lymphoid tissue (MALT). MALT lymphomas often have a prolonged clinical course and a deceptively benign histological appearance which can be misinterpreted as lymphocytic interstitial pneumonitis and pseudolymphoma in lung, and as benign lympho-epithelial lesion in salivary gland. It can arise on a background of auto-immune sialadenitis from which it may be difficult to distinguish.

Tuberculosis in the elderly

A.D. MacKAY, R.B. COLE We studied tuberculosis notifications from 1976-80 in the North Staffordshire Health District (NSHD), which has only a small immigrant population. The notification rate for new cases of TB in white patients over 55 years of age in NSHD was twice that reported for England and Wales by the MRC (B.M.J. 895-8, **281**, 1980). Of 433 cases in all ethnic groups, 52 (12.0%) were diagnosed only at necropsy, and 48 (11%) died before treatment was completed. TB was the only cause of death in 39 of these 100 cases and contributed to death in a further 19 cases, the major site of disease being thoracic in 86 cases. Of those dying before completion of treatment, TB was the cause of death or contributory in 23; 16 of those 23 (70%) had been treated for less than 13 weeks. The percentage of deaths occurring before or during treatment rose with increasing age. Major drug-induced unwanted effects occurred in one-third of all treated cases in the over-65 age group, mostly related to rifampicin. This survey highlights the problems of TB in the elderly, who present with advanced disease, are diagnose late and whose course is complicated by other diseases and a poor tolerance of therapy.

Nebulised lignocaine anaesthesia for fibreoptic bronchoscopy—is it to be preferred?

I. GOVE, J. WIGGINS, D.E. STABLEFORTH The use of prior nebulised lignocaine for topical anaesthesia was studied in 52 patients undergoing fibreoptic bronchoscopy (FOB) without supplementary oxygen. All patients received atropine premedication, and were randomised as follows: 19/52 received bolus lignocaine and i.v. diazepam (BLD), 15/52 had nebulised lignocaine and i.v. diazepam (NLD), and 18/52 had nebulised lignocaine (NL) alone.

NL alone had no significant effect on basal pO_2 (mean change -1.3%) whilst i.v. diazepam caused a significant fall in both groups BLD (mean change -13.6%, $2p<0.01$) and NLD (mean change 16.5%, $2p<0.01$). During FOB the pO_2 fell in 15/19 of group BLD (mean max change: -18.8%) and in 13/15 of group NLD (mean max change: -14.8%) but in only 5/18 of group NL ($2p<0.05$). Continuous ECG recording showed significant arrhythmias in only 2 patients, 1 from each of groups BLD and NLD.

The procedure took significantly longer for group BLD (mean $\pm$ SD min, 12.7 $\pm$ 5.9) than for group NL (8.5 $\pm$ 3.0, $2p<0.01$). The NL technique was preferred by the bronchoscopists, but there was no difference in patient acceptibility between the three groups.

Although additional lignocaine was needed in 10/15 in group NLD (mean 118mg) and 13/18 in group NL (mean 82 mgs), mostly to achieve adequate nasal anaesthesia, the total amount given did not differ between the groups (mean $\pm$ SD mg; BLD 540 $\pm$ 102, NLD 479 $\pm$ 86, NL 454 $\pm$ 77).

The early fall in Po_2 seen with intravenous diazepam premedication was not seen in patients receiving nebulised lignocaine alone. These results suggest that compared with bolus administration nebulised lignocaine gives equally good local anaesthesia, is well tolerated without premedication, and is quicker.

The distribution of house dust mites in Liverpool

M.J. WALSHAW, C.C. EVANS Vacuumed samples of dust from the bed, bedroom carpet, and lounge carpet of 50 Liverpool houses were analysed using a standard technique[1] involving incubation with 90% lactic acid and identification of mites with a stereo-microscope. *Dermatophagoides pteronyssinus* was the commonest mite found. However, *Euroglyphus maynei* was the predominant mite in 48% of beds examined, and formed 39% of all adult mites in bed dust — more than in any other published series.[2] The highest levels of this mite were found in bed dust, fewer in bedroom carpet dust, and even fewer in lounge carpet dust (although here it still made up 18% of the total adult mite count). There was a correlation ($p<0.01$) between lowering social class and the prevalence of this mite, and also between lowering social class and Na+ concentrations in bed dust ($p<0.01$). Furthermore, there was a correlation ($p<0.05$) between Na+ concentration and *E maynei* levels in bed dust. These are new findings.

1. M.E. Blythe. Some aspects of the ecological study of the house dust mites. Br. J. Dis. Chest. 3-31, **70**, 1976.
2. M.E. Blythe, J.D. Williams, J. Morrison Smith. Distribution of pyroglyphid mites in Birmingham with

particular reference to Euroglyphus maynei. Clinical Allergy. 25-33, 4, 1974.

Treatment of sputum retention by minitracheotomy

H.R. MATTHEWS, R.B. HOPKINSON Retention of sputum remains a serious cause of morbidity and mortality in thoracic medicine and surgery, as it frequently leads to respiratory failure, bronchopneumonia and death. Conventional treatment involves tracheostomy or endotracheal intubation, both of which abolish glottic function and are highly invasive. A simple method of percutaneous tracheal cannulation for suction has therefore been developed, in which a 4.0 mm paediatric endotracheal tube (Portex) is inserted through a 1 cm incision in the cricothyroid membrane, using a specially designed guarded scalpel and introducer. The procedure can be performed in the ward, ICU or theatre, using local or general anaesthesia.

Since October 1981 more than 50 patients have been treated for sputum retention from a variety of causes. Ages ranged from 12-80 and the period of cannulation from 1-45 days. Following minitracheotomy 39 patients made a full recovery without any other treatment for sputum; 2 died from respiratory failure and 9 died from non-pulmonary causes. Following decannulation healing occurred within 6 days in all surviving patients and there were no long-term sequelae.

The method is much simpler and less invasive than existing alternatives for the treatment of sputum retention and when used early frequently prevents the development of respiratory failure and the need for artificial ventilation.

The relationship between neutrophils and hyperresponsive airways

E.H. WALTERS, P.M. O'BYRNE, M.J. HOLTZMAN, J.A NADEL We have previously reported that ozone-induced airway hyperresponsiveness in dogs correlated with the development of airway inflammation. In particular, dogs that became hyperresponsive after ozone inhalation developed a marked increase in the number of neutrophils in the airway epithelium. We have now studied whether ozone-induced hyperresponsiveness could be inhibited by neutrophil depletion. Responsiveness was assessed with dose-response curves of acetylcholine aerosol concentration versus pulmonary resistance; depletion was assessed by counting neutrophils in venous blood and in biopsies of the airway epithelium. Each was assessed 5 days and 1 day before ozone and 1 hour after ozone exposure (3.0 ppm for 2 hrs) in 6 untreated dogs and in 6 dogs treated with hydroxyurea (200 mg/kg daily) for 5 days before ozone. In untreated dogs, responsiveness and neutrophil numbers before ozone did not change, but responsiveness and epithelial neutrophils increased markedly after ozone. In treated dogs, circulating neutrophils decreased from 8.9 ± 2.2 to $0.6 \pm 0.01 \times 10^3$ per mm^3 (mean $\pm$ SEM), and responsiveness before ozone did not change. However, increases in responsiveness and epithelial neutrophils did not occur after ozone. Six weeks after stopping hydroxyurea, responsiveness and epithelial neutrophils again increased markedly after ozone. The results suggest that induced hyperresponsiveness may depend upon the mobilisation of neutrophils into the airways.

A "new" role for eosinophils in the pathogenesis of asthma

R.J. SHAW, O. CROMWELL, A.B. KAY The sulphidopeptide leukotrienes C_4, D_4, and E_4 (LTC_4 LTD_4, LTE_4) which comprise the activity of slow reacting substance of anaphylaxis (SRS-A) are believed to be involved in the pathogenesis of asthma. We have measured the leukotriene-generating capacity of peripheral blood leucocytes from 21 asthmatic patients and 12 non-asthmatic atopic controls. Leucocytes were purified by Ficoll-Hypaque and stimulated for leukotriene generation by the calcium ionophore (A23187). Leukotrienes C_4/D_4 and B_4 were measured by specific radio-immunoassay and further identified by high pressure liquid chromatography. The amounts of LTC_4/D_4 generated were dependant upon the dose of A23187, and peak release was observed after 15 minutes incubation. The amounts of LTC_4/D_4 were found to be directly related to the number of eosinophils in the cell suspension concentration, and appeared to be generated predominantly by this cell type. In contrast, the majority of LTB_4 was derived from the neutrophil. These observations indicate that the eosinophils, which are known to infiltrate in large numbers into bronchial tissue in asthma, have the capacity to generate preferentially the SRS-A/sulphidopeptide leukotrienes and that this in turn might lead to mucus production and constriction of bronchial smooth muscle, which are characteristic of the pathophysiology of this disease.

