# *Proceedings*

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### Arterial embolisation in the management of life threatening haemoptysis from tuberculous cavities colonised by aspergillus

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Many patients with life threatening haemoptysis secondary to a pulmonary aspergilloma or an old tuberculous (TB) cavity are unfit for surgical resection by virtue of their poor pulmonary function (*Arch Intern Med* 1983;**143**:303–8). An alternative approach in these cases is to attempt to occlude the blood vessels supplying the wall of the cavity by selective arterial embolisation. We report the results of such management in four patients (three female, one male; aged 64–66 years) with severe life threatening haemoptyses (> 200 ml blood/day) in whom poor pulmonary function precluded surgery (mean $FEV_1$ 0·76 litres, range 0·45–1·05; mean FVC 1·44 litres, range 0·85–1·90). Pulmonary, bronchial and intercostal arteriography were performed via the right femoral approach using Judkins and Amplatz coronary catheters. The vessels supplying the cavity wall were demonstrated as arising from bronchial (two cases) or intercostal (two cases) arteries. Embolic materials (finely-cut gelatine, dura mater, Tambrez, Ivalon and Terbal) were used to occlude the vessels involved. There were no complications during or immediately after embolisation and the patients were discharged after one, one, five and 15 days. None of these patients has reported any further haemoptysis during the follow up period (mean 16 months, range 5–48), though one patient's pulmonary TB relapsed one month after embolisation. These encouraging results suggest that treatment by arterial embolisation is of value in patients suffering life threatening haemoptysis from old tuberculous cavities, in whom surgical treatment may not be feasible by virtue of poor pulmonary function.

### Audit of bronchial artery embolisation for major haemoptysis

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During 1984–9 40 consecutive bronchial artery embolisations (BAE) were attempted for acute major haemoptysis (> 100 ml) in 26 patients (cystic fibrosis 16, aspergilloma six, bronchiectasis three, unknown one). $FEV_1$ median 35% predicted (range 13–96%). The median total volume of haemoptysis prior to BAE was 680 ml (270–2200). Abnormal vessels were embolised successfully on 33/40 occasions. Further major haemoptyses occurred within one week in 16/33. Five patients (three aspergillomas, two cystic fibrosis) died from haemoptysis during the episode in which BAE was performed despite subsequent surgery in four (cavernostomy, bronchial artery ligation, and/or resection). Haemoptysis stopped for at least one week in 17/33 and has not recurred at all in seven patients (follow up time four months to five years). On 7/40 occasions embolisation was not possible (five no abnormal vessels found, two unstable catheter placement); four of these were undertaken within nine days of a technically successful BAE. There were no major complications. Although there was a high failure rate for BAE we consider that it still has a place in the menagement of patients with major haemoptysis for whom surgery carries an unacceptably high risk and patients with cystic fibrosis awaiting heart-lung transplant.

### Short course chemotherapy for pulmonary tuberculosis: experience with a regimen of Z2H6R6 in routine clinical practice

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Patients with pulmonary tuberculosis in West Ham (1981–3), Newham (1984–June 1988) and Blackburn (1987–June 1988) treated by the above physicians were routinely given a six month regimen of rifampicin and isoniazid, supplemented by two months initial pyrazinamide (Z2H6R6). Patients with isoniazid resistant organisms or a history of previous chemotherapy were excluded. Two hundred and thirty seven patients were notified, 214 being eligible for inclusion. One hundred and seventy completed treatment as planned, 93 had culture positive disease, and 77 culture negative disease or pleural effusion. One hundred and thirty four were asian, 27 white and nine of other ethnic origin. Patients have been followed up for a mean duration of 16·6 months (range 3–42 months). Drug reactions requiring modification of treatment occurred in only seven patients (3·3%). To date five relapses have occurred, all in culture positive patients, within 12 months of cessation of treatment. Of the relapsed patients, three admitted major non-compliance and one was given additional pyridoxine 100 mg daily for the first two months. The overall relapse rate was 2·9% (95% confidence limit 0·96–6·73%), for culture positive disease the relapse rate was 5·4% (95% confidence limit 1·76–12·1%). The results of this regimen in routine clinical practice are as good as those achieved in clinical trials (six months' therapy with rifampicin/isoniazid and two months' initial pyrazinamide with or without ethambutol.

### Bronchoscopy and mucosal biopsy in the diagnosis of Wegener's granulomatosis

MH OLIVER, M GEORGE, CMD ROSS *North Devon District Hospital, Barnstaple*
In four patients presenting with Wegener's granulomatosis (WG) to the department of medicine we have been struck by a marked similarity in the endoscopic and histological appearances of the bronchial mucosa. These changes have been sufficiently distinctive to lead us to believe that bronchoscopy and mucosal biopsy are of value in early diagnosis of this condition. The diagnosis was based on the following criteria present in all four patients: (*a*) pulmonary disease, (*b*) evidence of involvement of at least one other organ system, (*c*) positive antineutrophil cytoplasmic antibody (ANCA), (*d*) response to cyclophosphamide plus prednisolone. At bronchoscopy widespread and severe inflammation of the mucosa was seen in all four patients, virtually occluding one or more segmental bronchi in two. Mucosal biopsy revealed florid necrotising granulomatous inflammation with scattered giant cells, and squamous metaplasia which amounted to dysplasia in three. Vasculitis was not seen. There was no suggestion of tuberculosis or invasive carcinoma. Vasculitis is not invariably found in biopsy specimens from other sites. We feel that the demonstration of the changes described above, together with compatible chest *x* ray appearances and a positive ANCA test result, may permit early diagnosis of WG before life threatening involvement of other organ systems and without recourse to open lung biopsy.

### Lung crackle characteristics determined by computed lung sound analysis

N AL JARAD, S DAVIES, R LOGAN SINCLAIR, RM RUDD *Department of Thoracic Medicine, London Chest Hospital, London*
We studied the features of lung crackles in six patients with bronchiectasis (BE), six patients with congestive heart failure (CHF), six patients with asbestosis (AS) and eight healthy smokers (HS). A condenser microphone was positioned on the chest wall 4 cm below the scapular angle for 30 seconds of slow deep breathing in a sitting position. The flow was detected by a pneumotachograph and superimposed on the sound signal. The timing of the crackles and their duration were detected by using a time expanded wave form. Maximum frequencies of five crackles from each patient were analysed using a power-frequency spectrogram generated by a fast fourier transform. Crackles were detected in all patients and in one normal subject. Crackles in CHF occurred in inspiration (56%) and expiration (46%). They started during the first third of inspiration and lasted

to the end of inspiration and started at the beginning of expiration and finished half way through expiration. Crackles in AS were predominantly inspiratory (92%). They started at mid inspiration and lasted until the end of inspiration. Crackles in BE occurred mainly in inspiration (68%) but also in expiration. They were confined to the first half of inspiration and of expiration. Duration of crackles and frequency are shown in the table (mean and SD). Discriminant analysis, taking into account the timing of crackles as well as their duration and frequency, showed that the three conditions could be clearly distinguished. We conclude that lung sound analysis of pulmonary crackles may discriminate between different lung pathologies.

| | *Crackles duration (ms)* | *p* | *Highest frequency (Hz)* | *p* |
|---|---|---|---|---|
| CHF | 5·5 (1·2) | NS | 722 (311) | NS |
| AS | 5·1 (0·5) | <0·01 | 531 (111) | <0·01 |
| BE | 8·2 (3·0) | | 299 (150) | |

## Survey of respiratory physicians' involvement in and management of opportunist pneumonia in immunocompromised patients

PA CORRIS *on behalf of the BTS Research Committee Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne*
The management of pneumonia in immunocompromised hosts represents an increasing clinical problem. We were interested to survey both the degree of involvement and methods used by UK respiratory physicians in the management of such patients. Three hundred questionnaires were sent to consultant members of the BTS and 228 returned (76%). Eighty five per cent of respondents had been referred such patients undergoing chemotherapy for solid tumours or haematological malignancies and 39% following solid organ transplantation. Seventy two per cent of physicians had seen HIV positive patients. Thirty three per cent stated that it was usual for them to see all immunocompromised patients admitted to hospital with pneumonia, but only 10% had seen more than five patients in the preceeding three months. The usual request was for a diagnostic bronchoscopy alone in one third of cases and request for advice on management, including choice of therapy in the remainder. Forty two per cent felt that patients were generally referred too late. Seventy five per cent had written a protocol for the investigation and management of such patients. A 24 hour bronchoscopy service was available in 65% of units. Although routine microbiology and cytology of bronchoalveolar lavage fluid was available in 95% of units a rapid diagnostic virology service was available in only 36%. There was no consensus in the management of those immunocompromised patients whose clinical features were described in the three case histories. It was particularly noteworthy that 30 different combinations of antibiotics were selected by those choosing to give empirical treatment to the cases. The results of the survey suggest the majority of respiratory physicians are involved in the management of such patients but approaches to management are not uniform. Fifty one per cent of physicians expressed an interest in multicentre prospective clinical studies of prophylaxis and treatment of opportunist pneumonias.

## Characterisation of bronchial intraepithelial lymphocytes in bronchiectasis

JR LAPA, E SILVA, PJ COLE, LW POULTER *Host Defence Unit, Department of Thoraxic Medicine, National Heart and Lung Institute, Brompton Hospital, and Department of Immunology, Royal Free Hospital School of Medicine, London*
T lymphocytes are prominent constituents of the bronchial inflammation in bronchiectasis. (Lapa e Silva JR, *et al. Thorax* 1989;44:668–73). We have investigated the phenotype of intraepithelial lymphocytes present in biopsy samples from affected areas of bronchus in 15 patients with bronchiectasis and have compared it with that of intraepithelial lymphocytes from five normal controls. Consecutive cryostat sections were stained with monoclonal antibodies recognising T cell receptor subsets and other relevant antigens. A large increment in absolute numbers of CD3+ intraepithelial lymphocytes and subsets of T cell receptor were noted in bronchiectasis but their relative proportion and the CD4:CD8 ratio remained the same as in controls. A large majority of T cells was CD8+/CD5− both in bronchiectasis and controls. However, in bronchiectasis specimens there were significantly more CD8+ intraepithelial lymphocytes coexpressing CD45RO and HLA-DR. We suggest that the increased population of intraepithelial lymphocytes seen in bronchiectasis represents an expansion of the normal population of intraepithelial lymphocytes present in the bronchus, and that these cells have been activated and are immunologically committed.

| | *CD3** | *TCRdl** | *BFl** | *CD3/8* |
|---|---|---|---|---|
| BX | 7·4 (2·3) | 1·2 (0·5) | 4·9 (1·9) | 84·9 (11·2) |
| C | 3·2 (0·8) | 0·3 (0·2) | 2·4 (0·2) | 79·4 (10·5) |
| p | + | + | <0·02 | NS |

| | *CD3/4* | *CD8/5* | *'8/45RO* | *'8/DR* |
|---|---|---|---|---|
| BX | 15·1 (11·1) | 9·5 (3·4) | 75·5 (8·8) | 15·9 (7·3) |
| C | 9·0 (6·6) | 14·6 (7·4) | 54·8 (11·7) | 4·2 (2·4) |
| | NS | NS | <0·002 | + |

BX—bronchiectasis; C—control.
*Mean (SD) of No of positive cells/$10^4$ or percentage of double labelled cells.
†$p \leqslant 0{\cdot}0001$.

## Gamma delta T cells in the lungs of RS virus infected mice sensitised with recombinant vaccinia viruses expressing single RS virus proteins

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It has been proposed that T cells bearing a novel (gamma delta, $\gamma\delta$) form of the T cell receptor (TCR1), rather than the conventional $\alpha\beta$ TCR (TCR2), are a major component of first line defence against epithelial infections. Evidence for such cells in the murine lung has so far been indirect, being based on detection of mRNA rather than T cell surface antigens. Respiratory syncytial (RS) virus is an important cause of acute respiratory infection in man, especially in infancy. Mice infected with RS virus develop strong pulmonary lymphocytosis demonstrable by bronchoalveolar lavage (BAL). In order to study the phenotype of these cells, groups of BALB/c mice were infected intranasally with RS virus, and subjected to BAL at various timepoints. Recovered cells were stained with antibodies to CD3 (145-2C11) TCR1 (UC713D5, kindly given by Dr J Bluestone) and TCR2 (H57-597, kindly given by Dr R Kubo). Cells were simultaneously stained for CD4 (GK 1·5) and CD8 (53–6·7), and subjected to three colour flow cytometry. Exfoliated cells from mice undergoing primary infection (and those previously primed by scarification with recombinant vaccinia encoding influenza nucleoprotein) gave rise to $CD3^+CD4^+TCR2^+TCR1^-$, $CD3^+CD8^+TCR2^+TCR1^-$ and $CD3^-CD4^-8^-TCR^-SIg^-$ cells. A minor subset of $CD4^-CD8^-TCR2^+CD3^+TCR1^-$ cells was also identified in these mice. By contrast, mice previously scarified with recombinant vaccinia encoding single RS proteins gave rise to $4^-8^-$ cells bearing either TCR1 or TCR2 in approximately equal numbers. Whether these cells have TCR gene rearrangements typical of cutaneous or pulmonary TCR1 cells remains to be determined.

## IgG subclasses in sputum from patients with chronic bronchial sepsis

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Immunoglobulin G exists as four subclasses, each with different biological properties. The presence of these subclasses in secretions may be important for the elimination of micro-organisms from the bronchial tree. We have therefore measured IgG subclasses in sputum and serum from a total of 28 patients with bronchiectasis, classified according to the usual nature of their secretions into mucoid (M), mucopurulent (MP) or purulent (P) groups, when clinically stable. No significant differences were observed in serum concentrations in any of the patient

| | *M* | *MP* | *P* |
|---|---|---|---|
| IgG1 g/l | 0·16 (0·06–0·26) | 0·26 (0·15–0·37) | 0·55 (0·25–0·84) |
| % serum | 2·0 (1·3–7·8) | 3·7 (1·1–7·5) | 9·9 (5·1–37·5) |
| IgG2 g/l | 0·035 (0·07–0·1) | 0·27 (0·11–0·43) | 0·23 (0·05–0·49) |
| % serum | 0·7 (0·3–4·8) | 8·8 (3·5–27·5) | 5·0 (1·8–13·7) |
| IgG3 g/l | 0·04 (0·004–0·10) | 0·14 (0·06–0·22) | 0·22 (0·09–0·35) |
| % serum | 4·2 (0·7–40·6) | 12·7 (6·2–57·1) | 24·9 (14·1–54·7) |
| IgG4 g/l | 0·003 (0·001–0·21) | 0·13 (0·03–0·3) | 0·19 (0·02–0·28) |
| % serum | 4·5 (0·2–150) | 88·9 (30·0–175) | 42·9 (7·7–172·7) |

groups for the four IgG subclasses. The table shows the sputum IgG concentrations and results expressed as % of serum concentrations. All results are shown as median (range). The concentrations of all four subclasses in mucoid samples were significantly lower than in mucopurulent or purulent samples ($p < 0.01$). The IgG1 and IgG3 concentrations were significantly higher in purulent samples than in mucopurulent samples ($p < 0.01$). Similarly, the mucoid samples had significantly lower proportions of IgG2, IgG3, and IgG4 than mucopurulent or purulent samples ($p < 0.05$). The proportion of IgG1 present was also significantly higher in the purulent samples than in mucopurulent samples ($p < 0.005$). The results suggest a significant degree of local synthesis of IgG subclasses (especially IgG1 and IgG3) by plasma cells in the lung particularly in response to increased bacterial load.

## Detection of pneumocystis by DNA amplification

AE WAKEFIELD, FJ PIXLEY, K SINCLAIR, S BANNERJI, R MILLER, JM HOPKIN *Institute of Molecular Medicine and Osler Chest Unit, Oxford, and Department of Medicine, Middlesex Hospital, London* We have cloned and characterised DNA sequences from *Pneumocystis carinii*. Sequence analysis has identified the gene that encodes for mitochondrial ribosomal RNA of the parasite. Oligonucleotide primers were constructed from this sequence for use in polymerase chain reaction amplification of parasite DNA from various test samples. Efficient DNA amplification was obtained in samples from human and rat lungs infected with *Pneumocystis carinii* but none from isolates of other pulmonary pathogens. Subsequent sequencing of amplified products showed small but consistent differences in the DNA of pneumocystis obtained from the rat and human hosts, thus allowing us to choose an internal oligonucleotide specific to human pneumocystis for Southern hybridisation on amplified sequences. We then studied 50 individuals (HIV+ with documented pneumocystis pneumonia, HIV+ without pneumocystis pneumonia and immunocompetent patients) providing alveolar lavage samples. DNA amplification recognised the parasite in each of the 16 cases with proved pneumocystis pneumonia, but also distinguished lesser degrees of pneumocystis infection in HIV+ individuals without clinical pneumonia. DNA amplification provides a highly sensitive and specific assay for the detection of *P carinii*.

## Proliferation of bronchial epithelium in experimental bronchiectasis

D GUERREIRO, J ROHDE, H TODD, JR LAPA E SILVA, M SHEPPARD, PJ COLE *Host Defence Unit, Department of Thoracic Medicine, and Department of Lung Pathology, National Heart and Lung Institute, London* Experimental bronchiectasis was induced in rats by partial ligation of the apical lobe bronchus (LIG) and distal intrabronchial (ib) injection of live *Pseudomonas aeruginosa* (PaL). Seven groups of five rats each, constituted the test group (PaL+LIG) and six control groups: age matched normal rats, LIG alone, sham operated rats, and ib killed Pa both alone and with LIG. Rats were killed at four, eight and 12 weeks, their lungs inflated, apical lobes orientated and sectioned uniformly, and sections stained with H&E, PAS alone and alcian blue/PAS. The epithelial cell nuclei were counted in a blind fashion, always in alternating 0·3 mm lengths down the apical lobe bronchus starting 0·6 mm distal to the ligation, in each of the sections at each time point using $\times 400$ magnification. Results were analysed by Kruskal-Wallis non-parametric analysis of variance. The Pa+LIG group alone developed bronchiectasis with an increase in number of H&E stained bronchial epithelial cells (mean (SD) at three months: 636·4 (36·9) (Pa+LIG) *v* 178·7 (13·8) (normal group); $p < 0.0001$). Similarly, this group of rats showed a significant increase in the total number of goblet cells (76·9 (4·4) (Pa+LIG) *v* 27·0 (5·2) (normal group); $p < 0.0001$) and acidic glycoprotein producing cells (74·8 (2·6) (Pa+LIG) *v* 21·7 (2·7) (normal group); $p < 0.0001$) at three months. This experimental model demonstrates a proliferative epithelial component to the inflammation associated with the development of bronchiectasis.

## Interpretation of the $\dot{V}CO_2$–$\dot{V}O_2$ relationship during incremental exercise

CB COOPER, WL BEAVER, K WASSERMAN *Harbor-UCLA Medical Center, Torrance, California* The $\dot{V}CO_2$–$\dot{V}O_2$ relationship during incremental exercise (V-slope) can be described by two linear components. The lower component (S1), presumed to represent aerobic muscle metabolism, has a slope $\simeq 0.95$, suggesting that glycogen is the predominant substrate. The upper component (S2) is steeper because additional $CO_2$ is generated from $HCO_3^-$ buffering of lactic acid. The intersection of these two component slopes thus represents the transition from purely aerobic to mixed aerobic and anaerobic metabolism: the anaerobic threshold (AT). We have examined the effect of muscle glycogen depletion and alterations in the rate of increase in work rate during incremental exercise, on S1, S2 and AT. Ten normal men with a mean age of 31·4 years (SD 6·2) performed incremental and constant work rate exercise protocols on three different days. Before day 2 they were depleted of glycogen by strenuous exercise and fasting overnight. S1 was reduced from 0·95 (SEM 0·02) on control days to 0·79 (SEM 0·03, $p < 0.001$) after glycogen depletion; S2 was reduced from 1·54 (SEM 0·09) to 1·34 (SEM 0·06, $p < 0.01$) whereas AT and the difference S2–S1 was unchanged. The slope of the relationship between steady-state $\dot{V}CO_2$ and $\dot{V}O_2$ from serial constant work-rate tests below AT correlated with S1 on both control and glycogen depleted days ($r = 0.702$, $p < 0.0001$). Seven normal men with mean age 20·6 years (SD 2·4) performed a random sequence of six incremental tests with different rates of increasing work rate (15 watt/min, 30 watt/min, 60 watt/min). S1 was unaffected by the rate of work rate increase but S2 increased systematically with work rate: 1·27 (SEM 0·02), 1·42 (SEM 0·04, $p < 0.01$) and 1·65 (SEM 0·05, $p < 0.01$). These findings support the hypothesis that S1 is a measure of muscle RQ and that S2 depends on muscle RQ plus the rate of lactic acid buffering.

## A progressive shuttle walking test of functional capacity in patients with chronic airflow limitation

SM SCOTT, DA WALTERS, SJ SINGH, MDL MORGAN, AE HARDMAN *Department of Respiratory Medicine, Glenfield General Hospital, Leicester, and Department of Physical Education and Sports Science, Loughborough* Laboratory assessment of disability in respiratory disease is not widely available and existing field tests of walking ability may be overly influenced by motivation. We have examined the feasibility and reproducibility of an incremental, externally paced 10 metre shuttle walking test to measure functional capacity in patients with chronic airflow limitation. The test involves walking a 10 m shuttle around two cones. The speed of walking was dictated by a prerecorded audio signal, which increased each minute while heart rate was monitored by short range telemetry. Different protocols were tested in two groups of patients. In group A (age 54–73 y, 9 M $FEV_1$ 0·36–1·45 l) the walking speed was 0·62 m/s for the first minute increasing by 0·1 m/s for each minute for 10 levels. In group B (age 52–74 y, 6 M, $FEV_1$ 0·6–2·1 l) the walking speed was 0·5 m/s for this first minute increasing by 0·17 m/s for 12 levels. Each patient was tested on three occasions one week apart during a period of clinical stability ($FEV_1$ within 5%). The test was terminated by achievement of 85% maximum predicted heart rate or failure to complete a shuttle. The distances walked ranged from 20 metres (level 1, shuttle 2) to 510 m (8, 9) in group A and 140 m (3, 2) to 630 m (9, 0) in group B. In group A the mean difference between tests 1 and 3 was $-13$ m (95% CI 55 to 29) and between 2 and 3 was $-11$ m (95% CI $-28$ to 6). In group B the mean difference between tests 1 and 3 was $-36$ m (95% CI $-53$ to $-19$) and between 2 and 3 was $-2$ m (95% CI $-22$ to 18). After one practice the 10 metre shuttle appears to be a reproducible test of respiratory disability and worthy of further investigation.

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## Effect of low and high intensity aerobic training on physical fitness in adult cystic fibrosis

W FREEMAN, DE STABLEFORTH, RM CAYTON, MDL MORGAN *Departments of Respiratory Medicine, East Birmingham Hospital, Birmingham, and Glenfield General Hospital, Leicester* The value of exercise training in adult cystic fibrosis (CF) is unclear. Eighteen adult (15–35 years, 13 M) patients with "stable" CF volunteered for a six week home based cycle exercise progamme. They were randomly assigned, single blind, to low (30–40% $\dot{V}O_2$ max, 3 × week, 15–20 min) or high (60–90% $\dot{V}O_2$ max, 3–4 × week, 20–30 min) intensity aerobic training regimens. Laboratory tests including a progressive maximal cycle exercise test (40 W start, 10 W (F) and 15 W (M) increments/min) and endurance capacity at 80% $\dot{V}O_2$ max, were performed at baseline, after a 3–6 week control period and after six weeks of training. Of the 18 patients, two withdrew in the control period (exacerbation of infection, non-compliance); 10 undertook high intensity training, of whom two withdrew (pregnancy, exacerbation of infection); whereas six undertook and completed

| | $FEV_1$ (l) | $\dot{V}O_2$ max (ml/kg/min) | Lowest $SaO_2$% | Endurance 80% $\dot{V}O_2$ max (min) |
|---|---|---|---|---|
| LOW (n = 6) | | | | |
| Baseline | 2·43 (1·00) | 32·4 (7·7) | 93·2 (3·1) | 26·59 (11·73) |
| Control | 2·50 (0·95) | 30·7 (5·9) | 92·0 (4·3) | 25·68 (12·74) |
| Training | 2·38 (0·99) | 30·4 (6·2) | 92·7 (4·3) | 31·67 (14·52) |
| HIGH (n = 8) | | | | |
| Baseline | 1·94 (0·61) | 32·6 (5·6) | 88·4 (4·8) | 18·25 (8·74) |
| Control | 1·93 (0·64) | 31·7 (7·4) | 89·3 (4·7) | 13·63 (10·47) |
| Training | 1·83 (0·67) | 32·1 (8·0) | 86·3 (5·5)* | 20·77 (12·76) |

*$p < 0·05$ control *v* training.

low intensity training. Results are mean (SD). Overall, the physiological benefits of both levels of training were marginal. Three patients after high intensity and two patients after low intensity training, had >15% reduction in $FEV_1$ or FVC compared with control, which was accompanied by a deterioration in exercise performance. Improvement in aerobic fitness (>10 min increase in endurance at 80% $\dot{V}O_2$ max and/or >10% increase in $\dot{V}O_2$ max) was observed in six patients with stable spirometry, three from each regimen, suggesting that in patients who did improve high intensity training offered no obvious advantage over low intensity training.

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## Exercise performance six months following heart lung (HLT) and single lung transplantation (SLT)

I OMAR, J WHITE, A KIRK, J DARK, P GLASPER, GJ GIBSON, PA CORRIS *Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne* Although one would predict the functional result following HLT to be better than SLT, we were interested to note that in the short term, exercise capacity as assessed by six minute walking distance (6MD) were equivalent. Accordingly we have carried out formal progressive symptom limited exercise testing using a bicycle ergometer at six months in six patients following HLT and five patients following SLT for pulmonary fibrosis. All tests were carried out with patients breathing room air and work load was increased by 10 watts every minute. None of the patients had evidence of lung rejection or infection within one month of the study. Three of the patients in the HLT and one in the SLT group stopped exercise on account of leg fatigue rather than breathlessness. There were no significant differences in exercise results observed between HLT and SLT groups and we conclude that at six months exercise performance following SLT is as good as that following HLT.

## The importance of breathlessness scoring in the assessment of exercise performance

JG HAY, P STONE, J CARTER, MG PEARSON, AA WOODCOCK, PMA CALVERLEY *Fazakerley Hospital, Liverpool, and Wythenshaw Hospital, Manchester* Disability and therapeutic response in chronic obstructive lung disease may be assessed by exercise testing. Progressive tests assess peak performance whereas self paced tests may better reflect activity in daily living. We studied 32 patients with severe air flow obstruction (mean $FEV_1$ 0·72 (SD 0·28) l, mean age 65 (8) years). After four practice six minute corridor walks (6MD) patients attended on two consecutive days. They performed a baseline 6MD on each day with breathlessness scoring by a modified Borg category score (BS) before and at the end of exercise. Then they received either 200 μg oxitropium bromide (Ox) or placebo by MDI in a randomised crossover trial. Forty five minutes later the 6MD was repeated, and 45 minutes after this a progressive cycle exercise test performed (CE). $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$ and BS were recorded at minute intervals. Cycle duration (mean 4·0 (SD 1·9) min) and walking distance (397 (105)m) were closely correlated following placebo ($r = 0·75$) and both significantly increased following Ox (4·3 (1·9) mins $p < 0·02$; 420 (90)m; $p < 0·02$) yet remained correlated ($r = 0·64$). Six MD correlated with the change from resting to peak values of $\dot{V}E$ after placebo ($r = 0·69$) and Ox ($r = 0·45$). The increase in breathlessness while walking corrected for distance and while cycling corrected for duration correlated closely (placebo $r = 0·79$, Ox $r = 0·85$). Self paced walking tests can induce less distress but at the cost of a shorter walking distance. During progressive cycle exercise maximum ventilation is rapidly reached and the test stops. Breathlessness and the amount of exercise may have independent roles in the response to treatment.

## Exercise testing and supplemental oxygen in obstructive and interstitial lung disease

AC DAVIDSON, RM LEACH, NT BATEMAN, IR CAMERON *Department of Thoracic Medicine, St Thomas's Hospital, London* The endurance walking test (END) may be more sensitive than the six minute walk (6 MW) in detecting change in severe airflow obstruction (Davidson *et al. Thorax* 1988;43:965–71). We have now compared the use of the two tests in patients with severe airflow obstruction (n = 6, mean (SEM) $FEV_1$ 0·6 (0·3) l, FVC 1·7 (0·15 l, $Pao_2$ 59 (4) mm Hg) and with interstitial lung disease (n = 6, FVC 1·9 (0·35) l, $Pao_2$ 64 (6 mm Hg)). The sensitivity of the two tests was assessed by the change in walking distance with oxygen (at 2, 4, and 6 l/min) using a patient carried Care-Ease liquid oxygen system or, for the control walk, air (4 l/min) from a sham liquid oxygen system. Oxygen increased walking distance in both patient groups ($p < 0·05$ in all cases). Mean (SEM) increase over control in obstructive patients was 59 (12)%, 119 (23)% and 120 (21)% at 2, 4 and 6 l/min $O_2$ for END and 25 (9)%, 47 (15)% and 44 (13)% for 6MW. For the interstitial group mean increase was 47 (8)%, 98 (14)% and 112 (18)% for END and 25 (2)%, 45 (5)% and 42 (5)% for 6MW. END and 6MW were equally repeatable following training with a coefficient of variation below 7% for both tests. Instructions for END were simple and readily understood by the patient when compared with those for the 6MW. These results suggest that the END is more sensitive to the benefit of oxygen than the 6MW in both airflow obstruction and interstitial lung disease. Both tests are repeatable but the END is easier to perform.

| | HLT | SLT |
|---|---|---|
| Age (years) | 32·5 (3·0) | 51·5 (2·9) |
| $\dot{V}O_2$ max (ml $min^{-1}$ $kg^{-1}$) | 15·8 (1·9) | 14·5 (1·2) |
| $\dot{V}O_2$ max (% predicted) | 42·4 (5·4) | 49·4 (4·1) |
| $\dot{V}E$ max (l $min^{-1}$) | 39·2 (4·2) | 48·7 (6·2) |
| HR max (b $min^{-1}$) | 123 (1·7) | 132 (6·8) |
| $SaO_2$ at end of exercise (%) | 93·2 | 95·2 |
| 6MD (m) | 512 (25·9) | 514 (32) |

## Respiratory morbidity on industrial Teesside: role of socioeconomic factors and smoking

AK SIMONDS, RN HARRISON *North Tees General Hospital, Stockton on Tees, Cleveland* Mortality from respiratory disease in Cleveland is 25% above the national average and the Townsend report on health inequality in the Northern Region has highlighted an area along the south bank of the Tees which is associated with a substantial excess of premature respiratory deaths, particularly in women. To examine the link between respiratory mortality and morbidity, the health care load imposed, and the role of smoking and socioeconomic factors, a study of respiratory morbidity in the Teesside electoral ward of Portrack and Tilery has been carried out. A random sample of 1139 subjects (one in four of eligible 18–65 year olds) was interviewed at home using an expanded MRC respiratory questionnaire with additional detailed questions on socioeconomic activity. It was found that 57·3% of males and 53·1% of females were current smokers; 24·4% and 31·4% of males and females respectively had never smoked. Prevalence of symptoms included: wheeze 48·3% (persistent wheeze 20·8%), chronic cough 25·9%, sputum production for three months of the year 21·4%, breathlessness at rest 9·3%. Asthma had been diagnosed in 6·5%, 26·5% had consulted their GP with a chest condition in the past two years and 9·3% had more than one serious chest illness in the last three years. Presence of symptoms was associated with smoking and age, but there was no marked difference between sexes or across socioeconomic groups. Morbidity in non-smokers was significant—wheeze 29·8%, chronic bronchitis 11·1% and GP consultation rate for chest conditions 23·8%. This suggests that factors other than smoking and socioeconomic status may be contributing to respiratory pathology in this population, and the role of air pollution is being investigated.

### Aetiology of cryptogenic fibrosing alveolitis: a case-control study of environmental dust exposure

J SCOTT, IDA JOHNSTON, JR BRITTON *City and University Hospitals, Nottingham* We have previously reported that mortality from cryptogenic fibrosing alveolitis (CFA) is increased in industrial regions of England and Wales (Britton *et al. Thorax* 1989;44:870–1P). We now report a case-control study of the role of occupational and domestic dust exposure in the aetiology of CFA. Our cases comprised all 46 live patients with CFA known to the Nottingham hospitals; up to four controls individually matched for age, sex and general practitioner were selected for each case from family practitioner committee records. Forty cases (87%) and 106 of their matched controls (60%) completed a self administered questionnaire assessment of lifetime exposure to dust, animals or smoke at home or at work. We found that CFA cases were more likely to report occupations involving exposure to atmospheric dust (matched odds ratio (OR) 3·1, 95% confidence limits 1·2–7·9, $p < 0·01$), and particularly to metal dust (OR = 11·0, (2·3–52·4), $p < 0·001$) or wood dust (OR = 2·9, (0·9–9·9), $p = 0·08$). Cases were also more likely to have worked with cattle (OR = 10·9 (1·2–96·0), $p = 0·01$), and to have lived in a house heated by a wood fire (OR = 12·6 (1·4–114), $p = 0·009$). There was no association between disease status and exposure to coal, sand or stone dusts, or to cigarette smoking or occupational social class. However, CFA cases were more likely to report allergic symptoms in response to exposure to household dust (OR = 2·6, (1·3–5·4), $p = 0·001$) or to tree, grass or flower pollen (OR = 2·3, (1·1–4·9), $p = 0·03$). These findings demonstrate that environmental dust exposure is likely to be involved in the aetiology of CFA, and suggest that atopy may also be a risk factor for the disease.

### Regional incidence of work related respiratory disease in the UK, 1989

SK MEREDITH, VM TAYLOR, JC McDONALD *Epidemiological Research Unit, National Heart and Lung Institute, London Chest Hospital, London* The "Surveillance of Work Related and Occupational Respiratory Disease" (SWORD) project collects information monthly on *new* cases of work related respiratory disease reported by 348 thoracic and 346 occupational physicians in the UK. There is a participating consultant in 94% of chest clinics. In 1989, the first year, 2075 cases were reported. These have been analysed by region according to residence of the patient. Incidence rates have been calculated using 1988 labour force survey regional estimates of the working population. Asthma was the most frequently reported diagnosis (549 cases, 26% of total). The annual incidence was 22 per million working population; the rate in men was twice that in women, and rose steadily with age in both sexes. Four regions had rates well above the national average—West Midlands Metropolitan County (66/$10^6$), Northern (47/$10^6$), Merseyside (40/$10^6$) and Tyne and Wear (39/$10^6$). Four diseases, mainly attributed to asbestos, formed 38% of cases: malignant mesothelioma (337 cases; 13/$10^6$), asbestosis (184; 7/$10^6$), lung cancer in the presence of pulmonary fibrosis (49; 2/$10^6$) and benign pleural disease (214; 8/$10^6$). A similar geographical distribution was observed in all four. Tyne and Wear had by far the highest rates, at least four times the national average (combined rate of 217/$10^6$). High rates of lung cancer and mesothelioma were observed in the Northern region (32/$10^6$), Merseyside (25/$10^6$), Central Clydeside (22/$10^6$) and the rest of Scotland (25/$10^6$). These regional differences reflect substantial variation in the geographical distribution of new cases of work related respiratory disease. A regional analysis of cases in each diagnostic group will be presented as well as the geographical and age related distribution of suspected agents.

### Randomised controlled trial of an intervention package designed to reduce morbidity from undertreated asthma in primary school children

RA HILL, J WILLIAMS, JR BRITTON, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* We have assessed an intervention package designed to identify and reduce morbidity from under-treated asthma in school children. Questionnaires on respiratory symptoms were sent to parents of all 17 432 5–10 year olds in 102 schools, and from 13 585 replies we identified 451 children with evidence of under-treated asthma (343 reporting absence from school because of wheezing in the last year, but taking no asthma drugs, 108 absent for more than one week but taking one asthma drug only). Two hundred and twenty eight children were randomised to receive an "active" intervention comprising general practitioner (GP) consultation for reassessment of therapy and education for their teachers by the school nurse; 223 (controls) received no intervention. One hundred and fifty two (67%) "active" children consulted their GP, who made a new diagnosis of asthma in 39 (26%), and introduced or increased asthma therapy in 58 (38%). Over the next year parent-reported absence, due to wheezing, fell by approximately one week in both groups, with no difference between them. Mean school registered absence fell in the active group by 0·14 (SEM 0·49) days/term, and increased in the controls by 0·22 (0·73) days; the difference was not significant (95% CI −2·25 to +1·53 days). There was also no difference in parent or school reported absence relative to controls in the 58 children who had asthma therapy introduced or changed by their GP, or in the subgroup reporting more than two weeks' absence in the past year. There were no differences between groups for participation in games or swimming. School nurse teaching was well attended by teachers, whose knowledge of asthma was significantly better at the end of the study in "active" schools; children in these schools were also more likely to be allowed to keep their inhalers with them, and to take prophylactic treatment for games. Our intervention therefore, improved teachers' knowledge and management of asthma, but did not measurably reduce morbidity.

### High incidence of respiratory symptoms in Birmingham school children in the UK

JG AYRES, S PANSARI, P WELLER, A SYKES, D LOWE, N BUTLER *Birmingham Chest Clinic, Department of Respiratory Medicine and Community Unit, East Birmingham Hospital, Birmingham* As part of a schools asthma study, a respiratory questionnaire (based on that used in the North Tyneside Study) was sent to the parents of all children (age 4–11) attending two primary schools in inner city Birmingham. Questionnaires were returned by 359/520 (69%) in school 1 and 466/512 (91%) in school 2 ($p < 0·0001$), 825/1032 (79%) overall. No respiratory history or symptoms were reported in 177/359 (49%) and in 241/466 (51·7%) of the two schools respectively. A diagnosis of "probable" asthma was made in 111/359 (31%) (school 1) and in 88/466 (18·9%) (school 2). These rates fell to 20% and 14·6% if a sole positive answer to the question on recent recurrent wheeze was not taken to mean asthma. If the total number of pupils were taken as denominators, these rates fell to: "probable" asthma 21·4% (school 1) and 17·2% (school 2); "probable" (without recurrent wheeze) 13·9% (school 1) and 13·3% (school 2). For 98/825 (11·9%) the question "If your child develops a cold or 'flu, does it settle on the chest?" was the only question answered positively. In a further 54 this question plus one other symptom question was answered positively. This group of "chesty" children may contain a number of patients with undiagnosed asthma and should be studied further with particular reference to passive smoking and family history. The findings suggest a high incidence of respiratory symptoms among Birmingham school-children.

AS is supported by a grant from the National Asthma Campaign.

### Cystic fibrosis: current survival and population estimates to the year 2000

JS ELBORN, DJ SHALE, JR BRITTON *Respiratory Medicine Unit, City Hospital, Nottingham* Survival from cystic fibrosis (CF) is increasing rapidly. It is important to estimate the extent of this improvement so that health care facilities can be planned to deal with the expanding CF population. Estimates of life expectancy are also essential if accurate information on current prognosis is to be given to parents of an affected child, or to prospective parents deciding whether to proceed with a potentially affected pregnancy. We have used logistic linear models to estimate survival trends from CF mortality data for England and Wales between 1959 and 1986, and have extrapolated these to produce estimates of the likely size of the CF population over the next decade, and to predict the current life expectancy of children born with CF. We estimate the current CF population in England and Wales to be approximately 5200, of which 3300 (63%) are aged under 16 years. By the year 2000 the total population will increase to 6000, of which 3400 (57%) will be aged under 16. Thus the number of children with CF will remain fairly constant over the next 10 years, while adult numbers will increase by approximately 36% (from 1901 to 2577). We estimate the median life expectancy of children with CF born in 1990 to be 40 years, this figure having doubled in the last 20 years. This study suggests that health service provision for children will not need to change substantially over the next 10 years, but services for adults will need to increase by about a third. Parents can be counselled that the median life expectancy of a newborn child with CF is currently of the order of 40 years.

### Effect of dexamethasone on lung injury after oxygen exposure in the preterm guinea pig

I TOWN, M LANDREAU, J LOUDEN, G PHILLIPS, S HOLGATE, F KELLY *Departments of Human Nutrition and Medicine I, University of Southampton, Southampton* In the preterm infant with developing or established bronchopulmonary dysplasia (BPD), dexamethasone is widely used and has been shown to improve short term outcome. The mechanism of this effect has not been determined, although there is some evidence to suggest that the anti-inflammatory action of dexamethasone may be of importance. We have studied the effects of dexamethasone in the preterm guinea pig, an animal model which provides a number of parallels with the human infant, including the development of pulmonary inflammation in response to oxygen exposure. Three day premature guinea pig pups were delivered caesarian section and exposed to either 95% $O_2$ or 21% $O_2$ for 72 hours, then maintained in room air for up to 96 hours. Subgroups of animals were given a daily sc injection of either dexamethasone (10 mg/kg) or an equivalent volume of 0·9% NaCl. Bronchoalveolar lavage (BAL) was performed three, five or seven days after delivery. Exposure to 95% $O_2$ resulted in pulmonary inflammation as evidenced by an increase in BAL leucocytes. Inflammatory cell numbers (mean (SD)) in BAL from saline and dexamethasone treated animals (7–9 per group) following 95% oxygen exposure are shown in the table. In conclusion, dexamethasone attenuates the pulmonary inflammatory response in the preterm guinea pig exposed to hyperoxia. These data provide some insights into the mechanism of action of corticosteroids in neonatal lung disease.

| | | *3 days* | *5 days* | *7 days* |
|---|---|---|---|---|
| Total cell count | Saline | 8·7 (2·0) | 16·9 (8·4) | 11·7 (8·6) |
| ($\times 10^5$/ml) | Dex | 5·0 (1·6)* | 7·6 (2·0)* | 10·6 (9·2) |
| Neutrophil count | Saline | 15·1 (12·3) | 51·26 (59·6) | 31·7 (60·8) |
| ($\times 10^4$/ml) | Dex | 9·1 (6·4) | 4·5 (5·1)* | 26·2 (59·2) |

*$p < 0.01$.

### Radionuclide assessment of pulmonary endothelial and epithelial permeability in HIV positive patients

DN HUNTER, R LAWRENCE, CJ MORGAN, JV COLLINS, TW EVANS *Brompton and Westminster Hospitals, London* Patients who are seropositive for the human immunodeficiency virus (HIV) and have *Pneumocystis carinii* pneumonia (PCP) have been shown to have a decreased pulmonary transfer factor for carbon monoxide (TLCO) (Shaw RJ *et al. Thorax* 1988;**43**:436–40) and abnormal $^{99m}$Tc DTPA clearance curves and half times (O'Doherty *et al. Respir Med* 1989;**83**:395–401) compared with asymptomatic HIV positive patients. This implies an abnormality of the alveolar epithelial barrier. No studies of the integrity of the pulmonary endothelial barrier have yet been undertaken in HIV positive patients. Pulmonary endothelial permeability can be independently assessed by measuring the protein accumulation index (PAI), a double isotopic technique involving the labelling of transferrin with $^{133m}$In and red blood cells with $^{99m}$Tc. We studied the TLCO, $^{99m}$Tc DTPA clearance, and PAI in seven asymptomatic HIV positive patients receiving inhaled pentamidine therapy for PCP prophylaxis. All of the subjects had reduced TLCO (mean 57% of predicted). Six of the seven patients had biphasic $^{99m}$Tc-DTPA clearance curves with a mean (SEM) half time of 5·06 (0·76) mins (normal >40 mins). PAI × 10–3 was 0·37 (0·11) in 14 lungs (7 subjects) (normal PAI <1). We conclude that asymptomatic HIV positive patients receiving pentamidine prophylaxis may have a reduced TLCO together with increased alveolar epithelial permeability but pulmonary endothelial permeability remains normal. These alveolar epithelial diffusion abnormalities may be due to an effect of inhaled pentamidine therapy or reflect frequent subclinical PCP infection in these patients.