Effect of vagal blockade on adenosine-induced bronchoconstriction in asthma

J.S. MANN, M.J. CUSHLEY, S.T. HOLGATE Adenosine has recently been proposed as a bronchoconstrictor mediator in asthma, whose effects are specifically antagonised by methylxanthines. Since bronchoconstriction produced by a number of bronchial provocants may be mediated reflexly, we have investigated the role of the vagus in adenosine-induced bronchoconstriction. On 4 separate days, 8 asthmatic subjects (5M, 3F, mean age 26 years) underwent bronchial challenge with increasing concentrations of nebulised adenosine (A) or methacholine (M), 1 hour after inhaling either saline placebo or 1mg ipratropium bromide (IB).

Airway calibre was measured as sGaw and changes expressed as percentage of baseline values. Cumulative dose-response curves were constructed and analysed for position and slope. Following placebo, A and M produced parallel dose-related falls in sGaw, mean geometric PC_{35} values being 1.2 and 0.1mg/ml respectively. IB caused an increase in sGaw which did not significantly differ prior to challenge with A ($58 \pm 15\%$) or M ($62 \pm 11\%$). After IB, both A and M caused bronchoconstriction, but compared to their effects after placebo, the dose-response curves were displaced in a parallel fashion to the right. This displacement reached statistical significance for M ($p<0.001$) (dose-ratio, 196) but not A (dose-ratio, 1.3). The

lack of effect of IB in protecting against adenosine-induced bronchoconstriction while producing cholinergic blockade suggest that this nucleoside does not produce its airway effects through stimulation of vagal reflexes.

Inhibition of Paf-acether action by theophylline

J. MORLEY, H. BILANI, J.M. HANSON, C.P. PAGE, P.J. THOMPSON Paf-acether is a phospholipid that produces bronchoconstriction in experimental animals and elicits sustained inflammatory responses in both animals and man. We have measured airflow obstruction in response to Paf-acether in the anaesthetised guinea-pig by the Konzett-Rossler technique with concurrent monitoring of thoracic accumulation of platelets by an isotopic method. In such animals, Paf-acether induced bronchospasm could be inhibited by theophylline. As responses to Paf-acether in this species are platelet dependent, we have also examined the capacity of theophylline to affect aggregation of human platelets *in vitro*. Theophylline had no effect on the aggregation of human platelets in response to adenosine diphosphate or collagen, but abolished responses to arachidonic acid and significantly reduced responses to Paf-acether.

Paf-acether can be produced from a variety of cell types by allergic or non-allergic stimuli and has properties appropriate to a mediator of asthma. Paf-acether are reported to be inhibited by steroids or ketotifen in experimental animals and by cromoglycate in man. The present observations that platelet-dependent pulmonary reactions to Paf-acether are inhibited by theophylline imply that such an effect may contribute to the anti-asthma activity of theophylline.

Leucocyte activation following antigen- and histamine-induced bronchoconstriction

S.R. DURHAM, MARY CARROLL, G. WALSH, A.B. KAY We previously reported that neutrophils were "activated" following exercise-induced asthma (EIA), as shown by an increase in the percentage of complement rosettes (CR), and that this was inhibitable by prior administration of disodium cromoglycate (DSCG) (Thorax. 234, **38**, 1983 abs.). These changes in neutrophil CR were preceded by elevations in neutrophil chemotactic activity (NCA) indicating that activation might be dependent on the release of mast cell products. We now report similar findings in antigen-induced bronchoconstriction and, in addition, have observed similar changes in monocyte CR. When susceptible individuals inhaled specific allergen there was a time-dependent increase in the percentage of both neutrophil (13/13 patients) and monocyte (9/9 patients) CR which was preceded by elevations in the concentrations of serum NCA. The magnitude of the increases in CR observed with neutrophils and monocytes after allergen inhalation were similar, whereas no changes in neutrophil and monocyte CR and NCA were observed after histamine challenge (7/7 patients). These findings support the view that mast cell activation, induced either by antigen or the respiratory heat exchange of exercise (Lancet. 520, **1**, 1983) leads to subsequent activation of phagocytic cells; a finding of potential importance in our understanding of the inflammatory aspects of day to day asthma.

Platelet activation in allergic asthma

I.A. GREER, J.H. WINTER, D. GAFFNEY, K. REGAN, J.J.F. BELCH, G. BOYD, C.D. FORBES There is some evidence that platelet activation and the products of cyclooxygenase may be involved in experimental asthma. We have attempted to confirm and extend these observations by the measurement of B-thromboglobulin (a platelet specific protein) and thromboxane B_2, by radio-immunoassay, and platelet aggregation to adenosine diphosphonate and collagen, in 6 asthmatic subjects sensitive to house dust antigen, who underwent inhalational challenges. Thromboxane B_2 is the stable metabolite of thromboxane A_2, a pro-aggregatory prostaglandin and potent bronchoconstrictor released by activated platelets. Each subject underwent 2 separate inhalational challenges with house dust mite antigen and histamine. Inhalation of these reduced the forced expiratory volume in one second (FEV_1) to below 80% of pre-inhalation values within 30 minutes in all subjects. Blood samples were taken before and at 5 and 15 minutes following antigen challenges, and before and after the reduction of the FEV_1 to less than 80% of pre-inhalation values with histamine challenge. We did not demonstrate any significant difference in B-thromboglobulin, thromboxane B_2, or in platelet aggregations, following challenge with histamine or antigen. These observations suggest that platelet activation is not involved in the initial bronchoconstriction following antigen challenge.

Circadian variation in number and affinity of beta$_2$ adrenoceptors in lymphocytes of asthmatic patients

S.J. TITINCHI, M. AL-SHAMMA, K.R. PATEL, J.W. KERR, B. CLARK The numbers and affinity of beta$_2$-adrenoceptors on peripheral lymphocytes in five normal subjects and five asthmatic patients were measured at 18.00 and 8.00 hours on and off oral salbutamol. FEV_1 and FVC were also recorded at these times. The asthmatic patients were in remission and were taken off all sympathomimetic drugs for one week and none were on corticosteroid therapy. The lymphocyte beta$_2$-adrenoceptors were characterized using ^{125}I hydroxybenzyl-pindolol (^{125}I-HYP) and 7-9 standards were used for each assay to determine the receptor numbers (Bmax) and affinity (Kd) from Scatchard analysis.

A significant circadian variation in Bmax was observed in both the controls and asthmatic patients which was unaffected by oral salbutamol. Both groups appeared to compensate for loss of receptor numbers induced by salbutamol administration by increasing receptor affinity. For comparable combinations of drug/time, there was no significant difference between the controls and asthmatic patients. Our results suggest that asthmatic patients have intact beta-adrenoceptor function and that the 'morning-dip' observed in these patients cannot simply be explained by changes in beta adrenoceptor numbers or affinity.

The effects of an inhaled beta-agonist on cough chemoreceptor threshold

DAVID GODDEN, RACHEL LOWRY, COLIN BORLAND, TIM HIGENBOTTAM Cough is induced by inhaling fine aqueous mists of solutions deficient in chloride ions (Godden et al, Clin. Sci. p. 350, **65**, 1983 Abstract). Using solutions of progressively diminishing chloride ion content a dose response curve for cough chemoreceptors may be constructed. Inhaled beta-agonists suppress cough (Corroa et al, N. Eng. J. Med. 633-637, **300**, 1979). We have studied whether inhaled beta-agonists alter the threshold of airway chemoreceptors to cough.

Ten smokers and ten non-smokers with normal lung function were studied. Each inhaled from an ultrasonic nebulizer (Devilbiss 65), for periods of 1 minute at intervals of 5 minutes, solutions containing 147, 113, 75, 31 and 0 mmol/l chloride ions. Expired volume was recorded during each challenge through a 2 way valve using a pneumotachograph, allowing identification and recording of cough. Two challenges on separate days were undertaken, and 15 minutes before each, in random order double blind fashion, fenoterol 0·36 mg or placebo was inhaled.