Work supported by the Edith Walsh and Ivy Powell awards of the British Medical Association.

### Fibroblast proliferating activity in neonatal bronchoalveolar lavage fluid

JM GRIGG, NK HARRISON, GJ LAURENT, M SILVERMAN *Department of Paediatrics, Royal Postgraduate Medical School, and Biochemistry Unit, National Heart and Lung Institute, London* A proportion of preterm infants with respiratory distress syndrome (RDS) develop bronchopulmonary dysplasia (BPD) and subsequently lung fibrosis. We investigated whether bronchoalveolar lavage fluid (BALF) from six ventilated neonates with complicated RDS had the potential to stimulate fibroblast proliferation in vitro. All subjects were seven days of age. Lavage was performed down the right main bronchus using 2 ml/kg normal saline. The mitogenic activity of BALF on human fetal lung fibroblasts was measured using a colorimetric assay based on the uptake and subsequent release of methylene blue (*J Cell Sci* 1989;**92**:513–8). Results of BALF cell counts and fibroblast proliferation, expressed as % of media controls, are shown in the table.

BALF from all six infants showed significant stimulation of fibroblast proliferation. The mean value of 125% is equivalent to that obtained from known mitogens such as platelet derived growth factor. In three cases this occurred in the apparent absence of alveolar macrophages. The origin and nature of mediators in BALF which stimulate fibroblast proliferation are unknown, but results indicate sources in addition to the alveolar macrophage may be important.

| *Gestation (weeks)* | *Outcome* | *BALF cells × $10^4$/ml* | | *Fibroblast proliferation (%)* |
|---|---|---|---|---|
| | | *Total* | *Macrophages* | |
| 28 | BPD | 448 | 77 | 141 |
| 27 | BPD | 573 | 2 | 127 |
| 24 | BPD | 28 | 1 | 121 |
| 28 | BPD | 10 | 0 | 111 |
| 28 | BPD | 17 | 0 | 130 |
| 30 | Died | 4 | 0 | 120 |

### Increased numbers of NORs in bronchiolar lining cells in cryptogenic fibrosing alveolitis and peribronchiolitis

DC ROWLANDS, JG AYRES, J CROCKER *Departments of Histopathology and Respiratory Medicine, East Birmingham Hospital, Birmingham* It has been suggested that the number of intranucleolar silver staining structures (AgNORs) is related to proliferative activity in lymphomas, mesothelioma and squamous cell carcinoma of the lung, but the method has not been applied to inflammatory disorders of the lung. Open lung biopsies from nine cases of cryptogenic fibrosing alveolitis (CFA), 13 cases of bronchiolitis and 10 specimens of normal lung were studied. A combined AgNOR-immunoalkaline phosphatase technique using antibodies against suitable cell antigens allowed enumeration of AgNORs in specific cell types (Murray *et al. J Pathol* 1989; **159**:169). In the nine cases of CFA the mean (SD) cell AgNOR counts were: type I pneumocytes 1·21 (0·08); type II pneumocytes 1·43 (0·18); intra-alveolar desquamated pneumocytes 1·61 (0·18); intra-alveolar macrophages 1·43 (0·15); lymphocytes 1·11 (0·09); stromal fibroblasts 1·28 (0·09); perivascular spindle cells 1·2 (0·05); endothelial cells 1·21 (0·07). These are similar results to values from previous studies for these cell types. In bronchiolar epithelial lining cells the mean AgNOR count for the cases of CFA (2·7) and peribronchiolitis (3·87) were significantly greater than for normal lung (1·9) (CFA *v* normal $p < 0.05$; peribronchiolitis *v* normal $p < 0.001$). Thus bronchiolar lining cells appear to show increased proliferative activity in both bronchiolitis and CFA. Further studies are required to determine the role of the bronchiolar lining cell in the pathogenesis of these two conditions.

This work was supported by a grant from the Chest, Heart, and Stroke Association.

### Concentrations of free radical products in bronchoalveolar lavage fluid in patients with BCNU related pulmonary fibrosis

C BLEASDALE, R O'DRISCOLL, S WILKES, S KALRA, AA WOODCOCK, MJ JACKSON, CRK HIND *Cardiothoracic Centre, Liverpool; Wythenshawe Hospital, Manchester; and Royal Liverpool Hospital, Liverpool* BCNU (carmustine) is a recognised cause of pulmonary fibrosis, which may occur some years after treatment. The mechanism of the lung damage is unknown, but it is postulated that it may be mediated by the action of toxic free radicals. In order to investigate this possibility, we measured the free radical products in bronchoalveolar lavage (BAL) fluid obtained from eight patients (6 male, 2 female; mean age

24·5 years, range 21–29 at the time of study), who had developed histologically proved pulmonary fibrosis up to 17 years after treatment with BCNU for malignant brain tumours (*Thorax* 1990;45(in press)). BAL fluid free radical activity was measured by simultaneous assay of levels of 9,11-linoleic acid (9,11-LA') and 9,12-linoleic acid (9,12-LA). The results are expressed as a molar ratio (%MR) of 9,11-LA'/9,12-LA × 100 (*Am Rev Respir Dis* 1990;141 (in press)). We found that the mean %MR was 3·1 (range 0·8–6·4). This was significantly higher than in patients without evidence of pulmonary fibrosis (mean level 1·8) ($p < 0·1$). When compared with the levels in BAL fluid of patients with proved cryptogenic fibrosing alveolitis (mean 4·3) there was no significant difference. The level of free radical activity in lavage fluid did not correlate with the pulmonary function tests (vital capacity, total lung capacity or treatment or transfer factor), or with the differential cell counts in the BAL fluid. These results support the hypothesis that the active inflammatory process in BCNU related pulmonary fibrosis is probably mediated in part by toxic free radicals.

This work is supported by the British Lung Foundation.

### Late BCNU pulmonary fibrosis: light and ultrastructural findings

PS HASLETON, A WEBSTER, BR O'DRISCOLL, HR GATTAMANENI, AA WOODCOCK *Departments of Respiratory Medicine and Pathology, Wythenshawe Hospital, Manchester* We have performed transbronchial lung biopsies on seven patients who had clinical evidence of lung fibrosis 13–17 (mean 14) years after exposure to BCNU chemotherapy for cerebral tumours. The age at treatment ranged from 5 to 16 years (mean 10 years) and the age at biopsy ranged from 21 to 30 years (mean 24 years). Light microscopy revealed focal interstitial pulmonary fibrosis with an associated mild lymphoplasmacytic infiltrate and some intra-alveolar histiocytes and neutrophil polymorphs. Cuboidalisation of epithelium was seen ultrastructurally. Electron microscopy demonstrated changes on both sides of the basement membrane. Type I (membranous) pneumocytes exhibited electron lucency and had been shed in some areas, leaving a bare basement membrane. Type II cells showed no obvious increase in number but had an increased complement of lamellar bodies and some of these cells contained multiple large vacuoles. Endothelial cells displayed degenerative changes with electron lucency of the cytoplasm. Focal but marked interstitial fibrosis was seen along with an increase in thickness due to elastin. These changes indicate ongoing damage to alveolar epithelial and endothelial cells together with interstitial pulmonary fibrosis. Postmortem findings are demonstrated in one female patient who died of lung fibrosis 13 years after BCNU chemotherapy. We conclude that BCNU chemotherapy may cause continuing damage to the alveolar wall many years after treatment has been given.

### Effect of inhaled histamine on plasma histamine concentrations in normal volunteers

R WOOD-BAKER, JP FINNERTY, ST HOLGATE *Medicine 1, Southampton General Hospital, Southampton* Histamine has a number of biological actions which suggest that it may play a role as a mediator in asthma. In the laboratory setting the increase in plasma histamine concentrations seen following allergen inhalation have been used as evidence of this involvement. It has been suggested that the histamine found in the plasma originates from mast cells within the lung, which after release spills over into the systemic circulation. Alternatively, the source may be from circulating basophils and thus not directly related to pulmonary histamine release. We have studied this by measuring the changes in plasma histamine occurring following inhalation of histamine aerosol by normal subjects at concentrations which would produce profound bronchoconstriction in many asthmatics. Nine normal male volunteers, mean age 23·6 (SD 5·2) years participated in the study. Following a rest period and venous cannulation, two baseline blood samples and airflow measurements ($FEV_1$) were performed. Subjects then inhaled saline placebo aerosol by a method modified from Chai *et al* (Chai H *et al. J Allergy Clin Immunol* 1975;56:323–7), with further $FEV_1$ measurements and blood sampling at 1, 3, 5, 10 and 15 minutes. This procedure was repeated with increasing concentrations of histamine up to a maximum of 16 mg/ml. Following sampling, plasma was immediately separated by centrifugation at 4°C, 3000 *g* for 10 minutes and stored at −20°C until analysis of histamine concentrations by radioimmunoassay (Immunotech, Marseille). $FEV_1$ and plasma histamine concentrations were compared by Student's *t* test for paired data. The baseline measurements of $FEV_1$ and plasma histamine concentration were 5·36 (0·7) l/s and 0·24 (0·15) ng/ml. There was no significant change in $FEV_1$ or plasma histamine concentration following inhalation of saline placebo. Inhalation of histamine aerosols at concentrations of 0·5, 1, 2 and 4 mg/ml also failed to show any significant difference from baseline measurements. Four subjects also underwent challenge with 16 mg/ml of histamine aerosol, which caused an increase in mean plasma histamine concentration to 0·54 (0·33) ng/ml at 1 minute and 0·41 (0·26) ng/ml at 3 minutes before returning to baseline, although these were not statistically significantly different to baseline values. The finding that plasma histamine concentrations do not change significantly after inhalation of concentrations of histamine sufficient to cause marked bronchoconstriction in asthmatics, suggests that the changes in plasma histamine following allergen challenge do not directly represent histamine release within the lung.

### Bronchial reactivity to histamine and bradykinin in non-asthmatic volunteers after experimental rhinovirus infection

O SUMMERS, P HIGGINS, I BARROW, D TYRRELL, S HOLGATE *Southampton General Hospital, Southampton, and MRC Common Cold Unit, Salisbury* Twenty seven non-asthmatic healthy volunteers (12 M, 15 F; 11 atopic), mean age (SEM) 38·6 (1·6) y, were inoculated intranasally with two strains of rhinovirus, RV 2 and RV EL. $PC_{15}$ $FEV_1$ histamine and bradykinin were measured before and seven and 21 days after inoculation. Infection was determined by four-fold rises in antiviral antibody titres in blood taken before and 21 days after inoculation, by viral culture from nasal washings collected on days 3–6 after inoculation by symptomatic response or by clinical assessment. PEF was recorded three days before and for 21 days after inoculation, as were diary card scores of cough, chest tightness, wheezing and dyspnoea. All 27 underwent the first two challenges, and 22 the third challenge. For the whole group and for atopic subjects there were significant correlations between the PC values for bradykinin and histamine ($r = 0·82$, $p < 0·0001$; $r = 0·849$, $p < 0·0001$ respectively). The PC values for atopics and non-atopics were significantly different ($p = 0·0019$ for histamine, $p = 0·0068$ for bradykinin, Wilcoxon signed rank test). Twenty subjects were infected by any criteria; six had clinical colds, and nine were atopic. For these 20 the median (range) $PC_{15}$ $FEV_1$ for the three histamine challenges was 35·5 (0·89–64), 62·3 (1·5–64) and 34 (0·94–64) mg/ml respectively, and 32 mg/ml for each bradykinin challenge (ranges: 0·015–32, 0·088–32 and 0·033–32). For infected subjects there was a significant difference between the second and third histamine challenges ($p = 0·0249$); this was also found for the whole group (median $PC_{15}$ 64 and 42·6 mg/ml, $p = 0·0032$), and for the subgroups of non-atopic infected subjects ($p = 0·0464$), and of infected subjects without clinical colds ($p = 0·018$). There was no significant change in mean $PEF_1$ or symptom scores after viral infection. We conclude that there is a negligible change in airways reactivity to histamine after experimental rhinovirus infection, and no change in bradykinin reactivity.

### Airway responses to inhaled metabisulphite and methacholine in heart-lung transplant (HLT) recipients

BJ O'CONNOR, V TSANG, PJ BARNES, MH YACOUB, KF CHUNG *Department of Thoracic Medicine, National Heart and Lung Institute, Brompton Hospital, London, and Harefield Hospital, Middlesex* Bronchial hyperresponsiveness (BHR) to methacholine (MC) develops following HLT. This may be an index of pulmonary denervation or airway inflammation. Inhaled metabisulphite (MBS) provokes bronchoconstriction in asthmatic subjects that correlates with BHR to MC (Nichol GM *et al. Thorax* 1989;44:1009–14.). MBS stimulates neural pathways and may act on locally exposed and intact airway subepithelial nerves. To evaluate mechanisms of BHR post HLT we measured airway responses to MC and MBS in eight stable HLT recipients on standard immunosuppressive therapy (mean (SEM)% predicted $FEV_1$ 84 (7). A control group of eight heart transplant recipients on similar therapy (% predicted $FEV_1$ 89 (5)) were studied in identical manner. Doubling increments of MC (0·5–64 mg/ml) and MBS (1·25–80 mg/ml) were nebulised from a dosimeter until the highest concentration was delivered or specific airway conductance (sGaw) fell by 40% from baseline ($PC_{40}$). Responses to MC were increased in HLT patients when compared with control group (HLT group—median $PC_{40}$ 14·62 mg/ml; control group—median $PC_{40}$ 50·17 mg/ml, $p < 0·05$). In contrast, both groups reacted similarly to MBS, which did not induce significant bronchoconstriction, provoking only small changes in airway calibre (median % decrease in sGaw 11·3 and 12·5 for HLT and controls respectively). Thus MC induced bronchoconstriction post HLT is independent of previous surgery and immunosuppressive therapy

and, unlike in asthma, does not correlate with responses to MBS. Vagal nerve pathways may mediate MBS induced bronchoconstriction.

### Inhaled sodium metabisulphite does not show immediate tachyphylaxis in asthma

BJ O'CONNOR, M CHEN-WORSDELL, SM RIDGE, RW FULLER, PJ BARNES *Department of Thoracic Medicine, National Heart and Lung Institute, Brompton Hospital, London* Generation of sulphur dioxide ($SO_2$) may underlie the indirect bronchoconstrictor response to nebulised sodium metabisulphite (MBS) in asthma. $SO_2$ challenge is tachyphylactic. Previous studies have suggested similar tachyphylaxis to MBS. To investigate this mechanism we performed two studies in 15 mild atopic asthmatic subjects. Initially (study 1) we examined the effect of inhalation challenge with MBS on direct challenge with methacholine (MCh). On the same day, eight subjects inhaled MCh on two occasions, MChl—60 minutes before and MCh2—60 minutes after inhalation of MBS. In another study (study 2), seven subjects underwent two MBS challenges, MBS1 and MBS2, separated by an interval of one hour. Doubling increments of MCh (0·6–16 mg/ml) and MBS (0·06–40 mg/ml) were nebulised from a dosimeter until $FEV_1$ fell by 20% from baseline; log $PC_{20}$ was calculated by linear interpolation. Inhalation of MBS did not affect MCh responsiveness. Similarly, log-$PC_{20}$ values after repeated challenge with MBS did not differ significantly. Thus the direct spasmogenic effect of methacholine is unchanged by MBS. Furthermore, unlike $SO_2$ and other indirect stimuli, MBS fails to exhibit tachyphylaxis. Its mechanism of bronchoconstrictor action, which remains uncertain, may differ from that of $SO_2$.

| | *Study 1* | | | *Study 2* | |
|---|---|---|---|---|---|
| | *log$PC_{20}$* | *$PC_{20}$* | | *log$PC_{20}$* | *$PC_{20}$* |
| MCh1 | 0·16 (0·23) | 1·45 | MBS1 | 0·91 (0·14) | 8·13 |
| MCh2 | 0·24 (0·22)* | 1·74 | MBS2 | 1·01 (0·12)* | 10··23 |

Results are mean (SEM) log$PC_{20}$ and geometric mean $PC_{20}$ mg/ml with analysis by paired *t* test. *NS.

### Time course of bronchodilation and functional antagonism of histamine induced bronchoconstriction after salmeterol

OP TWENTYMAN, JP FINNERTY, ST HOLGATE *University of Southampton, Medicine I, Southampton General Hospital, Southampton* Salmeterol is a novel long acting beta$_2$ agonist. We have investigated the duration of functional antagonism of histamine induced bronchconstriction due to this compound. We studied eight atopic asthmatics (3F, 5M) median age 22 (range 21–32) y, mean (SEM) $FEV_1$ 88·4 (4·2)% predicted and geometric mean provocative concentration of histamine (H) causing a 20% fall in $FEV_1$ ($PC_{20}$) 0·38 mg/ml. A double blind placebo controlled study of salmeterol 50 μg was performed. The $PC_{20}$ H was measured at 18.00 and 20.00 h and then the following morning prior to drug administration. After spontaneous recovery of $FEV_1$ salmeterol or placebo were inhaled 10 minutes prior to the inhalation of nebulised saline (0·9%). $PC_{20}$ H measurements were repeated at two hourly intervals from 1·5 to 9·5 h post saline and again the following evening at 32 and 34 h. Changes in $FEV_1$ were followed over the same time frame. In one subject the 9·5 h readings were omitted. Following placebo and saline mean (SEM) $FEV_1$ rose by 3·1 (1·5) and 5·8 (2·7)% from baseline at 20 minutes and 9·5 h respectively (NS). After salmeterol and saline $FEV_1$ rose by 7·4 (2·1) and 6·9 (2·6)% at the same time points ($p < 0.006$, $p < 0.031$ respectively). After placebo $PC_{20}$ H decreased by a mean of 0·09 and 0·13 doubling dilutions from the morning baseline at 1·5 and 9·5 h respectively (NS). After salmeterol the mean increases in $PC_{20}$ H of 4·0 and 3·2 doubling dilutions at 1·5 and 9·5 h were both significant ($p < 0.001$). There were no significant differences between bronchial responsiveness measured on the first evening and the values at 32 and 34 h after either placebo or salmeterol. We conclude that salmeterol produces significant bronchodilation and functional antagonism of histamine induced bronchoconstriction that lasts longer than 9·5 hours, but less than 32 hours.

### Effect of increasing doses of beclomethasone dipropionate (BDP) on bronchial hyperreactivity (BHR) in asthma

S OWEN, CAC PICKERING, A WOODCOCK *Regional Department of Respiratory Physiology, Wythenshawe Hospital, Manchester* Inhaled corticosteroids reduce BHR in asthma but there is little information on the dose-response relationship. We therefore carried out a double-blind crossover study over 24 weeks comparing the effects of 0, 600, 1200 and 2400 mg of BDP daily using a breath activated system (Becodisk) on BHR. 20 atopic subjects were recruited, of whom 17 completed (7M:10F; age range 17–57). All had mild to moderate asthma (mean % predicted $FEV_1$ 91%). Following a two week placebo run in period the subjects received four differing monthly treatment regimens in random order, each separated by a two week placebo washout period. BHR was measured using histamine before and after each treatment period. BHR was unchanged on placebo but improved significantly on each dose of BDP ($p < 0.001$). There was, however, no significant difference in effect between the three doses. We conclude that (1) BDP reduces BHR in asthma; (2) this effect does not appear to be dose dependent in mild/moderate asthma; and (3) BHR was not abolished even with high dose BDP.

| *Daily dose BDP (μg)* | *Geometric mean histamine $PC_{20}$ (mg/ml)* | |
|---|---|---|
| | *Before* | *After* |
| 0 | 2·04 | 1·42 |
| 600 | 1·52 | 3·42 |
| 1200 | 1·30 | 3·05 |
| 2400 | 1·62 | 3·82 |

### Muscarinic receptor subtypes in normal human lung

JFJ MORRISON, TW HIGENBOTTAM *MRC Molecular Genetics Unit, Cambridge, and Papworth Hospital, Cambridge* Muscarinic receptors are important modulators of airway calibre in man. Studies have demonstrated the effectiveness of receptor antagonism in asthma, especially at night and during acute exacerbations. Currently five subtypes of human muscarinic receptors ($m_1$ . . .$m_5$) have been cloned and expressed in mammalian cells. Each subtype consists of seven transmembrane regions with three intracellular and extracellular domains, and belongs to the family of receptors which couple G proteins. In this study we set out to determine which subtypes are present in normal human lung. The polymerase chain reaction (PCR) was used to amplify the messenger RNA (mRNA) extracted from the lungs of five subjects. Two lung specimens were from subjects receiving heart-lung transplantation for Eisenmenger's syndrome, and three from pneumonectomy specimens for lung carcinoma. Total RNA was extracted from samples of distal and proximal lung from each subject. The RNA was then enriched for mRNA using an oligo dt cellulose column. Each sample was DNAsed to ensure no DNA contamination. Then 2 μg of mRNA was reverse transcribed (RT) to yield single stranded complementary DNA (sscDNA). Oligonucleotide primers (35 bases) were designed to selectively amplify the third intracytoplasmic domain of each subtype of receptor in which least homology of base pair sequence is seen. Using these selective primers 35 cycles of PCR were performed using thermostable *Thermus aquaticus* (Taq) DNA polymerase on a Techne thermal cycler. As a negative control each DNAsed sample was RNAsed prior to RT and PCR, and as a positive control human cortex rRNA was subjected to RT and PCR. The results reveal the presence of only $m_1$, $m_2$ and $m_3$ in both proximal and distal normal human lung. The localisation of these subtypes of receptors awaits the results of in situ hybridisation studies.

### Neuropeptide containing nerves in human airways in vivo: a comparative study of atopic asthma, atopic non-asthma, and non-atopic non-asthma

PH HOWARTH, KM BRITTEN, RJ DJUKANOVIC, JW WILSON, ST HOLGATE, DR SPRINGALL, JM POLAK *Medicine I, Southampton General Hospital, Southampton, and Department of Histochemistry, Royal Postgraduate Medical School, London* The distribution and localisation of neuropeptide containing nerves in the airways in vivo was investigated using flexible fibreoptic bronchoscopy to obtain endobronchial biopsies from the subcarinae of the major airways. Biopsy samples, immediately placed into Zamboni's fixative, were stained by immunofluorescent techniques for the presence of nerves (PGP 9·5) and for the neuropeptides, vasoactive intestinal polypeptide (VIP), substance P (SP), neuropeptide tyrosine (NPY) and calcitonin gene related peptide (CGRP). The localisation was defined as epithelial (EPI), smooth muscle (SM), glandular (GL) or vascular (BV). Comparisons were made between atopic asthmatics (n = 10), on salbutamol only ($PC_{20}$M 0·37 mg/ml), atopic rhinitics (n = 7, $PC_{20}$M > 11·73 mg/ml), and non-

atopic healthy volunteers (n = 10, $PC_{20}M$ > 16·0 mg/ml). Immunofluorescent nerves (PGP 9, 5) were identified in the biopsy specimens in all groups at all sites with no significant differences between asthmatics (A), rhinitics (R) and controls (C). No VIP staining was identified in association with BV and was found in EPI in only 1 subject (A). VIP staining in SM and GL did not differ between A, R and C, nor did NPY staining, which was confined to SM and GL. No immunofluorescent nerves to SP could be identified in any group. These findings identify the presence of neuropeptides in human airways in vivo but do not support the idea that an absence of VIP is an underlying abnormality contributing to enhanced bronchial reactivity in asthma.

### Hypoxaemia and right to left shunt in patients with chronic liver disease

OA BJERKAN, JS FLEMING, AJ PEACOCK *Wessex Right Heart Group and Department of Nuclear Medicine, Southampton General Hospital, Southampton* It has been known for over 100 years that patients with cirrhosis of the liver may become hypoxaemic and, in some cases, the hypoxaemia is due to right to left (R–L) shunting in the lung. What is not known, however, is the prevalence of either the hypoxaemia or the R–L shunt. We have studied 53 consecutive patients presenting to the liver unit with chronic liver disease. Nineteen of these showed evidence of hepatic decompensation at the time of presentation. Arterial oxygen saturation ($Sao_2$) was measured in each patient by oximetry (Ohmeda 3700). We found that 21/53 (40%) of all patients and 10/19 (53%) of those with liver decompensation were hypoxaemic ($Sao_2$ 95% or less). Of the 21 who were hypoxaemic, 13 consented to measurement of R–L shunt. These patients had normal lung function ($FEV_1$ and FVC). The measurement of R–L shunt was obtained by quantifying the proportion of $^{99m}Tc$ labelled albumin microspheres (mean diam 34 $\mu$m) reaching the systemic circulation following intravenous injection. This method compares the counts over the right kidney with the total counts injected as a measure of shunt (Chilvers ER, *et al. Clin Radiol* 1988;**39**:611–4). Eight of the 13 patients had demonstrable R–L shunt (% shunt > 10% cardiac output) and there was a linear correlation (r = 0·7; p < 0·05) between measured $Sao_2$ and measured shunt. Mean shunt in the hypoxaemic patients was 13·6 (SEM 2·6)% of cardiac output. In seven normal controls mean shunt was 6·8 (1·8)%. The difference between these was significant (p < 0·05). We conclude that hypoxaemia is common in patients with chronic liver disease and may be due to abnormal R–L shunting of blood. Both of these variables can be measured by simple and relatively non-invasive techniques.

### Is oxygen a renal vasodilator in patients with hypoxic chronic obstructive airways disease (COAD)?

SV BAUDOUIN, J BOTT, C DEANE, A WARD *Departments of Thoracic Medicine and Medical Engineering, King's College Hospital, London* The origin of the oedematous state "cor pulmonale" in patients with chronic respiratory failure remains controversial. It has been proposed that changes in renal function may be important and this view is supported by radioisotope studies showing reduced renal blood flow in patients with hypoxic COAD. However, no causal link has been established between arterial oxygenation and changes in renal flow. We have measured renal blood flow profiles, non-invasively by Duplex doppler ultrasound, in nine hypoxic patients with COAD (mean $Pao_2$ 7·2 kPa; mean $Paco_2$ 6·2 kPa, mean $FEV_1$ 0·75 l) while breathing room air and controlled oxygen. Six normoxic ($O_2$ saturation 97% or greater on air) healthy, aged matched volunteers acted as controls. $O_2$ saturation and transcutaneous $CO_2$ were continuously monitored (calibrated with arterialised capillary samples). Subjects breathed room air while the mean of five separate recordings of renal pulsatility index PI (a non-dimensional measure of renal vascular resistance) was taken. Controlled $O_2$ was then given to achieve a stable $O_2$ saturation of 95% or greater for 15 minutes without a significant rise in $Taco_2$ and five further recordings of PI were taken. Controls showed no significant difference in PI on air or oxygen. The PI of COAD patients on air was significantly greater than controls (p < 0·001) and fell significantly (p < 0·02) on oxygen. Renal vascular resistance is increased in patients with hypoxic COAD and significantly falls with oxygen therapy.

| | *n* | *$O_2$ sat (SD)* | *PI (SD)* |
|---|---|---|---|
| Controls (air) | 6 | 97 (1) | 1·01 (0·09) |
| Controls ($O_2$) | 6 | 99 (1) | 1·03 (0·15) |
| COAD (air) | 9 | 88 (6) | 1·44 (0·28) |
| COAD ($O_2$) | 9 | 95 (2) | 1·26 (0·14) |

### Atrial natriuretic peptide (ANP) attenuates pulmonary vascular remodelling by chronic hypoxia in rats

RJD WINTER, L ZHAO, JMB HUGHES *Respiratory Division, Department of Medicine, Hammersmith Hospital, London* We have previously shown that plasma ANP concentration is increased both in rats with pulmonary hypertension after seven days' exposure to chronic hypoxia (*Clin Sci* 1989;**76**:95–101) and in patients with hypoxic pulmonary hypertension (*Thorax* 1989;**44**:58–62). We propose that release of ANP by the hypertrophied right ventricle and the right atrium during chronic hypoxia modifies the remodelling of pulmonary blood vessels during hypoxic exposure. We have tested this hypothesis by continuous infusion of two doses of ANP in rats during chronic hypoxia. Alzet 2ML1 mini osmotic pumps were implanted subcutaneously into albino male Wistar rats (n = 48) connected by cannula to the jugular vein. Dose regimens were: (i) vehicle, (ii) ANP 300 ng/rat/h, (iii) ANP 800 ng/rat/h either in hypoxia ($Fio_2$ 10%) or normoxia for eight days. Animals were then anaesthetised and measurements of systemic blood pressure (systolic and diastolic, SAP and DAP, mm Hg) and pulmonary artery pressure (PAP, mm Hg) were made. Right and left ventricular weights (RV and LV) were measured. Right ventricular hypertrophy was expressed by RV/LV (%). Microhaematocrit (Hct, %) and body weight gain were measured and vascular remodelling was assessed by counting the percentage of thick walled peripheral vessels (TWPV, %). Results mean (SD)) are given in the table (n = 8 all groups).

Thus ANP, which is naturally released in increased amount during chronic hypoxia, attenuates pulmonary hypertension and vascular remodelling.

### Does oxygen desaturation during sleep cause release of erythropoietin in patients with chronic obstructive pulmonary disease?

MF FITZPATRICK, G MCMAHON, KF WHYTE, MB ALLEN, RC TAM, PM COTES, NJ DOUGLAS *Respiratory Medicine Unit, Department of Medicine (RIE), University of Edinburgh, and Haemostasis Research Group, Clinical Research Centre, Harrow* Patients with chronic bronchitis and emphysema (CB and E) become hypoxaemic during sleep, especially during REM phase (Douglas NJ, *et al. Lancet* 1979;i:1–4). This nocturnal hypoxaemia is thought to contribute to secondary erythrocytosis in these patients by increasing erythropoietin production, although there is no direct evidence to support this contention and daytime serum erythropoietin (EPO) was normal in 50% of patients with CB and E and erythrocytosis (Wedzicha JA *et al. Clin Sci* 1985;**69**:413–22). We have now compared EPO over 24 hours in nine patients with CB and E and nine age matched normal subjects. Mean age was 68 (SD 10) years. In those with CB and E mean arterial $Po_2$ was 7·1, range 3·95 to 8·6 kPa, and $PCo_2$ 6·3, 5·3 to 9·3 kPa. Serum was sampled every two hours during the day and hourly at night. Total sample volume was less than 150 ml per subject. Serum samples were stored at −70°C until estimation of EPO by radioimmunoassay. Serum EPO was raised in the three most hypoxic patients with CB and E who also had the lowest dips in overnight saturation. In two of these EPO was continuously above normal and in the third it was increased in 10 out of 11 samples taken between 20.00 and 07.00 h. In these patients EPO tended to increase from about 02.00 until 06.00 or 07.00 h. In the remaining six patients with CB and E, despite reduced $Sao_2$ during sleep, serum EPO was not significantly different from that

| | *Normoxia* | | | *Hypoxia* | | |
|---|---|---|---|---|---|---|
| | *Vehicle* | *ANP 300* | *ANP 800* | *Vehicle* | *ANP 300* | *ANP 800* |
| PAP | 28 (6) | 29 (5) | 28 (4) | 45 (6)* | 39 (5)* | 38 (6)† |
| SAP | 145 (24) | 140 (14) | 138 (16) | 143 (21) | 147 (32) | 146 (31) |
| DAP | 125 (18) | 122 ((11) | 124 (15) | 125 (15) | 124 (24) | 128 (25) |
| RV/LV | 29 (2) | 29 (1) | 28 (2) | 37 (4)* | 35 (5)* | 37 (4)* |
| Hct | 49 (4) | 46 (6) | 47 (9) | 59 (5)* | 55 (8)* | 56 (7)* |
| BW | 37 (8) | 41 (12) | 39 (13) | 16 (4)* | 9 (19)* | 14 (20)* |
| TWPV | 4 (1) | 6 (3) | 6 (3) | 25 (6)* | 19 (4)‡ | 17 (7)*‡ |

*p < 0·001 compared with normoxic vehicle treated;
†p < 0·05; ‡p < 0·01 compared with hypoxic vehicle treated.

of the normal controls. Thus nocturnal desaturation was associated with increased EPO production in 33% of our patients with CB and E (those who were most severely hypoxic). It is not, however, a consistent stimulus to increased EPO release.

### Does air temperature influence breathlessness and exercise performance in chronic obstructive lung disease (COPD)?

DR GRAHAM, J AHMAD, MG PEARSON, PMA CALVERLEY *Fazakerley Hospital, Liverpool* Cold air is known to cause wheezing in asthma while in normal individuals cold air may reduce breathlessness (Schwartzstein. *Am Rev Respir Dis* 1987;136:58–61). The effect of air temperature on symptoms and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) is unknown. Twenty one patients with stable COPD and less than a 20% response to bronchodilators were studied (mean (age 64 (6) y, $FEV_1$ 0·99 (0·28 l). Each patient performed a symptom limited, progressive cycle test (10 watt/minute increments) on consecutive days in random order while breathing either room air (mean 24·5°C) or cold air (mean 7·5°C) from a mouthpiece. Pulse rate, ECG, $Sao_2$, $PetCO_2$, Borg Score and work load were recorded each minute. Spirometry was measured before and 10–15 minutes after exercise. Mean $FEV_1$, $Sao_2$ and maximum pulse rate on both study days were similar. In contrast to patients with asthma, no COPD patient had a greater than 10% reduction in $FEV_1$ after exerrcise, mean $FEV_1$ rising by 12% after room air and by 6% after cold air. Breathing cold air, 11 patients exercised further than when breathing room air and 10 achieved the same work load. Mean maximum work load was 43 (18) watts with cold air and 35 (14) watts breathing room air ($p < 0·001$). End exercise Borg scores were similar, but at the same levels of work 12 patients reported less breathlessness with cold air, seven were unchanged and only two were more breathless. Mean $PetCO_2$ levels were higher after cold air (5·9 (1·4) *v* 5·3 (1·7) kPa, $p < 0·001$), suggesting relative hypoventilation. These results show that patients with COPD behave differently from asthmatics when breathing cold air. They were able to do more work yet were less breathless at a given work load. The reasons for these improvements are not clear but may be related to an effect of cold air on the perception of breathlessness.

### Changes in lung mechanics in patients with chronic obstructive pulmonary disease in the supine posture

JCH YAP, A WATSON, H JOYCE, NB PRIDE *Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London* Patients with chronic obstructive pulmonary disease (COPD) often complain of orthopnoea when they lie supine. However, almost all assessments of their airway mechanics are made in the sitting posture. We have examined changes in total respiratory resistance (Rrs) and reactance (Ra), both at 6 Hz, resonant frequency (Res.Fr.) and frequency dependence (Fr. Dep.) of Rrs in the sitting ($S_1$ and $S_2$) and supine (Su) positions, using the pseudo-random noise oscillation technique of Landser (*J Appl Physiol* 1976; 41:101) in seven men with COPD and a mean (SEM) age of 66·9 (2·5) years, forced expiratory volume in one second ($FEV_1$)% predicted of 41·0 (4·4)%, $FEV_1$/VC of 41·0 (5·0)% and total lung capacity (TLC)% predicted of 119·8 (5·6)%. Their measurements were compared with those of seven male controls with a mean (SEM) age of 61·1 (1·2) years, $FEV_1$% predicted of 111·0 (5·8)%, $FEV_1$/VC of 75·4 (3·4)% and TLC% predicted of 105·1 (4·3)%. We also measured mid tidal lung volume (MTLV), vital capacity (VC), oxygen saturation ($Sao_2$) and visual analogue score (VAS) for dyspnoea in both positions. The absolute changes in the above measurements from sitting to supine position are greater in COPD (all $p < 0·05$) and they did not go back to the initial sitting values even after 15 minutes. These changes occurred despite a smaller fall in MTLV in the patients (99 *v* 910 ml, $p < 0·01$). Their VC decreased by 283 ml as compared to 121 ml in the control. There was also a fall in $Sao_2$ of 2%, $p < 0·01$ and a small increase in VAS. Thus, although patients with COPD do not show the normal fall in MTLV in the supine posture when awake, they still have increases in Rrs. If MTLV falls in sleep, these increases would be even larger.

| | *COPD* | | | *Control* | | |
|---|---|---|---|---|---|---|
| | $S_1$ | *Su* | $S_2$ | $S_1$ | *Su* | $S_2$ |
| Rrs ($cmH_2O$/l/s) | 4·8 | 6·1 | 5·5 | 2·2 | 2·8 | 2·1 |
| Ra ($cmH_2O$/l/s) | − 2·1 | − 3·6 | − 2·4 | −0·3 | −0·6 | −0·2 |
| Res. Fr (Hz) | 20·6 | 28·6 | 22·1 | 7·5 | 9·8 | 7·3 |
| Fr.Dep. ($cmH_2O$/l/s/Hz) | 0·3 | 0·6 | 0·4 | −0·2 | 0·03 | −0·2 |

### Five year survival with nocturnal cuirass assisted ventilation in chest wall disorders

WJM KINNEAR, JM SHNEERSON *Assisted ventilation unit, Newmarket General Hospital, Newmarket* During a 12 month period in 1984–5 we started 25 patients with respiratory failure due to chest wall disease on nocturnal cuirass assisted ventilation. Eight had a thoracic scoliosis or kyphosis, nine had neuromuscular disease (including two with a postpoliomyelitis scoliosis) and eight had undergone a thoracoplasty. Two patients with scoliosis discontinued nocturnal assisted ventilation and both died within a year. Cuirass assisted ventilation became ineffective in maintaining adequate ventilation overnight in three patients, two with scoliosis and one with a thoracoplasty. Two of these patients were successfully transferred to intermittent positive pressure ventilation via a nasal mask or tracheostomy, but one patient with a scoliosis died at night shortly after an elective tracheostomy had been performed. Fourteen patients were alive after five years, representing 61% of the patients who continued with assisted ventilation. In addition to the deaths mentioned above, two patients with a scoliosis, three with progressive neuromuscular disease and three with a thoracoplasty died. Mortality was not related to age, vital capacity or arterial blood gases at the time of presentation.

### Lung function and pulmonary haemodynamics in cryptogenic fibrosing alveolitis

D VEALE, JC DOIG, J WHITE, RS BEXTON, GJ GIBSON, PA CORRIS *Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne* Cor pulmonale is a recognised complication of cryptogenic fibrosing alveolitis (CFA) but there is little published information on pulmonary haemodynamics in this disorder. We have performed right heart catheterisation on 12 patients with advanced CFA as part of an assessment for single lung transplantation and have related the findings to levels of pulmonary function at rest and on exercise. All patients had raised pulmonary vascular resistance, with a mild to moderate increase in pulmonary artery pressure. Patients had a normal cardiac output and had normal pulmonary artery wedge pressure. No significant correlations were found between individual tests of pulmonary function and cardiac data in this study. The values of PA pressure for a given $Pao_2$ in these patients were, however, similar to those reported in a larger group with chronic airways obstruction (Boushy and Worth. *Chest* 1972;5:565).

| | *Median* | *Range* |
|---|---|---|
| $FEV_1$ % predicted | 45 | 21–76 |
| Vital capacity % predicted | 46 | 26–73 |
| $Pao_2$ (breathing air) kPa | 7·9 | 5·9 –10·5 |
| $Paco_2$ kPa | 5·1 | 4·4 – 6·1 |
| Exercise capacity (breathing 50% oxygen) watts | 40 | 30–80 |
| Cardiac output l $min^{-1}$ | 5·19 | 4·39– 9·35 |
| Mean PA pressure mm Hg | 28 | 20–48 |
| Pul artery wedge pressure mm Hg | 11 | 7–15 |
| Total pul resistance units × $m^2$ | 8·62 | 5·83–18·9 |

### Diagnostic pick up rate of polysomnography

N RAJAGOPALAN, NJ DOUGLAS *Respiratory Medicine Unit, Department of Medicine (RIE), University of Edinburgh* It is often argued that patients suspected of having the sleep apnoea-hypopnoea syndrome should undergo full polysomnography rather than a simple respiratory investigation because other clinically important diagnoses may be detected at polysomnography. These may be the only abnormalities detected or may coexist with sleep apnoea, making the interpretation of studies based on respiratory monitoring alone difficult. However, the basis for this assumption is relatively flimsy, largely depending on one study only published in abstract form (Rutherford *et al. Am Rev Respir Dis* 1987;135:A48). We have therefore examined the ultimate diagnoses obtained in 100 consecutive patients referred for investigation as to whether they had the sleep apnoea-hypopnoea syndrome, each of whom underwent full overnight polysomnography including anterior tibial EMG recordings. Fifty one proved to have the sleep apnoea-hypopnoea syndrome, defined as the

coexistence of symptoms plus at least 15 apnoeas + hypopnoeas per hour of sleep (Whyte *et al. Q J Med* 1989;72:659–66). Forty five patients had entirely normal polysomnography, including one with narcolepsy, one with the Klein-Levin syndrome and two whose symptoms were ascribed to psychological causes. Three patients were found to have nocturnal myoclonus; two of these had coexisting sleep apnoea, which was considered to be less important in both cases. Three patients were found to be nocturnal hypoventilators with no evidence of the sleep apnoea-hypopnoea syndrome. We conclude that in only three (those with myoclonus) of 100 subjects referred for consideration of the diagnosis of the sleep apnoea-hypopnoea syndrome did polysomnography contribute to an alternative diagnosis being achieved. The value of this expensive procedure must thus be questioned.

### Domiciliary polysomnography in Duchenne muscular dystrophy

Y KHAN, JZ HECKMATT *Department of Paediatrics, Hammersmith Hospital, London*
We report a study of sleep hypoventilation in non-ambulant adolescents with Duchenne muscular dystrophy. Polysomnography was carried out with an Oxford Medilog multiparameter analysis recorder with Respitrace inductance plethysmography and an Ohmeda Biox 3700 pulse oximeter. The following channels were recorded: electroencephalogram C4-A1, electro-oculogram, submental electromyogram, chest and abdominal movements, oronasal airflow and oxygen saturation. Nineteen patients have been studied and we are currently involved in studying age matched controls. All subjects had two consecutive nights studied at home. Full sleep staging was possible in 14 patients. Of these, 10 had episodes of hypoxia defined by $\geqslant 4$ falls in oxygen saturation of $\geqslant 5\%$ from the previous baseline value during sleep and associated with apnoea. There was no significant difference in selected sleep parameters between nights 1 and 2 (table, n = 14). The number of hypoxic events of 10% desaturation between night 1 and night 2 was, however, significant. Hypoxia was associated with apnoea of greater than 10 seconds and on screen analysis the apnoeas were predominantly "central" in origin. We conclude that it is possible to get high quality domiciliary polysomnography. However, despite the advantages of home based studies the necessity of an "adaptation" night remains. Our patients with sleep hypoventilation will be further studied in a trial comparing theophylline with nasal ventilation.

| | *Night 1* | *Night 2* | *p* |
|---|---|---|---|
| Actual sleep time (min) | 423 (94) | 452 (96) | NS |
| REM sleep | 96 (77) | 77 (40) | NS |
| Sleep efficiency (%) | 90 (6) | 91 (7) | NS |
| Hypoxia 5% | 4 (4) | 6 (6) | NS |
| Hypoxia 10% | 2 (3) | 4 (5) | 0·02 |

Values are mean (standard deviation).