No significant differences in cough frequency occurred between smokers and non-smokers. Inhaled beta-agonists however appear to suppress chemoreceptor induced cough.

Inhaled mist chloride ion concentration (mmol/l)	Cough frequency (mean ± se) per minute		
	Fenoterol	Placebo	Significance level
147	0	0	NS
113	0	0	NS
75	0.1 (± 0.1)	1.9 (± 0.9)	$p<0.05$
31	4.5 (± 1.5)	7.3 (± 1.6)	$p<0.02$
0	7.8 (± 1.6)	13.6 (± 2.6)	$p<0.001$

Bronchial reactivity during the menstrual cycle

C.J. GIBBS, I.I. COUTTS, R.J. WHITE We have shown previously that 40% of asthmatic women have a subjective and objective deterioration in their asthma premenstrually. The present study was performed to see whether a cyclical variation in bronchial reactivity existed during the menstrual cycle to account for this. Histamine reactivity was measured premenstrually, during menstruation and at midcycle in 10 normal and 12 asthmatic women of whom 6 reported premenstrual deterioration. Two asthmatics showing greater than 15% change in baseline FEV_1 between 2 of their studies were excluded from the relevant parts of the analysis. No significant differences were found in PC_{20} in either normal or asthmatic women during the menstrual cycle but the normal women had a significantly ($p<0.05$) lower FEV_1 at midcycle than during the menstrual period. It seems unlikely that the premenstrual deterioration in asthma is due to cyclical variation in bronchial reactivity.

Analysis of the effect of adrenaline on histamine-induced acute inflammation in man

D.V. McGIVERN, G.S. BASRAN It has been shown that histamine-induced cutaneous responses in man can be inhibited by the selective $beta_2$ agonist salbutamol (S). Animal experiments suggest this is primarily an anti-permeability effect. However, the effect of the natural beta agonist adrenaline (Ad), which is known to reduce angioneurotic oedema and possesses additional alpha agonist activity (vasoconstrictor), has not been studied in this context in man. We have now studied the effect of Ad on histamine-induced weal responses. Furthermore, in order to clarify the contribution made by the beta component, we have compared Ad with the alpha agonists noradrenaline (NA) and phenylephrine (PhE) which show diminishing beta activity (in the rank order Ad > NA > PhE). S was used as a control.

Weals were induced on the volar surface of the forearm in 7 healthy volunteers (aged 22-27) by injecting intradermally a fixed volume of solution (50μl) containing histamine alone (0.75 μg/site) or mixed with adrenoceptor agonists at the doses shown in the table. Weal volumes were estimated by a method previously described (Lancet, i, 935, 1982).

	Inhibition of weal volume (% control site)						
Agonist (μg/site)	0.001	0.01	0.1	1	10	100	ID 50
Ad	18	44	62	-	-	-	0.02
NA	-	11	49	65	-	-	0.13
PhE	-	-	27	46	63	-	1.58
S	-	-	-	32	39	51	89.1

The results show a dose-dependent inhibition of weal volume by all 4 drugs and the doses required to produce 50% inhibition (ID 50) were of the rank order Ad > NA > PhE, paralleling their beta activity. Ad clearly has powerful antiflammatory activity (approx. 5000 times that of salbutamol) at local concentrations which could be achieved by standard therapeutic doses.

Mechanism of propranolol induced bronchoconstriction in asthma

P.W. IND, PETER J. BARNES The mechanism of ß-blocker induced bronchoconstriction in asthma is obscure, as airways ß-receptors are not under tonic stimulation by sympathetic nerves and circulating adrenaline concentrations are not raised. In animals propranolol may induce bronchoconstriction which is independent of ß-receptor blockade (J. Maclagan and U.M. Ney. Br. J. Pharmac. 409-418, **66**, 1979) and may be related other properties such as local anaesthetic activity. We have compared the effect of DL-propranolol (10 mg) and D-propranolol (5 mg) administered intravenously in randomised double blind fashion. We studied 6 subjects (3 male) aged 28 ± 4.1 years (mean ± SEM) with mild asthma. Mean maximum fall in FEV_1 after DL-propranolol was 17.6 ± 1.4% of baseline compared with 5.0 ± 3.5% after D-propranolol ($p<0.01$). The extent of ß-receptor blockade was then determined using incremental infusions

of isoprenaline. The mean isoprenaline dose required to increase heart rate by 20 beats per minute was 0.36 μg/kg/min after DL-propranolol compared with 0.03 μg/kg/min after D-propranolol; the dose of isoprenaline to increase FEV_1 by 8% was 8.4 ± 2.3 fold higher after DL- compared with D-propranolol, confirming cardiac and airways ß-blockade. Circulating adrenaline concentrations were normal (0.23 ± 0.05 nmol/l), were unrelated to the fall in FEV_1 after DL-propranolol and were unchanged by propranolol.

We conclude that ß-blocker induced bronchoconstriction is due to ß-adrenoceptor antagonism rather than local anaesthetic activity. Whether this is due to a direct effect on airway smooth muscle or on pulmonary mast cell ß-receptors has not been determined.

Dose strong coffee alter airways calibre?

P.J. STURGISS Strong coffee was recommended in the Edinburgh Medical Journal as "One of the commonest and best reputed remedies of asthma" (H. Salter. Edinburgh Med. J. 1109-1115, 1859). Caffeine, as a methylxanthine, shares many of the pharmacological properties of theophylline, and, since it might cause bronchodilation, subjects are often asked to refrain from caffeine containing drinks before participating in bronchodilator studies.

To determine whether this is necessary we studied 12 normal and 6 asthmatic subjects in a randomised double blind comparison of change in specific airways conductance (sGaw) after drinking a cup (250ml) of standard or decaffeinated coffee (4g). Measurements of sGaw were made before and 20, 40, 60 and 80 min after drinking the coffee.

Subjects repeated the same protocol on one further occasion except that no drink was given. Data were analysed in terms of the area under the % Δ sGaw/time curve, and values compared by the Wilcoxon Signed Rank test.

Mean sGaw increased with each regime, though this was only significant for decaffeinated coffee ($p = 0.04$). Since there was no significant difference in the areas under the % Δ sGaw curves following standard coffee, decaffeinated coffee and no drink, we conclude that strong coffee as given in this study does not cause bronchodilation, and that the bronchodilation seen was due to diurnal variation in sGaw. Our results suggest that with sensitive measurements of airways function diurnal variation is likely to be a greater source of bias than any pharmacological effect of caffeine.

Disodium cromoglycate relieves symptoms in symptomatic young smokers: a double blind placebo controlled trial

A.G. LEITCH, ELIZABETH M. LUMB, A.B. KAY We have previously shown that there was a significant increase in sputum histamine, and a higher sputum/serum ratio of IgE in young symptomatic cigarette smokers who regularly expectorated when compared to non-smokers (Clin. Allergy. 257, **11**, 1981). This observation indicated that mast cell/mediator cells might be involved in the manifestation of these smoking-associated symptoms. For this reason we have undertaken a double blind placebo controlled study of disodium cromoglycate (DSCG) in 32 symptomatic young smokers. All had regular morning cough and sputum with the sensation of wheeze, but were not asthmatics as determined by the usual criteria. No significant changes were observed in sputum or serum eosinophils, IgE, IgG or IgA, or sputum histmine concentrations following the administration, for 3 weeks, of either DSCG (20 mg) or placebo, thrice daily, However, DSCG, but not placebo, was associated with significant improvements in the symptoms of cough ($p<0.01$) and wheezing ($p<0.025$). We suggest that these changes may be due to an effect of DSCG on the irritant receptor-mediated reflex response to cigarette smoke rather than the involvement of mast cells.

Disodium cromoglycate as an anti-inflammatory agent

A.B. KAY, T. NAGAKURA, G. WALSH, MARY CARROLL We reported previously that neutrophils were activated following exercise-induced asthma (EIA) (as shown by an increase in the percentage of complement rosettes) and that activation was inhibitable by prior administration of disodium cromoglycate (DSCG) (Thorax. 234, **38**, 1983 abstract). In the present study we tested the hypothesis that DSCG might act directly on neutrophils and other inflammatory cells. This was undertaken by determining whether the compound affects leucocyte activation in vitro Neutrophils, eosinophils and monocytes were stimulated with the synthetic bacterial analogue f-met-leu-phe and activation was assessed by measuring enhancement of complement and IgG (Fc) receptors. Enhancement of neutrophils and eosinophils and monocytes was inhibited by DSCG in a time- and dose-dependent fashion. The EC_{50}, with C3b and IgG (Fc), was approximately 5×10^{-9} moles l^{-1} for monocytes. Chemotactic factor-induced activation was also inhibited by dibutyrl cyclic AMP and other agents such as theophylline and salbutamol, which increase the intra-cellular levels of cyclic AMP. These findings indicate that DSCG has "anti-inflammatory" effects with an order of potency which is 100 to 1000 more than the required for mast cell stabilization.

Simplifying the use of respiratory inductance plethysmography

J.R. STRADLING, G.A. CHADWICK, C. QUIRK, T. PHILLIPS Surface measurements of ribcage (RC) and abdominal (AB) expansion have gained popularity because of artefacts induced in breathing patterns by mouthpieces or masks. We have developed a computer aid to using respiratory inductance plethysmography (RIP) utilising 'basic' on a BBC B microcomputer with no extra interfacing. The calibration system uses multiple linear regression (MLR) to devolve the RC and AB volume motion coefficients (VMCs) and thus subject cooperation need only be minimal.

We have compared calibration by MLR and the isovolume manoeuvre (IVM) in 10 normal subjects and 9 patients with chronic airways obstruction (CAWO). The accuracy of VMCs was assessed by producing voluntary

changes in RC/AB contributions to breathing whilst on the spirometer (minimum of 90 breaths). The same posture was maintained throughout.

Multiple linear regression was at least as good as the IVM in developing VMCs in both normals and patients with CAWO. The table shows the accuracies found for the MLR technique.

	95% confidence limits on:- 1) Individual breaths	2) Mean of 10 breaths	Average error from 10% change in RC/AB contribution
NORMALS	± 7%	± 2.2%	1.8%
PATIENTS	± 15%	± 4.8%	4.8%

Transcutaneous oxygen tension accurately reflects changing arterial oxygen tension during exercise

B.J. GRAY, R.W. HEATON, J.M. CALLAGHAN, D.C.S. HUTCHISON We have previously shown that after single point in vivo calibration, transcutaneous oxygen tension ($tcPO_2$) is an extremely accurate method of estimating arterial oxygen tension (PaO_2) in steady state conditions in adult subjects.

During muscular exercise, the response characteristics of the electrode may not enable rapid detection of changes in PaO_2, and changes in skin blood flow could theoretically influence the relationship between $tcPO_2$ and PaO_2.

We have compared $tcPO_2$ and PaO_2 during and after exercise in six male patients with severe chronic obstructive airways disease. The electrode was calibrated in vivo on each patient who then performed a progressive exercise test. $tcPO_2$ was continuously measured during and after exercise period and PaO_2 was measured at frequent intervals from an indwelling arterial cannula. $tcPO_2$ and PaO_2 showed a closely related biphasic pattern in each patient. Both parameters fell during exercise, but during recovery there was a rapid rise in $tcPO_2$ (32 ± 5.5 mmHg) and PaO_2 (32.3 ± 7.5 mmHg) which overshot resting values and peaked at 3.4 ± 1.3 minute.

Throughout exercise and recovery 62 simultaneous comparisons of $tcPO_2$ and PaO_2 were made. The relationship was very close and is given by the equation $tcPO_2 = 0.975\ PaO_2 + 1.1$ mmHg (standard error of estimate = 1.5, r = 0.984, $p<0.001$).

We conclude that transcutaneous oximetry is a reliable method of monitoring PaO_2 during exercise, and when calibrated in vivo $tcPO_2$ reflects accurately both the magnitude and timing of rapid changes in PaO_2.

Sleep apnoea in myxoedema

A.D. MacKAY, R.A. COOPER, S. BRADBURY, J. STAINFORTH, D.J. GAWKRODGER, A. ALLEN, K. PROWSE, W. VAN'T HOFF Obstructive sleep apnoea has been reported frequently in myxoedema. We studied 9 patients with myxoedema presenting consecutively to an endocrine clinic. Polygraphic sleep recordings were carried out in all with a trained observer present throughout. Six patients, 2 male and 4 female, had symptoms of sleep disordered breathing and 5 of these showed an abnormal number of episodes of sleep apnoea: 22-137 episodes during six hours recorded sleep (Apnoea Index range 3.7-22.8). The majority of apnoeic episodes appeared central in type. Small changes in oxygen saturation or heart rate were found in 4 patients. The episodes occurred in those with the longest symptomatic histories of myxoedema but there was no correlation with age, weight or serum levels of thyroxine, TSH or prolactin. The presence of arousal was not related to the occurrence of apnoea although sleep patterns were markedly disturbed. The male patient with extensive apnoea died of a myocardial infarct six months after study. The 4 female patients studied again when euthyroid, showed no significant apnoea and normal sleep patterns. Sleep apnoea appears common in myxoedema. In contrast with previous reports our series showed predominantly central episodes but these were also abolished by thyroxine.

Respiratory drive in pregnancy

W.V. EVANS, A. MORROW, T.J. COADY, D. SEATON Dyspnoea is a common feature of early pregnancy[1] when standard tests of respiratory function show only minimal changes.[2] The mechanism of this remains obscure but may be related to the level of plasma progesterone which is produced in increasing quantities through pregnancy and which is known to stimulate ventilation, probably by a central effect.[3]

Mouth occlusion pressure 100 msec after inspiration from functional residual capacity ($P_{0.1}$) reflects the motor output of the respiratory centres and serial measurements of $P_{0.1}$ have not previously been reported in pregnancy. We have measured $P_{0.1}$ in nine healthy pregnant subjects both breathing air and a 5 per cent CO_2/95 per cent oxygen mixture at 14, 20, 32 and 36 weeks of gestation and post-partum and have correlated the results with plasma progesterone levels. In addition a respiratory questionnaire was completed and static lung volumes were recorded at each visit.

$P_{0.1}$ increased significantly during air breathing in the third trimester ($p<0.05$) and during CO_2/O_2 mixture breathing from the 20th week onwards ($p<0.05 - <0.01$). There was also a significant correlation between plasma progesterone level and $P_{0.1}$ during air breathing ($p<0.01$). Although mechanical changes in pregnancy affect the pattern of breathing our results imply that the circulating level of progesterone is also influential.

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Oral high frequency ventilation by jet (HFJV) or oscillator (HFOV) reduces minute ventilation ($\dot{V}E$) in normal subjects

R.J.D. GEORGE, R.J.D. WINTER, M.A. JOHNSON, I.P. SLEE, D.M. GEDDES HFV is the delivery of volumes of gas less than

anatomical dead space at frequencies exceeding 1Hz. It is established as an alternative to IPPV in animals and man. The small volumes are delivered either as sinewaves by a loudspeaker (HFOV) or as a pulsetrain of gas from a jet source (HFJV). As spontaneous breathing is unhindered, the potential for assisting ventilation in conscious subjects is great. We report the effect upon resting $\dot{V}E$ in 2 studies of superimposed HFV using (1) an 8" bass loudspeaker and (2) a solenoid valve based jet ventilator both delivered through a standard mouthpiece in 7 healthy volunteers. Ventilation was monitored by Respitrace and blood gases by transcutaneous electrodes. Following 10 minutes run in, 10 minutes' HFV alternated with 5 minutes' control. Frequencies between 1 and 33 Hz were delivered in random sequence. The final 4 minutes of each ventilatory period were analysed and expressed as a percentage of control (mean of the last minute of all control periods). Ventilation fell significantly at all frequencies ($p<0.01$). Savings were maximum (54%) using HFJV where there was also a significant at all frequencies ($p<0.01$). Savings were maximum (54%) using HFJV where there was also a significant fall in $tcPCO_2$ at 3.3 Hz. The ventilatory savings achieved by this noninvasive ventilatory support in normal subjects merit its evaluation in those with breathing difficulties.

Ventilatory saving by high frequency chest wall compression (HFCWC)

R.J.D. GEORGE, R.J.D. WINTER, S.J. FLOCKTON, D.M. GEDDES We have shown that air column oscillation by jet or loudspeaker over a wide range of frequencies reduces spontaneous minute ventilation ($\dot{V}E$) in normal subjects. Here we report the effect of HFCWC upon $\dot{V}E$. At the resonant frequency (f_O) of an oscillating system, the amplitude of flow will be maximum for a given input pressure. We therefore studied frequencies including rib-cage resonance (f_O 60-80 Hz) and respiratory system resonance in 8 normal subjects (f_O 5-10 Hz) and 8 with COPD (f_O 13-26 Hz).