### Community based survey of objective sleep quality in asthmatic patients and in snorers

MF FITZPATRICK, K MARTIN, D PECK, CM SHAPIRO, NJ DOUGLAS *Respiratory Medicine Unit, Department of Medicine (RIE), and Department of Psychiatry, University of Edinburgh* A questionnaire consisting of 125 broadly based questions was sent to a random selection of 500 people at each of eight locations across Britain. Twenty two of the 125 (18%) questions related to sleep quality, asthma or snoring. One thousand four hundred and seventy eight people (37%) returned the completed questionnaire. Six per cent of the responders said they had asthma. Eighty five per cent of the asthmatics claimed to waken with nocturnal asthma symptoms from time to time, and 31% of the asthmatics were woken by asthma at least 20 times per year. Similarly, 82% of the asthmatics suffered asthma symptoms on getting up in the morning and these symptoms occurred more than 20 times per year in 38% of the asthmatic group. More asthmatics (38%) felt that they had too little sleep than non-asthmatics (29%; $p < 0{\cdot}01$). More of the asthmatic group felt that their sleep was rarely or never refreshing (27 *v* 16%; $p < 0{\cdot}001$). More of the asthmatics said that they had accidental naps during the day ($p < 0{\cdot}02$) and snoring was commoner in the asthmatics ($p < 0{\cdot}03$). Nineteen per cent of responders said they snored on at least one night per week. Deliberate daytime napping ($p < 0{\cdot}01$) and accidental daytime napping ($p < 0{\cdot}001$) were more common among the snoring group than non-snorers. Regular snorers more commonly took alcohol within an hour of going to bed at night ($p < 0{\cdot}01$). Falling asleep while driving or operating machinery was more common among snorers than non-snorers ($p < 0{\cdot}03$). We conclude that asthmatics and snorers in the community have significant morbidity from sleep disturbance and, possibly as a result of this, snorers are more likely to have daytime naps while driving or operating machinery.

### Is a symptom based questionnaire useful in the diagnosis of the sleep apnoea-hypopnoea syndrome?

MB ALLEN, NJ DOUGLAS *Respiratory Medicine Unit, Department of Medicine (RIE), City Hospital, Edinburgh* Investigation of the sleep apnoea-hypopnoea syndrome (SAHS) is both time consuming and expensive. It has been suggested that diagnosis from history alone may be possible (Williams *et al. Chest* 89;**96**:451–3). To determine if this is true, a 24 question self administered questionnaire was designed, based upon previously reported symptoms (Whyte *et al. Q J Med* 1989;72: 659). The questionnaire was prospectively completed by 140 consecutive patients referred for investigation of suspected SAHS. From the results of standard overnight polysomnography patients were divided into two groups, those with SAHS defined as 15 or more apnoeas plus hypopnoeas per hour of sleep (A+H/hr) and those without. The mean (SD) results between the two groups are shown in the table. The numbers of patients in the two groups with loud snoring, daytime sleepiness, unrefreshing sleep and excessive nocturnal movements were similar with no difference in the number of car accidents between the two groups. The only question with a significantly different response was "Has your bed partner ever noticed you stop breathing when asleep?"—which produced a positive response more often in the patients found to have the sleep apnoea-hypopnoea syndrome (75 *v* 46%; $p = 0{\cdot}01$). Thus, when applied to a group of patients referred for investigation of SAHS, our symptom based questionnaire is of relatively little value and cannot reliably identify patients with the sleep apnoea-hypopnoea syndrome.

| | | *No* | *Age* | *Collar size* | *% females* |
|---|---|---|---|---|---|
| 15 or more | A+H/h | 78 | 52 (12) | 16·3 (1·2) | 12% |
| Less than 15 | A+H/h | 62 | 49 (14) | 16·2 (1·2) | 28% |

### Sleep apnoea in chronic bronchitis and emphysema

M ALLEN, K PROWSE *City General Hospital, Stoke on Trent* Transient falls in oxygen saturation during sleep in patients with chronic bronchitis and emphysema (CB+E) have been attributed to episodes of upper airway obstruction (Wynne. *Am J Med* 1979; **66**:573). Although not confirmed (Catterall JR. *Am Rev Respir Dis* 1983;**128**:24), some patients with CB+E do have evidence of upper airway obstruction in the absence of sleep apnoea symptoms. To examine the frequency of upper airway obstruction and changes in sleep architecture with time, full polysomnography was undertaken at 0, 6, and 12 months on 10 patients (seven male) with stable CB+E. Their mean age (SD) was 60·5 (5·7) years with a mean $FEV_1$ of 0·85 l. Four patients had previous heart failure and all had daytime hypoxaemia, mean $Pao_2$ 7·9 kPa, $Paco_2$ 5 kPa. Sleep quality was good with sleep efficiencies (time asleep/time in bed) of 69·5%, 70·7% and 73·8% respectively. Times spent in different sleep stages were similar. On the basis of an apnoea plus hypopnoea index (A+Hl) of 5, four patients were normal, three had sleep apnoea in one out of three studies, two were abnormal in two out of three studies and one had evidence of sleep apnoea on all three study nights. If an A+Hl of 15 is used, seven patients are normal, two show sleep apnoea on one out of three nights, and one is abnormal on two out of three nights. Thus the discrepancy in incidence of sleep apnoea found in the literature may be due, in part, to the definition of what is "normal", along with some variability in the patients themselves.

### Inhaled salmeterol reduces nocturnal bronchoconstriction and improves objective sleep quality in nocturnal asthma

MF FITZPATRICK, T MACKAY, H DRIVER, KF WHYTE, NJ DOUGLAS *Respiratory Medicine Unit, Department of Medicine (RIE), University of Edinburgh* As conventional inhaled bronchodilators do not remain effective over eight hours of sleep, reliance has been placed on slow release oral beta agonists and theophyllines to reduce nocturnal bronchoconstriction in patients with more severe asthma. However, side effects can limit the efficacy of these oral agents, and theophyllines impair objective sleep quality in asthmatics (Rhind *et*

*al. Br Med J* 1985;**291**:1605). We studied the efficacy of inhaled salmeterol, a long acting inhaled Beta$_2$ agonist, in two doses (50 and 100 $\mu$g twice daily) on nocturnal bronchoconstriction and objective sleep quality in 18 patients with nocturnal asthma (defined as at least two nocturnal awakenings with asthma per week and a mean overnight fall in PEF of at least 15% over a two week run in). During this double blind, placebo controlled, cross-over study involving three two week treatment limbs, patients kept a diary card of PEF four times daily and at night, and had two consecutive overnight polysomnograms in the sleep laboratory at the end of each treatment period. Statistical analysis was by Wilcoxon signed rank test with the Bonferroni correction. Salmeterol in either dose significantly improved the lowest overnight PEF ($p < 0.05$), the mean percentage overnight fall in PEF ($p < 0.02$), PEF at final wakening ($p < 0.01$), and morning asthma symptoms ($p < 0.05$). Salmeterol also increased the time spent in deep (stage 4) sleep ($p < 0.02$) and reduced the time spent in wakefulness and drowsiness ($p < 0.05$). We conclude that salmeterol, unlike any other drug tested to date, improves both nocturnal bronchoconstriction and objective sleep quality in patients with nocturnal asthma.

### Platelet activating factor (PAF) induced bronchoconstriction in asthmatics: role of cysteinyl leukotrienes

IK TAYLOR, GW TAYLOR, RW FULLER *Department of Clinical Pharmacology, Royal Postgraduate Medical School, London* PAF is an ether linked phospholipid which is a potent smooth muscle spasmogen when inhaled into the human airway. The bronchoconstriction is transient but heightened bronchial reactivity may persist. Formation of PAF accompanies the stimulation of a number of inflammatory cells; further, PAF activates eosinophils, neutrophils and platelets. To evaluate the mechanism of PAF induced bronchoconstriction in vivo, we have studied 10 mild atopic asthmatics (six F, age 20–35, predicted $FEV_1$, 58–>100%). All medications were stopped at least 24 hours prior to study and each subject was studied on three occasions. Bronchial challenges were performed once each with methacholine (MC), isotonic saline (SAL) and PAF administered from a breath activated dosimeter delivering 8 $\mu$l/breath. The total dose of PAF delivered was 80 $\mu$g (five breaths, 2 mg/ml). Maximum bronchoconstriction to PAF was matched with methacholine administered in doubling doses via the dosimeter and specific airway conductance (sGaw) measured in a variable pressure, constant volume body plethysmograph. Urine was collected for four hours post-challenge and analysed by HPLC-RIA for $LTE_4$, the stable metabolite of $LTC_4$ and $LRD_4$. Results (mean (SEM)) are shown in the table. Whole body LT generation, as measured by urinary $LTE_4$, is significantly elevated following PAF compared to MC and SAL demonstrating secondary mediator release occurs in vivo following PAF administration to the airway. Whether the source of this increased LT generation is systemic or related to pulmonary sequestration of inflammatory cells remains to be evaluated. While a direct effect of PAF on airway smooth muscle cannot be excluded, the bronchoconstrictor actions of PAF may be mediated indirectly through the release of cysteinyl LTs (or via cyclo-oxygenase dependent mechanisms—Ward *et al*, this meeting) from activated inflammatory cells.

| | *PAF* | | *SAL* | | *MC* | |
|---|---|---|---|---|---|---|
| $LTE_4$ (ng/mmol Cr) | 366·0 | (66·9)* | 33·6 | (4·6) | 41·6 | (13·3) |
| Mean max % fall sGaw | 48·2 | (4·6) | 11·8 | (4·1) | 55·5 | (4·9) |

*$p < 0.01$.

### Effect of inhalation of sulphidopeptide leukotrienes on airways responsiveness to histamine in asthmatic and normal subjects

SP O'HICKEY, RJ HAWKSWORTH, JP ARM, AEG CREA, BW SPUR, TH LEE *Department of Allergy and Allied Respiratory Disorders, Guy's Hospital, London* To investigate the effects of prior inhalation of the sulphidopeptide leukotrienes (LT) C4, LTD4, and LTE4 on the airways responsiveness to histamine, six normal and seven asthmatic subjects underwent histamine inhalation challenge one, four and seven hours after saline control and bronchoconstriction induced by LTC4, LTD4, LTE4 and methacholine. Airways responsiveness was determined as the dose of agonist required to induce a 35% fall in specific airways conductance. In asthmatic subjects prior inhalation of LTC4 enhanced airways responsiveness to histamine when compared with saline inhalation by 2·8, 3·9 and 2·9 fold one, four and seven hours respectively after inhalation ($p < 0.001$). LTD4 enhanced histamine responsiveness by 2·1, 2·9 and 2·1 fold after inhalation ($p < 0.001$) and LTE4 enhanced histamine responsiveness by 2·4, 3·0 and 1·8 fold after inhalation ($p < 0.001$). Methacholine inhalation did not alter significantly the histamine responsiveness throughout the time course. In normal subjects inhalation of LTC4, LTD4 and LTE4 did not alter airways responsiveness to histamine. These results suggest that the sulphidopeptide leukotrienes may have a role in the pathogenesis of bronchial hyperresponsiveness.

### Leukotriene E4 enhances histamine responsiveness in guinea pig tracheal strips by a cholinergic neuronal mechanism

CAJ JACQUES, BW SPUR, TH LEE *Department of Allergy/Allied Respiratory Disorders, Guy's Hospital, London* Airway hyperresponsiveness is a prominent feature of bronchial asthma. Contractile response to histamine in guinea pig central but not peripheral airway tissue is enhanced by LTE4. LTE4 induced hyperresponsiveness is selective for histamine and is not seen with other contractile agents, such as carbachol, substance P or KCl. LTE4 did not modulate the relaxation of tracheal smooth muscle caused by isoprenaline. LTE4 (4nM) produces an approximate 10 fold shift to the left of the histamine dose-response curve as compared with control tissues incubated with buffer ($p < 0.005$) but there is no significant increase in the maximal response (Tmax) to histamine ($10^{-4}$M). Preincubation of tracheal strips with 20-COOH LTE4 or 11-trans LTE4, two analogues of LTE4, produced an approximate seven fold and three fold leftward shift, respectively, of the histamine dose-response curve. The cyclo-oxygenase inhibitor indomethacin and GR32191, a thromboxane (TP–) receptor antagonist, blocked the LTE4 induced hyperresponsiveness of tracheal strips. The thromboxane A2-mimetic U46619 was able to cause hyperresponsiveness to histamine on tracheal smooth muscle. Atropine (1$\mu$M) was also able to block LTE4-induced hyperresponsiveness. Tetrodotoxin, a nerve conduction blocker, inhibited the hyperresponsiveness produced by LTE4. Preincubation of tracheal strips with LTE4 potentiated the response to electrical field stimulation using parameters which did not result in direct muscle stimulation. Our results suggest that LTE4 selectively augments histamine responsiveness in guinea pig tracheal tissues, that the mechanism is via a facilitation of cholinergic neurotransmission, and that it is mediated by TP receptors.

### $TXA_2$ formation in vivo following inhaled PAF in human asthma

PS WARD, IK TAYLOR, RW FULLER *Department of Clinical Pharmacology, Royal Postgraduate Medical School, Du Cane Road, London* We have previously produced evidence of increased $TXA_2$ biosynthesis in acute spontaneous asthma (Taylor *et al. Thorax* 1989; 44:866P). PAF has been postulated to act via $TXA_2$ generation in inducing airway hyperresponsiveness and bronchoconstriction in the dog, without altering numbers of infiltrating inflammatory cells. To test whether PAF provokes $TXA_2$ generation in vivo in man, 10 mild atopic asthmatic volunteers were given, in a randomised, single blind fashion, saline vehicle (0·9%), PAF (80 $\mu$g; 2 mg/ml) or methacholine (MC), administered via a breath activated dosimeter delivering 8 $\mu$l/breaths (5 breaths/challenge). Maximal bronchoconstriction to PAF was matched with doubling doses of MC. sGaw was measured as an index of bronchoconstriction, and urine collected for four hours and assayed for metabolites of thromboxane $A_2$ and prostacyclin. Results (mean (SEM)) are shown in the table. (PG excretion is ng/mmol creatinine; D- is 2,3-dinor-D; ***$p < 0.01$). In conclusion, we have demonstrated secondary mediator production following PAF but not MC, demonstrating that bronchoconstriction per se does not itself generate $TXA_2$. Whether

| | *PAE* | | *MC* | | *Saline* | |
|---|---|---|---|---|---|---|
| sGaw (% max fall) | 48·2 | (4·6)*** | 55·5 | (4·9)*** | 11·8 | (4·1) |
| $TXB_2$ | 6·78 | (1·2) | 3·64 | (0·7) | 3·19 | (0·7) |
| D-TXB2 | 41·3 | (7·1)*** | 14·0 | (2·7) | 17·1 | (3·9) |
| 6-oxo-$PGF_{1\alpha}$ | 8·25 | (0·7) | 5·92 | (0·9) | 7·41 | (1·4) |
| D-oxo-$PGF_{1\alpha}$ | 22·2 | (1·4) | 13·9 | (1·8) | 18·6 | (3·3) |

the source of the increased $TXA_2$ is exclusively lung derived is open to question. Increases in this same study in leukotriene $E_4$ (Taylor *et al*, this meeting) point to the possibility that more than one mediator is involved in PAF induced bronchoconstriction, and further studies are necessary to elucidate which is more important.

This work was supported by the MRC and ARC.

### Neutrophil sequestration in normal human lung after inhalation of platelet activating factor (PAF)

FWK TAM, J CLAGUE, CMS DIXON, AWJ STUTTLE, BL HENDERSON, AM PETERS, JP LAVENDER, PW IND *Royal Postgraduate Medical School, Du Cane Road, London* PAF inhalation causes bronchoconstriction and transient reduction in peripheral neutrophil count in man and may induce bronchial hyperresponsiveness (Chung *et al. Thorax* 1989;44:102). We have studied seven male non-asthmatic subjects, including three smokers (mean age 31 (range 25–39) years). Six subjects received autologous $^{99m}$Tc labelled red cells as a blood pool marker, five received $^{111}$In neutrophils and one received $^{111}$In platelets. When lung radioactivity (gamma camera signal) was stable, subjects inhaled 96 $\mu$g of PAF via a dosimeter (Mefar). Peripheral neutrophil count fell in all subjects with a mean reduction of 57% (range 29–100%) at five min, recovering to 169% of baseline at 30 min. In the peripheral blood, there was a 49, 53 and 41% reduction of $^{111}$In neutrophil at five, 10 and 15 min respectively. After PAF there was immediate pulmonary sequestration of $^{111}$In neutrophils. Mean maximal increase in lung radioactivity of 107% (range 59–147%) at a mean time of 7·4 (range 4·5–10) min, returning to normal by 3 h. Circulating platelet count did not change in any subject and there was no pulmonary sequestration of platelets after PAF. Inhaled PAF caused bronchoconstriction in all subjects, as determined by partial flow volume ($\dot{V}p$) curves, with a mean reduction in $\dot{V}p_{40}$ of 59% (range 40–78%) at six minutes. We have demonstrated pulmonary neutrophil, but not platelet sequestration after PAF. This supports a role for PAF as an inflammatory mediator. Pulmonary sequestration of neutrophil after PAF was not accompanied by marked increase in $^{111}$In neutrophil influx in other tissues and therefore appears to be responsible for peripheral neutropenia. This may be a useful model for exploring mechanisms and new therapeutic approaches to pulmonary inflammation in man.

### Use of corticosteroids in patients with chronic airflow obstruction by physicians in the West Midlands

DC WEIR, P SHERWOOD BURGE *Department of Thoracic Medicine, East Birmingham Hospital, Birmingham* We have studied the use of corticosteroids in patients with chronic airflow obstruction by physicians in the West Midlands, by means of a case history based questionnaire. The case history described the history, clinical course, treatment, and changes in peak expiratory flow in an elderly smoker admitted to hospital with an acute exacerbation of his airflow obstruction. We compared the replies from general physicians (n = 60) and physicians with an interest in or specialty in respiratory medicine (n = 24). Eighty four of 137 questionnaires were returned. Respiratory physicians were more likely to use oral corticosteroids in the treatment of the acute episode (75% *v* 37%, $p < 0.002$), to follow up patients in the clinic (68% *v* 24%, $p < 0.002$), and to monitor progress in the clinic objectively using spirometry (88% *v* 36%, $p < 0.001$). General physicians labelled the patient "asthmatic" as frequently as respiratory physicians, but only 35% of the general physicians labelling the patient as such would prescribe long term inhaled corticosteroids, compared with 100% of respiratory physicians. This study has revealed major differences in the use of oral and inhaled corticosteroids by general and respiratory physicians in the treatment of chronic airflow obstruction.

### Bone turnover in patients with chronic obstructive airways disease (COAD) during short course prednisolone therapy

D MORRISON, NJ ALI, PA ROUTLEDGE, S CAPEWELL *Departments of Chest Disease and Clinical Pharmacology, Llandough Hospital, Cardiff* Although osteoporosis is well known following long term prednisolone, the effects of short courses are less clear. We therefore studied biochemical markers of bone turnover in 10 male patients with chronic obstructive airways disease (COAD) who required assessment of "steroid reversibility" (mean age 65, mean $FEV_1$ 1·0 l). Patients received, single blind, two weeks' placebo, four weeks' prednisolone 20 mg/day, then two weeks' further placebo. Following 400 $\mu$g salbutamol, seven patients showed $\geqslant$200 ml improvement in $FEV_1$ and nine in FVC; only three showed a corresponding FVC improvement following prednisolone. Mean (SEM) fasting urine hydroxyproline/creatinine ratio (a marker of bone resorption: Nordin. *Clin Endocrinol* 1978;8:55) increased by 65% on prednisolone (8·9 (1·4) to 14·7 (2·7), $p < 0.05$), and returned to baseline after placebo (9·4 (1·1)). Calcium/creatinine ratio rose by 40% (0·30 (0·05) to 0·42 (0·07), $p < 0.05$). Serum alkaline phosphatase, a marker of net bone formation, fell after prednisolone by 28% (113 (9) to 81 (9) U/l, $p < 0.05$); osteocalcin did not change significantly (3·4 (0·4) to 3·3 (0·7)), nor did serum calcium, phosphate or PTH. These responses may be compared with our previous study of high dose inhaled beclomethasone dipropionate (2000 $\mu$g/day) in normal subjects (Ali. *Thorax* 1989;44:900); hydroxyproline/creatinine ratio increased by 33% and alkaline phosphatase fell by 10%. It is concluded that short course prednisolone significantly increased bone resorption and inhibited bone formation. These data may have implications for patients already at risk of osteoporosis. The effect of high dose inhaled corticosteroids on bone turnover in patients with COAD should now be investigated.

### Why do patients with obstructive lung disease taking steroids become osteoporotic?

KARIM MEERAN, ANDREW HATTERSLEY, JACQUELINE BURRIN, PATRICIA HILL, ROBERT SHINER, KAYE IBBERTSON *Brompton Hospital; Department of Medicine, Hammersmith Hospital, London; and Section of Endocrinology, University of Auckland, New Zealand* Osteoporosis is a common complication of corticosteroid therapy. Corticosteroids have been claimed to increase plasma parathyroid hormone (PTH) and to reduce plasma calcitonin (CT) levels, changes which could increase bone resorption. Bone formation is reflected by serum osteocalcin and may be decreased by corticosteroids. We have studied 34 adult outpatients with symptomatic asthma or chronic obstructive airways disease receiving pharmacological doses of prednisolone (mean dose 9·8 (SD 3·7) mg for 9·2 (7·5)) years and compared them with 34 controls matched for age, sex, menopausal status and disease. There was a significant difference in the mean plasma osteocalcin (subjects 6·3 ng/ml, controls 8·6 ng/ml; $p < 0.01$) but not in mean plasma CT (13·8 pg/ml *v* 13·2 pg/ml) or plasma PTH (33·8 pg/ml *v* 34·6 pg/ml). In a parallel study of 10 healthy male volunteers the same biochemical indices were measured before and at the end of a seven day course of 15 mg prednisolone daily. Plasma CT was also measured after infusion of calcium gluconate (Ca 2 mg/kg over one minute). Basal and peak plasma CT and PTH levels were not significantly altered by this short course of steroids. There was, however, a significant fall in mean plasma osteocalcin from 11·8 ng/ml to 6·9 ng/ml ($p < 0.001$). The fall in osteocalcin suggests that the predominant effect of corticosteroids on bone is a reduction in formation. Calcitonin may be effective in treating steroid osteoporosis but we have found no evidence that patients on steroids have lower plasma levels of this hormone.

### Screening and prophylaxis in steroid induced bone disease: conflicting views of respiratory and bone physicians

CK CONNOLLY, RM FRANCIS, NK MURTHY, RJ PRESCOTT, S ALCOCK *Department of Medicine, Memorial Hospital, Darlington, and General Hospital, Newcastle upon Tyne* Steroid bone disease is probably the most frequent and feared complication of long term treatment with oral corticosteroids. The value of prophylaxis is controversial, so it was decided to compare the views of respiratory and bone physicians. A postal questionnaire was sent to the physician members of the British Thoracic Society and experts in bone metabolism. Two hundred and thirty six of 378 (62·4%) forms were returned from the respiratory physicians and all 13 from the bone physicians. Of the respiratory physicians, three (1·3%) establish a pretreatment baseline in men and in premenopausal women, and 10 (4·2%) in postmenopausal women. Six (2·5%) screen during oral steroid treatment in men and premenopausal women and 15 (6·4%) in postmenopausal women. Twenty one (8·9%) give prophylactic treatment to men, 22 (9·3%) to premenopausal women and 42 (17·8%) to postmenopausal women. The majority give calcium to all subjects and 50% prescribe oestrogens to postmenopausal women. The responses were not related to the doctor's age or hospital appointment. Six (46%) of the bone physicians would establish a baseline before treatment in men and premenopausal women, and seven (54%) in postmenopausal women. Screening is recommended by eight (62%) for men and premenopausal women, and by nine (69%) for postmenopausal women. Two

bone physicians do not see sufficient patients without gross evidence of steroid bone disease to comment on prophylactic treatment. Of the remaining 11, eight (73%) advised it in men and in premenopausal women, and nine (82%) in postmenopausal women. The treatment recommended is similar to that used by those respiratory physicians who do give prophylactic treatment. The responses of the bone physicians suggest that respiratory physicians may undertreat potential steroid bone disease. This may have medicolegal as well as therapeutic implications.

### Testosterone levels during systemic and inhaled corticosteroid therapy

SP REYNOLDS, S CAPEWELL, J THOMAS, D MORRISON, NJ ALI, G REID, R HENLEY, D RIAD-FAHMY *Departments of Tuberculosis and Chest Diseases, Tenovus Institute, and SAS Peptide Hormone Unit, Llandough Hospital and University Hospital of Wales, Cardiff* Testosterone has importance both as a sex hormone and an anabolic steroid promoting bone formation. Hypogonadism is associated with osteoporosis (Nordin *et al. J Steroid Biochem* 1981;**15**:171). Chronic oral prednisolone therapy in asthmatic men reduces testosterone levels by up to 50% (Reid. *Clin Endocrinol* 1989;**30**:83). High dose inhaled corticosteroids (HDICS) cause a variety of systemic effects including increased bone resorption and may cause reduction in total bone calcium. (Ali. *Thorax* 1989;**44**:900); Stead and Cooke. *Br Med J* 1989;**298**:403). Are testosterone levels affected? Testosterone, gonadotrophins (LH and FSH) and sex hormone binding globulins (SHBG) were therefore measured (between 9 and 11 am) in 35 male patients with respiratory disease attending an outpatient clinic (mean age 57, range 21–75 years). They were grouped according to steroid therapy and compared with 19 age matched controls. Mean (SD) testosterone levels were 33% lower in 12 men on long term oral prednisolone (14·5 (6·0) *v* 21·7 (6·3) nmol/l in controls, $p < 0.01$) but were not significantly lower in 10 patients on low dose beclomethasone (400–800 μg/day: 19·7 (3·7) or in 13 men taking HDICS (beclomethasone 1500–2250 μg/day: 17·9 (5·6) nmol/l). SHBG, FSH and LH levels were similar in the four groups. These data suggest that, although long term systemic corticosteroids reduce testosterone levels, long term inhaled corticosteroids do not. Other mechanisms for the increased bone resorption and reduced total bone calcium reported in patients taking high dose inhaled corticosteroids should now be investigated.

### Bone mineral density in women taking inhaled corticosteroids

RJ STEAD, A HORSMAN, NJ COOKE, P BELCHETZ *Departments of Respiratory Medicine and Endocrinology and MRC Bone Mineralisation Group, General Infirmary, Leeds* Corticosteroids are known to cause osteoporosis and biochemical studies indicate that high doses of inhaled corticosteroids may increase bone resorption (Ali NJ *et al. Thorax* 1989;**44**:900). We studied bone mineral density in 11 asthmatic women (median age 55, range 36–73 years) taking high dose inhaled corticosteroids. Three were premenopausal, seven were postmenopausal and one, aged 51, had undergone hysterectomy aged 39. Eight patients had been taking beclomethasone dipropionate (Becloforte) for a median (range) duration of 2 (1–10) years and two had been taking budesonide (Pulmicort) for one year and 14 months respectively. One patient had used beclomethasone and then budesonide for a total of four years. At the time of study dosages of beclomethasone were: 1000 μg, six patients; 750 μg, one; 2000 μg, one; and of budesonide: 800 μg, one; 1200 μg, one; and 1600 μg, one. All patients had previously taken courses of prednisolone not exceeding two weeks duration. Bone mineral density was measured using a Lunar DPX dual photon beam bone densitometer. Ten patients had a second scan and eight of these had a third at intervals of 2–7 months. Bone mineral density of the lumbar spine was reduced by 13·4% ($p < 0.001$) and that of the forearm by 8·6% ($p < 0.05$) in the asthmatics compared with healthy age-matched control women. There was no statistical difference at the femoral neck. The longitudinal study did not indicate progressive bone loss in patients. These preliminary data indicate that this group of asthmatic patients have clinically significant reductions in lumbar spine bone density but do not indicate that rapid bone loss is actively occurring. It is possible that the abnormalities are due to previous oral corticosteroid therapy.

### Clinical features and outcome of 36 adults presenting to hospital with proved influenza

AC JONES, JT MACFARLANE, S PUGH *City Hospital and PHLS, Nottingham* Following the recent winter influenza epidemic we have studied 36 adults (16 female) who presented to the Nottingham hospitals with proved influenza. Fourteen (39%) died. The median age of survivors was 72 years (range 21–83) and in the fatal cases 72·5 years (range 22–88). Only nine (25%) had been in previous good health, underlying respiratory disease (in 16 (44%)) and cardiac disease (in 12 (33%)) being common. Respiratory symptoms were the commonest: cough in 26 (72%); dyspnoea in 25 (69%) and discoloured sputum in 17 (47%). "Flu" symptoms were reported in only a third. Focal chest signs were present in 24 (67%) though radiographic pneumonia was found in only 14 (39%). Bacterial pathogens were identified in 12 cases: *Haemophilus influenzae* in four; *Staphylococcus aureus* in two (one bacteraemic); *Pseudomonas aeruginosa* in three (one cystic fibrosis on admission, two late nosocomial infections); *Streptococcus bovis* bacteraemia in one; *Streptococcus pyogenes* from one empyema and pneumococcal antigen from another empyema. Preadmission antibiotics had been given to only 17 (47%), only eight effective against *S. aureus*. Fifteen different inpatient antibiotics were used; 12 patients did not receive antistaphylococcal cover. Eleven deaths were directly attributable to influenza, including one *S aureus* endocarditis. Survivors were more likely to have cough and chest pain whereas fatal cases were more likely to be confused and have a raised urea. The mean inpatient stay was 16 days. In this small retrospective series most patients with proven influenza had pre-existing disease and suffered respiratory symptoms but not always pneumonia. Antibiotic therapy was not always ideal and should be directed against streptococci, *H influenzae* and *S aureus*. Death and prolonged inpatient stay were common.

### Importance of oropharyngeal flora in the development of chest infection after upper abdominal surgery

JP DILWORTH, RJ WHITE, EM BROWN *Departments of Medicine and Microbiology, Frenchay Hospital, Bristol* Chest infection commonly occurs after abdominal surgery. The bacteria causing the infections may be found in the oropharynx. The oropharyngeal flora of patients undergoing abdominal surgery have therefore been investigated. Swabs from the oropharynx were taken preoperatively from 127 patients undergoing upper abdominal surgery and repeated on the first, third and fifth postoperative days. The isolation of *Haemophilus influenzae*, *Streptococcus pneumoniae*, and coliforms was noted. Patients were assessed for evidence of chest infection until discharge. The incidence of oropharyngeal colonisation by *H influenzae* was 16% and remained constant postoperatively. *Strep pneumoniae* was present in the oropharynx in only six patients preoperatively and this incidence fell. In contrast, there were only two patients with coliforms colonisation preoperatively, but this transiently increased to 12 patients by the third postoperative day and then fell again by the fifth day. Twenty four patients developed a chest infection. In eight of these the bacterial cause was established. Seven had *H influenzae* and two had *Strep pneumoniae* in the sputum. There was a significant relationship between the carriage of *H influenzae* preoperatively and the subsequent development of chest infection ($p < 0.001$). *H influenzae* was found significantly more often in cigarette smokers. The transient growth of coliform organisms was not related to the development of infection. This study shows that the high incidence of chest infection in cigarette smokers may in part be due to preoperative colonisation of the oropharynx by pathogens.

### Diagnosis of respiratory infections in the immunocompromised child with sputum induction

ABM FOOT, A OAKHILL, JR CATTERALL *Royal Hospital for Sick Children and Royal Infirmary, Bristol* Respiratory infection is common in the immunocompromised child, especially following bone marrow transplantation (BMT), cytomegalovirus (CMV) pneumonitis often proving fatal. Sputum is rarely produced, and diagnosis often requires bronchoscopy. Recently, sputum induction (SI) has been used to facilitate diagnosis of Pneumocystis carinii (PCP) pneumonia in adults with AIDS. However, its application in other groups and for other organisms has not been documented. Over a 10 month period SI with 5% saline administered by ultrasonic nebuliser was performed in 13 immunocompromised children (4–14 y) on 15 occasions when respiratory symptoms ($n = 13$) and/or respiratory signs ($n = 8$) and/or CXR changes ($n = 8$) were suggestive of infection (Group A). In addition, four CMV + ve BMT recipients at high risk of virus reactivation underwent SI serially on 15 occasions when asymptomatic (Group B). Three samples from group A were positive. CMV was identified by immunofluorescence and cell culture in a CMV + ve BMT recipient (tachypnoea, temperature 39°C, $Sao_2$ 90%) 62 days after transplantation, SI having previously been negative, and this was

followed by clinical response to anti-CMV therapy. Two others were positive for *Haemophilus influenzae*. Organisms were identified by other means in three cases: adenovirus in upper respiratory tract secretions (n = 2) and *Mycoplasma pneumoniae* by serology (n = 1). Bronchoalveolar lavage was performed in four patients in whom SI was negative, and in each case no organisms were identified. All induced sputum samples in group B were negative. SI failed in two children and was generally poorly tolerated in children ≤6 y. Retching/vomiting occurred in four children, and two complained of a foul taste. Alveolar macrophages were seen in 11 of 12 specimens examined cytologically. In summary, SI can be performed in immunocompromised children, and for pathogens other than PCP. It may be useful for early diagnosis of active CMV infection. However, its use should be limited to the cooperative symptomatic child.

### Double blind comparison of the efficacy and tolerance of clarithromycin and erythromycin stearate in the treatment of community acquired pneumonia

G ANDERSON, TF ESMONDE *Newport Chest Clinic, Newport* The objective of this multicentre, double blind, randomised study was to compare the efficacy and tolerance of clarithromycin (C) and erythromycin stearate (ES) in the treatment of community acquired pneumonia. Two hundred and eight adult patients were randomised to receive either C 250 mg 12 hourly (96 patients) or ES 500 mg six hourly (112 patients) for a duration of 14 days. One hundred and eight patients were evaluable for efficacy, 64 receiving C and 44 in the ES group. There was no difference between the two groups in terms of clinical success rate when assessed as clinical cure and improvement (89% for C, 98% for ES), or for radiological response (90% for both groups). Considering all patients who entered the study, an intention to treat analysis revealed significant differences in favour of C. Clinical cure was achieved in 50% of patients who received C compared with 33% in the ES group ($p = 0.03$), while improvement in cough was observed in 97% and 80% of patients receiving C and ES respectively ($p = 0.007$). Adverse effects, mainly gastrointestinal, caused discontinuation of treatment in 4% (4/96) of patients in the C group compared with 19% (21/112) treated with ES ($p < 0.01$). These results demonstrate that C is as effective as ES for the treatment of community acquired pneumonia, and is better tolerated. A further benefit of C is that it can be given twice daily.

### Tuberculosis in patients infected with the human immunodeficiency virus

ELC ONG, BK MANDAL *Regional Department of Infectious Diseases and Tropical Medicine, Monsall Hospital, Manchester* A British retrospective study (Helbert M *et al. Thorax* 1990;45:45) documented 15 human immunodeficiency virus (HIV) infected patients with *Mycobacterium tuberculosis* (TB) infection but needed invasive procedures like bronchoalveolar lavage and transbronchial biopsy to obtain positive bacteriological results. We report our study of seven HIV infected patients (five British, one Indian, one African), mean age 38·6 years, with TB infection. None were intravenous drug abusers. All patients on presentation had symptoms; fever (seven patients), cough (7), loss of weight (6) and neck swelling (2) were common. There were two patients with extrapulmonary tuberculosis therefore fulfilling the diagnostic criterion for the acquired immunodeficiency syndrome (AIDS). Four patients (1 AIDS, 3 AIDS related complex—ARC) had pulmonary TB and one other patient with AIDS had disseminated TB. The mean CD4 count of the patients with ARC and AIDS were 466/mm$^3$ and 32/mm$^3$ respectively at the time of diagnosis of TB. The five British had BCG previously but only one had grade 3 reaction to Mantoux testing. Chest radiographs from four patients were normal while the others showed cavities, reticulonodular shadowing, consolidation and pleural effusion. Positive TB cultures were obtained from induced sputum (4 patients), lymph node biopsy material (2), stools (1), bone marrow (1) and pleural fluid (1). All but two isolates were fully sensitive to standard anti-TB drugs. Response to treatment was rapid and uncomplicated, apart from one AIDS patient who had hypersensitivity reactions to seven anti-TB drugs. Our small survey showed that TB may occur at any stage of HIV disease and is an important cause of fever in HIV infected British patients even with normal chest radiograph and previous BCG vaccination. Induced sputum with nebulised hypertonic saline was an important aid to diagnosis and therefore none of our patients was bronchoscoped. Standard chemotherapy was adequate in all patients with sensitive isolates.

### Distribution and time course of pneumococcal capsular antigen in the body fluids of 21 patients with pneumococcal pneumonia

P VENKATESAN, K SOLE, J T MACFARLANE, RG FINCH *City Hospital, Nottingham* Twenty one patients with evidence of pneumococcal pneumonia (12 blood culture positive, 2 sputum culture positive, 21 pneumococcal capsular antigen (PCA) positive) were studied prospectively for the distribution and time course of PCA in saliva, sputum, serum and urine. The presence of PCA was the only evidence of pneumococcal pneumonia in eight patients. Countercurrent immunoelectrophoresis was used to detect PCA. Saliva was positive for PCA in 13 (62%) patients. Two patients had positive saliva for several days before a sputum specimen was provided. Therefore analysis of saliva in patients unable to expectorate may be helpful. Sputum was positive in 16 (76%) patients. Of the four body fluids collected, sputum was the most likely to be positive on the first specimen. Serum was positive in 11 (52%) patients and urine, concentrated in Lyphogel, was positive in 13 (62%) patients. In three patients PCA persisted in the urine after it had disappeared from the serum. Antigenaemic patients (median age 68 years) were older than non-antigenaemic patients (median age 41 years). All but two antigenaemic patients had positive blood cultures. In 11 patients PCA persisted longer than seven days, being in serum and urine longer than in saliva and sputum. At 6 weeks one patient still had positive saliva, two had positive sputum and three had both positive serum and urine. Patients with persistent antigenaemia tended to have a clinically more severe pneumonia and four developed pleural effusions, two of these being PCA positive. Investigation for PCA can contribute to microbiological diagnosis in culture negative cases, even several days after commencing antibiotics. Prolonged antigenaemia and antigenuria was associated with severe infections, some complicated by pleural effusions.

### Nasal intermittent positive pressure ventilation in the management of airways disease on a general medical ward

RC GODFREY, A BROWN, ST HOLGATE, RA HITCHCOCK, JH CONWAY, M CARROLL *Southampton General Hospital, Southampton* We report the use of nasal intermittent positive pressure ventilation (NIPPV) in the emergency management of nine patients admitted with acute on chronic respiratory failure. Eight patients had chronic obstructive airways disease, one cystic fibrosis; in all cases $FEV_1$ was less than 50% predicted. Mean age was 61 years (32–76). The average duration of NIPPV was 25 hours, usually broken into several periods of two to three hours. Seven patients returned home and two died. The patient with cystic fibrosis retains NIPPV at home. Length of stay in hospital varied from two days to several weeks, being influenced by social factors as well as by clinical recovery. Blood gases before NIPPV showed a mean $Pao_2$ of 4·98 kPa (3·45–7·48) and $Paco_2$ of 9·32 kPa (7·22–14·2). Mean values on NIPPV (with supplemental $O_2$ at 2 litres/minute) were $Pao_2$ 11·7 kPa (7·1–24·35) and $Paco_2$ 6·3 kPa (5·8–10·83). In all cases the rise in $Pao_2$ was significant. $Paco_2$ showed a trend downwards in all but the two patients who died. Compliance was satisfactory in all but one case. We conclude that NIPPV may be a helpful component in management of acute respiratory failure on a general ward.

### Domiciliary nasal positive pressure ventilation in chronic obstructive pulmonary disese (COPD)

MW ELLIOTT, M CARROLL, JA WEDZICHA, MA BRANTHWAITE *Brompton Hospital, London* Nasal intermittent positive pressure ventilation (NIPPV) is effective in controlling nocturnal hypoventilation (*Thorax* 1988;43:349–53). We have evaluated NIPPV using the "Bromptonpac" (Pneupac Ltd, Luton) at home in 12 patients with severe COPD (median and range $FEV_1$ 0·571 (0·26 to 1·1), FEV/FVC 30% (19 to 44), $Pao_2$ 6·5 kPa (5·6 to 8·4), $Paco_2$ 7·8 kPa (6·3 to 9·9). Following acclimatisation in hospital (median stay 2 days, range 1 to 10) and four weeks' home use, effective overnight ventilation was confirmed by ear oximetry and transcutaneous $CO_2$ measurements. Seven patients elected to continue NIPPV after the trial ended. Median (range) changes in $Pao_2$ and $Paco_2$, after six months' NIPPV, taken after 15 minutes' rest in the mid afternoon, breathing air, were +0·7 kPa (−1 to +1·1) and −0·5 kPa (−1·5 to +0·5) respectively. Bicarbonate ion concentration fell by 3·9 mmol/l (8·8 to 1·4). Six with symptomatic sleep disturbance initially, including five already using oxygen, reported improved sleep quality, confirmed on formal testing. Six minute walking distance increased by 24 m (−10 to +113) and quality of life questionnaire scores showed small improvements. Three patients withdrew within six months because of difficulty sleeping and all showed slight deterioration in arterial blood gas tensions at 6 months. One

patient, who failed to master the technique, died after six weeks NIPPV and another, who was poorly compliant, was withdrawn at 9 months because of worsening cor pulmonale. It is concluded that NIPPV can be used successfully overnight at home to treat some patients with severe COPD. Motivation is an important ingredient and success is more likely in patients with symptomatic sleep disturbance unrelieved by oxygen therapy.