The study was performed in a sound box with the subject breathing through a rigid tube connected to the outside. $\dot{V}E$ was measured by Respitraces, air column oscillation by pneumotachograph and blood gases by transcutaneous electrodes and ear oximeter. Frequencies were delivered in random sequence at 132dB ($8mmH_2O$) 10 minutes' oscillation alternated with 5 minutes' control. In normals the maximum fall in $\dot{V}E$ (20%) occurred at 5-10 Hz ($p<0.01$). In those with COPD the maximum fall in $\dot{V}E$ (15%) occurred between 13 and 26 Hz ($p<.01$).

We conclude that significant ventilatory saving may be achieved with external chest wall compression. This saving can be achieved with very low pressures and may be related to a resonance of the respiratory system.

Effects of high frequency chest wall compression in normal subjects and COPD patients

P.M.A. CALVERLEY, H.K. CHANG, D. WHITE, A. ZIDULKA High frequency of oscillation of gas via an ET tube is an effective method of ventilation but is not suitable for use in conscious subjects. To overcome this problem we have used the rapid inflation and deflation of a modified double blood pressure cuff wrapped round the lower thorax to oscillate intra-thoracic gas. We have studied the effects of oscillation at 3, 5 and 8 Hz in a randomised order on minute ventilation measured by respiratory induction plethysmography and on arterial blood gas tensions in five normal subjects (3M, 2F) and five patients with COPD (4M, 1F) (FEV_1 0.67 ± 0.16 litres/min, FVC 1.76 ± 0.73 litres/min). In the normal subjects after 15 minutes of oscillation mean minute ventilation ($\dot{V}E$) fell from 6.5 ± 0.6 litres/min. to 4.24 ± 0.92 litres/min. at 3 Hz and from 5.8 ± 0.46 litres/min to 4.3 ± 0.45 litres/min. at 5 Hz but did not change with 8 Hz oscillation. Despite the fall in $\dot{V}E$ Pa_{O_2} rose slightly while Pa_{CO_2} was unchanged. In the patients a similar but less pronounced fall occurred at 3 Hz (9.12 ± 1.04 litres/min to 6.67 ± 91 litres/min) but not at 5 or 8 Hz. Again blood gas tensions did not change when $\dot{V}E$ was reduced. Similar changes in $\dot{V}E$ occurred when the cuff pressure was reduced to half the initial maximum tolerated pressure in both groups studied. Serum CPK and haptogloblins were unaffected by oscillation and no local complications occurred. High frequency chest wall compressions may be useful in assisting ventilation in patients who might otherwise need ventilatory therapy.

The individuality of chest wall motion in tetraplegia

M.D.L. MORGAN, ANDRÉ DE TROYER In tetraplegia the impairment of respiratory function is greater than would be predicted from the loss of intercostal and abdominal muscle power alone. Abnormal chest wall motion contributes to this, and gradual improvement of respiratory function is said to be due to the development of rib cage stiffness resulting from joint immobility and muscle spasticity.[1] We examined the relationship between thoraco-abdominal motion, muscular activity, rib cage stiffness and the duration of injury in eight tetraplegic subjects. The duration of injury ranged from 2 weeks to 25 years. Optical mapping was used to record and measure thoraco-abdominal motion and volume change, during quiet and exaggerated breathing. Simultaneous electromyograms were obtained from the parasternal intercostals, scalenes and sternomastoids. An index of rib cage stiffness was derived from the volume change during a static inspiratory mouth pressure manoeuvre.

Paradoxical rib cage motion was present in 5 of 8 subjects during tidal and 6 of them during exaggerated breathing. The range of abnormality was wide and unrelated to duration of injury or pattern of muscular activity. A stiff rib cage from any cause was associated with less abnormality.

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An optical method of studying the shape and movement of the chest wall in recumbent patients

M.D.L. MORGAN, A.R. GOURLAY, D.M. DENISON We describe a development of an optical mapping technique which allows

the shape and motion of the chest wall to be studied in recumbent patients. It employs a single still or video camera at a fixed view point to determine the 3-dimensional co-ordinates of the surface of the body, and use them to measure volume or demonstrate shape change. Measurements on different test objects (volumes 228 ml to 7807 ml) in different positions suggest a reproducibility of volume measurement of ± 27 ml and a maximum volume error of 150 ml. Studies of inspiration/expiration CT scans show that one can expect to capture 99% of respiratory motion by this method. The measurement of expired volume in six subjects has a random error ± 76 ml (standard deviation) within individuals. There were small systematic difference between subjects. A flow volume loop has been derived from a normal subject by this method.

Low frequency fatigue reduces sternomastoid endurance

J. EFTHIMIOU, R.A.E. HOLMAN, M. BELMAN, M.A. SOLOMON, S.G. SPIRO, R.H.T. EDWARDS Low frequency fatigue (LFF) reflects impaired force generation at low frequencies of electrical stimulation, but it is not known whether its presence will affect the voluntary contractile properties of a muscle. In order to evaluate this we studied five normal subjects who performed an isotonic endurance exercise consisting of repetitive neck flexion to 35% of a previously determined maximum voluntary force. The endurance time — the duration the subject was able to attain this target force was recorded (a) one hour after 150 head lifts, which consistently produced sternomastoid LFF (i.e. $>15\%$ fall in the '20/50 ratio', the force generated at 20 Hz compared to that at 50 Hz stimulation), and (b) without preceding head lifts (control run). These two runs were performed one week apart and in random order.

The mean (±SD) '20/50 ratio' immediately before the endurance exercise for the control run was 75.2% (±6.9) compared to 55.3% (±7.2) for the head lift run ($p<0.01$). The mean (±SD) endurance time for the control run was 20.9 (±6.1) min compared to 12.8 (±6.3) min for the head lift run ($p<0.01$). We conclude that the presence of LFF was associated with reduced sternomastoid endurance during a repetitive submaximal exercise. LFF maybe a useful index in the evaluation of respiratory muscle failure.

Changes in transfer factor and transfer coefficient after pneumonectomy for carcinoma of the bronchus

P.A. CORRIS, D.A. ELLIS, T. HAWKINS, S. NARIMAN, G.J. GIBSON Changes in carbon monoxide transfer factor (TLCO) and transfer coefficient (KCO) after pneumonectomy are poorly documented and it is not clear whether the changes are related to the preoperative distribution of perfusion. We performed ^{99m}Tc perfusion lung scans preoperatively and measured TLCO and KCO by the single breath method both preoperatively and 4 months postoperatively in 28 patients undergoing pneumonectomy for carcinoma of the bronchus. There was a mean decrease in TLCO of 20.2% predicted and a mean increase in KCO of 13.6% predicted. The mean decrease in single breath alveolar volume (VA) was 26.7% predicted TLC. Significant linear correlations were found between the percentage preoperative perfusion (% $\dot{Q}$) of the resected lung and the decrease in TLCO ($r = 0.68$), increase in KCO ($r = 0.71$) and decrease in VA ($r = 0.85$). The relationship between increase in KCO % predicted (y) and % $\dot{Q}$ of the resected lung (x) is described by the equation $y = 0.41x + 2.1$. Thus to take the extreme example of an individual with equal blood flow to each lung preoperatively, the blood flow to the surviving lung is potentially doubled after pneumonectomy but the KCO is observed to rise by only 22%.

Changes in TLCO and KCO after pneumonectomy are linearly related to the preoperative distribution of perfusion.

Balloon occlusion of the bronchi at fibreoptic bronchoscopy: application to physiological assessment before lung resection for bronchogenic carcinoma

L.R. BAGG, I.D. COX Patients with bronchial carcinoma frequently have some loss of function in the affected lung. This impairs the accuracy of predictions of post-operative ventilatory outcome based on conventional pulmonary function tests. A technique is described for determining regional function by balloon occlusion of the bronchus to the lung or lobe to be resected, using a Fogarty balloon catheter introduced at fibreoptic bronchoscopy. Twenty two of 25 consecutive patients with bronchial carcinoma admitted for resection were studied successfully. Considerable loss of function in the affected lung was seen in the majority. Significantly greater functional impairment was found in the lungs of the 5 inoperable patients than in the 17 who had resections, but there was an overlap in values between the operable and inoperable cases. Twelve of the 17 patients who had a resection were followed up at least 2 months after operation. A highly statistically significant correlation was seen between pre-operative prediction of postoperative VC ($r = 0.88$) and FEV_1 ($r = 0.98$) and the values measured at follow up. The method is readily available and provides an accurate prediction of postoperative ventilatory function after pneumonectomy or lobectomy. These attributes offer potential advantages over the main alternative methods for assessing regional lung function.