### Guidelines for assessment of patients with chronic lung disease for portable oxygen therapy

SH LOCK, RM RUDD, JA WEDZICHA *Department of Thoracic Medicine, London Chest Hospital, London* Portable oxygen therapy produces variable benefit in patients with chronic lung disease and may have placebo effects. As portable treatment is expensive, full assessment is required. No definite guidelines for response are available as previous studies were limited in patient numbers. We reviewed our assessments for portable oxygen in 50 patients (mean $FEV_1$ 0·86 (SD 0·32) l; $Pa_{O_2}$ 7·5 (1·6) kPa), 44 patients with chronic airflow obstruction (CAO) and six patients with restrictive lung disease. The standard protocol for assessments included six minute walking tests with oxygen and air cylinders in all patients, visual analogue scales (VAS) for breathlessness in 31 patients, oximetry, and a subjective assessment by patients as to whether they had improved on oxygen. The median percentage increase in six minute walking distance was 7·9 (95% confidence interval (CI) 4·8–11·9)% on oxygen compared with air cylinders and this correlated with the fall in $Sa_{O_2}$ during a baseline walk on air ($p < 0·05$). There was an increase in distance walked on air compared with baseline of 4·9 (1·3–9·8)%, presumably representing a placebo response. The median VAS scores on oxygen decreased by 8·8 (0–24·1)% compared to air and this change was greater in patients with symptomatic improvement ($p < 0·01$), but was not related to walking distance. Patients with restrictive lung disease showed similar responses to those with CAO. We suggest that assessments should include walking tests with air cylinders to detect placebo effects, VAS scores and oximetry. An improvement on any test of 8% will identify patients likely to benefit from portable oxygen therapy.

### Modulation of elevated pulmonary vascular resistance in systemic sclerosis and primary pulmonary hypertension

JM MORGAN, DN HUNTER, C BLACK, R DU BOIS, TW EVANS *Brompton and Royal Free Hospitals, London* The reduction of elevated pulmonary vascular resistance (PVR) by a high inspired oxygen concentration is a common but not universal phenomenon in patients with pulmonary vascular disease of varying aetiology and may determine their response to long term domiciliary oxygen therapy. We therefore determined changes in PVR during oxygen therapy in two patient populations not previously studied: systemic sclerosis (SS: n = 8, mean (SEM) age 44·5 (5·4) years) and primary pulmonary hypertension (PPH: n = 7, mean age, 38 (7·8) years). All patients were hypoxaemic ($Pa_{O_2}$ on air 9·5 + 1·2 kPa for SS and 8·3 (0·6) kPa for PPH, $p > 0·05$). Right atrial pressure, pulmonary artery pressure, pulmonary artery occlusion pressure, systemic arterial pressure, $Pa_{O_2}$ and cardiac output by thermodilution were measured at three 20 minute intervals while inspiring air and after inspiring 60% oxygen for 30 minutes. There was a significant fall in PVR with oxygen in patients with SS (from 797·6 (179·2) to 616 (160) dyne.s.cm$^{-5}$, $p < 0·05$) and this fall correlated inversely with baseline PAP and $Pa_{O_2}$ prior to oxygen therapy ($r = -0·86$, $p < 0·025$; $r = -0·76$, $p < 0·05$ respectively). In the PPH patients PVR did not fall significantly with oxygen (from 969 (80) to 852 (91) dyne.s.cm$^{-5}$, $p > 0·05$) and no predictor of a vasodilator response in individual patients was found. We suggest that in SS increased PVR may be principally due to hypoxic pulmonary vasoconstriction while elevated PVR in patients with PPH is also modulated by other factors, and this may have implications in the success of long term domiciliary oxygen therapy.

| | *YC (n = 53)* | *AA (n = 10)* | *EC (n = 21)* | *COAD (n = 26)* |
|---|---|---|---|---|
| Blanching 10 μg/ml | 48 | 9 | 17 | 11*† |
| With BDP 100 μg/ml | 51 | 9 | 20 | 17**† |

$\chi^2$ tests with Yates's correction; *$p < 0·02$ *v* EC; **$p < 0·05$ *v* EC; †$p < 0·001$ *v* YC.

### Severe pulmonary hypertension in the vasculitides: a comparison of symptoms and signs with primary pulmonary hypertension (PPH)

G CREMONA, TW HIGENBOTTAM, AT DINH XUAN, J WALLWORK *Papworth Hospital, Papworth Everard, Cambridge* The vasculitides (VS) rarely cause severe pulmonary hypertension but can cause difficulty in diagnosis. We report four cases of VS with severe pulmonary hypertension and compare their clinical and haemodynamic characteristics (pulmonary artery pressure (PAP), cardiac index (CI) and mixed venous saturation ($Sv_{O_2}$) with those reported by the National Institutes of Health Registry of PPH (Rich S, *et al. Ann Intern Med* 1987;**107**:216) on PPH. All four patients were treated with corticosteroids and continuous intravenous infusion of prostacyclin and two of them with immunosuppressive drugs. The therapy resulted in an acute decrease in total pulmonary vascular resistance, an improved exercise tolerance and a satisfactory control of vasculitic symptoms. One patient died of atypical mycobacterial pneumonia. One patient successfully underwent heart-lung transplantation and the other two are alive respectively at 18 and 28 months from diagnosis. There is considerable overlap in the signs and symptoms presented by these patients and only subsequent evidence of the vasculitic process permitted a correct diagnosis in each case. Careful attention to clinical signs of vasculitis as well as complete autoantibody screening should aid in the diagnosis and appropriate treatment of these patients.

| | *Vasculitis* | *PPH* |
|---|---|---|
| Sex (M/F) | 1:3 | 1:1·7 |
| Age (y) | 32 (7) | 36 (15) |
| Dyspnoea | 75% | 60% |
| Syncope | 25% | 8% |
| Leg oedema | 100% | 37% |
| Serosal involvement | 75% | 0% |
| Raynaud's phenomenon | 0% | 10% |
| Autoantibodies | 75% | 29% |
| V/Q scan | Diffuse patchy (50%) | Diffuse patchy (75%) |
| Mean PAP (mmHg) | 64 (17) | 60 (18) |
| CI (l/min.m$^2$) | 1·6 (0·7) | 2·27 (0·9) |
| $Sv_{O_2}$ | 65·5 (7·1) | — |

### Cutaneous response to beclomethasone dipropionate (BDP) in severe chronic obstructive airways disease (COAD)

PH BROWN, S TEELUCKSINGH, I WILLIAMSON, SP MATUSIEWICZ, AP GREENING, GK CROMPTON *Respiratory Unit, Northern General Hospital, Edinburgh* Persistent smokers may develop COAD, but it is not clear why some patients develop more severe airflow limitation than others with comparable smoking histories. It is common practice to perform a "trial" of prednisolone to determine whether airways obstruction can be ameliorated by corticosteroids. We have observed that asthmatics sensitive to corticosteroids exhibit blanching of similar degree to that in healthy subjects when BDP is applied to their skin. In contrast, asthmatics relatively resistant to a corticosteroid trial show reduced blanching. We have now studied this vasoconstrictor response in patients with severe ($FEV_1 < 1$ l) COAD who show no significant change in $FEV_1$ with bronchodilators or a corticosteroid trial. BDP, dissolved in ethanol at concentrations between 1 and 100 μg/ml, was applied to forearm skin, occluded under plastic overnight and the degree of blanching assessed the following day. Twenty six patients with COAD (21F, 5M; mean age 65 y) were studied. Eight were taking regular inhaled corticosteroids and seven long term prednisolone (< 10 mg daily). Six were also taking high dose prednisolone at the time of testing. Results were compared with young healthy controls (YC); elderly subjects (mean age 78·8 y) with no significant respiratory disease (EC) and patients with acute asthma taking high dose prednisolone (AA). It is concluded that patients with severe irreversible COAD show a reduced vasoconstrictor response to topical BPD. The mechanism underlying this and its relevance to the pathogenesis of irreversible COAD is unknown.

### Decreased response to ipratropium bromide by nebuliser in acute severe asthma.

C TEALE, JFJ MORRISON, MF MUERS, SB PEARSON *Respiratory Unit, Killingbeck Hospital, Leeds* A combination of ipratropium bromide (IB) and a $beta_2$ agonist is increasingly used in the treatment of acute severe asthma although out patient studies have shown that inhaled anticholinergic agents decrease in efficacy as $FEV_1$ falls (*Thorax* 1964;**19**:406). To determine whether there are changes in response to inhaled

anticholinergics in acute severe asthma we have examined the effects of nebulised IB and terbutaline (T) in hospitalised patients recovering from acute asthma. We studied nine patients admitted to hospital with acute severe asthma, mean age 47 years. At 6 am each day baseline PEF was recorded. IB 1 mg was nebulised and PEF measured one hour later. Following this T 5 mg was nebulised and PEF repeated 15 mins later. The table shows mean PEF responses to IB followed by T in acute asthma (p values from paired *t* tests). Hence IB produced 96% of available bronchodilatation on patients best day but only 71% when baseline was lowest a highly significant change in response ($p < 0.01$). We conclude that in acute severe asthma as baseline PEF rises response to inhaled IB improves compared to response to combined IB+T suggesting either increased reflex vagal bronchoconstriction or reduced cholinergic receptor access in acute severe asthma.

| | *Base* | *Ipratropium* | *Terbutaline* |
|---|---|---|---|
| Worst day | 157 | 212 $p < 0.01$ | 235 $p < 0.01$ |
| Best day | 300 | 342 $p < 0.01$ | 346 p NS |

### Terfenadine in nocturnal asthma

C TEALE, JFJ MORRISON, SB PEARSON *Respiratory Unit, Killingbeck Hospital, Leeds*
Vagal blockade with atropine corrects part of the nocturnal fall in PEFR in asthma suggesting that diurnal variation in vagal tone is important but other factors are likely to be involved (*Br Med J* 1988;**296**:1427–9). In a single blind study we have measured the nocturnal dip in asthmatics before and after atropine (At) and terfenadine (T) to determine if diurnal variation in histamine mediated effects contribute to nocturnal asthma. Eight asthmatics with diurnal variation in PEFR >20% were studied. At 4 am and 4 pm on sequential days PEFR was measured before and 10 mins after IV atropine 30 mcg/kg. Six hours before PEFR measurements subjects received, on a single blind basis, either placebo (P) on day one, or terfenadine 120 mg on day two. Results were analysed by paired *t* tests. The table shows effect of terfenadine (T) or placebo (P) and atropine on mean PEFR at 4 am and 4 pm in eight asthmatics (p values show effects of At). The nocturnal dip of 41 l/m ($pp < 0.05$) after P was maintained after either terfenadine (38 l/m, $p < 0.05$) or atropine (58 l/m, $p < 0.05$) but was reduced to a non-significant 16 l/m ($p = 0.4$) on combined terfenadine plus atropine. We conclude that terfenadine reduces nocturnal bronchoconstriction and modifies the effect of vagal influences.

| *4am* | *Base* | *Atropine* | *4pm* | *Base* | *Atropine* |
|---|---|---|---|---|---|
| P | 242 | 273 ($p < 0.01$) | | 283 | 331 ($p < 0.01$) |
| T | 278 | 295 (NS) | | 316 | 311 (NS) |

### Propranolol reduces the diurnal variation in peak flow in normal subjects

C TEALE, SB PEARSON *Respiratory Unit, Killingbeck Hospital, Leeds*
The precise mechanisms leading to nocturnal bronchoconstriction in asthmatics remains uncertain, although it probably represents an exaggeration of a normal circadian rhythm in airway calibre (*Thorax* 1980;**35**:723). It has been suggested that diurnal variation in circulating adrenaline may contribute to nocturnal asthma (*N Engl J Med* 1980;**303**:263) but recent work has challenged this view (*Thorax* 1989;**44**:889P). In an open study we have measured night time and morning PEF in normal subjects on and off propranolol to determine if beta adrenergic mediated effects influence nocturnal dipping. Eight normal subjects mean age 26 years, range 24–30 years, measured twice daily PEF, recording the best of three, on waking and on retiring to bed for 28 days, taking propranolol 80 mg bd on days 15–28. A placebo control was not used because of the obvious cardiovascular effects of propranolol. Results were analysed by paired *t* tests. Morning mean PEF was not influenced by propranolol (baseline 550 l/m, propranolol 551 l/m, NS). However, propranolol produced a significant fall in mean diurnal variation in PEF from 17·9 l/m to 8·0 l/m ($p < 0.01$). We conclude that in normal subjects propranolol does not influence morning PEF but reduces the diurnal variation in PEF by more than 50%. This supports the suggestion that daytime increases in beta adrenergic effects, presumably due to increases in plasma adrenaline, contribute to diurnal variation in bronchial calibre.

### Diurnal variation and perception of asthma

AH KENDRICK, G LASZLO *Respiratory Department, Bristol Royal Informary, Bristol*
Perception of asthma may be studied by relating changes in a visual analogue self assessment scale (VAS) to changes in peak expiratory flow using a coded meter (Higgs *et al. Thorax* 1986;**41**:671). Whether there is a diurnal variation in the perception of asthma is unclear. Forty four asthmatics, (27F: aged 17–65 y) recruited from health centres recorded VAS and coded PEF in the early morning (AM) midday (MD), early evening (EE) and before going to bed (BED), for 14 days. Linear regression analysis determined the significance of the relationships of VAS to loge (% predicted PEF), and the slope, intercept and correlation obtained. Comparison of the effects of time of day on PEF, VAS, slope and intercept was by Friedmann's analysis of variance. The results are given as mean (range) with PEF as % predicted, VAS in mm along a 100 mm scale and intercept in mm. PEF and VAS varied significantly ($p < 0.01$) with the time of day, but slope and intercept did not. We conclude that, although there is a significant diurnal variation in VAS and PEF, there is no significant diurnal variation in the discrimination (slope) or perceptive threshold (intercept) of asthma. Similar findings were obtained when the group was divided into the 19 subjects who showed a significant correlation of VAS to loge (% predicted PEF) and the 25 subjects who did not.

| *Time* | *PEF* | *VAS* | *Slope* | *Intercept* |
|---|---|---|---|---|
| AM | 50·0 (18–121) | 15·5 (0–56·7) | −14·0 (−64–+13·6) | 58·0 (−46–166) |
| MD | 57·9 (18–26) | 11·1 (0–38·7) | −6·5 (−40–+60·5) | 26·0 (−26–198) |
| EE | 55·7 (19–125) | 12·2 (0–48·8) | −7·2 (−59–+20·9) | 31·1 (−31–143) |
| BED | 52·9 (18–123) | 13·3 (0–53·8) | −11·6 (−75–+12·2) | 54·3 (−21–242) |

### Elevated plasma atrial natriuretic factor and its effect on histamine responsiveness in asthmatic subjects

G HULKS, A JARDINE, JMC CONNELL, NC THOMSON *Department of Respiratory Medicine and MRC Blood Pressure Unit, Western Infirmary, Glasgow*
We have previously demonstrated that significant bronchodilation may be achieved in patients with moderately severe asthma by the intravenous infusion of atrial natriuretic factor (ANF). The current study was designed to ascertain whether alteration in circulating ANF affected airway reactivity. Eight male asthmatics were studied, mean (SD) age 31·5 (6·8) years and $FEV_1$ 3·50 (0·73) litres, equivalent to 87 (12)% predicted. Following a screening visit, subjects attended at the same time of day on four further occasions at least one week apart. After 20 minutes rest baseline measurements of $FEV_1$, ANF, catecholamines, pulse and blood pressure were recorded. Thereafter an intravenous infusion was commenced consisting either of placebo or ANF (1, 3 or 10 pmol/kg/min) given in a randomised, double blind manner. After 20 minutes infusion a histamine challenge was performed, commencing with a dose 0·0625 mg/ml and doubling thereafter until the $FEV_1$ fell by 20% ($PC_{20}$). These results demonstrate that at both physiological and pathophysiological plasma levels atrial natriuretic factor causes a significant reduction in airway reactivity in asthmatic patients.

| | *Rate ANF infusion (pmol/kg/min)* | | | |
|---|---|---|---|---|
| | *Placebo* | *1* | *3* | *10* |
| Baseline $FEV_1$ (litres) | 3·52 (0·28) | 3·55 (0·30) | 3·63 (0·30) | 3·59 (0·27) |
| Plasma ANF (pg/ml; N ⩽50) | 17 (3) | 41 (4) | 157 (15) | 500 (3) |
| Plasma adrenaline nmol/l; N ⩽1) | 0·21 (0·07) | 0·24 (0·09) | 0·31 (0·11) | 0·26 (0·09) |
| $PC_{20}$ (geometric mean; mg/ml) | 0·77 | 1·15* | 1·90** | 3·38** |

*$p < 0.05$, **$p < 0.001$.

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### Bronchial responsiveness in patients with chronic left ventricular failure

DP MOORE, JCH YAP, JGF CLELAND, JMB HUGHES, NB PRIDE, CM OAKLEY *Divisions of Clinical Cardiology and Respiratory Medicine, Royal Postgraduate Medical School, London*
Bron-

chial responses (BR) were assessed after exercise, hyperventilation and methacholine challenge in 12 patients (11 males) with chronic left ventricular failure (LVF) and a mean (SEM) age of 55 (6) years, mean forced expiratory volume in one second ($FEV_1$) of 2·31 (0·75) l, mean $FEV_1$ % predicted of 78·0 (15·0) % and mean $FEV_1$/VC of 80·0 (6·0)%. None had a history of bronchial asthma atopy or chronic cough but four had positive skin-prick test responses to common aeroallergens. The patients were exercised on a bicycle ergometer to more than 70% of maximum predicted minute ventilation and at the end of exercise they showed a normal bronchodilator response (mean $FEV_1$: 2·21 to 2·33 l, $p < 0·01$) and $FEV_1$ did not fall below baseline in the 20 minutes following peak exercise. Their BR to methacholine was examined using a Wright nebuliser for two minutes with doubling concentrations up to 16 mg/ml. Only one patient had $PC_{20}$ $FEV_1$ (the concentration of methacholine that caused a 20% fall in $FEV_1$) < 16 mg/ml. As methacholine response was less than expected in our group of LVF, we repeated the test in eight patients but using the forced oscillation technique of Landser (*J Appl Physiol* 1976; 41:101) to measure total respiratory resistance (Rrs) at 6 Hz, so avoiding the effect of deep inflation on $FEV_1$. Increase in Rrs of more than 50% was found in four of the eight patients whose challenges were previously negative. $FEV_1$ immediately after the end of the challenge did not show any change from baseline in three. Six of the patients also had hyperventilation tests. Hypocapnic voluntary hyperventilation did not have any effect on their $FEV_1$ but eucapnic hyperventilation tended to increase their mean $FEV_1$ (1·84 to 1·98 l, $p = 0·07$) after three minutes. In summary, our patients with chronic LVF did not develop post-hyperventilation or exercise induced bronchial narrowing. They were also not as sensitive to methacholine as in some previous studies. Measurements with Rrs instead of $FEV_1$ may increase the sensitvity of methacholine testing.

## Effect of supine posture on lung mechanics in chronic left ventricular failure

JCH YAP, DP MOORE, JGF CLELAND, C OAKLEY, NB PRIDE *Divisions of Respiratory Medicine and Clinical Cardiology, Royal Postgraduate Medical School, London* The mechanisms of orthopnoea in left ventricular failure (LVF) are still not understood. We have used the forced oscillation technique of Landser (*J Appl Physiol* 1976;41:101) to measure total respiratory resistance at 6 Hz (Rrs), in the sitting and supine positions in 10 patients (9 male, mean age 61·4 years) with chronic LVF (NYHA II-III) and 10 matched controls (9 male, mean age 62·6 years). We also measured lung volumes: total lung capacity (TLC), vital capacity (VC), mid-tidal lung volume (MTLV), forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), maximum expiratory flow rate at 25% VC (MEF 25% VC), oxygen saturation ($Sao_2$) and visual analogue score (VAS) for breathlessness. In the sitting position Rrs in patients was larger than control, 3·4 *v* 2·6 $cmH_2O/l/s$, $p = 0·05$. TLC, $FEV_1$ and VC were reduced to 70–82% of predicted in patients, but mean $FEV_1$/FVC was 81%. On their adopting the supine position, their mean VAS increased from 2·2 to 3·9. Despite a smaller fall in MTLV in the patients (112 *v* 690 ml, $p < 0·01$), there was a greater rise in Rrs (80·5% *v* 37·6%, $p = 0·02$) and their $Sao_2$ fell by 1·7%. The declines in VC were 255 *v* 114 ml respectively. There was a 53·5% decrease in MEF 25% VC in patients compared with 6·4% in control, ($p < 0·001$). On their resuming the sitting position, all the measurements almost reverted to the initial sitting values within five minutes. Rrs was further studied in five patients and four controls before and 30 minutes after inhaling 250 μg of ipratropium (table—mean (SEM) values). In summary, we found a substantial reversible increase in Rrs accompanied by subjective dyspnoea while patients were lying supine despite a small fall in MTLV in LVF patients. This increase was slightly less after treatment with ipratropium.

| | *Sitting* | *Supine* | *Sitting* |
|---|---|---|---|
| Rrs cm $H_2O/l/s$ | | | |
| LVF (before) | 3·3 (0·6) | 6·5 (0·7) | 4·0 (0·8) |
| LVF (after) | 3·4 (0·6) | 6·0 (0·8) | 3·6 (0·7) |
| Control (before) | 2·2 (0·5) | 3·1 (0·5) | 2·1 (0·3) |
| Control (after) | 1·8 (0·3) | 2·8 (0·5) | 1·8 (0·3) |

## Effect of salbutamol controlled release on exercise induced asthma

EC SMITH, RA CLARK, DP DHILLON, G LASZLO *Respiratory Medicine, Bristol Royal Infirmary, Bristol, and Respiratory Medicine, King's Cross Hospital, Dundee* Inhaled salbutamol usually prevents exercise induced asthma (EIA) but oral salbutamol is not equally effective (Anderson *et al. Am Rev Respir Dis* 1976;114:493). Salbutamol controlled release tablets (SCR) 8 mg bd were assessed by two centres in a double blind crossover study to determine the efficacy of SCR as a prophylactic agent for EIA, and were compared with placebo. Twenty subjects aged 17–33 years (9 male and 11 female) were recruited. All showed a fall of at least 25% in one second forced expiratory volume ($FEV_1$) after running on a treadmill for 6 min while inspiring dry air at room temperature through a valve box (Weinstein *et al. J Allergy Clin Immunol* 1976;57:250). The subjects were otherwise fit with a $FEV_1 > 70\%$ predicted. Inhaled bronchodilators were withheld for six hours and meals for two hours prior to each test. Only very mild exercise (normal walking) was permitted before the test. Three more exercise tests at the same workload were carried out at the same time of day on three separate days. The first test confirmed that the chosen work load reproduced EIA. The second and third tests were carried out after the subject had been admitted to the trial and medication had been taken for 3–7 days. The subjects were given either placebo or active SCR 8 mg bd in random order. For each exercise test baseline $FEV_1$ was measured and repeated post exercise at 2 min and 5 min, and at 5 min intervals for a total of 30 min. Changes in the mean $FEV_1$ baseline between exercise tests was small (mean baseline $FEV_1$ after the first treatment period was 4·16 l, which decreased by 0·11 l after the second treatment period). Analysis was carried out on the maximum fall in $FEV_1$ [$\Delta FEV_1$max] after exercise. Mean $\Delta FEV_1$max for all subjects using active SCR was 1·18 l (SD 0·76) and after placebo was 1·31 l (SD 0·76). There was no significant difference between the two treatments ($t = 0·819$, $p > 0·10$]. Regular medication with salbutamol controlled release does not prevent or attenuate exercise induced asthma.

## Effect of inhaled bronchodilators in normal volunteers of different ages

EC SMITH, J POUNSFORD, G LASZLO *Department of Care of the Elderly, University of Bristol, Bristol and Department of Respiratory Medicine, Bristol Royal Infirmary, Bristol* It has been suggested that after the age of 40 years the bronchodilator response to salbutamol decreases in asthmatics (MI Ullah *et al. Thorax* 1981;36:523). We investigated whether age modified the bronchodilator effect of a $beta_2$ agonist and an anticholinergic on the airways in normal volunteers. Thirty normal non-smoking volunteers between the ages of 22 and 89 years entered a double blind study. Six subjects were selected from each of five age groups: under 35 years, 35–44, 45–54, 55–64, and over 65 years. The response of specific airways conductance (sGaw) to inhaled cumulative doses of terbutaline sulphate and ipratropium bromide were compared with a placebo in random order on three separate days. Standard metered dose inhalers were used with a Volumatic spacer and doubling doses given every 35 minutes to a cumulative maximum dose of 3·75 mg for terbutaline and 0·30 mg for ipratropium. Airway resistance and thoracic gas volume were measured at 15 and 30 minutes after each dose in a body plethysmograph, and sGaw calculated. Dose-response curves of sGaw were constructed for each drug and for each age group. The bronchodilator response was measured as the percentage change from baseline in the area under the sGaw curve (ΔAsGaw%). For Terbutaline ΔAsGaw% was found to significantly decline with age (Spearman's rank correlation coefficient $r = -0·724$, $p = 0·001$), but for ipratropium age was not found to have a significant effect ($r = -0·004$, $p = 0·98$), and no effect was seen with placebo ($r = 0·185$, $p = 0·64$). These findings suggest that in normal volunteers the bronchodilator effect of terbutaline sulphate decreases with increasing age and the effect of ipratropium bromide is independent of age.

## Production of maintained bronchoconstriction of chosen size in man as an aid to bronchodilator drug evaluation

RW FOSTER, K RAKSHI *Smooth Muscle Research Group, Department of Physiological Sciences, University of Manchester* With normal volunteers whole body plethysmography and log specific airway conductance (sGaw), the measurement of dose-effect relationships for bronchodilator drugs is difficult because bronchomotor tone is small in relation to its variability. A constant imposed bronchoconstriction of predetermined size can provide the requisite response range. A method of achieving this (Foster RW, Atanga GK. *Br J Clin Pharmacol* 1988;25:113P) uses inhaled nebulised methacholine (MeCh) in a loading dose plus maintenance dose regime. In brief, each subject undergoes three sessions to determine the sensitivity to MeCh, slope of its log dose-effect curve ($\delta E/\delta \ln D$) and rate of offset of its effect ($\delta E/\delta t$). These allow estimation of the local elimination rate constant ($k_{el}$) of MeCh. The chosen target magnitude of bronchoconstriction was a 67–

75% reduction in sGaw. Interpolation at this level in $\delta E/\delta \ln D$ provides the loading dose ($D_0$). $k_{el}$ provides the fractional maintenance dose rate. Experience with this method has now been gained in 15 further volunteers. The validity of the method has been assessed by testing the validity of each of its parts. (1) Straightness of the $\delta E/\delta \ln D$ curve segments used to calculate the local $k_{el}$. MeCh slope = $-0{\cdot}158$ (SD 0·028). Each of the 16 subjects' lines was not different ($p > 0{\cdot}05$) from straight; median $r^2 = 0{\cdot}85$. (2) Reproducibility of the effect of $D_0$. Median $D_0 = 3{\cdot}2$ mg. Target effect = $-1{\cdot}200 \pm 0{\cdot}097$; effect of $D_0$ produced in subsequent experiments = $-1{\cdot}200$ (0·108). The two sets of mean effect data correlated ($r^2 = 0{\cdot}62$). (3) Straightness of the $\delta E/\delta t$ curve segments used to calculate $k_{el}$. Slope = 0·00424 (0·00114). Each subject's line was not different from straight; median $r^2 = 0{\cdot}84$. (4) Constancy of effect under the maintenance dose regimen. Slope of $\delta E/\delta t = 0{\cdot}00016$ (0·00053); median $r^2 = 0{\cdot}08$. The method has been used in the assay of reproterol versus salbutamol, and AH 21-132 (*Br J Pharmacol* 1990;**99**:193P).

## Evaluation of transit time in normal and asthmatic children

TK NINAN, M HUDSON, V MILNE, G RUSSELL *Department of Child Health, University of Aberdeen* Mean transit time (MTT) was measured in 100 children aged from 6 to 14 years (mean = 10·23) with no history of respiratory problems. Mean transit time varied from 0·187 to 0·800 seconds (mean 0·362, SEM 0·011) and there was no significant correlation between MTT and height, body surface area, peak expiratory flow (PEF) or forced expiratory volume in one second ($FEV_1$), although there was a slight positive correlation with forced vital capacity (FVC) ($r = 0{\cdot}2056$; $p = 0{\cdot}02$). To determine the value of this test in the assessment of bronchodilator therapy in children with asthma, MTT was measured before and after the use of a salbutamol aerosol in 50 asthmatic children. Although MTT decreased after treatment ($t = 2{\cdot}36$; $p = 0{\cdot}022$), the improvement was less significant than the changes in FVC ($t = -3{\cdot}97$; $p = 0{\cdot}000$), $FEV_1$ ($t = -5{\cdot}01$; $p = 0{\cdot}000$), and PEF ($t = -7{\cdot}67$; $p = 0{\cdot}000$). Indeed, it is interesting to note that the parameter which is most easily measured (PEF) is also that which showed the most significant change in response to an effective bronchodilator. Although further evaluation is necessary, it is doubtful if MTT offers any advantage over simpler tests in the assessment of response to treatment in asthma.

## Evaluation of standardised residuals in clinical practice

S SAPIANO, A PARKES, W FREEMAN, JF MILES, RM CAYTON *Department of Respiratory Physiology, East Birmingham Hospital, Birmingham* Previous studies have advocated the use of Standardised Residuals (SR) to assess lung function data as opposed to percentage predicted values of forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC) and peak expiratory flow rate (PEFR). (Miller MR, Pincock AC. *Thorax* 1988;**43**:265-7). Lung function data were recorded at two community health council promotion days at a leisure centre in the East Birmingham District. One hundred and eighty six subjects were evaluated and their lung function data expressed as both % predicted and SR. After exclusion of people less than 18 years of age, those with a past or current history of chest disease and those with technique too poor to produce reliable vitalograph tracings, the data from 149 subjects were compared. In the SR evaluation a value of less than $-1{\cdot}65$ at the lower 90% confidence limit of a normally distributed population was taken as the cut off point for normality. Overall, 11 people had an $FEV_1$, FVC and/or a PEF of less than 80% while only six people had an SR of less than $-1{\cdot}65$. In addition, normal $FEV_1$, FVC and PEF values were recorded in seven people with an SR of less than $-1{\cdot}65$. The use of SRs may alter the definition of "abnormal" and "normal" interpretations of lung function data and may thus influence the advice given to the patients concerned.

## Comparison of cellular profiles in sequential aspirates of bronchoalveolar lavage (BAL) fluid and in bronchial biopsy specimens

M DUDDRIDGE, P GEDDY, P V GARDINER, C WARD, E H WALTERS *Chest Unit, Newcastle General Hospital, University of Newcastle upon Tyne* The relative importance of BAL and bronchial biopsy specimens in assessing the inflammatory process in asthma remains controversial. We have therefore compared cellular profiles in BAL and bronchial biopsy specimens in nine asthmatic (four smoking) and 10 control (six smoking) subjects. Each aspirate from a 3 × 60 ml BAL was analysed separately, and three bronchial biopsy specimens were taken from the subcarinae of the right or left lower lobes. Cytocentrifuge preparations were obtained before filtration and centrifugation and stained with Diff-Quick. A differential count was obtained on at least 500 cells assessed by two experienced observers. The biopsies were fixed in formalin and stained with $\alpha_1$ antitrypsin immunoperoxidase with haematoxylin-eosin counterstain. A differential count was performed on at least 200 cells without knowledge of the diagnosis. No significant difference was detected between the cellular profile of biopsy specimens in asthmatics and normals. In BAL fluid the only significant difference between asthmatics and controls was in the percentage of eosinophils (table). In biopsy specimens lymphocytes accounted for 57·4% of cells (range 43–68·5), histiocytes 14·8% (3–41·0), neutrophils 1·8% (0–6·5), eosinophils 1·0% (0–8·8), plasma cells 1·0% (0–9·8) and null cells 18·2% (7–27·6). The cellular profile of the first BAL aspirate differed significantly from the second and third, but none seemed to reflect the distribution of cells on biopsy. We conclude that in this population BAL was more sensitive in detecting asthmatic eosinophilia.

*% eosinophils (median (range)) on BAL and biopsy specimens*

| *BAL* | *Controls* | *Asthmatics* |
|---|---|---|
| Aspirate 1 | 0·2 (0–1·1) | 0·9 (0–4·0) |
| Aspirate 2 | 0·1 (0–1·3) | 0·2 (0–2·4) |
| Aspirate 3 | 0·0 (0–0·9) | 0·2 (0–1·6) |
| Biopsy specimen | 1·7 (0–8·8) | 0·8 (0–4·2) |

## Urinary leukotriene $E_4$ concentrations increase in asthmatic attacks induced by aspirin

PE CHRISTIE, P TAGARI, AW FORD-HUTCHINSON, S CHARLESSON, P CHEE, JP ARM, TH LEE *Department of Allergy and Allied Respiratory Disorders, Guy's Hospital, London, and Merck-Frosst, Quebec, Canada* Urinary leukotriene $E_4$ ($LTE_4$) concentrations have been measured in six asthmatic patients with aspirin sensitivity and in five asthmatic subjects tolerant of aspirin, before and after provocation with aspirin or placebo. Aspirin sensitive subjects showed an average 24% fall in $FEV_1$ after aspirin challenge whereas control individuals had a 1·6% fall in $FEV_1$ after ingestion of 100 mg aspirin. The resting urinary $LTE_4$ concentrations in asthmatic subjects sensitive to aspirin were 243 (range 50–1041) pg/mg creatinine and these were on average seven fold greater than those in control asthmatic subjects. Further, there was a mean 4·5 fold increase in urinary $LTE_4$ level 3–6 h after aspirin, but not placebo, challenge in aspirin sensitive asthmatic subjects which was not seen in the control asthmatic individuals. Leukotriene release may have a central role in the mechanisms of asthmatic attacks produced by aspirin ingestion.

## Effect of cetirizine on platelet activating factor (PAF) induced bronchoconstriction in patients with asthma

SK GHOSH, P RAFFERTY, KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow* Inhalation of platelet activating factor (PAF) produces bronchoconstriction in normal and asthmatic subjects. It has been suggested that PAF induced bronchoconstriction is mediated at least in part by histamine release (Lewis *et al. Am Rev Respir Dis* 1988;**137**:1015). We have examined the effect of cetirizine, a potent and specific $H_1$ receptor antagonist without anticholinergic and antiserotonin activity, on bronchoconstriction induced by PAF in 10 patients (five male, mean (SEM) age 37·4 (3·6) y) with mild atopic asthma in a placebo controlled, double blind crossover study. Airway responses were assessed by measuring specific airway conductance (sGaw). Patients were challenged with a single dose (12 $\mu$g to 96 $\mu$g) of PAF that had previously produced 35% fall in sGaw. PAF challenges were performed after single dose (15 mg) and one week's treatment (15 mg twice daily) of cetirizine. There was no significant difference in pretreatment baseline value of sGaw on different study days and the changes after cetirizine and placebo were also not significant. The mean (SEM) maximum % fall in sGaw after single and one week's treatment with cetirizine was 38·7 (7·01) and 45·6 (5·52) compared with 50·2 (2·89) and 43·9 (7·26) with placebo respectively. Similarly mean (SEM) area under curve (AUC-sGaw/time course response) was 391 (143) and 514 (85) with cetirizine compared with 565 (37) and 461 (94) with placebo respectively. The difference was not statistically significant. There was no difference in facial flushing and feeling of warmth between cetirizine and placebo. We conclude that PAF induced bronchoconstriction in man is not mediated by histamine release and that $H_1$ receptor antagonists do not modify PAF induced bronchoconstriction.

### Effect of nedocromil sodium on platelet activating factor induced airways reactivity in normal subjects

SK GHOSH, P RAFFERTY. KR PATEL *Department of Respiratory Medicine, Western Infirmary, Glasgow* Platelet activating factor (PAF) is a phospholipid with potent inflammatory properties. Recently it has gained importance as a mediator involved in the pathogenesis of asthma because of its ability to induce non-selective airways reactivity in normal subjects. Nedocromil sodium has recently been introduced in the management of asthma and has been shown to reduce airways hyper-responsiveness in pollen sensitive subjects. We have examined the effect of nedocromil sodium on bronchial reactivity to methacholine on the third and seventh day after PAF inhalation in nine normal subjects (age range 23–36 y) in a double blind cross-over study. Baseline methacholine challenge (2–256 mg/ml) was performed to determine $PD_{20}FEV_1$ or $PD_{10}FEV_1$ (where fall in $FEV_1$ was $< 20\%$ following the highest dose of methacholine). Patients were challenged with a single dose of PAF (96 $\mu$g) using a dosimeter 30 min after inhalation of nedocromil sodium or placebo administered via a Wright's nebuliser. Methacholine challenges were repeated on the third and seventh day. Baseline mean $FEV_1$ and methacholine PD values ($PD_{10} = 3$, $PD_{20} = 6$) were comparable in both treatment periods. In the whole group there was a significant increase in methacholine reactivity on the third day after placebo. Following nedocromil there was no significant change in reactivity. However, in five subjects there was more than a twofold decrease in PD values on the third day after placebo (responders) and this increased reactivity was inhibited by nedocromil ($P < 0.01$). Our results (table) suggest that nedocromil sodium inhibited PAF induced airways responsiveness in subjects who show an increased airways responsiveness following PAF.

| | *PD methacholine* | | | |
|---|---|---|---|---|
| *n = 9* | *Control* | *Day 3* | *Day 7* | |
| Placebo | 183·2 | 100·0 | | 134·5 |
| | | 0·05 | | |
| | | | NS | |
| Nedocromil | 198·6 | 169·4 | | 107·6 |
| | | NS | | |
| Responders n = 5 | | | | |
| Placebo | 398·1 | 138·0 | | 172·2 |
| | | 0·01 | | |
| | | | 0·01 | |
| Nedocromil | 354·8 | 407·4 | | 193·6 |
| | | NS | | |

### Effect of cardiopulmonary bypass on cytokine release from cells of the monocyte-macrophage line

AB MILLAR, T TREASURE, SJG SEMPLE, GAW ROOK *Departments of Medicine, Cardiothoracic Surgery, and Medical Microbiology, University College and Middlesex School of Medicine, London* Increased alveolar-capillary permeability is a marker of acute lung injury and has been demonstrated in patients with the adult respiratory distress syndrome (ARDS) and postcardiopulmonary bypass (CPB). We have previously suggested that tumour necrosis factor (TNF) may be responsible for the development of this increase in permeability in ARDS (Miller *et al. Lancet* 1989;ii:712) and have now investigated TNF production in patients undergoing CPB. Eight patients undergoing coronary artery bypass grafting were studied, with a mean age of 59 (SD 6) years. All the patients had no previous history of lung disease, normal chest radiographs and had stopped smoking for a minimum of six months prior to surgery. Each patient had blood taken before and after operation and fibreoptic bronchoscopy (FOB) and bronchoalveolar lavage (BAL) after operation while still ventilated. Four control patients undergoing vascular surgery were studied as controls and had blood taken before and after operation. Monocytes and macrophages were separated from blood and lavage fluid respectively by adherence to plastic. These cells were cultured alone and with lipopolysaccharide. The cell culture supernatants were assayed for TNF using a double sandwich ELISA method. The results (mean (SD) IU/ml) are shown in the table. These results suggest that cardiopulmonary bypass increases the spontaneous and stimulated production of TNF from peripheral blood monocytes—that is, they are primed for TNF release—but has no direct effect on alveolar macrophages.

| | | *CPB* | | *Controls* | |
|---|---|---|---|---|---|
| | | *Preop* | *Postop* | *Preop* | *Postop* |
| Monocytes | Spontaneous | 16 (15) | 58 (42) | 18 (12) | 20 (10) |
| | Stimulated | 62 (43) | 217 (47) | 57 (34) | 61 (31) |
| Macrophages | Spontaneous | — | 21 (11) | — | — |
| | Stimulated | — | 51 (23) | — | — |

### Reversibility of the late asthmatic reaction by inhaled beta$_2$ agonists

OP TWENTYMAN, ST HOLGATE *Medicine I, University of Southampton, Southampton General Hospital, Southampton* There is uncertainty about the relative contributions of bronchial smooth muscle contraction, mucosal oedema and mucus plugging to airflow obstruction in the allergen induced late asthmatic response (LAR). We have investigated the reversibility of the LAR using a selective inhaled beta$_2$ agonist to determine the rapidly reversible component of late phase bronchoconstriction. We studied eight atopic asthmatics (3F, 5M), median age 22 (range 21–31) years, mean (SEM) $FEV_1$ 90·7 (5·6)% predicted and geometric mean provocative concentration of histamine (H) causing a 20% fall in $FEV_1$ ($PC_{20}$) 0·32 mg/ml. Data from subjects in the placebo limb of double blind studies were used for this analysis. The $PC_{20}$ H was measured before allergen challenge, and at two hourly intervals from 1·5 to 9·5 h during the LAR. With two subjects the final LAR readings were made at 7.5 h. Changes in $FEV_1$ were followed over the same time frame. Placebo was inhaled 10 min prior to the $PC_{20}$ allergen known to elicit a LAR in each subject. After the final $PC_{20}$ H measurement salbutamol 200 $\mu$g was inhaled from a MDI followed by 2·5 mg in 4 ml saline (0·9%) inhaled by tidal breathing from an Inspiron Mini-neb nebuliser. $FEV_1$ was recorded 5 and 10 min after salbutamol. Following placebo allergen caused a mean (SEM) 30·6 (7·5)% fall in $FEV_1$ at 20 min in the early asthmatic response (EAR) and a 29·8 (6·7)% fall at the end of the LAR prior to salbutamol. Salbutamol completely reversed the LAR, 10 min post salbutamol $FEV_1$ was 0·6 (4·4)% above the morning baseline (NS). Expressed another way, $FEV_1$ was 87·4 (6·3)% of predicted 10 min post salbutamol, which compares with the entry value of 90·7 (5·6)% predicted measured at the same time of day the previous evening (NS). We conclude that falls in $FEV_1$ during the LAR are reversible with an inhaled selective beta$_2$ agonist. This may indicate that bronchial smooth muscle constriction contributes a relatively large proportion to the total airflow obstruction during the LAR.

### Effect of the TP receptor antagonist GR32191 on the allergen induced late phase asthmatic response

OP TWENTYMAN, ST HOLGATE *Medicine I, University of Southampton, Southampton General Hospital, Southampton* GR32191 is a specific antagonist of the TP receptor and blocks the actions of thromboxane A2 (TxA2) and prostaglandin $D_2$ ($PGD_2$). We have investigated the effect of this compound on allergen induced late phase bronchoconstriction and increased bronchial responsiveness. Eleven atopic asthmatic subjects (3F, 8M), median age (range) 24 (20–52) years, mean (SEM) $FEV_1$ 87·8 (5·3)% predicted and geometric mean provocative concentration of histamine (H) causing a 20% fall in $FEV_1$ ($PC_{20}$) 0·45 mg/ml, were studied. The trial was performed in a randomised double blind, placebo controlled fashion in three treatment periods separated by at least two weeks. GR32191 80 mg was administered either once, one hour prior to allergen challenge, or twice, one hour before allergen and again three hours after allergen. The previously identified $PC_{20}$ allergen for each subject was administered in each study period. The $PC_{20}$ H was measured in the evening and the following morning prior to allergen challenge, then again three and eight hours after allergen. $FEV_1$ was followed at 30 min intervals over the same time frame. Baseline $FEV_1$ and $PC_{20}$ H did not differ between treatment periods. After placebo allergen caused a mean (SEM) 35·6 (3·9)% fall in $FEV_1$ from baseline at 20 min, not significantly different from the early asthmatic response (EAR) at 20 min on either of the two active treatment days. After placebo $FEV_1$ recovered to within 9·2 (3·4)% baseline at three hours and fell again by 23·1 (5·8)% eight hours post allergen. GR32191 administered once before allergen challenge had no significant effects on $FEV_1$ in the late asthmatic response (LAR) compared to placebo, but when administered before and after the EAR a significantly greater fall in $FEV_1$ of 31·7 (6·0)% occurred at eight hours ($p = 0.016$). After placebo 0·79 (0·29) and 1·87 (0·42) doubling dilution increases in responsiveness to H occurred at three and eight hours following allergen challenge, not

significantly different from either active treatment day. We conclude that GR32191, administered before and three hours after the EAR, exacerbates the allergen induced LAR but does not affect the associated increase in bronchial responsiveness.

### Red blood cell sodium transport in asthma

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Epidemiological studies have suggested a link between dietary sodium (Na) and asthma mortality in men and children in England and Wales (Burney P. *Chest* 1987;**91**:143S). A high Na diet causes increased bronchial reactivity and a deterioration in symptoms in asthmatic men (Carey OJ *et al. Thorax* 1990; 45:XXP). The mechanism is unknown, although it has been suggested that abnormal Na transport processes may result in increased intracellular [Na], and, via increased Na/Ca exchange, increased intracellular [Ca] and cell activity. We have measured red blood cell (rbc) intracellular [Na], Na/K cotransport and Na/K ATPase activity in 12 male subjects with mild asthma and 12 controls matched for 24 h Na excretion and age. Seven asthmatic subjects were taking no regular treatment, the rest were taking infrequent inhaled salbutamol only. Control measurements were made before and two weeks after inhaled salbutamol 800 $\mu$g daily. Na transport was derived by comparing intra and extracellular $^{22}Na$ and $^{86}Rb$ activity after incubation of washed rbc in the presence and absence of the cotransport inhibitor bumetanide and the Na/K ATPase pump inhibitor ouabain. Intracellular [Na] was measured by flame photometry of rbc lysate. Mean (SEM) intracellular [Na] was 11·42 (0·81) and 9·09 (0·47) $\mu$mol/ml cell in subjects and controls respectively ($p < 0·05$). There was no significant difference between bumetanide and ouabain sensitive flux: bumetanide 0·309 (0·038) *v* 0·290 (0·056), ouabain 1·325 (0·134) *v* 1·303 (0·042) $\mu$mol/ml cell/h in subjects and controls respectively. Intracellular [Na], ouabain sensitive and bumetanide sensitive fluxes were not significantly different after controls had been treated with salbutamol. These results suggest a defect in regulation of intracellular [Na] in asthma, which may be relevant to its pathogenesis.

### Evidence of free radical activity in asthma

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Many of the cell types implicated in the airway inflammation of asthma are capable of producing oxygen derived free radical species. Diene conjugation is a useful marker of free radical activity and exists in vivo mainly in the form of 9,11-linoleic acid (LA). We therefore measured serum levels of this and its stable parent compound 9,12-LA using a high performance liquid chromatography technique in three groups of subjects: healthy adults (25); stable asthmatics (98) and acute asthmatics seen in casualty (25) (mean PEF 143 l/min). There was a significant difference in 9,11-LA levels between the controls and stable asthmatics and also between these and the acute asthmatics ($p < 0·001$) but no significant changes in 9,12-LA.

*Geometric means (with 95% confidence limits) $\mu$mol/l*

| Group | 9,11-LA | 9,12-LA |
|---|---|---|
| Controls | 8·98 (7·49–10·76) | 871 (795–955) |
| Stable asthma | 14·22 (12·98–15·59) | 945 (902–990) |
| Acute asthma | 18·65 (15·56–22·36) | 888 (810–973) |

We conclude that
(1) systemic free radical activity is increased in asthma, and
(2) the increase appears to be related to asthma severity.

### Inhaled frusemide inhibits exercise induced asthma (EIA) but bumetanide does not

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Inhaled frusemide has been shown to inhibit EIA but the mechanism is unknown, though an effect on transepithelial ion or water flux may be involved. We have compared prior inhalation of frusemide with another loop diuretic bumetanide in a randomised, double blind, placebo controlled study in 10 mild asthmatics with documented EIA. The relative diuretic dose of bumetanide (1 mg) was twice that of frusemide (20 mg) and all treatments were given by minineb nebuliser. Subjects ran for 6 min on a treadmill on four occasions, minute ventilation being recorded during the last minute. There were no significant differences in baseline $FEV_1$, PEF, temperature, humidity, heart rate or minute ventilation on the different days. Mean baseline $FEV_1$ was 94% and mean PEF was 89% predicted. Frusemide produced significant ($p < 0·05$) inhibition of fall in $FEV_1$ at 10 and 15 min compared to placebo. Bumetanide did not significantly affect EIA. Mean maximum fall in $FEV_1$ after exercise was 32·8% after placebo, 16·9% after frusemide ($p < 0·05$) and 25·0% after bumetanide (NS). We conclude that, assuming drug delivery does not differ, frusemide does not protect in exercise induced asthma by inhibition of $NA^+/K^+/Cl$ cotransport.

Supported by the Royal North Shore Hospital centenary fellowship.

### Influence of inhaled beclomethasone on airway inflammatory cell populations in asthma and the clinical correlates

PH HOWARTH, RJ DJUKANOVIC, JW WILSON, KM BRITTEN, SJ WILSON, AF WALLS, WR ROCHE, ST HOLGATE *Medicine I and Pathology, Southampton General Hospital, Southampton*

In an open study parallel assessment was made of the clinical and bronchial biopsy findings in atopic asthmatics before and after corticosteroid therapy. Nine symptomatic atopic asthmatics whose sole medication was salbutamol participated. Each recorded their symptoms and bronchodilator usage daily on diary cards for two weeks prior to their first brochoscopy and underwent methacholine inhalation challenge, to define the provocative concentration required to produce a 20% fall in $FEV_1$ ($PC_{20}M$) during this period. Bronchial biopsy specimens were taken for (*a*) immunohistochemical staining with $EG_2$ for eosinophils, AA1 for mast cells and MT1 for T lymphocytes and (*b*) transmission electronmicroscopy. Each subject then received inhaled beclomethasone diproprionate (BDP) 2000 $\mu$g daily for two weeks followed by 1000 $\mu$g daily for four weeks. Diary recordings were continued for six weeks, $PC_{20}M$ was measured in the second and sixth weeks and repeat bronchoscopy and biopsy undertaken at the end of treatment. There was clinical improvement in all subjects ($p < 0·01$) with symptom reduction, increase in $FEV_1$, improvement in $PC_{20}M$ and a reduction in bronchodilator usage. These findings were paralleled by significant ($p < 0·05$) reductions in eosinophil and mast cell numbers in the epithelium and submucosa. No significant change was seen in T cell numbers nor in the ultrastructural appearances of mast cell degranulation. These findings provide direct evidence of an anti-inflammatory effect of corticosteroids in asthma and relate clinical improvement to a reduction in eosinophil and mast cell numbers in the airway mucosa.

### Albumin as a disease activity marker in lavage (BAL) fluid in sarcoidosis and asthma patients treated with steroids

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Albumin in BAL fluid principally originates from the lung lining fluid, suggesting that BAL fluid albumin levels may be a useful indicator of inflammatory disease activity. In 12 sarcoidosis and 21 asthmatic subjects undergoing serial BAL studies before and after treatment with oral prednisolone 40 mg daily (1 month) and inhaled beclomethasone dipropionate 2 mg daily (median 2·5 months) respectively, as previously reported, BAL fluid albumin levels have been measured by radioimmunoassay (Diagnostic Products Corporation). These were compared with those in 10 control patients (age 19–67) with normal pulmonary function undergoing diagnostic bronchoscopy in the absence of recent respiratory infection and lung pathology. Geometric mean (95% CI) albumin concentrations ($\mu$g/ml BAL fluid) are given and comparison between groups and between BAL before and after treatment made by ANOVA.

| | *Sarcoid* | *Asthma* | *Control* |
|---|---|---|---|
| Pre-steroids | 92* (49–173) | 44 (35–54) | 41* (33–52) |
| Post-steroids | 37* (24–56) | 37 (29–46) | — |

*$p < 0·025$.

BAL fluid albumin levels were not significantly increased in the asthma group and no significant fall was found following treatment. In the sarcoid group the BAL albumin

levels were significantly higher than in the control group ($p < 0.025$), but no relationship was found with pulmonary function, and there was a significant fall in BAL albumin levels following steroid treatment ($p < 0.025$). The fall in albumin concentration was not correlated with improvement in TLco (mean 11% (SEM 2%) predicted), unlike our earlier reported correlation between the latter and the fall in stimulated pulmonary macrophage superoxide release in vitro (*Sarcoidosis* 1989;6(suppl 1):63). BAL albumin is not a good marker of inflammatory disease activity in the asthmatic airway, whereas it may be useful to follow the disease activity in individual patients with pulmonary sarcoidosis.

### Assessment of genetic linkage of atopic asthma and rhinitis on chromosome 11 in 64 nuclear families

RP YOUNG, JR LYNCH, WOCM COOKSON, JM HOPKIN *Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford* IgE responsiveness (IGER) underlying atopic asthma and rhinitis is a genetic trait that has been assigned to chromosome 11q in a small number of extended families (lod score 5·6: Cookson *et al. Lancet* 1989;i:1292). To test this finding we have studied the segregation of IgE responsiveness and conducted linkage analysis in 64 nuclear families. Each family was identified through a single affected child. IGER (atopy) was assigned prior to genotyping by skinprick testing, specific IgE titres to common inhaled allergens or elevated total serum IgE. At least two criteria were positive in 89% and 76% of the atopic parents and children respectively. Seventy nine per cent of atopic patients admitted symptoms of atopic disease (57% asthma, 39% eczema and 56% hayfever) while 73% of non-atopics were asymptomatic. The proportion of atopic children (excluding the proband) in single affected parent families ($n = 43$) was 65%, in dual affected ($n = 16$) was 80%, and in neither affected ($n = 5$) 29%. These findings are consistent with dominant inheritance and 90% penetrance of the IGER trait. A positive lod score of 5·1 was obtained in the nuclear families between IGER and the chromosome 11q marker p lambda MS.51. The aggregate lod score in nuclear and extended families is therefore 10·7, assigning the atopy locus to chromosome 11q with conservative odds of $10^9$:1. Preliminary estimates of heterogeneity indicate that the locus accounts for more than 80% of atopic British families.

### Hong Kong 1997: the implications for tuberculosis in the UK

M NISAR, SL CHAN, PDO DAVIES *Tuberculosis Research Unit, Fazakerley Hospital, Liverpool and Wanchai Chest Clinic, Hong Kong* The lease back of the British Colony of Hong Kong to mainland China in 1997 may result in immigration of a substantial number of Hong Kong Chinese into the UK over the next seven years. Previous large scale immigration from the Indian Subcontinent (ISC), where rates of tuberculosis are very much higher than in the indigenous UK population, resulted in a very distinct decrease in the decline of the disease in the UK from the mid 1960s. Also the ISC immigrants showed a different pattern of disease with proportionally greater numbers with extrapulmonary sites. Government statistics for tuberculosis in Hong Kong have been analysed and compared with similar data for England and Wales. Rates of disease in Hong Kong for 1988 were 123·6 per 100 000. Rates for Whites in the UK are about 5 per 100 000, approximately 1/25th of rates in Hong Kong. Only 6% of Tuberculosis in Hong Kong Chinese, resident in Hong Kong was extrapulmonary, compared with 15% in the Whites in the UK and 45% in ISC patients in the UK. Drug resistance in a recent Hong Kong survey was 14% of all isolates, almost all due to resistance to streptomycin, isoniazid, or both. This figure is similar to resistance in the ISC population in the UK (12·8%), but much higher than in the White population (1·3%). Immigration of all Hong Kong Chinese to the UK, granted a British passport, would add about 6% to the annual number of notifications per annum. Awareness of the relatively high rates of disease compared with the White population is likely to be important for clinicians treating newly arrived immigrants from Hong Kong. The higher rates of drug resistance should be borne in mind.

### Tuberculin reactivity in the elderly in residential care

M NISAR, CSD WILLIAMS, RAL AGNEW, PDO DAVIES *Tuberculosis Research Unit, Fazakerley Hospital, Liverpool* Overall mortality from Tuberculosis (TB) has shown no appreciable recent change. This is mainly due to the increasing proportion of TB in the elderly, where mortality rates are highest. An increasing number of the elderly now live in residential care where communal living may predispose to reinfection with or recrudescence of TB. Evidence from the USA suggests that residents of homes for the elderly may be at increased risk of infection compared with those living in the community. As part of a TB prevalence study of the elderly in care in Liverpool, 1568 residents in 52 homes (42 private, 10 DSS owned) were tuberculin tested by Heaf gun. 1485 residents (95%) were aged 65 years or more (group 1, mean age 83 (7) years). The remaining 83 (5%) although long term residents in the homes, were aged less than 65 (group 2, mean age 57 (8) years). Tuberculin test results were as follows:

| | *Group by Heaf grade (%)* | | | | |
|---|---|---|---|---|---|
| *Heaf grade* | *0* | *1* | *2* | *3* | *4* |
| Gp 1 (n = 1485) | 73 | 9 | 10 | 5 | 3 |
| Gp 2 (n = 83) | 53 | 21 | 10 | 10 | 4 |

Although older residents are more likely to have encountered infection during their lives, tuberculin reactivity was seen less commonly in this group (27% vs 47% $p < 0.01$). Though this may be due to clearance of the original infection in the elderly survivors, the more likely explanation is that a decline in cell mediated immunity with advancing age results in loss of tuberculin skin test reactivity. Loss of immunity may be the cause of high mortality rates in the elderly. Greater awareness of this increased vulnerability of the elderly to TB is required.

The study has been funded by the British Lung Foundation and Evans Medical Limited.

### Chronic respiratory symptoms in adults in Birmingham

DAR BOLDY, JG AYRES *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham B9 5ST* A recent study from South West London suggested that, although respiratory symptoms are as common as in the 1950's, disabling chronic bronchitis is seen less frequently (Littlejohns *et al. Br Med J* 1989;298:1556). Using the age sex register of a group general practice in inner Birmingham, a respiratory questionnaire was sent to all 2242 patients aged 45–74 (with 2 reminders). 229 patients had moved away or died. 1536/2013 (76·3%) responded, the response rate being higher in females than males (78·6% v 73·7%, $p < 0.02$) and in older patients ($X^2 = 44.3$, $df = 5$, $p < 0.0001$). 32·5% of responders usually produced sputum first thing in the morning or in winter. 21·0% of the responders reported winter/morning cough with breathlessness on walking up an incline. 35·4% of subjects currently smoked (43·6% males v 28·4% females) as did 32% of asthmatics. 219/251 randomly selected patients attended for spirometry and PEF measurement. 30/251 (12%) reported a history of asthma (17 of whom had current symptoms); 85/251 (33·9%) reported cough in the morning/winter ("bronchitis"). Pulmonary function (% predicted, mean (SD)) showed (see table). 23/251 patients (9·2%) had both an $FEV_1$ <80% predicted and an $FEV_1$/FVC ratio <70% and 29 more (11·6%) had an $FEV_1$ <80% predicted: only 12 of these patients had been diagnosed as having asthma or had been to hospital for a chest condition. In this study, the findings of significant respiratory symptoms (21%) and evidence of airflow obstruction (20·7%), higher than SW London, suggests continuing considerable (often unrecognised) morbidity in the community and marked geographical variation in the UK.

| | *$FEV_1$* | *FVC* | *PEF* | *FEV/FVC* |
|---|---|---|---|---|
| A | 84·9 (21·6) | 98·2 (23·4) | 88·0 (21·2) | 70·9 (9·1) |
| B | 84·7 (19·3) | 94·2 (16·8) | 94·0 (22·4) | 72·6 (11·6) |
| N | 98·3 (16·8) | 104·3 (17·0) | 107·1 (17·3) | 77·5 (7·0) |

A or B *v* N $p < 0.0001$; A *v* B NS.

### Contribution of labelling shift to the recent rise in asthma deaths in the UK

EJ WHALLETT, JG AYRES *Birmingham University Medical School and Department of Respiratory Medicine, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST* Since 1972 there has been a slight

rise in asthma deaths in the UK for which no single cause has been determined. In children hospital admissions and acute attacks in general practice have increased perhaps partly due to labelling shift from acute bronchitis. We used the OPCS mortality tables to look for labelling shift from acute bronchitis to asthma with respect to the 1960's epidemic of asthma deaths and the recent rise in asthma mortality. Annual age specific mortality rates (per 100,000) for England and Wales were taken for acute bronchitis and asthma from 1950 to 1985 for the age groups 5–34, 35–64 and 65+ years. For the 1960's epidemic no consistent changes in acute bronchitis mortality were seen in any age group. In the 5–34 age group ("clean" for asthma) mortality for acute bronchitis was steady between 1950–72 with a mean rate of 3·1 (range 1·6–3·9) but fell linearly to 0·75 (−76%) by 1985. The mean number of deaths in the 5–34 group from 1950–72 was 50; the number of deaths from acute bronchitis saved from 1973–85 was, therefore, 292 (152 male). Using the 1975 rate as a baseline the number of asthma deaths "lost" during the same period was 349 (170 male). These findings support the hypothesis that the recent rise in asthma deaths may have been contributed to in part by a labelling shift from acute bronchitis to asthma.

## Infection with *Pneumocystis carinii* is common in British and African children

AE WAKEFIELD, TJ STEWART, ER MOXON, K MARSH, JM HOPKIN *Institute of Molecular Medicine and Osler Chest Unit, Oxford*

Pneumocystis carinii is a potent opportunistic pathogen yet the occurrence of pneumocystis pneumonia is apparently rare in Africa despite the high prevalence of immunosuppression due to HIV infection, malnutrition and parasitic disease. Serological studies have been valuable in studying the epidemiology of pneumocystis infection in Europe, where it has been shown that asymptomatic infection is common in healthy children. To test for the presence of pneumocystis infection in Africa we have conducted a comparative serological study of 150 healthy young individuals from both Oxford and the Gambia. Whole pneumocystis antigen was used in an ELISA assay to screen for IgG, IgM and IgA antibodies. Reference values of optical density were established as 48/104 (mean/+2SD). In both groups, equivalent increasing prevalence of antibody titres (OD 150–1000) to pneumocystis was found so that by ten years of age 80% of both populations were seropositive. Pneumocystis infection occurs commonly in the African children we have tested.

## The West Midlands cystic fibrosis register

DL SMITH, DAR BOLDY, J WEST, R GUPTA, P WELLER, DE STABLEFORTH *East Birmingham Hospital, Birmingham, Birmingham Children's Hospital, Expert Management Systems, University of Warwick*

The West Midlands Cystic Fibrosis Register was instituted to allow closer examination of morbidity and mortality amongst all cystic fibrosis patients within the region and to enable estimation of future demands in this area. To date, details

| <5 | 5–<10 | 10–<15 | 15–<20 | 20–<25 | ≥25 years |
|---|---|---|---|---|---|
| 6·1 (2·7) | 9·5 (3·4) | 11·4 (5) | 12·3 (4) | 17·1 (4·1) | 15·3 (6·9) |

on 474 patients (249 male, 225 female) have been entered. Fifty four per cent of patients are less than 10 years of age, 74% less than 16. Twenty two patients (4·65%) are over the age of 25. Of those patients over 16 years of age, one half are in employment, a quarter are attending further education or employment training. One fifth are unemployed. Sixty per cent of patients were diagnosed in the first year of life, a further 29% below the age of five. Nine patients (1·9%) were diagnosed aged 15 years or more and two aged 30 years or more. The most common presenting features were malabsorption (55%) and chest infection (47%). Meconium ileus accounted for 14·8% of diagnoses whilst 8·9% were diagnosed by screening procedures. In over 300 patients diagnostic sweat testing gave a mean sodium concentration (SD) of 91·65 (18·35) mmol/l and chloride concentration of 103·52 mmol/l. Current bacteriological results (available in 54% of patients) show increasing rates of Pseudomonas colonisation with age, with a peak of 79% in the 15–20 age group. Above this age the rate falls slightly to 68%. Twenty six per cent of the under fives grow Pseudomonas. Staph aureus is the next most common pathogen seen in 17·5% of patients, H. influenzae was seen in 10·5%. Mean IgG levels g/l (SD) show a rise with age (table). The register will be updated annually to allow longitudinal analysis of selected parameters and the effects of differing management regimens.

DL Smith and J West are supported by the CF Trust.

## Introducing the nuclear reactor in pulmonary medicine

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Multielement determination of trace metals in tissues or body fluids in exposed workers or in diseases of unknown origin is still an open question. We are trying to determine the usefulness of this approach in a number of pulmonary diseases, using Neutron Activation Analysis (NAA). Briefly, in 17 patients (12 with occupational disease, five with a disease of unknown origin, defined later) dried samples of lung tissue, BAL fluid, blood, urine, toe nails, pubic hair, sperm were irradiated for 10 hours in a Triga Reactor with a thermal neutron flux density of the order of $10^{13}$ n $cm^{-2}$ $s^{-1}$. Radiochemical separation was carried out one day after irradiation by NAA. In five of six patients with Hard Metal Disease, body fluids or tissues (excluding lung tissue) were studied yearly for two or three consecutive years. Control values were obtained on 40 unexposed patients submitted to BAL and open lung biopsy mostly for a lung cancer. The concentration of any single element is expressed as the ratio (R) between the level found in the sample and the mean value found in our 40 controls. Results:

1) In two cases of interstitial lung disease, NAA detected very high unsuspected levels of trace elements in the lung tissue: Al (R = 66) and La (R = 5800) respectively; in both the relation with the worker activity was clear only after this result, so that we could reach the diagnosis of Aluminium Lung and of Rare Earth Pneumoconiosis respectively. We suggest that NAA may detect the role of single elements in determining Pneumoconiosis.

2) In six patients with Hard Metal Lung Disease NAA has demonstrated that a) the concentration of Co, W, Ta in the lung tissue far exceeds (even over 100 times) the BAL fluid R value. In other words, BAL samples cannot be representative of the elemental pattern in the interstitial tissue. b) the link of W or Ta in the lung tissue seems far more persistent than Co. c) to our surprise, the clearance of Hard Metals by nails, pubic hair or urine may increase after the removal from exposure (the reason of this pattern is not clear). This suggest that NAA may detect the movements of the metals over the time in the body fluids or tissues of workers during the follow up of pneumoconiosis. d) NAA may prove useful when the diagnosis of pneumoconiosis is in doubt (this happened in two cases).

3) In two other patients with undetermined alveolitis, in one with a Granulomatous Disease of unknown origin, and in one with TB, all with suggestive occupational history and interstitial lung disease, NAA gave completely normal results, suggesting the exclusion of an occupational disease.

4) Finally, in three cases of sarcoidosis, one of idiopathic pulmonary fibrosis, one with alveolar cell carcinoma, multielement determination of trace metals in lung tissue gave completely normal results, excluding a metal as the cause of these diseases of unknown origin.

## Do platelets have a role in byssinosis?

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Previous in vivo and in vitro studies (*Int Arch Arbeitsmed* 1971;27:309; *Thromb Res* 1987;48:117) have implicated platelets in the aetiology of byssinosis. In order to investigate this, we have studied 26 cotton card room workers in two Lancashire mills exposed to medium grade cotton. Platelet levels and $FEV_1$ were measured for each operative prior to the first working shift of the week (following a weekend break) and immediately post shift. Twenty six paired values were obtained. The mean age of the operatives was 41 years (Standard Deviation 16·7). Mean platelet levels did not change significantly across shift (pre: 267 × $10^9$/l 95% confidence interval (CI) 249–285, post: 262 CI 246–278). Eleven operatives had a fall in $FEV_1$ across shift (mean −0·14 litres). There was no association between a fall in $FEV_1$ and change in platelet level across shift. Five operatives had symptoms of byssinosis. Mean pre-shift platelet levels in the byssinotic group (230, CI 198–262) were significantly lower than in the non byssinotic group (277, CI 256–298).

There was no significant shift effect in either of these groups. This preliminary study does not support an acute effect of cotton dust exposure on platelet levels, but raises the possibility of a chronic effect in byssinotic operatives.

### Microorganisms and byssinosis?

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Previous studies[1] have reported a significant correlation between gram negative bacteria concentrations and the prevalence of byssinosis, supporting a theory that endotoxin from gram negative bacteria may be a causative factor in byssinosis. We have investigated four cotton spinning mills and measured work area gram positive (GP) and gram negative bacteria (GN), fungi (F) and thermophilic organisms (TH) using an Anderson sampler and specific media. Work area (WAC) and personal breathing zone (PBZ) dust concentrations were also measured. Four hundred and four workers in 11 main work areas were interviewed with an MRC questionnaire. The prevalance of byssinosis, other work related symptoms (WRS: one or more of work related chronic bronchitis, persistent cough, chest tightness, wheeze and shortness of breath) rhinitis and eye symptoms (RHIN), were calculated per work area. Using Pearson equations, correlations were shown between the log concentrations of all forms of organisms and byssinosis (GP 0·70, GN 0·56, F 0·66 and TH 0·62); WRS (GP 0·45, GN 0·41, F 0·52 and TH 0·51) but only WAC correlated weakly with RHIN (0·32). Using multiple regression models, byssinosis was influenced by log GP, log GN and PBZ ($R^2$ = 0·62). WRS was predicted by log F and WAC ($R^2$ = 0·31). This study confirms the association between airborne gram positive and negative bacteria and byssinosis. A similar association is present between airborne fungi and other work related respiratory symptoms.

1 Cinkotai *et al, Am Ind Hyg Assoc J* 1977;38: 554–9.

### The epidemiology of occupational asthma in the West Midlands and Finland

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The West Midlands Region and Finland have similar sized populations (both working populations are 2·2 million) and are similarly industrialised. In Finland cases of occupational asthma which have been compensated are kept on a central register and it is figures from this that we compare with those produced by the Midland Thoracic Society's Surveillance Scheme. The incidence of occupational asthma in the general working population is 1 in 33 000 in the West Midlands and 1 in 8 000 in Finland. The incidences of occupational asthma in different occupational groups are shown in the table. These results could be due to true differences in incidence, but the higher incidence in Finland is likely to be due to under-reporting of occupational asthma in the West Midlands. Comparison of incidence in different occupational groups reveals that occupational asthma is particularly underreported in workers in the food and beverage industry, a group which includes bakers. This also appears to be true in the group containing agricultural workers. This suggests a need for greater vigilance for work-related respiratory symptoms in these groups.

| | *West Midlands* | *Finland* |
|---|---|---|
| Food, Beverage & Tobacco | 1 in 20 000 | 1 in 890 |
| Chemical, Plastics, Wood & Textiles | 1 in 7 700 | 1 in 5 500 |
| Electrical, Metal Product & Machine Manufacture | 1 in 28 000 | 1 in 11 000 |
| Agriculture & Forestry | 1 in 13 000 | 1 in 2 300 |

### Clinical features and management of allergic disease in seafood processors

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Asthma in prawn processors was first attributed to handling techniques which generated inhalable material (Gaddie, *Lancet* 1980;ii:1850). Subsequently the immunological influence of cigarette smoking was reported from case-control evidence obtained in a similar factory elsewhere where the meat was removed from the carapace by water jet extraction (McSharry, *Immunol Today* 1986;7:98). A further study in this group has now been completed. Of the 135 employees (all female), 23 had wheeze which mainly occurred during working hours. Work-related reductions in peak flow rate of up to 72% were recorded in comparison with holiday recordings. Sixteen symptomatic subjects were skin test sensitive to prawn extract including 8 sensitive to commonly inhaled antigens. Cigarette smoking was reported by 17/23. The development of symptoms appeared unrelated to duration of employment or age, and caused work absence in only 5 subjects. Symptoms improved in 7/13 after removal to distant sites within the factory, 4 improved with a respirator which was found intolerable by 7 others. Symptomatic control was reported in 19/23 using inhaled bronchodilator therapy alone. Work-related dermatitis (11/23 symptomatic, 37/135 overall) appeared more difficult to control. Airborne prawn antigen from filter-eluted personal air samples taken during work was not detected in areas isolated from the processing site. While the replacement of air blowing by water extraction has not resulted in control of this disorder, the incidence of chest symptoms in our study (15%) is lower than that of the original report (36%) suggesting that exposure to inhalable antigen has been altered. Allergy remains common in prawn processors, particularly in cigarette smokers, who appear to be more susceptible to the disorder than non-smokers.

### Changes in transepithelial potential difference (TEPD): a predictor of pulmonary oedema after phosgene inhalation

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Phosgene, an odourless colourless gas, achieved notoriety as a poison in the First World War, but is now widely used in organic chemical synthesis, over a million tons being produced each year in the USA (Currie *et al. Fund and Appl Toxicol* 1987;8:107–14). On accidental exposure the gas damages the respiratory tract: it is an acylator which reacts with and inactivates enzymes in the cells lining the airways and alveoli, resulting in loss of impermeability and subsequent potentially severe pulmonary oedema (PO). There is a latent period after exposure and no known predictors of incipient PO exist to identify patients requiring more aggressive management (Diller *et al. Toxicol and Ind Health* 1985;1:73–80). Generation of a TEPD in the airways depends on Na-K ATPase, known to be quickly inactivated after exposure to phosgene (Prosolono *et al. Arch Env Health* 1977;32:271–83) and we postulated that TEPD may fall before any other evidence of lung damage is detectable. In a preliminary study 8 sheep were anaesthetised and their TEPD measured by a standard method. Four were exposed to a toxic dose of phosgene and 4 acted as controls. TEPD was measured at various sites for 6 hours and the lungs were then examined for evidence of PO. Some results are shown below: all exposed animals did have pathological evidence of pulmonary oedema and throughout the period of observation their TEPD readings were lower than the controls, which had normal lungs. These early results do suggest that TEPD changes after phosgene inhalation may be a predictor of pulmonary oedema.

### Haemolytic anaemia in a case of occupational asthma due to maleic anhydride

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Occupational asthma due to a number of acid anhydrides including maleic anhydride has previously been described. Haemolytic anaemia has been described in workers exposed to trimellitic anhydride but not to the structurally similar chemical maleic

| *RESULTS* | *TEPD (expressed as mean (SE)) mV* | *Pre exposure* | *+60 min* | *+180 min* |
|---|---|---|---|---|
| MID TRACHEA | Control | −14·5 (2·8) | −14·3 (2·6) | −15·8 (2·3) |
| | Exposed | −13·0 (4·3) | −7·0 (1·6) | −5·3 (1·8) |
| SEG BRONCHUS | Control | −13·0 (2·9) | −11·8 (3·9) | −9·3 (1·4) |
| | Exposed | −12·3 (4·0) | −6·0 (2·3) | −5·6 (3·5) |

anhydride. We describe a case of autoimmune haemolytic anaemia in a patient with occupational asthma due to maleic anhydride. Occupational asthma was confirmed by history and positive specific IgE antibodies to maleic anhydride. Whilst working as a supervisor on a pilot plant producing maleic anhydride he was admitted to hospital with jaundice and lethargy with a haemoglobin of 5·8 g/dl (13–18 g/dl) and a bilirubin of 157 μmol/l (<15 μmol/l). His lactate dehydrogenase was 1472 U/l (100–500 U/l) and he had a positive Coombs' test. The anaemia responded rapidly to steroids and plasmapheresis and he returned to work in an office job away from exposure. Six months later he returned to his job as a supervisor on the maleic anhydride production process; at this point his haemoglobin was normal at 14·8 g/l. Three weeks after this he was readmitted to hospital with a recurrence of his haemolytic anaemia; admission haemoglobin was 6·9 g/l. Again this responded to treatment. He has had no further exposure and has had no further episodes of anaemia, his asthma has improved and his specific IgE to maleic anhydride is declining. This case suggests that maleic anhydride can also cause a haemolytic anaemia.

## Controlled trial of 3 or 6 courses of the ECMV regimen and of 6 courses of an ifosfamide regimen in the chemotherapy of small cell lung cancer (SCLC)

NM BLEEHEN, DJ GIRLING, PM FAYERS, RJ STEPHENS *for the Medical Research Council Lung Cancer Working Party, 20 Park Crescent, London W1N 4AL.* Four hundred and fifty nine patients with confirmed SCLC were admitted to the study between 1985 and 1989 from 21 centres. They were allocated at random to 3 chemotherapy regimens, each given on 3 consecutive days at 3-week intervals. In the first two, etoposide 120 mg/m$^2$, cyclophosphamide 1 g/m$^2$, methotrexate 35 mg/m$^2$ and vincristine 1·3 mg/m$^2$ (max 2 mg) were given IV over 30 minutes on day 1, and etoposide 120 mg/m$^2$ IV or 240 mg/m$^2$ orally on days 2 and 3, for a total of either 3 courses (ECMV3) or 6 courses (ECMV6). In the third, etoposide was given on days 1, 2 and 3, in the same dosages as above, together with ifosfamide 5 g/m$^2$ IV during 24 hours on day 1, for a total of 6 courses (EI6). Patients with limited disease (57% of the total) received radiotherapy to the primary site after the third course of chemotherapy in all 3 series. During the first 3 courses of chemotherapy, a partial response occurred in 41% of 157 ECMV3, 45% of 152 ECMV6, and 50% of 150 EI6 patients, and a complete response in 14%, 9%, and 13%, respectively. There was no survival advantage to any of the 3 regimens (P = 0·29, log-rank test). The estimated median survival time was 33 weeks in the ECMV3 series, and 39 weeks in the ECMV6 and EI6 series. At 1 year, 29%, 30%, and 33% of assessable patients were alive, and at 2 years 8%, 9%, and 10%, respectively. In patients with a partial or complete response, there was no statistically significant difference in survival (P = 0·15, log-rank test). The estimated median survival time was 38, 44, and 48 weeks, and the proportions alive at 1 year 30%, 37%, and 40%, and at 2 years 9%, 13%, and 13%, respectively.

## Controlled trial of palliative radiotherapy given in two fractions (F2) or one fraction (F1) for inoperable non-small cell lung cancer (NSCLC)

NM BLEEHEN, DJ GIRLING, PM FAYERS, RJ STEPHENS *for the Medical Research Council Lung Cancer Working Party, 20 Park Crescent, London W1N 4AL.* In a trial aimed at simplifying the palliative treatment of patients with a poor prognosis, 235 patients with inoperable NSCLC and poor performance status (WHO grade 2–4) were admitted during 1988 and 1989 from 10 centres. All had their main symptoms related to the chest even if metastases were present, and had tumour too advanced for radical radiotherapy. They were allocated at random to receive thoracic radiotherapy with either 17 Gy in 2 fractions of 8·5 Gy 1 week apart (117 patients), a regimen shown to be effective in a previous MRC study (report in preparation), or 10 Gy in a single fraction (118 patients). As assessed by the clinicians, the two regimens had similar palliative effect. Cough was palliated in 48% of 112 F2 and 56% of 108 F1 patients, haemoptysis in 75% of 55 and 72% of 54, and chest pain in 56% of 66 and 72% of 71, respectively. The median percentage of survival time during which there was palliation was 50% in the F2 series and 50% in the F1 series for cough, 73% and 71% for haemoptysis, and 50% and 50% for chest pain, respectively. As assessed daily by the patients using a diary card, the level of physical activity was higher in the F1 series, and the F2 regimen caused substantially more dysphagia which was recorded by 57% of patients compared with 23% in the F1 series. There was no difference in survival (p = 0·7 log-rank test); the estimated median survival time from allocation was 16 weeks in the F2 series and 18 weeks in the F1 series. In conclusion, the single fraction (F1) regimen is recommended.

## Prednisolone pharmacokinetics in patients with inoperable lung cancer

SM TARIQ, J THOMAS, PA ROUTLEDGE, S CAPEWELL *Departments of Chest Diseases and Clinical Pharmacology, Llandough Hospital, Cardiff CF6 1XX.* Prednisolone has long been used in patients with inoperable lung cancer to alleviate anorexia, weight loss and fatigue. However, the optimum dosage remains uncertain. There may be reduced absorption and plasma-protein binding. Hepatic metabolism may be impaired non-specifically or by liver metastases. We therefore studied the pharmacokinetics of prednisolone in 12 patients with inoperable lung cancer (4 small cell, 5 squamous cell and 3 large cell; 9 male and 3 female, mean age 66, range 54–83 y) compared with age and sex matched controls with chronic bronchitis. Patients with coexisting hepatic, renal or cardiac disease and those receiving oral steroids or drugs inducing/inhibiting liver microsomal enzymes were excluded. Prednisolone pharmacokinetics were studied over 10 hours on two occasions one week apart comparing 30 mg prednisolone given orally and IV in random order. The plasma clearance of prednisolone was reduced by 28% (oral) and 25% (IV) in lung cancer patients as compared to the controls [oral 84·4 vs 116·7 ml/min (p < 0·05), and IV 83·4 *v* 110·4 ml/min (p < 0·05)]. The differences were not related to albumin levels, evidence of liver metastases, or abnormal liver function tests. The area under the curve was correspondingly higher in lung cancer patients, by 37% and 32% respectively [oral 6225 *v* 4545; IV 6308 *v* 4792, both p < 0·02], and $t_{\frac{1}{2}}$ was prolonged [oral 4·89 *v* 4·04 hours; IV 4·36 *v* 3·78 hours, p < 0·05]. C max was also significantly higher after IV administration (1564 *v* 994 μg/l, p < 0·05). Bioavailability was 99% in cancer patients and 96·3% in bronchitics. In conclusion, prednisolone clearance is significantly reduced in patients with lung cancer, and lower doses should therefore be considered.

## Pleural fluid LDH: does it have a diagnostic role in mesothelioma?

J JOSEPH, SM VINEY, MJ SMITH, P BECK, GS BASRAN *Respiratory Unit, District General Hospital, Rotherham, South Yorkshire S60 2UD.* Although pleural fluid LDH analysis is widely used in USA, it has not gained popularity in the UK as a test in the differential diagnosis of pleural effusion. Biochemical data from 170 patients with pleural effusions due to a variety of causes were analysed for total protein, total LDH, LDH-5 isoenzyme. The table shows the fluid/serum ratio (mean (SEM)) for total protein, total LDH and LDH-5 for the 10 effusion groups: mesothelioma (Meso), bronchial carcinoma (Br. ca.), metastatic carcinoma (Met. ca.), autoimmune disease (AID), congestive cardiac failure (CCF), pulmonary embolism (PE), para-pneumonic effusion (PPE), empyema (Emp), miscellaneous (Misc.) and unknown (UKN). LDH-5 ratio was significantly higher in mesothelioma group as compared to other groups (p < 0·025) except in autoimmune disease. Thus a higher LDH-5 ratio in the absence of autoimmune disease may help to differentiate effusion due to mesothelioma from those due to non-mesothelial groups.

| *Group* | *n* | *T protein* | *Total LDH* | *LDH-5* |
|---|---|---|---|---|
| Meso | 7 | 0·57 (0·03) | 7·92 (7·10) | 3·49 (0·65) |
| Br. ca. | 44 | 0·61 (0·01) | 1·05 (0·11) | 1·29 (0·09) |
| Met. ca. | 29 | 0·59 (0·02) | 1·24 (0·15) | 1·75 (0·18) |
| AID | 3 | 0·65 (0·01) | 4·85 (2·60) | 3·63 (0·68) |
| CCF | 36 | 0·39 (0·02) | 1·80 (1·13) | 1·62 (0·12) |
| PE | 8 | 0·47 (0·05) | 1 (0·13) | 1·28 (0·11) |
| PPE | 15 | 0·64 (0·03) | 2·15 (0·60) | 1·70 (0·41) |
| Emp | 14 | 0·65 (0·04) | 41 (20·90) | 1·49 (0·14) |
| Misc. | 7 | 0·36 (0·07) | 1·11 (0·48) | 1·91 (0·34) |
| UKN | 7 | 0·65 (0·03) | 1·34 (0·46) | 1·71 (0·42) |

## National survey of primary tracheal tumours

CM GELDER, MR HETZEL *Department of Thoracic Medicine, University College Hospital* The management of primary tracheal tumours is poorly defined because of their rarity. We have therefore attempted a retrospective survey of all Thoracic Physicians and Surgeons, ENT Surgeons and Radiotherapists in the UK. We report the interim results from the first 200 patients. One hundred and seven patients had squamous carcinomas, 19 adenoid cystic carcinomas, 14 anaplastic/large cell carcinomas, 8 small cell carcinomas, 6 adenocarcinomas, 20 miscellaneous rarer tumours and in 26 cases no histology was obtained. The one and five year survivals using life tables were as follows: squamous (39%, 8%), adenoid cystic (89%, 65%), anaplastic/large cell (53%, 0%), small cell (13%, 0%), adenocarcinoma (83%, 42%), miscellaneous (89%, 74%), no histological diagnosis (35%, 15%). Tumour site appears to affect the survival of patients with squamous cell carcinoma with the longest survival with tumours in the upper third and the shortest with tumours in the lower third. The majority of patients (75%) were treated with radio therapy, its effect on survival is therefore difficult to assess without untreated cases for comparison. In contrast to Grillo's series (H C Grillo *American Journal of Surgery* 1982;**143**:67) in the USA relatively few patients were treated by surgical resection (19) and the majority of these had either adenocystic carcinoma or one of the miscellaneous rare tumours. It is difficult therefore to directly compare the success rate of radiotherapy and surgery (even in the adenocystic carcinoma group because of their low death rate). The survival of the no histological diagnosis group was 15% at five years, and greater efforts to obtain histology seem justified. Future prospective studies are needed to determine the relative merits of surgery and radiotherapy.

## Survival in non-small cell lung cancer (NSCLC): physician's opinion compared with prognostic factors

MF MUERS (on behalf of THE THORACIC GROUP OF THE YORKSHIRE REGIONAL CANCER ORGANISATION) *Respiratory Unit, Killingbeck Hospital, Leeds LS14 6UQ* An assessment of survival underpins choice of management in NSCLC. Prognostic factor (PF) models using presentation clinical and biochemical data correlate with survival, but it is not known how they compare with a physician's opinion (or whether they can enhance it). Two hundred and eighty nine consecutive patients (221 histologically confirmed) and all managed as NSCLC by 4 physicians and 2 oncologists were studied prospectively. At presentation we recorded anthropometric data, 12 symptoms on a 4-point scale, WHO activity score, cell type, 8 blood values, and disease extent (14 variables). At the time of treatment decision the doctors estimated survival in month. Sixty four patients had surgery, 122 radiotherapy and 113 supportive care initially. Two hundred and seventy seven patients were followed to death or for a total of 12 months. The best model used activity score, anorexia and lymphocyte count. The table compares this with physician's opinion:

| *% survivors at:* | *3 months* | *12 months* |
|---|---|---|
| (1) All patients | 73 | 30 |
| (2) Model | | |
| Good prognosis | 88 | 46 |
| Mod prognosis | 73 | 28 |
| Poor prognosis | 54 | 16 |
| (3) Opinion: will survive | 80 | 50 |
| Opinion: will not survive | 25 | 27 |

The physician's opinion was better than the model at 3 months and equally good at 1 year. The best potential use of a PF model would seem to be to enhance opinions rather than replace them.