Bronchial reactivity to histamine in young male smokers with normal lung function

R.G. TAYLOR, S.W. CLARKE The increased bronchial reactivity of middle-aged male smokers could be the result of reduced airway calibre, or according to the Dutch hypothesis, contribute to its cause (Taylor et al, Thorax. 710, 38, 1983). To test this, bronchial reactivity was compared in 13 nonasthmatic young male smokers (S) and 13 nonsmokers (NS) of similar median age (S 26y, NS 24y) and baseline FEV_1 (S 106%, NS 111% predicted), using 2-minute inhalations of saline followed by histamine in concentrations of 2, 4, 8, 16, 32 and 64 mg/ml. Median duration of smoking was 9y and consumption 20 cigarettes/day.

Similar numbers of smokers and nonsmokers had a PC_{20} (provocative concentration reducing post-saline FEV_1 by

20%) below 16 (S O, NS 2), 32 (S 1, NS 3) and 64 mg/ml (S 5, NS 6). No subject had a PC_{20}<8 mg/ml. Numbers with a threshold concentration (reducing post-saline FEV_1 by 2 SD of baseline values) were similar at 2 (S 1, NS O), 4 (S 1, NS 2), 8 (S 7, NS 6), 16 (S 10, NS 9), 32 (S 11, NS 11) and 64 mg/ml (S 12, NS 13), as was the reduction in FEV_1 with histamine 16 mg/ml (median reduction S 6.4%, NS 5.3%). PC_{20} did not correlate with baseline FEV_1 in smokers (rs = 0.26, p>0.3) or nonsmokers (rs = 0.27, p>0.3).

These results show that in young smokers whose FEV_1 is normal, bronchial reactivity is not increased, and is independent of baseline lung function. The increased reactivity of middle-aged male smokers is therefore acquired later, by which time FEV_1 is liable to have diminished, perhaps to an extent where it does become a determinant of bronchial reactivity.

Number of patients required in lung function studies

A.G. DAVISON, P.M. FAYERS, A.J. NUNN, K.M. VENABLES, A.J. NEWMAN-TAYLOR The number of patients required to demonstrate an important clinical difference, if one exists, depends on the levels of significance selected, usually at least 5%, the size of the difference and the power of the test, that is the probability of detecting that difference. The power is seldom considered when planning studies and consequently many studies are too small to detect even substantial differences. Lung function parameters are frequently compared between groups. As an aid to planning these studies we have constructed tables showing estimates of the total number of patients required for a t-test to detect, at the 5% significance level and with 90% or 80% power, differences in lung function parameters such as FEV_1, FVC, TLC and TLCO between independent groups. We will present full tables. As an example, with a total of 200 patients it is possible to detect, with 90% power, a difference of 239 ml at the 5% level. However, with only 20 patients, under the same conditions, the difference rises to 754 ml. Estimations of the standard deviation (SD) have been taken from normal populations, but SD may be higher in the study population and more patients will be required for a given difference. The tables do however provide an estimate of the order of the number of patients required.

Diagnosing ciliary dyskinesia

MICHAEL GREENSTONE, ANN DEWAR, PHILIP STANLEY, PETER COLE Clinicians are now aware of the association of Kartagener's syndrome and ciliary abnormalities. However, Afzelius (Science. 317, 193, 1976) predicted that 50% of patients with "immotile" cilia would have normal cardiac situs as the direction of rotation of the archenteron would become random.

In recent years ciliary dyskinesia has been diagnosed in eleven patients (mean age 23 years) with normal cardiac situs referred to this Unit. Ten had recurrent chest infections, eight had radiological evidence of bronchiectasis and ten suffered from sinusitis. All patients in whom this disorder was suspected were screened with a saccharin test (Andersen I et al. Arch. Environ. Hlth. 290, 29, 1974) to determine nasal mucociliary clearance (NMCC). Those with NMCC > 30 min (NR<20 min) had a nasal brushing (J. Rutland, P. Cole. Lancet 564, 2, 1980) for examination of ciliary ultrastructure and function. Ciliary beat frequency (CBF) was assayed photometrically and percent motility calculated using a graticule. All eleven patients had grossly dyskinetic ciliary movement on inspection. CBF varied from complete stasis to 12 Hz (NR 11-16 Hz). Five patients had > 40% motility confirming the term "immotile cilia syndrome" to be a misnomer. Ultrastructural appearances varied from normal to absent dynein arms.

Screening for ciliary dyskinesia should be performed in all patients with recurrent or chronic chest infections. A spectrum of motility and ultrastructural abnormality exists which traditional invasive techniques of diagnosis (e.g. nasal biopsy for ultrastructural examination of ciliary dynein arms) may fail to detect.

The biochemical response of sputum to antibiotic therapy in patients with stable purulent bronchiectasis

R.A. STOCKLEY, S.L. HILL In our previous studies we have shown that elastase activity is a feature of purulent secretions in patients with stable bronchiectasis (Hill and Stockley. Clin. Sci. 38, 62, 1982). Since this enzyme activity is potentially capable of damaging ciliated epithelium and lung connective tissue, we decided to study the effect of broad spectrum antibiotic therapy on 21 occasions in 15 patients with bronchiectasis in the clinically stable state. Sputum and serum samples were collected at the start, on the 7th and 14th days of treatment, and 7 days after cessation of therapy.

Elastase activity expressed as the equivalent of porcine pancreatic elastase fell (p<0.025) from the initial value of 6.51 μg/100 μl (SD $\pm$ 3.22) to 3.33 μg/100 μl (SD $\pm$ 4.71) within the first week of treatment (becoming absent in 12 studies) rising to 4.96 μg/100 μl (SD $\pm$ 3.28) within 7 days of stopping therapy.

A similar change was seen in the sputum to serum albumin ratio (p<0.01)—from 2.37×10^{-2} (SD $\pm$ 1.52) to 1.83×10^{-2} (SD $\pm$ 1.47) rising again to 2.13×10^{-2} (SD $\pm$ 1.28), indicating a beneficial effect on lung inflammation.

These results may have major implications in the management of patients with bronchiectasis and warrant further investigation.

The association of sputum purulence with elastase activity, protein transudation and lung function in bronchiectasis

R.A. STOCKLEY, S.L. HILL, H.M. MORRISON Elastase has been implicated in the pathogenesis of several chronic lung diseases and is a feature of secretions during acute exacerbations of bronchitis or of patients with cystic fibrosis in the stable clinical state. Since elastase is potentially of harm to ciliated epithelium (Tegner et al. Rhinology, 199, 17, 1979) we have investigated the nature of the secretions in 35 patients with bronchiectasis.

One hundred and twenty one sputum samples were assessed; 29 were mucoid; 30 mucopurulent and 62 purulent. Elastase activity was not detected in any mucoid

samples but was present in 6 (20%) of mucopurulent, and 55 (88.7%) of purulent secretions. The sputum/serum albumin ratio (a marker of inflammation) was related to the macroscopic appearances of the secretion being higher ($p<0.01$) in the mucopurulent samples (median = 1.19×10^{-2}; range = 0.19 — 6.52) than mucoid samples (median 0.71×10^{-2}; range = 0.22 — 4.7) and the purulent results were higher than the mucopurulent ones (median = 1.52×10^{-2}; range = 0.55 — 12.72: $p<0.005$), suggesting a greater degree of protein transudation from serum. Twenty five of the patients had abnormalities of air flow but this was not related to the type of secretion. On the other hand, patients who regularly produced purulent secretions had greater RV/TLC ratios than those who did not (mean = 44.4%, SD ± 9.0 compared to 38.0, SD ± 9.9: $p<0.025$). Whether this is cause or effect is worthy of further study.

The quantitation and function of proteinase inhibitors in sputum and bronchoalveolar lavage

R.A. STOCKLEY, H.M. MORRISON, S. SMITH, T. TETLEY Proteinase inhibitors are thought to play an important role in protecting the lungs from enzyme induced damage. However, there is some controversy concerning the relative importance of these inhibitors in different secretions and evidence has been presented suggesting that α_1 proteinase inhibitor (α_1PI) is the major elastase inhibitor in bronchoalveolar lavage fluids (BAL).

We have measured the concentrations of α_1PI and a low molecular weight bronchial inhibitor (BMPI) in both sputum and BAL from 10 patients with bronchitis as well as assessing their inhibitory function.

Both proteins were present in measurable quantities in all samples. The relative concentrations of both proteins were similar in sputum and BAL (sputum median value = 1.13 μg BMPI/μg α_1PI; range = 0.04 — 6.48: BAL = 1.96; range = 0.63 — 6.82).

By assessing the inhibition of porcine pancreatic and leucocyte elastase we were able to determine the function of both inhibitors. The results suggest that the majority of elastase inhibition in both sputum and BAL (57-100%) is due to inhibitors other than α_1PI. These data do not support the suggestion that α_1PI is the major elastase inhibitor in BAL fluids (Gadek et al. J.C.I. 889, **68**, 1981).

An investigation of the physical and biochemical properties of the sputum from chronic bronchitics treated with N-acetylcysteine

CHRISTOPHER MARRIOTT, CHARLES TURTON, STANLEY S. DAVIS Nine patients (8 men, 1 woman) with an average age of 63 (± 6.48) years were included in the study which consisted of a two week baseline period followed by four weeks of active therapy (200 mg t.d.s.) and two weeks washout. Each patient was encouraged to produce a sputum sample at each weekly visit. Rheological (viscoelasticity) measurements indicated that there was no significant change in physical properties. The volume and dry weight of the sputum produced also did not change significantly. The analyses for free sulphydryl (−SH) and disulphide (S-S) groups produced a significant ($p<0.05$) change only in the former, which is indicative of the penetration of N-acetylcysteine into the sputum. Purification of the sputum to release the mucus glycoprotein showed no difference in the hexose:protein ratio, which indicates that basic synthesis is unaltered. Furthermore, since neither ester sulphate, sialic acid nor fucose changed then the charge on the molecule will be unaffected. However, the disulphide bonds showed a significant ($p<0.5$) increase. Therefore, it is concluded that N-acetylcysteine affects the assembly of mucus glycoproteins by its involvement in disulphide bridges but that this is not reflected by changes in other biochemical or physical properties.

Oral N-acetylcysteine has no demonstrable effect on mucus clearances in chronic bronchitis

ANN B. MILLAR, D. PAVIA, J.E. AGNEW, MARIE T. LOPEZ-VIDRIERO, D. LAUQUE, S.W. CLARKE The effectiveness of mucolytic agents is likely to depend on both the mode of administration of the drug and the nature of the patients' secretions. N-acetylcysteine has recently been introduced in oral form. We have investigated its effect on lung mucus clearance in nine patients with chronic bronchitis (mean (± SEM) age 67 + 3 years; % predicted FEV_1: 67 + 13). Tracheobronchial clearance was measured for 6 hours after inhalation of 5 μm polystyrene particles labelled with ^{99m}Tc. After a baseline test following two weeks without any mucolytic expectorant therapy, the patients were randomly allocated to placebo or drug (200 mg t.d.s.) for four weeks. Mean ± SD sputum viscocity (5 patients) was 6400 ± 5200, 5600 ± 5300 and 3800 ± 1900 mPa in the control, placebo and drug runs respectively. The mean tracheobronchial retention curves after placebo and drug treatment were almost identical to that in the baseline study. We conclude that N-acetylcysteine has no effect on mucus clearance in chronic bronchitis.

Danazol reverses the biochemical abnormality of inherited antithrombin III deficiency

ANDREW FAIRFAX A Staffordshire family is described with an inherited deficiency of antithrombin III, an inhibitor of serine proteases in plasma. The pattern of inheritance was typical of an autosomal dominant trait. Affected members experienced recurrent spontaneous episodes of phlebitis, deep venous thrombosis and pulmonary embolism. Typical levels of antithrombin III in 7 subjects who could be traced were 60-68% (NR 72-128%) measured by antigenic assay, and 33-68% (NR 84-116%) by chromogenic assay.

Danazol, an anabolic steroid with mild androgenic effects (a 17 α-alkyl derivative of ethinyl testosterone), has been used in other antiprotease deficiency states such as hereditary angioedema (Gelfand et al. N. Engl. J. Med. 1444-8, **295**, 1976) and α-1 antitrypsin deficiency (Gadek et al. J. Clin. Invest. 82-87, **66**, 1980). To date, there are no published reports on the use of danazol in antithrombin deficiency. Danazol was given in a dose of 600 mg/day to two antithrombin-deficient males previously maintained on long-term warfarin therapy. A complete reversion to normal of plasma antithrombin III measured by both assays was observed with this therapy. This novel use of

danazol may offer an alternative to long-term anticoagulation in hereditary antithrombin III deficiency.

Ciliotoxicity of asthmatic serum is species dependent

M. GREENSTONE, W. GRIFFIN, P.J. COLE Asthmatic serum and sputum have been reported to be ciliotoxic in a variety of ciliated systems and may be relevant to the impaired mucociliary transport seen in acute and chronic asthma. We investigated the effect of asthmatic serum on respiratory cilia because asthmatic serum has been reported to be toxic to rabbit tracheal cilia (Wilson and Fudenberg, Nature, **463**, **266**, 1977) and asthmatic sputum sol toxic to human bronchial cilia (Dulfano and Luk, Thorax. **646**, **37**, 1982).

The nasal cilia from 12 patients with acute asthma (mean PEFR 115 ± 48 l min $^{-1}$) were incubated at 37°C with autologous serum and ciliary beat frequency (CBF) measured photometrically over 24 hours (Rutland and Cole, Lancet. 564, **2**, 1980). Mean CBF (± SD) at 0,6 and 24 hours was 12.5 ± 1.21, 10.00 ± 1.64 and 10.85 ± 1.88 Hz. Mean CBF of nasal cilia from 8 healthy controls in autologous serum was 12.39 ± 0.84, 10.14 ± 0.87 and 10.34 ± 0.87 Hz respectively, showing similar baselines and rate of decline. Bronchial cilia behaved comparably (n = 5). However acute asthmatic serum caused complete ciliostasis within 6 hours when incubated with rabbit tracheal cilia. Normal serum had no effect (n = 6).

There is marked interspecies variation in the effect of asthmatic serum on respiratory tract cilia. Furthermore any ciliostasis in asthma is unlikely to be directly related to a serum factor in sputum sol.

Prolonged nasal mucociliary clearance in healthy smokers

P.J. STANLEY, L. MacWILLIAM, M.A. GREENSTONE, C. DALY, P.J. COLE Many constituents of tobacco smoke are ciliotoxic in vitro (reviewed by Wanner, Am. Rev. Respir. Dis. 73, **116**, 1977). However, studies of the effects of long-term cigarette smoking on lung, tracheal and nasal mucociliary clearance have provided variable results.

We have measured nasal mucociliary clearance (NMCC) using a saccharin method in 27 non-smokers, 25 smokers (21 smoked > 20 cigarettes/day) and 5 ex-smokers (>1 year abstention). No subject had chronic chest or nasal disease or recent upper respiratory infection. The time between placement of a saccharin particle on an inferior nasal turbinate and its perception as a sweet taste was recorded. This test is satisfactory and reproducible provided certain precautions are observed (Stanley et al. Br. J. Dis. Chest. 1983, in press).

Mean NMCC time for non-smokers was 11.1 ± 0.7 (SEM) mins. One smoker failed to taste within 60 minutes, the remaining smokers had a mean time of 19.3 ± 1.6 min and the ex-smokers 16.0 ± 3.4 min. NMCC was significantly slower in the smokers compared to non-smokers ($p<0.001$, Mann-Whitney U test) but there was no significant difference between non and ex-smokers.

This study provides further evidence of an in vivo defect in mucociliary clearance caused by smoking. Our results in ex-smokers agree with Camner et al. (Arch. Environ. Hlth. 90, **26**, 1973), who found improved tracheobronchial clearance after 3 months' cessation of smoking.