## Role of palliative medicine in management of advanced respiratory disorders

S AHMEDZAI, IS JOHNSON, J BULMAN, PEA WOOD *Leicestershire Hospice, Groby Road, Leicester LE3 9QE* Hospices have traditionally been regarded as places for "the dying". With the establishment of palliative medicine as a new speciality of internal medicine, the appointment of consultants is leading to an expansion in the range of services being offered. At the Leicestershire Hospice (on a busy hospital site), we operate a relatively high-turnover, short-stay policy for patients with incurable malignancy and other conditions such as end-stage motor neurone disease, pulmonary fibrosis, cardiorespiratory failure. We also offer outpatient clinics, day care and home care support. From September 1985 to March 1990, we had 484 referrals of patients with lung cancer (66% from GPs, 34% from hospital consultants). Reasons for referral were: symptom control (46·5%); psychological support (23·1%); respite for carers (41·6%); actually in terminal phase (39·0%). In addition, we arranged 9·6% of admissions for "assessment" (usually of physical disability) and 14·0% for "rehabilitation". Fourteen per cent of patients were initially offered an outpatient visit. Severity of problems at first assessment were graded on a 3-point scale: 41·2% of patients had severe (overwhelming) physical problems; 9·7% emotional; 17·6% social. Treatments offered to patients with respiratory distress symptoms include: inpatient and home nebuliser therapy with bronchodilators; diamorphine (dyspnoea, pain); lignocaine (cough, dyspnoea). Patients are screened for possible active treatment such as oncological regimes or bronchial stent. Palliative care services in future may be able to offer considerable support in the management of patients with advanced respiratory disorders.

## Pseudolymphoma of the lung

PHB BOLTON-MAGGS, A COLMAN, GR DIXON, MW MYSKOW, JG WILLIAMS, RJ CONNELLY, CRK HIND *Royal Liverpool Hospital, Liverpool; Halton Hospital, Runcorn; and The Cardiothoracic Centre, Broadgreen Hospital, Liverpool L14 3LB* Though described in the pathology literature, there is no mention of pseudolymphoma of the lung in the standard English respiratory textbooks. This rare condition was thought originally to be a benign lymphoid proliferation because of the indolent behaviour of the tumour and long survival of affected individuals. Recent pathological studies, however, have demonstrated that these lesions are lymphomas of mucosa-associated lymphoid tissue (maltomas). Three such patients have presented to this Cardiothoracic Centre in the past two years (all female, aged 60, 68 and 78). Clinical features included breathlessness and weight loss (3), haemoptysis (2) and wheezing (1); none had peripheral lymphadenopathy. Their chest X-rays were all different, showing right middle lobe consolidation, or multiple large pulmonary nodules, or bilateral patchy infiltrates. Bronchoscopy was normal in all cases, though transbronchial biopsy in one raised the suspicion of lymphoma. In each the diagnosis was made by open lung biopsy, with middle lobectomy in one case. Both patients with widespread chest X-ray changes received chlorambucil and prednisolone with complete resolution of their symptoms and chest X-ray abnormalities. No evidence of relapse is evident after 9, 9 and 18 months follow-up. These cases highlight the varied clinical and radiological features of this rare pulmonary condition, and its good prognosis following surgical resection in localised forms and chemotherapy in more widespread cases.

## Endoscopic bougie and balloon catheter dilatation of multiple bronchial stenoses: 10 year follow up

JB BALL, J DELANEY, CC EVANS, RJ DONNELLY, CRK HIND *The Cardiothoracic Centre, Liverpool L14 3LB; and Arrowe Park Hospital, Wirral* In 1981 this Unit reported its experience of endoscopic dilatation of multiple endobronchial stenoses in four patients (two sarcoidosis, one berylliosis, one idiopathic). Dilatation using Chevalier-Jackson bougies resulted in immediate clinical and physiological improvement (*Thorax* 1981;**36**:784–6). Ten years later, the same patients have been reassessed clinically, physiologically and bronchoscopically. In two of the patients, one with sarcoid (male, 51 years) and the other with idiopathic bronchostenoses (male, 39 years), the improvement immediately following mechanical dilatation was sustained for nine years. Both then relapsed clinically and physiologically. Identical restenoses were demonstrated and redilated in the first case using a balloon catheter with good improvement. In the second case, stenoses had developed in the smaller segmental bronchi while the major bronchi remained patent; such stenoses were not amenable to further dilatation. The third patient (male, 53 years, berylliosis) relapsed after five years with recurrence of stenoses in the original distribution. These could not be dilated and although clinical and spirometric improvement were achieved with prednisolone therapy, the endoscopic appearances remained unchanged over the subsequent five years. The fourth patient (female, 43 years, sarcoidosis) obtained only very temporary respite following bougie dilatation and required 11 further dilatations over the following three years. In spite of this and prednisolone therapy, her initial post-dilatation clinical and physiological improvement has not been maintained. These results suggest that mechanical dilatation of bronchial stenoses result in long term improvement in the majority of patients, although all patients would appear to relapse eventually.

### Nd: YAG laser pulmonary lumpectomy for stage 1 bronchogenic carcinoma

J KUO, GN MORRITT *Department of Cardiothoracic Surgery, Freeman Hospital, Newcastle upon Tyne* Nd: YAG laser pulmonary lumpectomy were performed in 9 patients with stage 1 bronchogenic carcinoma at the Regional Cardiothoracic Centre, Freeman Hospital. Their age ranges from 50 to 69 years (mean 62·2 years). Eight patients had T1 No tumours with one T2 No tumour. Tumour size varies from 0·2–4·5 cm. Tumour excision takes between 5–10 minutes. Intra-operative blood losses were minimal and a mean post-operative blood loss of 419 ml. The drop in haemoglobin ranges from 0·2–1·9 g/dl. None of the patients required blood transfusion. Air leaks were minimal and 8 out of 9 chest drains were removed within 24 hours. There were no complications or early mortality. Mean hospital stay was 7·3 days. Patients' pulmonary functions were well preserved.

### Primary pulmonary lymphoma

R UPPAL, P GOLDSTRAW *Brompton Hospital* Primary Pulmonary Lymphoma (PPL) is an uncommon tumour and constitutes 3–4% of all extranodal lymphomas. This represents 0·3–0·5% of all primary pulmonary malignant tumours. Extranodal lymphomas arise from mucosal associated lymphoid tissue. It is thought that PPL develops from B lymphocytes. Six cases presenting to a single surgeon over a seven year period are described. The mean follow up period was 56 months, range 12 to 89 months, with a sex ratio of female to male of 4:2. All patients had a surgical resection. Three underwent pneumonectomies and three lobectomies. Of these six patients, three had adjuvant chemotherapy one of whom also had deep X-ray treatment for chest wall recurrence. Five patients are still alive. Mean survival = 50·4 months with a range of 12–89 months.

### Diffuse malignant mesothelioma of the pleura: an eight year experience with palliative therapy

DW MYERS, C FORRESTER-WOOD, N IBRAHIM *Departments of Thoracic Surgery and Histopathology, Frenchay Hospital, Bristol* We have treated 93 patients from 1982 through 1989 with biopsy proved diffuse malignant mesothelioma of the pleura. Eighty four per cent of patients were men and 16% women. The disease occurred on the right side in 65%, and 47% could remember an asbestos exposure (only 13% of women). Thoracoscopy and open pleural biopsy were most commonly required to determine the diagnosis. The sole intent of our treatment was palliation: patients received conservative medical therapy alone versus early pleurodesis or pleurectomy/decortication for significant pleural effusion. Median survival was 12 months for all groups. Forty three per cent of patients required only conservative medical therapy and experienced adequate palliation. Forty per cent underwent pleurodesis for significant effusion, and only 15% of these subsequently required pleurectomy (pleurodesis treatment failures). Seventeen per cent underwent initial pleurectomy/decortication and enjoyed good relief from effusion, but these thoracotomy patients suffered significantly more pain and seeding of their wounds with tumour. We conclude that in the absence of any curative therapy, conservative medical therapy coupled with chemical pleurodesis for significant effusion affords the best palliation for diffuse malignant mesothelioma of the pleura, with pleurectomy/decortication reserved for pleurodesis treatment failures only.

### Pulmonary function in the post-operative period after spinal surgery for idiopathic scoliosis

WJM KINNEAR, GC KINNEAR, L WATSON, JK WEBB, IDA JOHNSTON *Harlow Wood Orthopaedic Hospital, Mansfield and University Hospital, Nottingham* Although the long term effects of spinal surgery for scoliosis have been studied extensively, there have been few reports of the changes seen in the early post-operative period. We have studied 20 patients with idiopathic scoliosis undergoing spinal surgery, 10 through a thoracotomy incision (Ant) and 10 by a posterior approach (Post). Fourteen patients were female, the median age was 14 (range 12 to 35) years and median pre-op vital capacity (VC) of 68 (range 28 to 109)% of predicted. A mild fall in oxygen saturation persisting for several days post-operatively was seen in most patients. Oxygen saturation fell below 90% in 5 patients, 3 of whom had clinical evidence of pulmonary complications. On the 7th post-operative day, median VC was 45% of pre-op values for Ant compared to 78% for Post surgery ($p < 0·01$), median sniff mouth pressure (Sniff-Pm) was 56% for Ant and 85% for Post surgery (NS) and the maximum relaxation rate of Sniff-Pm was 94% for Ant and 98% for Post surgery (NS). No patient was hypercapnic beyond the 3rd day post-op and none of the 10 patients who were able to perform VC lying and standing on the 7th post-op day showed a postural drop of more than 5%. Both Ant and Post spinal surgery are associated with post-operative hypoxaemia. The loss of VC after surgery is consistent with reflex inhibition of inspiratory musculature.

### Load compensation during $CO_2$ rebreathing in normal man and sleep apnoea

JE CLAGUE, N CARROLL, T MCKEOWN, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* The ventilatory response to $CO_2$ is a relatively "pure" stimulus to breathing. Imposition of a resistive load modifies this response and the perception of effort associated with it (Clague. *Am Rev Respir Dis* A322, 1989). Patients with obstructive sleep apnoea (OSA) have chronic mass loading of their respiratory systems but little increase in daytime resistance. We wondered whether $CO_2$ responses differ in OSA and whether chronic sleep deprivation affects the relationship between "drive" and effort sensation (IES). We studied 12 normal subjects (N) and 12 patients with OSA (A + HI 65). Each performed duplicate $CO_2$ rebreathes both free-breathing (fb) and with a 10 $cmH_2O$ inspiratory resistive load (IRL). Minute ventilation ($\dot{V}E$), $CO_2$ tension, mouth occlusion pressure P0·1 and IES were recorded. Mean slopes are shown in the table in SI units:

| | $\dot{V}E/CO_2$ | $P0·1/CO_2$ | $IES/CO_2$ | $IES/P0·1$ |
|---|---|---|---|---|
| N fb | 19·3 | 2·8 | 2·3 | 0·88 |
| IRL | 12·4 | 3·7 | 3·2 | 0·78 |
| OSAfb | 16·3 | 5·8 | 2·9 | 0·59 |
| IRL | 15·6 | 11·1 | 4·7 | 0·63 |

In OSA the free-breathing $\dot{V}E/CO_2$ response required a higher drive reflected by $P0·1/CO_2$ to maintain it. Unlike normals OSA patients maintained their $\dot{V}E/CO_2$ responses in response to loading by increasing the $P0·1/CO_2$ response. OSA patients are more dependent on central drive to maintain ventilation and changes in this drive during sleep may contribute to apnoeic episodes. In both normals and OSA IRL did not affect the IES/P0·1 relationships supporting the importance of respiratory drive in the perception of inspiratory effort.

### The effect of exercise on nasal potential difference in asthmatics and controls

WE HARRIS, S ALSUWAIDAN, K GIEBALY, C ADAIR, DP NICHOLLS, CF STANFORD *Royal Victoria Hospital, Belfast* It is thought that exercise induced asthma is due to drying of the mucosa during exercise (Anderson, *J Allergy Clin Immunol* 1984;73:660–5). Delay in onset of nasal secretion in asthmatics during exercise has previously been demonstrated (Stanford *et al. Thorax* 1988;43:251P). The volume and composition of airway surface liquid may be under the control of active ion transport. Nasal transepithelial potential difference may serve as an index of membrane function and can be measured in vivo in humans (Knowles *et al, Am Rev Resp Dis* 1981;124:484–90). We have looked at the way nasal potential difference alters during exercise in 6 asthmatics and 6 controls. Maximum nasal potential difference values (PD max.) were measured. Resting values were measured and then every 2 minutes during 12 minutes exercise and 20 minutes recovery. Exercise took place on an ergometer to a level which achieved 85% maximum predicted pulse rate. The results were expressed as means and SEM. PD max. values for asthmatics and controls were −12·6 (3·7) and −13·7 (4·4) respectively. At the end of exercise values were −18·6 (5·8) and −17·4 (5·7), the values for asthmatics continuing to rise to the end of the 20 minute recovery period −21·9 (6·2) whereas the value for the controls reached a peak 14 minutes after the end of exercise −24·3 (6·6) and fell to −21·1 (6·3) by 20 minutes recovery. There was no statistically significant difference between the groups but the rise to maximum was for each group ($p < 0·05$). We conclude that nasal potential difference increases during exercise in controls and asthmatics with no significant differences between the groups.

### Lung function and respiratory disease in patients with rheumatoid arthritis (RA)

J BANKS, C BANKS, B CHEONG, V UMACHANDRAN, AP SMITH, J JESSOP, M PRITCHARD *Llandough Hospital, Cardiff* Remarkably high prevalence rates of airways disease and interstitial lung disease have been reported in several series of patients with RA and attributed to the RA process. Diagnoses have been based primarily on the finding of a low MMEF or

TLCO respectively but little attention has been given to any accompanying clinical and radiographic findings. We have measured $FEV_1$, FVC, MMEF and TLCO in 270 RA patients (88 non smokers). In addition each patient was assessed clinically and had a chest radiograph. Abnormal tests in individual patients, ie MMEF or TLCO >2 SD below mean predicted values, were interpreted together with the clinical and radiographic findings. Lung function tests ($FEV_1$, FVC, MMEF) in the RA patients were also compared with those measured in a control group of 254 subjects and respiratory symptoms in the two groups compared with a respiratory questionnaire. Thirty one (11%) RA patients had an abnormally low MMEF. Of these 27 were cigarette smokers and most had respiratory conditions usually associated with smoking. Only 4 non smokers had a low MMEF (1 with bronchiectasis, 1 asthmatic). Fifty one (19·5%) RA patients had a low TLCO corrected for Hb. Forty seven were smokers, the majority had cough and sputum and obstructed spirometry. Only 4 (1·5%) had fibrosing alveolitis. Compared with controls mean $FEV_1$, FVC and MMEF were reduced in RA non smokers by 0·28 l, 0·29 l and 0·33 l/sec respectively but MMEF/FVC ratio did not differ from controls suggesting that the reduction in *mean* MMEF in RA is due to a reduction in lung volume rather than airways disease. These changes were not accompanied by increased breathlessness nor wheezing in RA non smokers. RA smokers showed similar results but the MMEF was further reduced by cigarette smoking. As a group they had the lowest MMEF overall and also experienced more respiratory symptoms than control smokers. Smoking related disease appears to be the major cause of abnormal lung function in RA.

## Increased circulating platelet aggregate formation during pulmonary vascular remodelling by chronic hypoxia in rats

RJD WINTER, D SYNDERCOMBE COURT, T KRAUSZ, L ZHAO, JA WEDZICHA *Department of Medicine (Respiratory Division) and Histopathology, RPMS, Hammersmith Hospital; Department of Haematology, The London Hospital, and Department of Thoracic Medicine, London Chest Hospital, London* We have previously shown increased platelet aggregate formation in patients with severe hypoxia and pulmonary hypertension (*Thorax* 1989;44:837P). We have investigated whether there are abnormalities of platelet aggregation during the late stages of vascular remodelling in response to chronic hypoxia. Albino male Wistar rats, weighing 200–250 g (n = 25) were placed in an environmental chamber with $Fio_2$ maintained at 10% (*Am Rev Resp Dis* 1986;134:763–7). After 7 days rats were anaesthetised and blood obtained by ventricular puncture into: i) buffered EDTA/formalin and ii) buffered formalin at 4°C. Blood was taken for measurement of microhaematocrit (Hct). The right ventricle (RV) was dissected from the left ventricle and septum (LV) and (in parallel experiments) rat lungs were taken for morphometric studies. Right ventricular hypertrophy was expressed as RV/LV. Platelet aggregate ratio (PAR) was measured as before by a quantitative method, in which the PAR approaches 1·0 in the absence of aggregates and falls when platelet aggregates are present (*Lancet* 1974;ii:924–5). Results are tabled below (mean (SD)):

| | *Normoxia (n = 10)* | *Hypoxia (n = 15)* |
|---|---|---|
| RV/LV,% | 26·3 (3·5) | 37·4 (3·5)** |
| Hct % | 38·5 (0·4) | 46·4 (0·3)* |
| PAR | 0·900 (0·036) | 0·790 (0·101)* |

*p < 0·01, **p < 0·001.

Thus, increased circulating platelet aggregates are seen during hypoxic pulmonary vascular remodelling. Morphometric studies of the small pulmonary vessels at this time point will also be presented.

## The effect of inspiratory threshold loading on the release of atrial natriuretic peptide (ANP)

D SPENCE, I PAVORD, A COLE, S DUTT, RF BING, P EBDEN *Department of Medicine, Glenfield General Hospital, Leicester* The mechanism of release of ANP is unclear, it is thought to underlie the natriuresis observed in obstructive sleep apnoea (OSA) (presented winter BTS 1989, Pavord *et al*). One theory is that the large negative intrathoracic pressures seen in OSA result in atrial distension and ANP release, alternatively the increase in right heart pressure consequent upon hypoxic pulmonary vasoconstriction may result in ANP release. The former hypothesis is supported by work from Anderson (*Clin Sci* 1989;76:423–9) which showed an increase in ANP release during prolonged low level negative pressure breathing. We studied the effects of recreating the negative intrathoracic pressures seen in OSA (40 cm to 80 cm $H_2O$) on ANP release in 7 normal male volunteers (age 21–30, weight 65–80 kg). Subjects rested for 1 hour in the supine position before breathing for 2 minutes through an inspiratory loading value set to achieve a negative intrathoracic pressure of 40 or 80 cm $H_2O$ monitored using an oesophageal balloon. No hypoxia occurred during the period of loading. Venous blood was taken for ANP assay prior to the period of loading, and every 10 minutes for 1 hour following it and assayed using the Amersham radioreceptor assay (normal range 5·02–22·8 pmol/l). There was no significant rise in the level of ANP following loaded breathing, 10 min 14 (6·6) pmol/l, 20 min 14·6 (6·7) pmol/l, 40 min 20·5 (10·5) pmol/l compared with resting values 16·1 (5·9) pmol/l. These results show that a short period of breathing against a load does not result in an increase in ANP release, and are in agreement with the results of Warley (*Clin Sci* 1990;78:311–13) who used a more prolonged though lower threshold load. They suggest that negative intrathoracic pressure alone is not the stimulus to the release of ANP seen in OSA. Further work is required to examine the role of hypoxia both alone and in combination with negative intrathoracic pressure on the release of ANP.

## Effects of CPAP on psychometric performance in patients with the sleep apnoea/hypopnoea syndrome

HM ENGLEMAN, I DEARY, MF FITZPATRICK, NJ DOUGLAS *Respiratory Medicine Unit, Department of Medicine (RIE) and Department of Psychology, University of Edinburgh* Although the symptoms of patients with the sleep apnoea/hypopnoea syndrome (SAHS) improve following CPAP, there is relatively little objective data on improvement. One of the major complaints of patients with SAHS is the inability to concentrate and both we (Cheshire *et al*, *Thorax*, abstract in press) and others (Greenberg *et al*, *Sleep* 1987;10:254–62) have shown that psychometric performance is depressed in SAHS patients. We have, therefore, examined the effect of CPAP therapy on daytime psychometric performance in 9 male patients with SAHS (age 35–69 yrs; apnoea + hypopnoea frequency 25–95 per hr). The psychometric battery included simple reaction time, four subtests from the WAIS-R battery (Information, Arithmetic, Block Design and Digit Symbol Substitution), Trailmaking Tests A and B, National Adult Reading Test, Inspection time, Auditory-Verbal Learning Test, Paced Auditory Serial Addition Test (PASAT) at 2 and 4 second presentation rates and the Hospital Anxiety and Depression (HAD) scale. In addition, objective daytime sleepiness was assessed by multiple sleep latency test (MSLT; Carskadon *et al*, *Sleep* 1986;9:519–24). Following CPAP therapy, there were significant improvements in the patients' performance on the Digit Symbol Substitution Test ($p < 0·05$) and in the 4 second PASAT ($p < 0·05$) but in none of the other psychometric tests. The MSLT did not change after CPAP. Two of 9 patients showed borderline scores for anxiety and depression on the HAD scale. These did not improve following CPAP therapy. The results of this pilot study suggest a recovery of complex visuomotor performance skills and sustained concentration ability after starting CPAP therapy.

## The relaxation time constant of sniff transdiaphragmatic pressure in myotonic dystrophy

AT COLE, DPS SPENCE, H HALL, M WARRENER, MDL MORGAN *Depts of Respiratory Medicine and Clinical Measurement, Glenfield General Hospital, Leicester* Slowing of the relaxation rate of sniff trans-diaphragmatic pressure (Pdi) has been observed to follow fatigue of the respiratory muscles (Levy *et al*, *Am Rev Resp Dis* 1984;130:38–40). For analysis the expression of the relaxation rate as the time constant (t) is favoured since it is independent of amplitude. Myotonic dystrophy (MD) is a disorder of relaxation which can affect the respiratory muscles. We have compared the sniff Pdi time constant in 5 patients with MD (age 26–62 years) to 9 normal subjects (age 24–38 years). Sniff Pdi was derived from gastric and oesophageal balloons and the subtracted trace recorded on paper. Five reproducible sniffs from FRC were recorded from each subject and digitised to obtain the mean exponential decay time constant for the lower half of the curve. Reproducibility experiments on one subject performed on three occasions showed an intra-observation variability of 12·7% and inter-observation variability of 3·8%. In patients with MD, (t) was significantly prolonged ($p = < 0·05$) median 95 ms (range 60 ms to 119 ms). Compared to normal, median, 57 ms (range 46 ms to 93 ms): Mann-Whitney U. In three patients with MD the measurements were repeated at least 90 minutes after a single oral

dose of procainamide (500 mg). In each case there was a reduction in (t) (Δ −9 ms to −59 ms). In two patients measurement repeated after 1 week of regular treatment (250 ms tds) demonstrated continued improvement (Δ −71 ms and −28 ms). These data confirm the prolongation of the time constant of sniff Pdi in MD and indicate that treatment with procainamide may return the value towards normal.

### The effect of metacholine challenge on the power spectra of asthmatic breath sounds

DPS SPENCE, S BENTLEY, DH EVANS, MDL MORGAN *Depts of Respiratory Medicine and Clinical Measurement, Glenfield General Hospital, Leicester* In order to devise a method of monitoring changes in airway calibre as a non-invasive instrument for the study of asthma we have sought to define a relationship between the breath sound spectrum and $FEV_1$. Breath sounds were recorded in a soundproof room during tidal respiration before and during metacholine challenge in 6 asthmatic subjects on two separate days. Sounds were captured over the suprasternal notch and recorded digitally (Sony 1000 ES DAT) for off-line analysis. A real time spectrograph was displayed using a fast Fourier transform spectrum analyser to obtain a 9 second representative sample immediately prior to each $FEV_1$ measurement (F F Schlindwein *et al*, *Med Biol Eng Comput* 1988;**26**:228–32). For each spirometric measurement the mean power (arbitrary units) and mean frequency (Hz) of the corresponding breath sounds were derived. In 11 out of 12 challenges at the PD20 there was an increase in mean power and the power/frequency product and in each case the mean frequency (mean Δ323 (287) Hz). However, the starting sound frequencies within and between patients were widely different (range 204–627 Hz) and did not correspond to $FEV_1$. Furthermore, there was no correlation of power or frequency with $FEV_1$ and no reproducible level of $FEV_1$ at which wheeze appeared. These results suggest that even with digitally recorded breath sounds the relationship between airway calibre and sound spectra remains elusive.

### The effect of oxygen on ventilation and breathing pattern of patients with chronic renal failure during haemodialysis

JCH YAP, YT WANG, SC POH *Department of Medicine III, Tan Tock Seng Hospital, Singapore* Hypoxemia during haemodialysis is a well known phenomenon in patients with chronic renal failure. Many studies have demonstrated that the two main mechanisms responsible for the fall in arterial oxygen tension ($Pao_2$) are alveolar hypoventilation and ventilation-perfusion imbalance. The breathing pattern was shown to be irregular with apnoeas in the study by De Backer with a respiratory inductive plethysmograph (RIP) (*Am Rev Respir Dis* 1987;**136**:406–10). The aim of our study was to find out whether oxygen administration will abolish the irregularity in the breathing pattern during haemodialysis. We used the RIP to measure ventilation in 7 male patients with a mean (SD) age of 37·4 (8·1) years, over 2 hours of haemodialysis, with and without oxygen administration on 2 different days. Their blood gases were also monitored. The third day was studied without oxygen administration and haemodialysis. We found a significant mean (SD) fall in $Pao_2$ of 14·5 (7·1) mm Hg ($p < 0.01$) at the end of the two hour study. Their mean (SD) baseline pH was 7·393 (0·023). At the second hour, it became 7·418 (0·025) ($p = 0.03$). Their mean (SD) minute ventilation (VE) was decreased by 1·9 (1·1) l/min ($p = 0.02$). This was accompanied by a rise in mean (SD) expiratory time (TE) from 1·98 (0·46) to 2·56 (0·5) seconds and a fall in mean (SD) frequency of breathing (F) from 18·5 (3·9) to 14·6 (2·4) breath/min ($p < 0.01$). On the day of oxygen administration, there was no significant fall in VE (0·5 (0·9) l/min) or F (0·7 (1·9) breath/min). The increase in TE however remained significant ($p = 0.05$). There was significant improvement in pH ($p = 0.04$). No significant change in arterial carbon dioxide tension ($Paco_2$) was present on both days. Although oxygen administration abolished the hypoxemia, the breathing pattern remained irregular with episodes of central apnoea. In addition, we also found an unexpected number of central apnoeas with irregular breathing on a non-dialysis day. We postulate that $Paco_2$ is more important than $Pao_2$ in determining the stability of the breathing rhythm.

### Fatigue of the adductor pollicis induced by repetitive submaximal voluntary contractions—a model for respiratory muscle fatigue?

N CARROLL, H GIBSON, RHT EDWARDS, PMA CALVERLEY *Muscle Research Centre, Department of Medicine, University of Liverpool, PO Box 147, Liverpool L69 3BX* Respiratory muscle fatigue is thought to occur during acute ventilatory failure and has been demonstrated in patients weaning from assisted ventilation. Respiratory centre output as reflected by mouth occlusion pressure (P0·1) has been found to be reduced in such patients. Whether this is because the fatigued muscle cannot respond, develops central fatigue which prevents response, or is behaviourally adjusted to limit discomfort is not known. We have used the adductor pollicis as a well studied model to assess the influence of muscle fatigue on voluntary contractions. Seven subjects (4 M) performed repetitive submaximal contractions with a duty cycle of 0·5 and a frequency of 15/min to a target force of 75% of maximal voluntary contraction (MVC). This activity ended when the subject was unable to achieve 75% MVC on three consecutive contractions. A programmed stimulation electromyogram was performed before and 1 min after the study. The force rise in the first 100 msec of a submaximal contraction (F1) as determined by analogy with P0·1 was measured, as was the time taken for the voluntary contraction to decline by 50% (SF50). Submaximal contractions were continued for 9 (2·8) mins. Fatigue occurred with a fall of 18 (5·3)% stimulated force at 100 Hz with relaxation (MRR) slowing from 10·9 (0·6) to 6·6 (1·3)% force/10 msecs. Contraction as reflected by F1 was unchanged from beginning to end of the study whilst voluntary relaxation slowed. SF50 increasing from 0·13 (0·02) to 0·2 (0·03) seconds. These data suggest that fatigued muscle can contract normally after both voluntary and involuntary stimulation although relaxation rates slowed in each case. High levels of occlusion pressure could occur when low frequency fatigue is present whilst the low P0·1 seen during weaning may be due to central rather than peripheral mechanisms.

### Is computerised *x* ray planimetry a reliable measure of lung volumes in normal subjects?

D SPENCE, J AHMED, A SUMNER, PMA CALVERLEY, MG PEARSON *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Static lung volumes are usually measured either by a helium dilution method or in a body plethysmograph but both these techniques produce significant under and over estimates of lung volumes in patients with severe COPD. *X* ray planimetry provides an alternative and when computerised can produce comparable results (Pierce *et al*, *Thorax* 1979;**34**:726–34). We have evaluated a newly available *x* ray planimeter which uses these principles and looked at the reproducibility of its measurements compared to other techniques. Twelve normal male volunteers (25–40 y) had standard PA and lateral chest radiographs taken breath holding at TLC and FRC whilst breathing into a spirometer. Radiographs were taken seated to make the technique comparable with other measures. Two physicians (A & B) estimated lung volumes planimetrically from these radiographs whilst a technician (C) repeated the lung volume measurements on each film on three different days. Lung volumes were measured on the same day by steady state helium dilution and in a constant volume body plethysmograph both seated and with arms elevated to mimic the radiographic posture. All equipment was supplied by P K Morgan Ltd, Kent.

| *Observer* | *A* | *B* | *C* | *He* | *Box* |
|---|---|---|---|---|---|
| TLC | 8·09 (0·84) | 7·51 (0·99) | 8·49 (1·2) | 6·29 (1·2) | 6·45 (1·0) |
| FRC | 4·89 (1·1) | 4·85 (1·2) | 5·0 (1·4) | 3·0 (0·83) | 3·27 (0·78) |

Helium dilution and box volumes at both TLC and FRC were in close agreement but differed significantly from planimetry. Reproducibility between days for a single observer was good (CV 4·7%) but was worse between observers (CV 7·5%). Elevation of the arms did not effect box lung volumes. Although differences in thoracic tissue and blood volume may account for 1·2 l of the difference between the *x* ray and box values, our values suggest other factors must be present. Even when care is taken to standardise radiographic technique computerised planimetry has significant drawbacks and highlights the need for careful field trials before marketing new equipment for routine laboratory use.

### Hypoxia primes human alveolar macrophages for enhanced release of TNF and IL-1

AP GREENING, MH BAIN, M GORDON, NJ DOUGLAS *Department of Medicine, University of Edinburgh* Alveolar macrophages (AM) differentiate from the monocyte precursor in an environment of higher oxygen tension than other tissue macrophages. In

patients with a number of respiratory disorders, but particularly emphysema and fibrosing conditions, there are areas of the lung that have low ambient oxygen tensions. We have shown previously that culture of human AM under conditions of relative hypoxia for a period of 16 h or more primes them for an enhanced stimulated release of hydrogen peroxide. One explanation would be that hypoxia-induced synthesis of cytokines might act as an intermediary AM activator. We have examined the lipopolysaccharide (LPS) stimulated release of tumour necrosis factor (TNFα) and interleukin 1 (IL-1β). AM were obtained by bronchoalveolar lavage from 23 patients (16 men; 16 smokers, 4 exsmokers; mean age 57 y) at diagnostic bronchoscopy. AM were adhered for 1 h, washed and cultured for 20 h in sandwich boxes gassed to give environments of 21% $O_2$, 74% $N_2$, 5% $CO_2$ or 2·5% $O_2$, 92·5% $N_2$, 5% $CO_2$. They were cultured in RPMI 1640 supplemented by 5% LPS free foetal calf serum to which was added 0, 1, 10 or 100 ng/ml LPS. The cell free supernatants were assayed for TNFα and IL-1β by ELISA. There were no differences between the normoxic and hypoxic cultures for the unstimulated release of either IL-1β or TNFα. However, for stimulated cells (LPS 100 ng/ml), hypoxic culture primed for enhanced release ($p < 0·001$; Wilcoxon signed rank test) of both IL-1β (n = 23) and TNFα (n = 19). We conclude that environmental hypoxia can prime AM for an enhanced stimulated release of IL-1β and TNFα.

| LPS (ng/ml) | IL-1β (ng/10⁶AM) 21%$O_2$ | IL-1β (ng/10⁶AM) 2·5%$O_2$ | TNFα (ng/10⁶AM) 21%$O_2$ | TNFα (ng/10⁶AM) 2·5%$O_2$ |
|---|---|---|---|---|
| 0 | 0·75 (0·1) | 0·7 (0·2) | 4·6 (1·2) | 5·3 (1·4) |
| 100 | 3·1 (0·8) | 5·4 (2·1) | 25·7 (6·6) | 30·7 (7·1) |

## Characterisation of a chloride channel from airway epithelium

EWFW ALTON, PJ SCHLATTER, SD MANNING, AJ WILLIAMS, DM GEDDES *National Heart and Lung Institute, Dovehouse St, London SW3 6LY* The unequal distribution of ions such as $Na^+$ and $Cl^-$ moving across epithelial surfaces through specific ion channels, results in consequent flux of water by osmosis. This process is likely to be involved in the regulation of the sol phase of airway secretions and in turn mucociliary transport. In cystic fibrosis both $Na^+$ and $Cl^-$ channels are abnormally regulated. We have therefore begun to study the characteristics of single chloride channels isolated from sheep trachea, a tissue very similar to that of human airways with respect to ion transport. Apical and basolateral membrane vesicles were separated by differential centrifugation and magnesium precipitation. Vesicles were added to planar phospholipid bilayers and fusion induced by high osmotic gradients in the presence of 2 mM $Ca^{2+}$. The most frequently seen anion-selective channel was characterised by subconductance states of 1/3 and 3/4 the fully open level. Selectivity for chloride over sodium was 7:1 and slope conductance 80 pS in symmetrical 200 mM NaCl. The channel was strongly voltage-gated and calcium-dependent with a minimum requirement of 100 μM free $Ca^{2+}$. The chloride channel blocker NPPB produced a dose-related flickering block at 10–50 μM, with complete block at 100 μM. We have identified very similar channels from human airways suggesting that reconstitution of membrane vesicles into phospholipid bilayers may provide a useful technique for the study of the regulation of airway chloride channels.

## Endothelial dysfunction in isolated pulmonary arteries from chronically hypoxic rats

RM LEACH, CHC TWORT, JPT WARD, IR CAMERON *Division of Medicine, UMDS, St Thomas's Hospital, London SE1 7EH* The role of the endothelium in pulmonary arteries (1–2 mm) and arterioles (100–300 μm) from normoxic and chronically hypoxic (10% $O_2$, for 6 weeks) rats was studied using a small vessel myograph. Endothelial function was examined using acetylcholine which releases endothelium derived relaxing factor (EDRF) and serotonin which has both a direct contractile effect on smooth muscle and which may also release EDRF (Furchgott, Vanhoutte, *FASEB Journal* 1989;3:2007–18). In pulmonary arteries from control rats, precontracted with noradrenaline ($1·5 \times 10^{-6}$ M), acetylcholine ($10^{-5}$M) resulted in a 74 (6)% relaxation of the stable contraction (n = 8). Mechanical removal of the endothelium from the artery almost entirely abolished this relaxation, 4 (4)% (n = 8, $p = <0·01$) and chemical inhibition of the release of EDRF with *N*-monomethyl-L-arginine acetate (N-MMAA) reduced the relaxation to 26 (4)% (n = 4, $p = <0·05$). In arteries from chronically hypoxic rats, with an intact endothelium, the relaxation demonstrated was 46 (8)%, a significant reduction when compared with the control vessels (n = 13, $p = <0·05$). The contraction to serotonin ($2 \times 10^{-4}$ M), expressed as a percentage of the maximum $K^+$ depolarisation, in the pulmonary artery and arteriole of the control rats was 37 (4)% and 12 (2)% respectively (n = 23). The response was significantly increased ($p < 0·05$) following mechanical removal of the endothelium (104 (4)% and 54 (7)%, n = 8) or after preincubation of the vessels with N-MMAA (88 (5)% and 60 (4)% n = 4). Vessels from chronically hypoxic rats showed a similar significant increase ($p < 0·05$) in sensitivity to serotonin (89 (6)% and 51 (5)%, n = 19) when compared with control vessels. These results suggest that there is a defect in pulmonary artery endothelial function following prolonged exposure of rats to a hypoxic environment.

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## Steroid induces phenotypic changes in alveolar macrophage populations from patients with sarcoidosis

LSG MARIANAYAGAM, LW POULTER *Department of Immunology, Royal Free Hospital School of Medicine, London* Efficaceous therapy with inhaled budesonide is associated with changes in the proportions of phagocytes and antigen presenting macrophages identified with monoclonal antibodies (MoAb) (MA Spiteri *et al*, 1988). In this study we used in vitro methods to determine whether corticosterods can directly alter cell phenotype, and thus, by implication, cell function. Alveolar macrophages were obtained from 5 sarcoid patients and 5 normal volunteers by bronchoalveolar lavage (BAL). The cells were washed, resuspended in supplemented RPMI medium and incubated in vitro for 24 and 48 h with budesonide, at a concentration of $5 \times 10^{-4}$ mg/$10^5$ cells. Parallel control cultures, omitting budesonide, were also set up. At 24 and 48 h intervals, cells were harvested, viability assessed and cytospin preparations made. In all cases some cytospins were prepared prior to culture. The proportions of cell subsets were determined by immunoperoxidase methods with MoAb: RFD7, a marker for mature phagocytes and RFD1 identifying antigen presenting cells. Class II MHC expression was studied using MoAb $RFDR_1$. In sarcoids, culture with budesonide caused a fourfold increase over controls, in the number of $RFD7^+$ cells. In normals, a twofold increase was seen in RFD7 positivity. In both sarcoid and normal cells budesonide reduced expression of D1 by 48 h. Similar trends in D1 and D7 expression occurred in lymphocyte-free isolated subsets of $D1^+$ and $D7^+$ cells in normals. HLA-DR expression was raised by budesonide culture in sarccoid BAL, but down regulated in normals. These results show a direct effect of steroids on alveolar macrophage populations which may result in altered function.

## Albumin—a potential marker of disease activity in BAL fluid: its principal origin from lung lining fluid

M DUDDRIDGE, JD FENWICK, C WARD, S WILLIAMS, DJ HENDRICK, EH WALTERS *Chest Unit and Department of Medical Physics, Newcastle General Hospital, Newcastle upon Tyne* Albumin levels in BAL fluid are used as an index of disease activity and as a denominator in the expression of solute mediator concentrations. Urea is principally derived from the circulation at BAL (*Am Rev Respir Dis* 1989;**139**:A459). To investigate the origin of albumin found in BAL fluid, a 3 × 60 ml BAL was performed (middle lobe) 5 min after 1·48 MBq iv $^{125}$I-human albumin was given to 5 control patients (normal pulmonary function; age 27–72) and 5 asthma patients (baseline $FEV_1$ 39–82%; age 24–61) undergoing bronchoscopy. Venous blood was simultaneously sampled with the lavage. BAL albumin concentrations were measured by radioimmunoassay, plasma albumin by Hitachi continuous flow analyser, and BAL and plasma $^{125}$I-albumin marker by gamma-counter. $^{125}$I-albumin flux from the circulation into BAL fluid was determined and corrected for the flux accounted for by the low number of red blood cells (haemo-

| | | Aspirate 1 | Aspirate 2 | Aspirate 3 |
|---|---|---|---|---|
| Controls | Flux | 4 (0–15) | 2 (0– 7) | 2 (1– 9) |
| | Total | 79 (61–96) | 57 (45–95) | 41 (26–85) |
| Asthma | Flux | 4 (2–31) | 5 (2–18) | 16 (2–24) |
| | Total | 53 (18–104) | 48 (22–67) | 52 (19–54) |

cytometer count) present in each BAL aspirate (<1 μg/ml albumin rbc associated flux in 27/30 aspirates). Median (range) BAL albumin concentrations (μg/ml) are given and patient groups and aspirates compared using ANOVA. In the asthma group there was a significantly higher albumin flux from the circulation than in the controls ($p < 0.005$), with no aspirate effect. Baseline $FEV_1$, smoking status and age also influenced the albumin flux ($p < 0.05$). Albumin flux into the combined BAL aspirates would have accounted for 13% of the total albumin in 1 control patient (other four <3%), but >20% in 3 of the asthma patients (74% in one patient). In a "disease" group the albumin levels in BAL may not exclusively represent an epithelial lining fluid origin.

*RESULTS*

| | *CRP* | *$\alpha_1$AT* | *$\alpha_1$ACT* | *$\alpha_1$AGP* |
|---|---|---|---|---|
| Normal | <8 mg/l | <4000 μg/l | <600 mg/l | <1000 mg/l |
| Sarcoidosis | *15 (3) | 5050 (375) | 730 (80) | 1122 (62) |
| Active | 19 (5) | *5689 (742) | †860 (141) | 1162 (115) |
| Inactive | 12 (3) | *4605 (362) | †639 (92) | 1099 (81) |
| TB | *48 (7) | 5783 (928) | 777 (185) | ‡1883 (184) |
| Crohn's | *50 (17) | 5243 (890) | 642 (163) | ‡1665 (249) |

Mean (SE), *$p < 0.05$, †$p < 0.02$, ‡$p < 0.001$ Student's $t$ test.

## Effect of rhamnolipid on guinea pig (GP) tracheal mucus velocity (TMV) in vivo and in human respiratory epithelium (HRE) in vitro

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Rhamnolipid is a small hydrophobic molecule secreted by *Pseudomonas aeruginosa* which is present in secretions of patients with cystic fibrosis at concentrations up to 60 μg/ml. We measured its effect on anaesthetised GP TMV in vivo using radiolabelled erythrocytes. A single injection of 10 μg rhamnolipid in Ringers solution on to the tracheal mucosa reduced TMV to 27 (13) (SE) per cent of baseline by 20 minutes ($n = 7$, $p = 0.028$ cf controls of Ringers alone) with gradual recovery by 2 h. We further assessed its effect on GP tracheal epithelium and HRE from nasal brushings and resected turbinates by measuring in vitro ciliary beat frequency (CBF) using a photometric technique and by transmission electron microscopy (TEM). Rhamnolipid at 1 mg/ml and 250 μg/ml of Ringers slowed CBF of GP epithelium but doses of ⩽64 μg/ml did not. Rhamnolipid caused immediate CBF slowing of nasal brushings but only at doses ⩾64 μg/ml of Ringers. Mono- and di-rhamnolipid had equal effects. To assess the longer term effect of rhamnolipid, CBF of turbinate HRE in Medium (M) 199 was examined; CBF was modestly slowed by rhamnolipid at ⩾32 μg/ml (CBF test: 9·87 (0·41); Cont.: 11·48 (0·27), $p < 0.001$, $n = 7$) after 4 h with subsequent recovery at 14 h but further modest slowing at 24 h (CBF test: 10·2 (0·4); Cont.: 11·4 (0·3)). Tissue was more sensitive in Ringers than in M199. By TEM rhamnolipid exposed GP epithelium in vivo and HRE at the time of early CBF slowing in vitro were normal, as was ciliary ultrastructure. After 24 hours, turbinate tissue exposed to ⩾ 32 μg/ml displayed mitochondrial abnormalities. We conclude that clinically relevant concentrations of rhamnolipid immediately reduce TMV in vivo, but this may be independent of direct cilio-inhibition or epithelial damage. Longer exposure to rhamnolipid damages HRE ultrastructure.

## The acute phase response in sarcoidosis and other granulomatous diseases

NM FOLEY, AB MILLAR, NMCI JOHNSON, GAW ROOK, MW MCNICOL *University College and Middlesex School of Medicine and Willesden Chest Clinic, London*

Acute phase proteins such as C-reactive protein (CRP), alpha$_1$ antitrypsin ($\alpha_1$AT), alpha$_1$ antichymotrypsin ($\alpha_1$ACT) and alpha$_1$ acid glycoprotein ($\alpha_1$AGP) are released from the liver in response to trauma, infection and inflammatory diseases. CRP levels and the erythrocyte sedimentation rate (ESR) are usually normal in sarcoidosis but elevated in tuberculosis and Crohn's disease. We have measured the levels of CRP, $\alpha_1$AT, $\alpha_1$ACT and $\alpha_1$AGP in the serum of 86 patients with granulomatous diseases. Fifty six patients had biopsy-proven pulmonary sarcoidosis, 23 of whom were deemed on clinical grounds to have "active" disease. Sixteen patients had pulmonary tuberculosis (TB) and had measurements made prior to commencing treatment. Fourteen patients had Crohn's disease, six having clinical scores compatible with active inflammation. Mean CRP and $\alpha_1$AGP were higher in TB and Crohn's disease, but patients with sarcoidosis showed a marked rise in the levels of the protease inhibitors $\alpha_1$AT and $\alpha_1$ACT, which were significantly higher in patients with active compared with clinically inactive disease. This elevation of protease inhibitors and the fact that they are significantly higher in active disease suggests that there is an acute phase response in sarcoidosis and that it may play a role in the pathogenesis of this disease.

This project was sponsored by the British Lung Foundation.

## Nucleolar organiser regions in squamous metaplasia of the bronchus

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A simple silver staining technique (the AgNOR technique) that demonstrates nucleolar organiser regions associated proteins can be applied to tissue sections to show silver staining structures (AgNORs) in interphase cells. A number of studies have suggested that there is an increased number of AgNORs in squamous cells showing changes of intraepithelial carcinoma of the uterine cervix, which is a premalignant lesion (Egan *et al. Histopathology* 1988;**13**:561). It is thought that squamous metaplasia (SM) of the bronchus is a marker for increased risk of bronchial carcinoma. This study investigated the possibility that there may be an increase in the AgNOR count of bronchial epithelial cells showing SM in association with a carcinoma elsewhere in the lung. The AgNOR stain was applied to tissue sections of bronchial mucosa showing SM from nine pneumonectomy specimens for carcinoma (8 squamous carcinomas and 1 adenocarcinoma). Eight of these specimens were from male patients, age range 53–73 years. In all cases the area of squamous metaplasia studied was at least 1 cm from the nearest tumour margin. For each section, the number of AgNORs in 200 nuclei were counted and the mean value used in analysis. The mean (SD) AgNOR count was 3·08 (0·69) for SM cells compared to 2·64 (0·89) for adjacent normal respiratory epithelial cells ($p = 0.26$; NS). When the mean values for SM and respiratory epithelium were compared in individual patients (paired $t$ test) the difference was significant ($p < 0.05$) although small in degree. In 6/9 cases the metaplastic values significantly exceeded the normal epithelial values suggesting that some cases of SM show increased proliferative activity. However assessing the AgNOR count in cases of squamous metaplasia is unlikely to be useful in predicting risk of development of malignant carcinoma.

This study was supported by a grant from the Chest, Heart and Stroke Association.

## Endotoxin induces a redistribution of iron to the lungs—a contribution to ARDS?

JG HAY, RHT EDWARDS, MJ JACKSON *Department of Medicine, University of Liverpool*

A frequent precipitating event in the evolution of the adult respiratory distress syndrome (ARDS) is sepsis. Endotoxin appears to redistribute body iron by blocking the release of iron from reticulo-endothelial cells to the plasma (Kampschmidt *et al, Am J Physiol* 1965;**208**:68–72). The role of the lung in this redistribution is not clear. We have examined the changes in lung iron distribution following endotoxin. Two groups of 6 rats were studied, one group received a peritoneal injection of saline, and the other 1 mg *E coli* endotoxin (strain 0127: 13% butanol extract). Six hours later both groups received 0·25 ml of packed rat red blood cells previously labelled over a 10 day period with Fe-59 together with 0·25 ml I-125 labelled albumin. Both groups were sacrificed 20 hours later by exsanguination. The vascular space of the lungs was flushed with saline, and the whole lungs and 0·1 ml of blood counted for Fe-59 and I-125 activity. Endotoxin resulted in an increase in the ratio of Fe-59 counts in the lung to that in the blood (0·37 SD 0·21) compared with saline controls (0·18 SD 0·11, $p < 0.05$). There were no differences seen in the lung to blood albumin ratios following endotoxin (1·65 SD 0·17) compared with saline (1·55 SD 0·13). The lung to plasma iron ratio was still significantly elevated following endotoxin when corrected by the lung to plasma albumin ratio (saline 0·12 SD 0·07, endotoxin 0·22 SD 0·10, $p < 0.05$). Endotoxin therefore produced no evidence of lung injury as assessed by albumin space measurement, but redistributed iron to the lungs. Since iron is a potent catalyst of free

radical reactions, this redistribution may play a part in the evolution of ARDS.

### Neutrophils in the airways of cigarette smokers: in vitro adhesivity and chemotaxis

C SELBY, E DROST, D BROWN, K DONALDSON, W MACNEE *Unit of Respiratory Medicine, Department of Medicine (RIE), and Institute of Occupational Medicine, Immunology Unit, City Hospital, Edinburgh, Scotland, UK* Central to the current proteolytic theory of the pathogenesis of emphysema is an increased elastolytic activity in the airways of cigarette smokers, suggesting activated leukocytes. However, peripheral blood neutrophils (PMN), exposed in vitro to particulate cigarette smoke (Sm) do not show enhanced proteolysis as assessed by fibronectin (FN) digestion (MacNee *et al. Thorax* 1989;44:333). Leukocyte adhesion and movement is necessary to digest a FN matrix in vitro and probably also to damage airspace epithelium and interstitium in vivo. We therefore measured the chemotaxis of PMN and their adherence to monolayers of alveolar epithelial (A549) cells before and after in vitro Sm exposure (>98% cells excluding trypan blue). Chemotaxis of Sm-exposed PMN towards zymosan-activated human AB serum (ZAS) was similar to control cells (PMN 24·4 (1·8), Sm PMN 34·7 (2·4) cells/hpf). However $^{51}$Chromium labelled PMN exposed to PCS exhibited significantly less spontaneous adherence when compared to control PMN at 5 minutes (table) and 30 minutes ($p < 0·01$). In addition, the increased adherence of PMN following stimulation with phorbol myristate acetate (PMA) was blunted in the Sm-exposed cells (table). Moreover, Sm exposed PMN adherence to a FN matrix was also suppressed. Glutathione (3 $\mu$M) protected the PMA-stimulated adherence (22·4 (0·7)%) of Sm PMN to epithelial cells. We conclude that reduced adhesivity rather than impaired chemotaxis of Sm-exposed PMN may help to explain the failure of Sm exposure to enhance FN digestion by PMN. Alternative explanations are necessary to explain epithelial damage and excessive proteolysis seen in cigarette smokers' airways.

*% PMN adherent to A549 epithelial cells*

| *Condition* | *n* | *5 min* | *p** |
|---|---|---|---|
| Control | 11 | 19·7 (3·5) | |
| Control + PMA | 9 | 28·4 (4·6) | <0·01 |
| Smoke | 11 | 13·6 (2·6) | <0·01 |
| Smoke + PMA | 9 | 11·8 (2·7) | (>0·05 of smoke) |

Mean (SEM); *compared with unstimulated control (Wilcoxon).

### Physiological and histological correlates of pulmonary endothelium dependent relaxation in human chronic obstructive lung disease

AT DINH XUAN, TW HIGENBOTTAM, J PEPKE-ZABA, G CREMONA, CA CLELLAND, J WALLWORK *Papworth Hospital, Papworth Everard, Cambridge CB3 8RE* Endothelium-derived relaxing factors (EDRF) are potent vasodilators released by endothelial cells in a variety of vascular beds, including human pulmonary arteries. However, the role of EDRF-mediated pulmonary relaxation in human chronic hypoxic lung disease is unknown. We have therefore investigated pulmonary endothelium-dependent relaxation mediated by EDRF in 12 patients undergoing heart-lung transplantation for end-stage chronic obstructive lung disease (COLD). Pre-transplanted values of $FEV_1$, $Pao_2$, $Paco_2$ of these patients were 20 (4)% of predicted (range, 9–60%), 6·7 (0·5) kPa (range, 4·3–10·9 kPa) and 6·8 (0·5) kPa (range, 4·8–9·4 kPa), respectively. Control pulmonary arteries (PA) were obtained from 12 patients undergoing lobectomy for lung carcinoma. None of the control patients had evidence of COLD. All vascular rings were studied immediately after lung excision. PA rings from control patients dose-dependently relaxed to cumulative doses ($10^{-10}$ to $10^{-5}$ M) of acetylcholine (ACh) and adenosine diphosphate (ADP), achieving a maximal relaxation of 81·3 (3·9)% and 85·3 (2·6)% from precontraction with phenylephrine, respectively. By contrast, PA rings from COLD patients only achieved 41·1 (7·2)% and 47·6 (6·4)% of maximal relaxation with ACh and ADP, respectively ($p < 0·001$; compared to controls). There was a negative correlation between intimal thickening and maximal relaxation of COLD PA rings ($r = -0·60$; $p < 0·001$). The latter was also correlated with pre-transplanted values of $Pao_2$ ($r = 0·65$; $p < 0·05$) and $Paco_2$ ($r = -0·61$; $p < 0·05$) but not with those of $FEV_1$ ($r = 0·18$, NS). We conclude that pulmonary endothelium-dependent relaxation mediated by EDRF is impaired in patients with end-stage COLD, and suggest that such impairment may contribute to/or accompany the development of pulmonary hypertension in chronic hypoxic obstructive lung disease.

### Pulmonary endothelium derived nitric oxide is reduced but still present in human end stage lung disease

AT DINH XUAN, TW HIGENBOTTAM, J PEPKE-ZABA, G CREMONA, FC WELLS, J WALLWORK *Papworth Hospital, Papworth Everard, Cambridge CB3 8RE* Impairment of pulmonary endothelium-dependent relaxation is a hallmark of a variety of human end-stage chronic lung disease (Dinh Xuan *et al. Eur J Pharmacol* 1989;163:401–3; *Br J Pharmacol* 1990;99:9–10). In order to investigate the role of endothelium-derived nitric oxide (EDNO) in the pathogenesis of such impairment, we have compared the effect of the L-arginine analogue, NG-monomethyl-L-arginine (L-NMMA), a specific inhibitor of EDNO synthesis, on pulmonary endothelium-dependent relaxation of isolated pulmonary arteries (PA) obtained from 8 patients undergoing heart-lung transplantation (HLT) for end-stage lung disease. Control PA were obtained from 8 patients undergoing lobectomy for lung carcinoma, none of whom had evidence of chronic lung disease. All PA rings were studied immediately after lung excision. Endothelium-dependent relaxation to acetylcholine ($10^{-10}$ to $10^{-5}$ M) was markedly impaired in PA rings obtained from HLT compared to controls (maximal relaxation = 43·4 (11·8) vs 73·8 (5·8)% from precontraction to phenylephrine in HLT and control PA rings, respectively; $p < 0·01$). Pretreatment with L-NMMA ($10^{-4}$ M) caused a greater rise ($p < 0·05$) in tension in PA rings obtained from controls (20·4 (5·1)%) compared to HLT PA rings (7·4 (1·6)%). Furthermore, pretreatment with L-NMMA ($10^{-4}$ M) reduced pulmonary endothelium-dependent relaxation to ACh in PA rings from both controls and HLT patients (maximal relaxation = 44·6 (10·8)% and 12 (5)% in control and HLT PA rings, respectively; $p < 0·001$ compared to untreated rings). This implies that EDNO is still produced by pulmonary endothelial cells of patients with end-stage lung disease. However, since this production is markedly reduced compared to controls, we submit that such reduction may contribute to the elevated vascular tone in patients with end-stage lung disease.

### Effects of alpha adrenergic and cholinergic stimulation on cyclic guanosine monophosphate level of pig pulmonary vascular smooth muscle

J PEPKE-ZABA, TW HIGENBOTTAM, AT DINH XUAN, T KEALEY *Papworth Hospital, and Department of Clinical Biochemistry, University of Cambridge, Cambridge* Endothelium-derived nitric oxide (EDNO) causes vasorelaxation by increasing vascular smooth muscle (VSM) level of cyclic guanosine monophosphate ([cGMP]). In order to investigate the effects of alpha-adrenergic and cholinergic stimulation on cGMP level of pulmonary VSM, we have measured [cGMP], using a radioimmunoassay method (Steiner *et al. J Biol Chem* 1972;247:1106–8) in pig pulmonary artery rings obtained from 18 animals. In the first set of experiments (n = 10), the rings were studied under unstimulated (control) conditions, and at the maximal effects of phenylephrine (PE) and acetylcholine (ACh). [cGMP] (pmol/mg) under control conditions was 0·26 (0·1) corresponding to 0·68 (0·2) g of tension on the rings. However, with maximal contraction to PE (tension = 2·01 (0·2) g), [cGMP] = 0·36 (0·07) whereas relaxation with ACh (tension = 2·01 (0·2) g) elicited the same cGMP level (0·36 (0·1)), both of which significantly differed from control values ($p < 0·05$). Time-response curves of the effects of PE ($10^{-5}$ M), ACh ($10^{-6}$ M) and the alpha-1 agonist methoxamine (Mx, $10^{-3}$ M) on [cGMP] were obtained in the second set of experiments (n = 8). Both PE and ACh induced a significant ($p < 0·05$) rise in cGMP whose peak of concentration occurred at 45 s and 30 s after addition of the drugs, respectively. The corresponding level of cGMP were 1·41 (0·56) and 1·15 (0·5) for PE and ACh, respectively. By contrast, the alpha-1 adrenergic agonist Mx did not have any significant effect on cGMP level which remained unchanged from baseline. We conclude that a rise of [cGMP] accompanies both endothelium-dependent relaxation to ACh and contraction to PE. The absence of effects of Mx on [cGMP] suggests that the rise of [cGMP] induced by PE may be due to its alpha-2 component, whereas the alpha-1 component is responsible for the overall contractile effects.

### Thermic effect of food in patients with chronic obstructive lung disease

JH GREEN, MF MUERS *Department of Medicine, St James's University Hospital, Leeds LS9 7TF* Weight loss and malnutrition are common in patients with chronic obstructive lung disease (COLD) (Openbrier *et al. Chest* 1983;**83**:17–22), and weight loss may be secondary to an increased resting metabolic rate (RMR) (Goldstein *et al. Chest* 1987;**91**:222–4). While RMR is the major component of total energy expenditure in sedentary people, dietary-induced thermogenesis (DIT) accounts for 15–20% of the total (Ravussin, Bogardus, *Am J Clin Nut* 1989;**49**:968–75). The purpose of the present study was to quantify RMR and DIT, together with fuel oxidation rates (FORs), in patients with COLD. Eight patients and 6 healthy age-matched controls were studied after an overnight fast. Metabolic rate and FORs were calculated from measurements of respiratory gas exchange, urinary nitrogen and blood urea nitrogen. After a 1 hour baseline period they consumed a liquid meal (41·2 kJ/kg) and measurements were continued for a further 4 hours. The RMR of the COLD patients was higher than controls, 111·7 (13·7) *v* 81·7 (9·6) (SD) kJ/kg/24 hours ($p < 0·05$). DIT was observed in both groups but the integrated response was smaller in patients (9·6 (4·8)) than controls (15·8 (3·6%)) ($p < 0·05$). The major difference in FORs was a raised fasting fat oxidation in patients, providing 3·46 (0·98) compared with 1·95 (0·96) kJ/hour/kg in controls ($p < 0·02$). These data confirm an elevated RMR in COLD patients, but DIT was lower in these patients than controls. Although others have shown preferential use of glucose in fasting COLD patients compared with controls (Goldstein *et al. Chest* 1987;**91**:222–4), our data suggest preferential use of fat in these patients.

### The effects of mode of exercise on chest wall motion and the perception of breathlessness during progressive incremental exercise in normal subjects

LM COCHRANE, CJ CLARK, G FRAME *Department of Respiratory Medicine, Hairmyres Hospital, Glasgow* A previous study has shown that there is a greater reduction in end-expiratory lung volume (EELV) when running, compared with cycling (Henke KG, *et al. J Appl Physiol* 1988;**64**(1):135–46). Since diaphragm function is optimised by a reduced EELV, cycling may be associated with a decrease in diaphragm efficiency and hence a greater reliance on "thoracic" breathing. If true, this might explain the observed increase in breathlessness at equivalent levels of ventilation during cycling compared with treadmill exercise (Cochrane LM, Clark CJ. *Thorax* 1989;**44**: 885P). Eighteen healthy male subjects performed one progressive incremental test on the bicycle ergometer (BE) and one on the treadmill (TM) in random order within 7 days of each other. Chest wall displacement was measured by inductance plethysmography (Respitrace). There was no significant difference in the relationship of total chest wall displacement (rib cage + abdomen) with tidal volume (Vt) between the 2 modes of exercise (BE slope 20·2 (6·8) *v* TM slope 16·7 (9·1)). Rib cage displacement (RC) was also not significantly different on the BE and TM (slope RC *v* Vt 8·2 (4·2) and 9·4 (5·9) respectively). However there was a greater increase in abdominal displacement (ABD) on the BE compared with TM (slopes ABD *v* Vt 12·0 (6·7) *v* 6·3 (4·0), $p < 0·05$). The slope of breathlessness (modified Borg) with minute ventilation was significantly higher on the BE as compared with the TM (0·079 (0·02) *v* 0·069 (0·03), $p < 0·05$). In summary, there was no evidence of increased rib cage excursion during BE *v* TM exercise. However, abdominal volume displacement was significantly greater during cycling and may indicate a corresponding increase in diaphragm excursion. Alternatively the change in posture may have altered abdominal wall compliance. This study could not demonstrate a relationship between the differences in chest wall motion during the two modes of exercise and the altered perception of breathlessness.

### The St George's respiratory questionnaire—repeatability and sensitivity to change

PW JONES, FH QUIRK, CM BAVEYSTOCK, JG COLLIER, P LITTLEJOHNS *Division of Physiological Medicine and Depts of Clinical Pharmacology and Public Health Sciences, St George's Hospital, London* The St George's Respiratory Questionnaire (GRQ) is a 76 item questionnaire to quantitate the impact of diseases of airflow limitation on patients' lives. Its relationship to other measures in COAD is presented in another abstract at this meeting (Jones *et al*). To assess its repeatability, it was presented to 40 adult stable asthmatics two to four weeks apart. Their mean age was 45 years (range 21–80), mean $FEV_1$ was 78% predicted (range 33–113). The correlation coefficient (r) for the total GRQ score obtained on the two occasions was 0·93. To test the ability of the GRQ to change, it was completed twice, one year apart, by a separate group of 122 patients with chronic airflow limitation. On both occasions the patients performed spirometry and a 6 minute walk (6-MWD). They also completed the MRC Bronchitis Questionnaire and the Sickness Impact Profile (SIP)—a general health index. The patients mean age was 62 years (range 31–75), mean $FEV_1$ was 49% predicted (range 11–114). As a population, there was little mean change in measured variables over the year but there were differences in the way individuals changed: $\Delta FEV_1$ = 1 (13)% predicted; $\Delta FVC$ −3 (14)% predicted; Δ6 − MWD −3 (95) m; ΔMRC dyspnoea score 0 (1) grade; Δ total SIP score 0 (8)%; Δ total GRQ score 2 (13)%. Correlations (Pearson) between changes in total GRQ score and changes in other variables are tabulated:

| | *$FEV_1$* | *FVC* | *6-MWD* | *SIP* | *Dyspnoea* |
|---|---|---|---|---|---|
| r | 0·22 | 0·27 | 0·36 | 0·31 | 0·47 |
| p | 0·018 | 0·003 | 0·0001 | 0·0006 | 0·0001 |

The GRQ is a measure of "quality of life" with a high level of repeatability for this type of instrument. It demonstrates an ability to change with changes in disease activity, which is an important property for a measure designed to quantitate therapeutic response.

### The St George's respiratory questionnaire—a measure of "quality of life" for patients with airflow limitation

PW JONES, FH QUIRK, CM BAVEYSTOCK, P LITTLEJOHNS *Division of Physiological Medicine and Dept of Public Health Sciences, St George's Hospital, London* The St George's Respiratory Questionnaire (GRQ) is a 76 item questionnaire. Each item is weighted according to the degree of distress associated with the symptom or state described in the item. The weights were collected from 140 patients with asthma from six countries. The collection of the weights and the minimal influence of demographic and disease related factors on them has been described previously (Quirk and Jones, *Clinical Science*, in press). Separate scores are calculated for Symptoms, Activity and Impacts (including effects on social functioning and emotional factors). A total score is also calculated. Scores increase with worsening disease state, the most severe score in each category is 100%. The questionnaire was presented to 152 patients with chronic airflow limitation in whom the performance of the Sickness Impact Profile (SIP)—a measure of general health—has been described (Jones *et al. Am Rev Respir Dis* 1989;**111**:117–24). The patients also performed spirometry, a 6-minute walk (6-MWD) and completed the MRC Bronchitis Questionnaire and the Hospital Anxiety and Depression Scale. Their mean age was 63 years (range 31–76), mean $FEV_1$ was 48% predicted (range 11–114). Pearson correlations between total GRQ score and other variables are tabulated. A five component generalised linear model was calculated using responses to three items from the MRC Questionnaire: daily wheeze (the p value for this component of the model was <0·0001), three months daily cough ($p = 0·03$) and dyspnoea ($p < 0·0001$); together with 6-MWD ($p < 0·004$) and anxiety score ($p < 0·0001$). This model accounted for 69% of the total sum of squares in GRQ score. The GRQ is a single measure that reflects a number of factors related to chronic airflow limitation and the impact that these may have on patients' lives.

### A comparison of subjective and objective measurements of airflow obstruction

BR O'DRISCOLL, RJ TAYLOR, A BERNSTEIN *Wythenshawe and Hope Hospitals, Manchester* An increasing body of evidence suggests that pulmonary function tests may correlate poorly with a patient's subjective sensation of breathlessness (Wolkove N, *et al. Chest* 1989;**96**:1247–51). We have compared subjective and spirometric measurements among 20 patients with severe airflow ob-

| | *$FEV_1$* | *FVC* | *6-MWD* | *SIP* | *Dyspnoea* | *Anxiety* |
|---|---|---|---|---|---|---|
| r | −0·22 | −0·27 | −0·36 | 0·31 | 0·47 | 0·57 |
| p | 0·0002 | 0·0001 | 0·0001 | 0·0001 | 0·0001 | 0·0001 |

struction (6 asthma, 14 COPD; mean $FEV_1$ 0·89 l, mean FVC 2·2 l). All patients recorded breathlessness on a scale from 1 (not present) to 7 (worst possible). All patients received the following nebulised treatments at 9 am on sequential days in a random order, double blind fashion. (i) Saline 4 ml, (ii) salbutamol 5 mg, (iii) ipratropium bromide 0·5 mg, (iv) mixture of salbutamol and ipratropium. After each treatment, patients recorded their response on a scale from 1 (no benefit) to 7 (best possible). $FEV_1$ was measured before treatment and 30 minutes after each treatment. The baseline $FEV_1$ correlated poorly with the subjective breathlessness score (Spearmann correlation coefficient $R = -0·32$, $p = 0·01$). Although the subjective and objective measurements both showed the active treatments to be superior to saline ($p < 0·03$), the subjective response to treatment correlated poorly with the % rise in $FEV_1$ ($R = 0·27$, $p = 0·01$). Of the 80 treatments given, 23 produced an isolated subjective response (score 3–7 but $FEV_1$ rise <15%). Four treatments produced an isolated objective response. We conclude that subjective and objective assessments of airflow obstruction may differ in magnitude in individual patients. Both should be measured in clinical trials of bronchodilator drugs.

## Bronchial responsiveness to inhaled histamine and ultrasonically nebulised distilled water (USDW) in chronic airflow obstruction

DC WEIR, P SHERWOOD BURGE *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham B9 5ST* We have studied bronchial responsiveness to inhaled histamine and USDW in patients with chronic airflow obstruction, not clinically asthmatic, over a three week period as part of a trial of high dose inhaled corticosteroids. Patients were tested if their $FEV_1$ was >0·75 l prior to the test. Histamine responsiveness was determined by the method of Yan *et al* (*Thorax* 1983;**38**:760), to a maximum dose of 7·8 μmol histamine. Response to USDW was measured 3 weeks later by inhaling increasing volumes of the aerosol to a maximum of 310 litres. Response was measured as the volume of water delivered to the mouth causing a 20% fall in the $FEV_1$. Four of 73 patients showed a fall in $FEV_1$ <20% at a dose of 7·8 μmol histamine. In the 69 patients in whom a PD20 was obtained (mean $FEV_1$ 1·221) the geometric mean PD20 histamine was 0·43 μmol. There was a weak correlation between the baseline $FEV_1$ and the PD20 histamine, $r = 0·26$ $p < 0·05$. Sixty one patients had repeat PD20 measurements 6 weeks later after placebo therapy, in these the 95% range for repeatability was ± 1·4 doubling concentrations. PD20 USDW was obtained in 37 of 48 patients tested. In 11 patients the $FEV_1$ had fallen by less than 20% at the end of the test. The geometric mean PD20 USDW was 2·93 ml water (mean $FEV_1 = 1·23$). Once again a weak correlation was seen between PD20 USDW and $FEV_1$, $r = 0·33$, $p<0·05$. The correlation between the two methods of measuring bronchial responsiveness was not significant, $r = 0·26$. In this group of patients sensitivity to USDW is less than to inhaled histamine, and the poor correlation suggests that different mechanisms may be involved in the response to the two agents.

## Effects of carbohydrate rich versus fat rich meals on carbon dioxide production and walking performance in COPD patients

JP MOUNSEY, DN BENSON, J MORRIS, SJ COLES, J EFTHIMIOU *Osler Chest Unit, Churchill Hospital, Oxford* High calorie intakes, especially as carbohydrates, increase carbon dioxide production ($\dot{V}CO_2$) and may precipitate respiratory failure in patients with pulmonary disease. Energy obtained from fat results in less $CO_2$ than carbohydrate and may help avoid respiratory failure. This study compares the effects of a fat rich oral feed (Pulmocare) with a carbohydrate rich feed (Ensure-plus) on $\dot{V}CO_2$ and walking performance in patients with severe chronic obstructive pulmonary disease (COPD). Ten stable COPD patients ($FEV_1$ 0·65 (0·181)) underwent a six minute walk (6MW) before and 45 minutes after taking 920 calories of Pulmocare (P), Ensure-plus (E) or an equal volume of a non-caloric control fluid (C), on three separate study days, in a double blind randomised fashion. $\dot{V}CO_2$, minute ventilation ($\dot{V}E$), oxygen consumption ($\dot{V}O_2$), respiratory quotient (RQ) and arterial blood gas tensions ($PaO_2$ and $PaCO_2$) were measured before and 30 minutes after the test meal. The table shows the mean (SD) percentage changes of the measured variables following E and P and the significance of the differences between them as determined by the paired *t* test. There were no significant changes in any of the variables following C. The carbohydrate rich meal (E) resulted in a significantly greater increase in $\dot{V}E$, $\dot{V}CO_2$, $\dot{V}O_2$, RQ and $PCO_2$ and a greater fall in 6MW, compared with the fat rich meal (P). The change in $PaO_2$ following E and P, however, was similar. Baseline measurements were similar on the three test days. Fat rich meals increase $\dot{V}CO_2$ less than carbohydrate rich meals and may therefore be less likely to exacerbate respiratory failure in COPD patients. Furthermore, such meals may improve exercise performance and this improvement may in part be related to the lower $\dot{V}CO_2$.

*Mean (SD) percentage changes in measured variables*

| | $\dot{V}E$ | $\dot{V}CO_2$ | $\dot{V}O_2$ | RQ | $PaCO_2$ | 6MW |
|---|---|---|---|---|---|---|
| P | 14·1 (3·2) | 17·7 (4·1) | 6·9 (4·0) | 10·0 (2·5) | 0·1 (0·5) | −1·2 (2·5) |
| E | 18·8 (5·7) | 25·7 (5·4) | 9·9 (3·5) | 14·4 (3·1) | 3·9 (2·8) | −8·2 (3·7) |
| P | <0·02 | <0·001 | <0·05 | <0·01 | <0·05 | <0·001 |

## Low concentration oxygen delivery by nasal cannula

ADRIENNE MARTIN, ANNE BALLINGER, JOHN MOORE-GILLON *St Bartholomew's and Homerton Hospitals, London* We have assessed the effect of varying oxygen concentration and flow rate, whilst keeping total supplemental oxygen delivery constant, in chronically hypoxic patients ($SaO_2 \leqslant 90\%$). A Quantiflex air/oxygen mixer was used in 4 patients to deliver by nasal cannula 1 l/min $O_2$ in the form of 1 l 100% $O_2$ and 2 l 50% $O_2$. In a further 3 patients, 2 l/min $O_2$ was given as 2 l 100% $O_2$, 4 l 50% $O_2$, and 6 l 33% $O_2$. Oxygenation was recorded by oximetry (for $SaO_2$ %) and cutaneous electrodes (for $TcPO_2$). Increases in $SaO_2$ and $TcPO_2$ occurred at all flow/concentration combinations. Mean increment in $SaO_2$ with 1 l 100% $O_2$ was 6·8% and 5·7% with 2 l 50% $O_2$. Equivalent figures for $TcPO_2$ were 1·86 kPa and 1·15 kPa. With 2 l 100% $O_2$ and 4 l 50% $O_2$ figures were $SaO_2$ 7·3%, $TcPO_2$ 3·15 kPa and $SaO_2$ 6·1%, $TcPO_2$ 2·06 kPa respectively. With 6 l/min 33% $O_2$ mean $SaO_2$ increments were 5·4% and $TcPO_2$ 1·42 kPa. Conventional concentrators produce low flow/high concentration oxygen. The present study shows that intermediate flow/concentration devices might give acceptable relief of hypoxaemia, at least short-term. Such flow/concentration characteristics are offered by permeable polymer technology, suggesting the prospect of very simple, light and readily transportable equipment to aid the mobility of patients receiving long-term oxygen therapy.

## Respiratory sensation during $CO_2$ rebreathing and exercise in COPD

JE CLAGUE, MG PEARSON, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* Exertional breathlessness is the major symptom of COPD but its severity varies considerably between otherwise similar patients at the same workload. Biological variation in the ventilatory response to $CO_2$ ($\dot{V}E/PCO_2$) might account for these differences in exercise performance and perceived difficulty in breathing (IES) but we found no evidence of this in 11 normal subjects. We have now studied 11 stable COPD patients (age 63 yrs, $FEV_1$ 1·25 l). In each we measured the ventilatory ($\dot{V}E$), sensory (IES) and occlusion pressure (P0·1) responses to $CO_2$ during duplicate $CO_2$ rebreathes and the same responses to metabolic $CO_2$ production ($\dot{V}CO_2$) during progressive exercise tests both with and without an inspiratory resistive load of 10 cm $H_2O$. The unloaded $\dot{V}E/PCO_2$ was lower in COPD compared to normals (9·43 (4·8) *v* 19·7 (5·2) l/kPa) whilst the $P0·1/PCO_2$ and $IES/PCO_2$ responses were both higher. In COPD loading reduced the $\dot{V}E/PCO_2$ by 31% increased $P0·1/PCO_2$ by 82% but did not change the slope of the IES/P0·1 relationship. The ventilatory response to metabolic $CO_2$ during exercise ($\dot{V}E/\dot{V}CO_2$) was higher in COPD than normals but was uninfluenced by loading (34 (7)) free-breathing *v* 32 (9) l/min loaded. $P0·1/\dot{V}CO_2$ and $IES/\dot{V}CO_2$ slopes were greater with loading but IES/P0·1 was unaffected (0·59 (0·16) *v* 0·54 (0·18) units/cm$H_2O$ loaded, $p > 0·5$). There was no correlation between any measure of $CO_2$ responsiveness during rebreathing and the subsequent ventilatory or sensory responses to exercise. However the $P0·1/\dot{V}E$ slope during rebreathing, a measure of respiratory impedence was well correlated with the exercise $P0·1/\dot{V}E$ slope ($r = 0·84$, $p < 0·01$). These data show that in COPD perceived effort is well correlated with respiratory drive but the slope of the relationship is dependent on the test. Indices of neuromuscular ($P0·1/\dot{V}E$) rather than chemical drive ($\dot{V}E/\dot{V}CO_2$) are most relevant to exercise performance in these patients.

## Exercise tolerance and respiratory sensation in stable COPD

JE CLAGUE, MG PEARSON, PMA CALVERLEY *Regional Thoracic Unit, Fazakerley Hospital, Liverpool* We have previously shown that maximum exercise performance in normal subjects depends on the peak ventilation ($\dot{V}E$) achieved, the respiratory drive (reflected by the mouth occlusion pressure, P0·1) and inspiratory effort sensation (IES). We have now studied these responses in 11 subjects with stable COPD (age 63 y, $FEV_1$ 1·25 l). Progressive cycle exercise tests recording $\dot{V}E$, gas exchange, P0·1 and IES (Borg Scale) at 30 s intervals were performed free-breathing (fb) and with a 10 cm $H_2O$ inspiratory resistive load (IRL). COPD patients exercised for a shorter time than normals even when loaded (normals 11·5 min *v* 5·1 min COPD). Other peak comparisons with normals are shown below in SI units:

| | | $Pk\dot{V}E$ | $Pk\dot{V}CO_2$ | *PkIES* | *PkP0·1* |
|---|---|---|---|---|---|
| Normal | fb | 53·2 | 1882 | 4·6 | 10·2 |
| | IRL | 31·7 | 1243 | 6·5 | 17·1 |
| COPD | fb | 35·3 | 906 | 6·6 | 12·6 |
| | IRL | 19·2 | 507 | 7·0 | 16·1 |

Loading in normal subjects produced similar levels of PkP0·1 and PkIES to that in free-breathing COPD. Added loading in COPD reduced $Pk\dot{V}E$ but increased P0·1 further ($p < 0·01$). The product of IES × $\dot{V}E$ and P0·1 × $\dot{V}E$ no longer predicted when exercise stopped but COPD exercised to similar levels of IES with and without loading. $Pk\dot{V}E$ was not related to the chemical drive to breathe ($\dot{V}E/\dot{V}CO_2$ nor $P0·1/\dot{V}CO_2$). Maximum inspiratory mouth pressures (MIP) fell after loaded exercise (pre 61 (27) cm $H_2O$ to post 54 (31) cm $H_2O$, $p < 0·05$). These data show that loaded exercise can mimic the ventilatory loading of COPD. Maximum exercise performance in COPD is limited more by effort sensation than ventilation achieved. Further respiratory loading in COPD pushes respiratory drive to a point where muscle fatigue begins. Increasing dyspnoea acts to warn of this and promotes behavioural change which avoids it.

## Cardiopulmonary exercise capacity in patients with COLD and CAD: effect of salbutamol and oxitropium bromide

F VAN ERCKELENS, TH HÜRTER, CH REUPCKE, U KROBOK, TH EITELBERG, M SIGMUND, U DESCH, P HANRATH *Medical Clinic I, RWTH Aachen, FRG* In patients with both chronic obstructive lung disease (COLD) and coronary artery disease (CAD) cardiopulmonary exercise tolerance was measured to assess the benefits and adverse cardiac effects of inhaled salbutamol and oxitropiumbromide. Ten patients (1 f, 9 m, $\bar{x}$ = 62 y) suffering from COLD (mean $FEV_1$ 54·4% of predicted value) and CAD (3 two-vessel-, 7 three-vessel disease, mean ejection fraction 65%) underwent standardised spiroergometry. The following parameters were determined: maximal oxygen uptake ($\dot{V}O_{2max}$), carbon dioxide output ($\dot{V}CO_{2max}$), work load ($W_{max}$), minute ventilation ($\dot{V}E_{max}$) and heart rate (HR). By continuous measurement of gas exchange the anaerobic threshold (AT) was determined (V-slope method, Beaver *et al, J Appl Physiol* 1986;**76**:54; Wasserman *et al, Circulation* 1988;**78**:1060 to assess submaximal work capacity. Exercise test was performed before and after the administration of inhaled salbutamol (S), oxitropiumbromide (O)—with a dose of 0·2 mg each—and placebo (P). The study was carried out double-blind; the effects were compared intraindividually. Results: P improved $FEV_1$ by 2·8%, S by 12·9% and O by 11·4%. $\dot{V}O_{2max}$ was increased significantly ($p < 0·05$) following the administration of S (+28·1%) and O (+21·5%) compared to P (+9·7%). As for $\dot{V}E_{max}$ the same effect ($p < 0·05$) was shown (S: +17·5%, O: +18·1%, P: +9·5%; no significant difference between S and O for both parameters). Heart rate response to maximal work load was not markedly influenced by S (+3·8%), O (+3·6%) and P (+1·2%) compared to the preceding exercise test before the administration. S and O caused a significant increase ($p < 0·05$) of $W_{max}$ (S: +16·7%, O: +19·6%, P: +8·1%) and AT (S: +29·6%, O: +25·8%, P: +6·4%) versus the effects of P (no significant difference between S and O for both parameters). Stress ECG revealed neither additional exertional ST-T-wave changes nor aggravation of preexisting arrhythmias after bronchodilatation by S or O. Conclusion: In patients with both COLD and CAD inhaled salbutamol and oxitropiumbromide markedly improved cardiopulmonary work capacity. Adverse cardiac effects, eg an increase of exercise-induced ECG-changes or arrhythmias could not be detected.

| | *Baseline reversibility to S or I* |
|---|---|
| 1) 15% increase in $FEV_1$ | (>200 ml) SE = 27%, SP = 80% |
| 2) 20% increase in $FEV_1$ | (>400 ml) SE = 20%, SP = 93% |
| 3) 15% increase in FVC | (>350 ml) SE = 29%, SP = 71% |
| 4) 20% increase in FVC | (>700 ml) SE = 17%, SP = 86% |

## Laboratory tests do not predict response to home nebuliser therapy

JM GOLDMAN, C TEALE, MF MUERS *Respiratory Unit, Killingbeck Hospital, Leeds LS14 6UQ* Two small studies have shown little correlation between laboratory tests of reversibility to nebulised bronchodilators and home assessment of benefit using serial peak flow recordings (*Thorax* 1989;**44**:845P, *BTS* Winter 1989:P152). We report the results of 100 trials using both home and laboratory measurements in patients referred for nebuliser assessment. Fifty five men and 43 women were studied mean age 66 (range 35–84) years. Mean baseline $FEV_1$ 0·9 (SD = 0·41) l, FVC 2·0 (SD = 0·74) l, PEFR 169 (SD = 77) l/min. Ninety trials were suitable for analysis (3 patients died, 3 made inadequate PEFR measurements and 4 received courses of steroids). Each patient attended for baseline measurements followed by an assessment of reversibility to salbutamol 5 mg (S) followed by ipratropium 0·5 mg (I). They were then supplied with a nebuliser and a PEFR meter to make twice daily measurements for 3 weeks. They continued their normal medications and, for a week each, nebulised normal saline (P), S and S + I 4 times daily. After each week laboratory measurements of spirometry and PEFR were made. A positive trial was defined as a 15% increase in mean PEFR over a week of S or S + I compared to a week of P. By this criterion 28 trials were judged positive. A variety of parameters were assessed for ability to predict a positive trial and are displayed in terms of sensitivity (SE) and specificity (SP). The change in the weekly measurements of spirometry and PEFR compared to baseline were also unhelpful with $FEV_1$ SE = 27%, SP = 80%, and PEFR SE = 57%, SP = 74%. We conclude that the above parameters are not useful in predicting response to home nebuliser treatment and hence serial home measurements of PEFR must be made to assess the value of such therapy.

## The effect of inhaled beclomethasone dipropionate (BDP) on bronchial responsiveness to inhaled histamine in chronic airflow obstruction

DC WEIR, P SHERWOOD BURGE *Department of Respiratory Medicine, East Birmingham Hospital, Birmingham B9 5ST* We have examined the effect of inhaled BDP on bronchial responsiveness to inhaled histamine in a group of patients with chronic airflow obstruction, not clinically asthmatic. Histamine responsiveness was measured by the method of Yan *et al* (*Thorax* 1983;**38**:760) if the $FEV_1$ was >0·75 l. Measurements were made at least 12 hours after the last study medication, on the final day of each treatment phase. Patients refrained from oral bronchodilators for 12 hours, and inhaled bronchodilators for 6 hours prior to testing. Patients received three weeks treatment with placebo, followed by BDP 1500 μg or 3000 μg per day in a single blind, sequential trial. Sixty five patients, aged 49–78 (mean 66) years, were studied. There was no significant change in either $FEV_1$ or log $PD_{20}$ values with treatment. Only 4 patients showed an improvement of more than 2 doubling concentrations of histamine over baseline and placebo after inhaled BDP. In this group of patients inhaled corticosteroids do not alter bronchial responsiveness over three weeks.

## Varicella-zoster infection in adults with cystic fibrosis: role of acyclovir

P MULVENNA, ELC ONG, AK WEBB *Departments of Chest and Infectious Diseases, Monsall Hospital, Manchester* Varicella is a common, usually mild and self-limiting childhood infection. The risk of serious pulmonary complications increases with underlying immunosuppressive disorders, pregnancy and amongst smokers. Three children with cystic fibrosis (CF) have been reported[1] recently in whom deterioration in pulmonary function coincided with varicella infection as

| | *Baseline* | *Placebo* | *BDP* |
|---|---|---|---|
| $FEV_1$ (litres, mean (SEM)) | 1·30 (0·05) | 1·27 (0·05) | 1·34 (0·05) |
| $PD_{20}$ (μmol, geometric mean) | 0·55 | 0·48 | 0·61 |

no antiviral treatment was given. We report a retrospective study of 5 adults (mean age 22, range 16–35 years, 3 males) with CP who developed varicella-zoster infection and were treated with acyclovir. All patients had symptoms on presentation; skin rash, cough with increasing sputum weight, breathlessness, fever and one male patient had severe diarrhoea. Two male patients had herpes zoster and the other three had varicella. All were colonised with multiresistant *Pseudomonas* species (3 *maltophila*, 2 *aeruginosa*), and clinically had an infective exacerbation. High dose intravenous acyclovir (10 mg/kg 8 hrly) were given in all patients with additional anti-pseudomonal agents. Clinical improvement was noted within 72 hours in all but one patient who had worsening $FEV_1$ (decline of 10% predicted) until 4 weeks later. All other four patients had stable $FEV_1$, pre and post treatment. Our survey shows that varicella-zoster infection contributes to an infective pulmonary exacerbation in adults with CF and acyclovir is effective and well tolerated with other anti-pseudomonal agents.