Antimicrobial penetration into bronchial secretions in chronic respiratory sepsis

P.J. COLE, D.E ROBERTS It is probable that the variable and often low levels of antimicrobial agents achieved in bronchial secretions are relevant to the difficulties encountered in eradicating or preventing relapse of infection in the chronically **damaged** bronchial tree — in contrast to their probable irrelevance to treatment of acute infections of the **normal** respiratory tract.

With this as an hypothesis we carried out a small open study in severe bronchiectasis of a regimen of amoxycillin, which theoretically should have achieved useful levels of the drug in sputum, and found it to be effective in improving clinical symptoms, sputum volume and spirometry (P.J. Cole, D.E. Roberts, S.F. Davies, R.K. Knight. J. Antimicrob. Chemother. 109, **11**, 1983) and subsequently, when taken promptly at the start of infective exacerbations, reducing their severity, duration and frequency (P.J. Cole, D.E. Roberts. Lancet. 248, **1**, 1983).

We have now compared serum and sputum levels after single oral doses of two antimicrobial agents in patients with severe bronchiectasis. The mean serum level of amoxycillin is approximately 1.5 times that of ampicillin whereas the mean sputum level is approximately 5 times as high. Using oral doses of the drugs which achieved equal serum levels we have found a significant superiority of penetration of amoxycillin into bronchial secretions. There are significant clinical implications of such penetration in the management of progressive suppurative disease.

Detection of cystic fibrosis carriers by serum-induced rabbit tracheal ciliary inhibition

W. GRIFFIN, J. RUTLAND, P.J. COLE It has been widely reported that cystic fibrosis (CF) serum causes dyskinesia in several animal cilia models (Bowman et al. Science. 325, **164**, 1969).

Using a quantitative method of measuring ciliary beat frequency (CBF) (Rutland and Cole. Lancet. 564, **2**, 1980) we have confirmed Spock's original, but unquantitated, observation (Spock et al. Pediat. Res. 173, **1**, 1967) that CF serum disorganises and slows rabbit tracheal cilia.

In a blind pilot study, the CBF of rabbit tracheal epithelium was slower in 20 homozygote and 40 heterozygote (parents) CF sera than in 10 normal sera ($p<0.001$). The mean time to ciliostasis was less in homozygote than heterozygote sera ($p<0.001$). Sera from 20/20 chronic bronchitic and 18/20 bronchiectatic patients were not ciliostatic. Two bronchiectatic sera (one patient with chronic *Ps aeruginosa* carriage, one with panhypogammaglobulinaemia) and two normal sera were cilioinhibitory. These could be from carriers of the CF gene.

The evaluation of a quantitative enzyme linked immunosorbent assay (ELISA) for anti-Aspergillus fumigatus IgG

D.J. SHALE, J.A. FAUX Use of reported methods for the anti-*Aspergillus fumigatus* IgG ELISA produced a qualitative

assay with poor reproducibility of optical density values (±23%). Inclusion of a highly positive (hc) and a negative (lc) aspergillus precipitin serum as standards overcame these defects. Intra- and inter-assay variation and a specific binding index (SBI) were derived from these sera. Mean intra-assay variation as coefficient of variation was 8.5% (1:100 7.5%; 1:200 8.4%; 1:400 9.2%; 1:800 9.0% from 6 determinations/dilution in 6-8 assays). Mean inter-assay variation was 8.7% (1:200 10.6%; 1:400 8.2%; 1:800 7.4% from 22 assays). The SBI gave a 73 fold separation between 16 precipitin positive sera and 18 negative sera compared to only 3.5 fold for optical density readings. In three patients with allergic bronchopulmonary aspergillosis, with sera collected between 1979 and 1983, there was absolute coincidence of clinical and radiological exacerbation with antibody elevations. The response to treatment was also clearly demonstrated. In mycetoma patients similar fluctuations in antibody levels were not seen. Thus this ELISA has valuable clinical and research applications — in particular as a means of monitoring the response to anti-*Aspergillus fumigatus* therapy, where the objective demonstration of an effect can be difficult.

Comparison of the use of aspergillus precipitins and the enzyme linked immunosorbent assay (ELISA) for IgG antibodies to Aspergillus fumigatus in a chest clinic population

D.J. SHALE, J.A. FAUX, D.J. LANE The routine use of an anti-*Aspergillus fumigatus* IgG ELISA was evaluated. Sera from 98 positive and 18 negative aspergillus precipitin patients were assayed. Clinical details of the patients were reviewed. Four precipitin groups were defined (1,>3lines; 2, 1-2lines; 3, positive after concentration of serum; 4, dubious positivity). The previously reported relationship between ELISA values and precipitin line numbers was confirmed in groups 1 and 2 ($r = 0.7944$, $p<0.001$) (Sepulveda et al. Clin. Allergy 359, **9**, 1979). Each precipitin line group from 0 to 4 was significantly separated (0:1:2:3:4, $p<0.001$, $p<0.01$, $p<0.025$, $p<0.01$ respectively). Only group 4 was insignificantly different from negative controls. The advantage of the ELISA lay in separating the patients in groups 3 and 4. Allergic bronchopulmonary aspergillosis patients had significantly higher antibody levels than bronchiectatics and asthmatics with negative skin prick tests to *Aspergillus fumigatus*. This separation was supported by 11 out of 14 group 4 patients giving negative precipitins after concentration in a second serum sample. However, we do not recommend the ELISA for routine testing as the combination of the *Aspergillus fumigatus* skin test and precipitins are sufficient to determine the clinical relevance of weakly positive aspergillus precipitins.

Is gas flow rate clinically important for nebuliser therapy?

J.W. HADFIELD, G. LOWE, W.J. WINDEBANK, J.R.M. BATEMAN There is good evidence from radio-isotope studies that the particular size of a nebulised aerosol is critically important for optimum deposition. Nebulisers produce the correct sized particles if run at about 8 l/min. There is no clinical evidence that lower driving flow rates are less effective in nebulised bronchodilator therapy. We have, therefore, studied 6 patients (age $\bar{60}$) with stable reversible airways obstruction. Each received 1 mg of salbutamol in 2 ml of N saline via a Sandoz "Lifeline" nebuliser driven at 8, 6 and 4 l/min on separate randomly allocated occasions. Bronchodilator drugs were withheld for 12 hours and baseline lung function measurements did not vary by more than 10%. The times (mean ± SE sec) for nebulisation were 309 ± 26.5 at 8 l/min, 436 ± 32.9 at 6 l/min and 790 ± 37.6 at 4 l/min respectively. Fifteen minutes after nebulisation PEFR improved by 36 ± 6.5% (SE) at 8 l/min, 32 ± 5.3% at 6 l/min and 34 ± 4.7 at 4 l/min. FEV_1 and FVC changed similarly and this improvement was maintained for 2 hours at each flow rate. We conclude that the clinical response from nebulised salbutamol is independent of the driving flow rate between 4 and 8 l/min.

The effect of ultrasonically nebulised distilled water on airflow obstruction, regional ventilation and lung epithelial permeability in asthma

COLIN BORLAND, ANDREW CHAMBERLAIN, BOB BARBER, TIM HIGENBOTTAM We have previously demonstrated that inhaled "fog" increases lung epithelial permeability in normals but without provoking brochoconstriction (Borland et al. Thorax. 221, **38**, 1983 abstract). To determine whether an increase occurs in asthma and whether the degree of change is associated with the degree of bronchoconstriction we have studied 7 male volunteers who exhibited "fog" induced bronchoconstriction. Each was studied on two occasions, one after tidally breathing 80 l of "fog" from a DeVilbiss 65 Ultrasonic Nebuliser and the other a control. The order was randomised and vitalography performed before and after "fog" challenge. Regional ventilation and permeability was monitored on both occasions by monitoring the distribution and clearance of a ^{99m}Tc-DTPA aerosol (J.G. Jones et al. Br. J. Anaesth. 705-21, **54**, 1982) using a gamma camera. Inhalation of "fog" caused a mean reduction in FEV_1 of 37.8% ($p<.05$) and a mean fall in DTPA t1/2 of 38.8% ($p<.005$) in the peripheral lung field. The changes in FEV_1 and t1/2 were correlated ($r = .86$ $p<.02$). There was no correlation between fall in FEV_1 and change in peripheral ventilation ($r = 0.41$ $p = 0.4$).

"Fog" inhalation in asthmatics provokes a similar increase in permability to that observed in normals but is accompanied by bronchoconstriction.