1 MacDonald NE, Morris RF, Beaudry J. Varicella in children with cystic fibrosis. *Pediatr Infect Dis J* 1987;6:414–16.

## A study of *Aspergillus fumigatus* (AF) lung disease in cystic fibrosis (CF) patients in South Wales: I. Use of serum IgG to AF as a marker of AF disease; II. Evidence of increased exposure to AF among CF patients with substantial lung disease

M ALFAHAM, MC GOODCHILD, IA CAMPBELL, R NEWCOMBE, C PHILPOT, R FIFIELD, J EDWARDS *University of Wales College of Medicine* A spectrum of disease due to *Aspergillus fumigatus* (AF) was studied in 67 patients with cystic fibrosis (CF) (mean age (1 SD), 9·5 (6·2) years, range 0·5–27). Clinical lung function and laboratory tests were carried out, including measurement of serum IgG to AF (AFIgG) by ELISA (Edwards *et al*, *Clinical and Experimental Immunology* (in press)). Results were compared with those found in 23 normal subjects (age 18·8 (7·8), 4·6–31) and 42 patients attending a neurology clinic (age 10·3 (3·9), 1·6–15·5). Twenty nine CF patients (43%) showed a positive value for one or more of the following, as evidence of exposure to AF: AFIgG, precipitins, specific IgE, sputum culture and immediate skin reaction. AFIgG correlated with: age, $p < 0·01$; presence of Pseudomonas species in sputum, $p < 0·01$; Shwachman Score, $p < 0·001$; Chrispin-Norman score, $p < 0·001$. Other correlations were between AFIgG and AF specific IgE, $p < 0·001$ and AFIgG and degree of immediate skin reaction, $p < 0·01$. Seven of the 29 CF patients were known already to have allergic bronchopulmonary aspergillosis. These patients had the highest values for AFIgG and the worst values for lung function, Shwachman and Chrispin-Norman scores; serial measurements of AFIgG in 2 patients showed a positive correlation with disease activity.

## The CF genotype and the linked marker haplotypes in adult pancreatic sufficient patients

G SANTIS, L OSBORNE, R KNIGHT, ME HODSON *Department of Cystic Fibrosis, Brompton Hospital, London SW3* It has been suggested that the inheritance of a single mild mutation at the CF locus confers pancreatic sufficiency, while the inheritance of two severe mutations, such as delta $F_{508}$, results in pancreatic insufficiency. Thirty five adult PS patients (age 20–68 years, mean 30 years), nineteen of whom were siblings, were identified. There was complete concordance among all siblings for both pancreatic and pulmonary status. Two of the patients became pancreatic insufficient (PI) during the period of follow up, one at the age of 62 and the other at age of 53. The frequency of the delta $F_{508}$ mutation on PS chromosomes was 46%. This was significantly lower than in pancreatic insufficient (PI) CF chromosomes. Two of the patients were homozygous for the delta $F_{508}$ mutation while the remainder lacked the delata $F_{508}$ mutation on one or both chromosomes. The delta $F_{508}$ mutation was associated with a single haplotype for the polymorphic markers XV-2C, KM.19, pMP6d-9 and J44. The chromosomes lacking the delta $F_{508}$ mutation were associated with a range of different haplotypes. Although there was spectrum of pulmonary severity associated with the PS patients studied, a significantly greater number had very mild lung disease. This could not be explained by differences in the frequency of the delta $F_{508}$ mutation between PS patients with mild and severe lung disease. The identification of two adult PS patients who were homozygous for the delta $F_{508}$ brings into question the division of CF mutations into mild and severe. However, the strong family concordance for pancreatic status in this and previous studies strongly suggests that other genetic factors are relevant. Our results indicate that genes other than the CF gene influence the CF phenotype.

## High resolution computed tomography (HRCT) in adults with cystic fibrosis (CF) and mild pulmonary disease

G SANTIS, ME HODSON, B STRICKLAND *Department of Cystic Fibrosis, Brompton Hospital, London SW3* Thirty eight adult patients with cystic fibrosis (CF) (7·6% of adult clinic population) with an $FEV_1$ consistently within the normal range (>75%) were identified. All chest radiographs in this group of patients were evaluated in random order. In 17 patients the chest radiograph was normal, while in the remainder there was consistent evidence of bronchial wall thickening. Radiological features of bronchiectasis were present on the chest radiograph of only four patients. Involvement of the upper zones was seen in 87% of the chest radiographs, although 13% of the films showed sparing of the upper zones with involvement elsewhere. HRCT was performed in a group of 30 patients in whom the chest radiograph showed no evidence of bronchial dilatation. HRCT showed evidence of mild bronchiectasis in 77% of all patients and 65% of those whose chest radiograph was normal. However three patients had normal CT scans, while in four, there was evidence of only mild bronchial wall thickening. The appearances on HRCT were consistent and characteristic. Bronchial wall thickening involving the proximal upper lobe bronchi before becoming more widespread was the earliest abnormality seen. Lumen dilatation follows, initially in the upper lobe bronchi being always less pronounced than the wall thickening. The dilatation is always even and parallel. These features can distinguish CF from post infective bronchiectasis and bronchopulmonary aspergillosis. Ten of the patients studied were diagnosed late. In these patients, the chest radiograph underdiagnosed the presence of bronchiectasis, which was identified by HRCT in six. We conclude that the majority of adult CF patients with very mild pulmonary disease have evidence of mild bronchiectasis on HRCT. The changes are sufficiently characteristic to suggest the diagnosis in adults investigated because of mild but recurrent respiratory symptoms. Normal HRCT in adults does not, however, exclude the diagnosis of CF.

## The distribution of the delta $F_{508}$ mutation in adult CF patients with very mild or severe pulmonary disease

G SANTIS, L OSBORNE, R KNIGHT, ME HODSON *Department of Cystic Fibrosis, Brompton Hospital, London SW3* The frequencies of the delta $F_{508}$ mutation, the haplotypes at loci linked to the cystic fibrosis (CF) gene and clinical variables were compared between adult CF patients with mild and severe pulmonary involvement. Thirty four adult British CF patients (Group A) whose $FEV_1$ was consistently normal (>75% predicted) and whose chest radiograph was either normal or showed evidence of only mild localised bronchial wall thickening, were defined as having mild pulmonary disease. Twenty five adult patients (Group B), in severe respiratory failure, who either had, or were awaiting heart/lung transplantation ($FEV_1$ < 30%, oxygen saturation <80%, chest radiograph appearance of widespread severe bronchiectasis) were defined as having severe lung disease. Group A included 26 pancreatic insufficient (PI) and eight pancreatic sufficient (PS) patients, whilst Group B included 22 PI and 3 PS patients. The delta $F_{508}$ mutation was identified on a similar proportion of CF chromosomes in each group (72% *v* 78%) which was also comparable to the frequency found in clinically unselected populations. In each group, a similar proportion were homozygous for the delta $F_{508}$ mutation. There was no association between specific haplotypes for the polymorphic markers KM.19 and pMP6d-9 and the severity of lung disease. There was a trend for allele 2 for the marker pJ3.11 to aggregate with mild lung disease, although this did not quite reach significance. Although chronic sputum colonisation by *Ps aeruginosa* was significantly more common in Group B than in Group A, in a number of Group A patients this did not result in any progression of their pulmonary disease. None of the other factors known to influence the progression of lung diseae were significantly different between the two groups. We suggest that in patients homozygous for the delta $F_{508}$ mutation, genetic factors outside the CF gene influence the severity of lung disease.

## C-reactive protein in blood spots from patients with cystic fibrosis

SM CORDON, JS ELBORN, EJ HILLER, DJ SHALE *Respiratory Medicine Unit and Department of Paediatrics, University of Nottingham, City Hospital, Nottingham NG5 1PB, UK* Serum C-reactive protein

(CRP) is an acute phase protein indicative of the host inflammatory response to infection and antibiotic treatment in cystic fibrosis (CF). To be useful, repeated samples of venous blood are required, which may be unacceptable in infants. In order to overcome the need for repeated venepuncture an enzyme-linked immunosorbent assay was developed for use with dried blood spots (10 $\mu$l) collected on Guthrie cards. In 101 subjects (controls, CF and other inflammatory conditions) there was agreement between serum and blood spot samples; mean difference $-0{\cdot}6$ $\mu$g/ml, 95% CI $-3{\cdot}3$ to $2{\cdot}2$ $\mu$g/ml. Dried blood spots could be kept at $-70$, $-20$, $+4$°C or room temperature for 3 weeks and posting specimens to the laboratory has no effect on determined CRP. Serum, venepuncture blood spots and skin puncture blood spots were interchangeable as the sampling method and had no significant effect on CRP. In eight patients studied before and after a course of antibodies there was no significant difference between sampling techniques in the fall of CRP; mean reduction finger-puncture blood spot $18{\cdot}3$ $\mu$g/ml; venepuncture blood spot $20{\cdot}9$ $\mu$g/ml and serum $20{\cdot}9$ $\mu$g/ml. This method allows repeated sampling in young children in the clinic, ward or at home avoding the need for repeated venepuncture. It is also applicable to other bacterial infections and inflammatory conditions in infancy.

## Families' opinions on home intravenous therapy in cystic fibrosis (CF)

SF WYNN, FM CHEATER (introduced by DJ SHALE) *City Hospital, Nottingham, UK* The prognosis of patients with CF who develop chest infections has improved. The management of infection usually requires a two week hospital admission for treatment, which disrupts education and employment and is stressful. The advantages of home intravenous antibiotic treatment (HIAT) over hospital treatment have been reported (Gilbert *et al. Arch Dis Child* 1988;**63**:512–7). However, the responsibility of giving intravenous therapy at home in addition to the routine management of CF may prove too burdensome for the carers. We aimed to identify the practical and emotional difficulties for HIAT family carers; to examine their views about training for HIAT; to ascertain their needs for additional help and to determine their views, comparing HIAT with hospital treatment. Thirteen families in 3 Midland towns were studied. Semi-structured interviews were held at home. Eleven (85%) families felt they had been well prepared for HIAT and two adequately prepared. The main concern of carers was the potential to administer an incorrect dose of antibiotics and the major practical difficulty was that 3–6 hours/day were spent on HIAT alone. Nine (70%) of families found home treatment less stressful than hospital treatment. One carer found it more stressful and the remainder considered the methods equally stressful. All carers considered that HIAT was of great benefit to the lifestyle of the family compared with hospital inpatient treatment.

## Bacteria grown from sputum during serial admissions for infective pulmonary exacerbations in adolescent and adult cystic fibrosis

GE PACKE, ME HODSON *Department of Cystic Fibrosis, Brompton Hospital, London SW3* The results of sputum culture for bacteria were collected in 45 patients (24 males, 21 females) with cystic fibrosis (CF) during serial admissions to hospital for treatment of pulmonary infective exacerbations. The mean (SD) age of patients at the beginning of the period of observation was 20·5 (3·8) years. The mean period of observation was 5·4 (2·2) years. Sixteen patients died and 5 underwent heart-lung transplantation by the end of the period of observation. *Pseudonomas aeruginosa* was isolated from sputum in 43 patients, on one or more admissions, with mucoid strains of *P aeruginosa* additionally cultured in 42 patients. *Staphylococcus pyogenes* was isolated in 31 and *Haemophilus influenzae* in 28 patients. Other organisms were grown infrequently: *Bacteroides* in 6, *P cepacia* in 3, anaerobic bacteria in 3, *Proteus* in 2, *Klebsiella pneumoniae* in 2, *Strep pneumoniae* in 1 and *P maltophilia* in 1. A moving averages calculation was made on the data on each patient to create five observations for each patient and to facilitate comparison of changes in the number of organisms grown from sputum over time. This showed that there was no overall change in the number of bacteria grown in sputum over serial admissions (F test, p = NS). Similarly, there was no change in the frequency with which *P aeruginosa, H influenzae* and *S pyogenes* were grown from sputum with successive admissions. This suggests that once patients with CF reach the stage where they are requiring repeated admissions for treatment of pulmonary infective exacerbations the number of organisms grown from sputum does not change significantly over serial admissions.

## Costing an adult cystic fibrosis service

DL SMITH, AE DAVIES, PJ MILLIGAN, DE STABLEFORTH *Department of Respiratory Medicine, and Department of Pharmacy, General Unit Administration at East Birmingham Hospital, Birmingham B9 5ST* We have attempted to quantify all costs incurred by one hospital in the year 1989 in providing an adult cystic fibrosis (CF) service. Patient numbers registered with the CF clinic at East Birmingham Hospital (EBH) rose from 64 to 92 over the period and continue to rise at a similar rate. The average age was 22 years (range 14–30) with a male preponderance (1·14:1). Of the group of 92, 11 lived within the EBH District, a further 75 lived within the West Midlands Region and 6 elsewhere. All attended regular out-patient clinics. Forty seven patients required in-patient admission for an average of 11·6 days on a total of 100 occasions. One patient spent a total of 257 days in hospital and subsequently underwent successful heart-lung transplantation. In 1989 one further patient was successfully transplanted and two others died. The total cost of providing this service was £347 200. Staffing costs represented 27% of this total whilst the general service cost (the cost of attending or being in hospital) accounted for 33·8%. The provision of diagnostic and support services specific to CF and not included in the general service cost was 7·4% of the total. Consumable costs represented 31·7% of the total. In-patient drug costs included in consumables totalled £95 000, 85% of which represented antibiotics; 13·6% (£47 200) of the total cost to EBH was not funded by the NHS but by charitable sources. Outpatient drug costs, which are borne by the Family Practitioner Committee and are additional to the total cost to EBH, for the year were £216 000, 41% being for enzyme supplements and 43% for antibiotics. At present this health district receives no regional recognition or funding for providing this service.

D L Smith is supported by the CF Trust.

## Airways response to exercise and physiotherapy in cystic fibrosis (CF)

D BILTON, M DODD, B HIGGINS, J EVANS, A MACALLISTER, AK WEBB *Adult CF Centre, Department of Chest Diseases, Monsall Hospital; and Department of Respiratory Physiology, Hope Hospital, Manchester* Exercise (Ex) and Physiotherapy (consisting of the forced expiration technique and postural drainage) (FET + PD) can be complimentary in aiding sputum expectoration. We now examine their effects on the airways. During a study of 4 different regimens: 1) FET + PD alone for 20 mins, 2) Ex alone for 20 mins, 3) Ex for 10 mins followed by 10 mins FET-+ PD and 4) FET + PD for 10 mins followed by Ex for 10 mins; performed over 4 consecutive days in random order, maximum expiratory flow volume curves (MEFV) were obtained prior to and immediately post each treatment. Exercise consisted of cycling at 60% of previously assessed $VO_2$ max. Eighteen patients completed this study ($FEV_1$ 18–98% predicted). Baseline $FEV_1$ and FVC values did not change over the 4 day study period. $FEV_1$ and $FEF_{25}$ values increased significantly from baseline after 20 mins Ex (p 0·01, p 0·05 respectively). There was a positive correlation (r = 0·59 p 0·01) between the baseline $FEV_1$ and increases in both $FEV_1$ and $FEF_{25}$. FET + PD produced no significant change in $FEV_1$ immediately post treatment but a significant fall in $FEF_{26}$. It is notable that despite the bronchodilation achieved by exercise this was not associated with increased sputum expectoration. The order of the combination treatments did make a difference to the MEFV values. EX + FET + PD produced a net fall in $FEF_{25}$ and $FEF_{50}$ but FET + PD + EX produced no significant changes. As sputum is not expectorated as efficiently with exercise as with FET + PD, body box plethysmography was completed in 7 of the patients in the study to establish whether 10 mins Ex produced significant air trapping. This was not the case, the RV/TLC ratio did not change.

## Sleep hypoxaemia in cystic fibrosis—correlates with pulmonary function indices in adults

DL SMITH, W FREEMAN, RM CAYTON, DE STABLEFORTH *Department of Respiratory Medicine, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST* A simple measurement which accurately predicts the occurrence of nocturnal hypoxaemia in adult patients with cystic fibrosis (CF) would prove useful in the management of this condition. We have performed over-

night finger probe pulse oximetry ($Sao_2$) on 20 patients (11 male, mean age 22 yrs, range 19–30) with CF, whilst breathing air, on the night before discharge from hospital following a course of treatment for an acute respiratory exacerbation of CF. We have also measured a number of lung function parameters within 24 hours of each sleep study. The patients showed a wide range of severity:

| | Mean (SD) | Range |
|---|---|---|
| % predicted $FEV_1$ | 45 (23) | 18–108 |
| % predicted FVC | 69 (23) | 38–110 |
| Awake arterial $O_2$ (kPa) | 9·0 (1·8) | 5·7–13 |
| Awake arterial $CO_2$ (kPa) | 5·0 (0·9) | 4·0–7·4 |
| Asleep mean $Sao_2$ % | 93 (4) | 82–97 |
| Asleep min $Sao_2$ % | 83 (13) | 43–94 |

Correlation co-efficients between pulmonary function indices and nocturnal $Sao_2$ are shown:

| | Mean $Sao_2$ | Min $Sao_2$ |
|---|---|---|
| % predicted $FEV_1$ | 0·62 ($p < 0·01$) | 0·47 ($p < 0·05$) |
| % predicted FVC | 0·54 ($p < 0·05$) | 0·55 ($p < 0·05$) |
| % predicted TLCO | 0·61 ($p < 0·01$) | 0·41 (ns) |
| RV/TLC ratio | 0·64 ($p < 0·01$) | 0·52 ($p < 0·05$) |
| Resting awake: | | |
| Arterial $Po_2$ (kPa) | 0·84 ($p < 0·001$) | 0·64 ($p < 0·01$) |
| Arterial $Pco_2$ (kPa) | 0·81 ($p < 0·001$) | 0·78 ($p < 0·001$) |
| Arterial saturation % | 0·89 ($p < 0·001$) | 0·67 ($p < 0·01$) |

Like Versteegh *et al (Eur Respir J* 1990;3: 68–73), we have found the resting awake oxygen saturation to be the best predictor of nocturnal hypoxaemia in CF. In our group of adult patients an awake oxygen saturation of less than 94% predicted a significant risk of nocturnal hypoxaemia (mean nocturnal saturation of less than 90%).

DLS and WF are supported by the CF trust.

## Sleep hypoxaemia in cystic fibrosis—response to hospital treatment

DL SMITH, W FREEMAN, RM CAYTON, DE STABLEFORTH *Department of Respiratory Medicine, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST* We have performed overnight finger probe pulse oximetry ($Sao_2$) on 16 patients (9 male, mean age 22 yrs, range 19–29) with cystic fibrosis (CF) within 36 hours of admission and at discharge, during hospitalisation for acute respiratory exacerbations. All patients received therapy with intravenous antibiotics, to which their organisms were sensitive, together with physiotherapy. During all studies patients were breathing room air. Clinical improvement followed treatment in all patients. Changes in lung function and nocturnal $Sao_2$ are shown (mean values (SD)). In 3 patients minimum nocturnal $Sao_2$ measurements of 90% or less were eliminated by hospital treatment. We have shown nocturnal hypoxaemia before and after treatment of a pattern similar to that described in stable patients (Muller NL, *et al. Am Rev Resp Dis* 1980;121:463–9). We conclude that nocturnal hypoxaemia in CF is more severe during respiratory exacerbations and improves with hospital treatment.

DLS and WF are supported by the CF trust.

| | Pre treatment | Post treatment | p value |
|---|---|---|---|
| $FEV_1$ (l) | 1·4 (0·6) | 1·6 (0·7) | <0·05 |
| FEV (l) | 2·7 (1·0) | 3·0 (1·1) | <0·01 |
| Mean $Sao_2$ | 91 (6)% | 93 (3)% | <0·01 |
| Min $Sao_2$ | 79 (16)% | 84 (13)% | <0·05 |

## Patient selection in asthma trials—baseline values of asthma severity: the effects of existing treatment

AM EDWARDS *Fisons Pharmaceuticals, Derby Road, Loughborough, Leicestershire* The evaluation of any new therapy in asthma is dependent upon demonstrating improvement in asthma severity from baseline values. In a series of asthma trials, baseline values from 133 hospital or general practitioner centres involving 1949 patients are compared according to existing treatment. Asthma severity is measured by Pulmonary Function—$FEV_1$ at clinic visits: PEFR twice daily by patient: patients estimate of severity of four symptoms daily, night asthma, day asthma, cough, morning tightness: daily use of rescue bronchodilators. Inclusion criteria were based upon asthma severity in the baseline and existing treatment. Three groups were identified. A) Patients on bronchodilator therapy alone: B) Patients well controlled on bronchodilators and inhaled corticosteroids: C) Patients not well controlled on bronchodilators and inhaled corticosteroids. Group B had significantly better baseline values than Groups A or C for all measures apart from bronchodilator use. Group A was significantly better than Group C apart from day asthma and morning tightness. These data indicate that for trial purposes three discrete groups of patients can be identified based upon existing treatment and severity variables, specifically night asthma, cough and pulmonary function.

## The use of xamoterol in chronic airflow obstruction

JA ROBERTS, VF CHALLENOR, DG WALLER *Departments of Clinical and Immunopharmacology, Southampton General Hospital* Xamoterol is a new $B_1$-adrenoceptor partial agonist with positive inotropic effects which are of benefit in the treatment of mild to moderate heart failure. However, at higher doses $beta_2$ adrenoceptor blockade may occur. Xamoterol has been shown to adversely affect ventilatory function in some asthmatic patients. As chronic airflow obstruction (CAO) and ischaemic heart disease share a common aetiological factor, a deleterious effect on symptoms or lung function in patients with CAO would limit the use of xamoterol in clinical practice. We have used a double blind, randomised, crossover trial to examine the effect of xamoterol on airway function in 10 patients with CAO (defined as $FEV_1$/FVC 60% and 15% reversibility of $FEV_1$ and/or FVC). $FEV_1$, FVC and specific airways conductance (sGaw) were measured before and after exercise on three separate days, before treatment, after 7 days of placebo and after 7 days of xamoterol (200 mg bd). Symptom scores, exercise distance and morning and evening PEF were recorded, as was dose-response to salbutamol. Bronchial reactivity (BR) to methacholine was also measured in six patients before the trial and after each treatment. Results were compared by Student's paired $t$ test. There were no differences between placebo and xamoterol as assessed by $FEV_1$ ($t = 0·64$), FVC ($t = 0·68$), exercise distance ($t = 0·35$) or maximum response to salbutamol ($t = -0·04$). There was a significant increase in morning PEF ($t = -5·0$, $p = 0·001$). Results demonstrate that xamoterol did not alter baseline lung function, exercise tolerance or BR in these patients. Our results indicate that xamoterol given for the recommended dose for 7 days does not cause a deterioration in airway function or respiratory symptoms.

## Comparison of the bronchodilator, cardiovascular and hypokalaemic effects of fenoterol, salbutamol and terbutaline

CS WONG, ID PAVORD, J WILLIAMS, JR BRITTON, AE TATTERSFIELD *Respiratory Medicine Unit, City Hospital, Nottingham* In the late 1970s New Zealand experienced an epidemic of asthma deaths not seen elsewhere. Two recent case-control studies suggested that this increase in mortality may have been related to the use of fenoterol (Crane *et al. Lancet* 1989;i:917; Pearce *et al. Thorax* 1990;45:170). The possible mechanisms for this association were not examined; two possibilities are that fenoterol is less $beta_2$ selective or is marketed at a higher dose than other $beta_2$ agonists. We therefore compared the effects on the airways with the effects on plasma potassium and the cardiovascular system of 2, 6 and 18 puffs of fenoterol 200 $\mu$g, salbutamol 100 $\mu$g, terbutaline 250 $\mu$g and placebo by metered dose inhaler in 10 asthmatic subjects. Subjects were studied at the same time on four non-consecutive days. Measurements of $FEV_1$, $PD_{20}$, heart rate, QTc and plasma potassium were made before and after three doses of each drug given at 90 minute intervals. The change in $FEV_1$ with the cumulative doses of the three active agents was similar. Terbutaline caused a smaller increase in $PD_{20}$ than fenoterol and salbutamol ($p < 0·05$). Fenoterol at these doses caused a greater increase in heart rate ($p < 0·05$) and also caused a greater prolongation of the QTc interval and fall in plasma potassium than salbutamol and terbutaline. Thus our data demonstrate that for a given bronchodilatory effect fenoterol has more unwanted cardiac effects than salbutamol or terbutaline.

## Rationalising nebuliser trials

JM GOLDMAN, C TEALE, MF MUERS *Respiratory Unit, Killingbeck Hospital, Leeds LS14 6UQ* Home nebuliser therapy for chronic airflow limitation is expensive, we therefore perform trials to identify patients who will gain objective benefit. Such trials should ideally be cheap and simple. We have analysed the results of 100 consecutive detailed nebuliser trials to identify factors which will predict patient response and allow us to rationalise trial design. We have accepted the evidence that the best measure of response to home nebulised bronchodilators is serial PEFR recordings (*Thorax*

1989;44:845P, BTS Winter 1989:P152) In each trial twice daily PEFR measurements were made during consecutive weeks of nebulised saline (P), salbutamol 5 mg (S) and S combined with ipratropium 0·5 mg (SI), taken 6 hourly. Patients made a subjective assessment of their response to therapy after each week. A positive trial was defined as a 15% increase in mean PEFR over a week on active treatment compared to placebo. Our results show: 1) The predictive value of the patients assessments had a sensitivity (SE) of 87% and a specificity (SP) of 49%; hence patient preference does not predict response. 2) If the best of 6 PEFR measurements over 10 minutes was used as baseline instead of a run in week on P, then SE = 73% and SP = 50%; a run in week is necessary. 3) Of the 28 patients with positive trials, 9 responded to S and SI, 16 to SI alone and only 3 to S alone (of these 1 had a cold during administration of SI and the other 2 had no subjective benefit from S); a single week of SI would have as good a predictive value. In conclusion we would suggest the following protocol for nebuliser trials. Patients should measure their PEFR during a week of nebulised saline followed by a week of nebulised SI. Those who have an increase of 15% in mean PEFR over a week on active treatment should be supplied with a nebuliser unless they feel no subjective benefit. Had we applied this regime in 100 trials we should have supplied 25 nebulisers.

## Steroid trials in the assessment of reversibility of airflow limitation: a survey of current clinical practice of chest physicians

J WIGGINS, MD FEHER, AF LANT, JV COLLINS *Department of Respiratory Medicine and Therapeutics, Westminster Hospital, London SW1P 2AP* To evaluate how steroid trials are currently used in the assessment of reversibility of airflow limitation a postal questionnaire was sent to 355 physicians with an interest in respiratory disease. Two hundred and fifty three questionnaires were returned (71% response rate). Only two respondents did not undertake steroid trials. Of the remainder 75% prescribed 30–40 mg of oral Prednisolone. The most common (61% of respondents) treatment period was two weeks. A high dose steroid inhaler was sometimes used as an alternative by 31% of respondents. Although 71% of respondents made lung function measurements on several occasions before starting steroids and 76% made measurements during treatment, 78% assessed patients only once at the end of the trial to assess its outcome. Walking tests and comprehensive lung function tests were used infrequently. Weight, blood pressure and urinary glucose were measured less frequently after than before steroid treatment. Blood glucose and electrolyte measurements were uncommon after treatment. There appears to be no consensus for a "steroid trial" regimen and there are variations in the measurements made. Current practice may neither detect a true benefit of treatment nor safeguard patients. However, more detailed trials may be restricted by practical constraints.

## Factors affecting drug delivery from jet nebulisers to patients

ML EVERARD, AR CLARKE, AD MILNER *Department of Child Health, University Hospital, Nottingham. Fisons Research and Development, Loughborough* Previous work with jet nebulisers has concentrated on the effect of variables such as driving gas flow (DGF) and fill volume on the output from nebulisers. Surprisingly little work has been done to determine how these variables affect drug delivery to the patient. The dose inhaled is not simply dependent upon the nebuliser output. To address this problem and that of the effect of changes in tidal volume with age, in vitro studies using a starling pump to simulate the respiratory pattern of an infant and an adult were performed. For the "infant", drug delivery is directly dependent upon the tidal volume and aerosol concentration. Increasing the DGF from 4 to 8 l/min more than doubled the output of drug from the nebuliser but had little effect on the aerosol concentration. The total dose inhaled in a 5 minute period of continuous nebulisation increased by only 1/3 though the dose inhaled within the respirable range increased 4 fold. Halving the concentration of the solution by diluting it with saline halved the total dose delivered in 5 minutes. The total dose inhaled by the "adult" was greater. However, the aerosol is diluted by entrained air and the drug delivered per litre inhaled and per kilogram body weight is much lower. Increasing the DGF from 4 to 8 l/min produced a 70% increase in total drug delivered largely by reducing the quantity of air entrained. If more concentrated solution were available this would enable nebulisation periods to be shortened hence improving compliance with prophylactic therapy. They would also have a role in the treatment of older subject to compensate for the dilutional effects of air entrainment.

## Performance characterisation of the DeVilbiss Ultraneb 99 ultrasonic nebuliser

TR LEIGH, T NAZIR, J WIGGINS, D GANDERTON, JV COLLINS *Department of Respiratory Medicine, Westminster Hospital, London. Chelsea Department of Pharmacy, Kings College, London* The performance characteristics of the DeVilbiss Ultraneb 99 ultrasonic nebuliser, which has been used successfully in the diagnosis of *Pneumocystis carinii* pneumonia in AIDS patients, have not been fully documented (TR Leigh. *Lancet* 1989;2:205–6). The nebuliser has three variables: a butterfly valve regulating flow of air over the nebulising solution, an intensity control which regulates the amplitude of impulses from the ultrasonic transducer, and the volume of water used as the energy couplant. We studied the effect on nebuliser performance of changes in each of these variables and volume of solution to be nebulised. Nebuliser performance was assessed by measurement of 1) Nebulised particle size, using a Malvern particle sizer to derive the median mass diameter (MMD), and 2) Nebuliser output (derived from the rate of loss of nebulised solution). We found that MMD remained constant over a wide range of intensity and butterfly valve settings, (mean MMD = 5·0 $\mu$m, SD = 0·46). However, as nebulised solution volumes increased, a critical volume (proportional to the intensity setting) was reached, beyond which MMD values fell, and the nebulised particle size distribution changed from normal to bimodal. Further increases in solution volume resulted in an unrecordable nebuliser output. Couplant volume was found to have significant effects on nebuliser output. At maximum intensity, nebuliser output rose from 0·13 to 2·5 ml/min following a 40 ml increase in couplant volume. MMD did not change significantly over a wide range of couplant volumes (mean = 4·5 $\mu$, SD = 0·78). Success of sputum induction may be related to several factors, including nebulised particle size, nebuliser output, nebulised solution tonicity, and induced cough response. We have found MMD to remain constant over a wide range of nebuliser settings. However, for optimal nebuliser output a defined volume of couplant fluid is required, and this should be considered when setting up the equipment.

## Comparison of apparatus for home nebuliser therapy

EC SMITH, AH KENDRICK *Respiratory Department, Bristol Royal Infirmary, Bristol* Nebulisers and compressors now form part of the potential home-based therapy for asthmatics. A wide variety of compressors and to a lesser extent nebulisers are available. We have compared the performance of 12 compressors as supplied by manufacturers with their nebuliser. These were 1) Medic-Aid Portaneb 50, 2) Inspiron, 3) Aeroneb Standard, 4) Aeroneb Super, 5) DeVilbiss Pulmo-aid, 6) Sinclair Atomolette II, 7) Medix AC2000, 8) Medix Minor III, 9) Medix World Traveller, 10) AFP nebuliser NO1, 11) AFP traveller T01 and 12) Nebupump. The cost ranged from £65 to £145, excluding VAT. Compressors 7, 8 and 9 used a Cirrus nebuliser, compressors 1 and 12 an Acorn, compressors 10 and 11 a Microneb, compressor 2 used a Minineb whilst compressors 3, 4 and 7 used their own. Assessment of sound level, weight, static pressure, free flow, flow at the nebuliser and percentage volume used after 10 minutes for a 2·5 and 5 ml start volume were assessed. Particle size distribution was assessed using a Malvern Master Sizer MS20 laser. Sound level ranged from 50 to 67 dB, and weight from 2·1 to 4·1 kg. Static pressure ranged from 95 to 452 kPa (mean 311) and free flow ranged from 7·0 to 12·2 l/min (mean 9·3). Flow at the nebuliser ranged from 3·6 to 6·9 l/min (mean 5·6). The percentage volume nebulised at 10 minutes ranged from 30 to 67% (mean 44) and 17 to 44% (mean 31·3) for 2·5 ml and 5 ml start volume respectively. The percentage of particles under 5 $\mu$m ranged from 16% to 62% (mean 45·8) and was independent of time of nebulisation and starting volume. Seven of the compressor units complied to BS5742 or its European equivalent. We conclude that some compressor/nebulisers combinations may fall below the apparent requirements for particle size and flow rate (Moren *et al. Aerosols in Medicine*, Elsevier) although little clinical evidence is available supporting these requirements. We recommend caution in supplying any device which does not conform to accepted performance standards.

## An audit of nebulisation techniques in a major teaching hospital: scope for improvement

R MILROY, N CALDWELL, J MCCABE, SW BANHAM, F MORAN *Department of Respiratory Investigation and Pharmacy Department, Glasgow Royal Infirmary* In response to

numerous requests for advice about the optimal methods for administering drugs via a nebuliser we determined to audit the techniques currently used in this large teaching hospital. An open-ended questionnaire survey was used at a total of 41 locations (including the Casualty Department) in the hospital. The audit sought information on the following topics: drugs nebulised; sequence of drug administration; measurement of drug solution; diluent and fill volumes; driving gas and flow rate; duration of nebulisation; and nebuliser care and cleanliness. A range of drugs were used, the commonest being Salbutamol (100%) and Ipratropium bromide (66%). A number of areas of deficiency were highlighted. Water was used as the diluent by 20% of the respondents. The resulting hypotonic solution may cause bronchoconstriction. Fifty per cent of respondents used a total fill volume of $<4$ ml. This results in a significant amount of drug remaining in the nebuliser dead space volume. Sixty per cent of respondents used a flow rate of $<6$ litres/minute which would result in inadequate nebulisation. Equal numbers used air or supplemental oxygen as the driving gas. Thirty per cent of respondents did not wash or care for the nebuliser at all between periods of use. The wide variety of procedures observed for administering drugs via a nebuliser in this hospital appears unsatisfactory. Differences in administration technique were noted in all aspects of the nebulisation process. The results of this survey highlight the need for a standardised procedure for administering nebulised drugs. Compliance with such guidelines could be monitored by a follow-up questionnaire in the future.

## Casualty assessment of asthma at a district general hospital (DGH)

S DAVIES, SF MOSS, P LONGSTAFF, PW IND *Ealing Hospital, Uxbridge Road, Southall, Middlesex* Despite the importance of Accident and Emergency (A/E) departments in the treatment of exacerbations of asthma there is little published information. Deficiencies of assessment of asthma in A/E have been highlighted (Reed *et al. Thorax* 1985;**40**:897). We have examined retrospectively the assessment and treatment of asthma in A/E at a District General Hospital serving a catchment population of approximately 200 000. On hundred and twenty nine patients presented with asthma on 141 occasions over a 3 month period. Mean age was 27 years and 91 (75%) patients were under the age of 40. Forty three (30%) were aged $<16$ years. Forty six per cent of patients were Asian though they account for about 30% of the population. One hundred and fourteen (81%) attendances were between 1800 and 0900 hours. Details of history recorded by Casualty Officers were limited but previous admissions were noted in 49 (35%). Usual asthma treatment was recorded in 98 (70%). Examination usually included auscultation, in 128 (91%), but heart rate was recorded in 110 (78%). Pulsus paradoxus was noted in 8 patients. Difficulty in speaking was commented upon in 68 (49%). Peak expiratory flow (PEF) was recorded in 128 (91%) before treatment and in 74 (52%) after nebulised salbutamol. Chest X-ray was performed in 27% and arterial blood gases measured in 30%. Forty two patients (30%) were admitted. Of those discharged 45% received a course of oral prednisolone. A/E attendance with asthma was high compared with previous studies at Southampton and Leicester. Assessment of asthmatic symptoms and signs was improved compared to the original Southampton study by Reed. Objective recording of airflow obstruction and particularly prescription of oral corticosteroids was greater than in the subsequent Southampton reassessment. These results in a busy DGH are encouraging but further efforts at education and attention to PEF documentation are required.

## A profile of asthma admissions

P LAWFORD *Walsgrave Hospital, Coventry CV2 2DX* We reviewed 113 adults admitted with acute severe asthma over a 3 month period. Eleven readmissions were excluded leaving 102 patients for analysis. Mean age was 43 (range 12–85), 38 were male, and 9 were of Asian extraction. Seventy six arrived between 1600 and 0800 hours. Thirty one were current or ex-smokers. Twenty seven had never been seen in a hospital before because of their asthma: only 7 of these were taking oral or inhaled corticosteroid. Of the remaining 75, 43 had been an in-patient with asthma at some time in the past, 32 had attended a hospital clinic and 60 were on oral or inhaled steroid. Forty two of 75 (56%) were currently or had been under the care of the two Chest Physicians in the city. As far as it was possible to enquire 31/102 had received a course of oral steroid, or a change of dosage, either on their own or on their GPs instigation, in the month prior to admission. During the same period 42 patients made 43 visits to the Casualty Department 3½ miles away. Four were of Asian stock and the average age was 26 (range 2–77). Twenty nine (69%) attended between 1600 and 0800 hours, and 12 were visitors from outside the city. Twenty had mislaid or run out of bronchodilator inhaler and were given an inhaler and discharged to their GPs. Eleven of 42 were taking oral or inhaled steroid. Only 7 peak flow measurements were recorded (mean 118 litres/min), but 12 received nebulised Salbutamol. Thirty two of 42 were discharged and a copy of the casualty card, often illegible, was sent to the GP. Ten of 42 were referred on to the Walsgrave Admissions. Of these 1 was admitted to ITU; 3 never showed up. During the 3 months, autopsy on 2 patients who died suddenly at home revealed changes consistent with status asthmaticus.

## A compliance monitor for inhaled aerosol therapy in asthma

SM YEUNG, GM COCHRANE, SA O'CONNOR *Thoracic Medicine, Guy's Hospital, London Bridge, London SE1 9RT, UK & Research Engineering, Smith Kline Beecham R & D, The Frythe, Welwyn, Herts AL6 9AR* Patient compliance to inhaled aerosol therapy is difficult to assess other than by cannister weighing. Ten aerosol actuators (Allen and Hanburys Ltd) were modified to incorporate an electro-mechanical system that counted and displayed actuations on a Liquid Crystal Display which could be made blind to the patient. The counter can be pre-set to ignore actuations within a given refractory period, in this case 3 seconds. Battery lifetime of a minimum 120 days is achieved by using a 3V Lithium Manganese Dioxide battery. Usage assessed by the counter (C) was compared with the change in cannister weight (W) in the laboratory (L) and by 21 patients (P) who substituted the trial actuator and continued with their normal steroid or beta agonist therapy for 2–3 weeks. (C) and (W) correlated well in the laboratory ($r = 0{\cdot}99987$, $p = 0$*). There was more digression from the expected correlation in (P) ($r = 0{\cdot}93585$, $p = 0$*), probably owing to (i) continued use of a cannister after it was empty in 1 patient and (ii) reactuation within the refractory period in 3 patients, despite repeated instruction on MDI technique. Removal of these 4 outliers resulted in improved correlation ($r = 0{\cdot}98724$, $p = 0$*). The counter could be reset and the actuator reused following sterilisation. This study confirms the accuracy of this counter in validating compliance with inhaled aerosol therapy both in the laboratory and clinical settings with regular steroid and symptomatic beta agonist usage. Again the importance of correct inhaler usage and the need for compliance monitoring are highlighted.

*Confidence in limits = 95%.

## How well do children use dry powder inhalers?

PC SEDDON, DP HEAF *Alder Hey Children's Hospital, Liverpool* Dry powder inhalers are being increasingly advocated in asthma, as they require less exact coordination than aerosols, and avoid the use of chlorinated fluorocarbons. However, they require a finite minimum inspiratory flow to release the drug. We assessed techniques using, and measured inspiratory flow through, two currently available dry powder devices: Rotahaler (R) and Turbohaler (T) in 81 children in 10 yearly age bands from 2 to 11 years. After written instructions only, 17% (R) and 28% (T) of children used the inhalers correctly at the first attempt. With coaching, 65% (R) and 72% (T) achieved correct technique by the third attempt. After coaching, following a single inspiration, less than a quarter of the dose remained in the Rotahaler in 51% and Turbohaler in 88%. Mean (SD) peak inspiratory flow in litres/min for the Rotahaler was 101 (46) and for the Turbohaler 56 (21). Flow rates above 50 l/min (R) and 22 l/min (T) are known to be needed for maximal bronchodilatation when $\beta$-agonists are delivered by the two devices. These values were exceeded by 79% (R) and 90% (T) of children respectively. Adequate inspiratory flow was achieved by all children aged 5 to 11 years with T and R, by more children aged 3 and 4 years with T (19/22) than R (11/22), and by few 2 year old children with T (2/7) or R (1/7).

## Atrial natriuretic factor in acute severe asthma

G HULKS, A JARDINE, RM ANGUS, JMC CONNELL, NC THOMSON *Department of Respiratory Medicine and MRC Blood Pressure Unit, Western Infirmary, Glasgow, G11 6NT* Elevated plasma levels of atrial natriuretic factor (ANF) and related hormones associated with volume and pressor homeostasis are found in a number of cardiopulmonary disorders. The altered ANF levels are assumed to be a result of atrial stretching. We have previously demonstrated that elevated plasma ANF has a significant bronchodilator effect on the constricted asthmatic airway and

| | Admission | Day 2 | Day 5 |
|---|---|---|---|
| PEFR (l/min) | 110 (13) | 261 (22) | 327 (26) |
| PR (bpm) | 120 (3) | — | — |
| $Po_2$ (kPa) | 8·80 (0·48) | — | — |
| $Pco_2$ (kPa) | 4·61 (0·24) | — | — |
| Hct | 0·45 (0·01) | 0·42 (0·01) | 0·42 (0·01) |
| ANF (pg/ml; N = 5–50) | 43 (6) | 42 (6) | 33 (6) |
| PAR (μunits/ml; N = 9–50) | 81 (17) | 65 (24) | 69 (17) |
| $A_2$ (pg/ml; N = 3–12) | 29 (9) | 25 (14) | 24 (10) |

therefore wished to examine the dynamics of plasma ANF in acute severe asthma (ASA). The subjects were 13 patients (2 subjects admitted twice) mean (SD) age 36·9 (14·1) years admitted to hospital with ASA, defined as severe or new onset bronchospasm not responding to usual bronchodilator therapy and associated with a pulse rate (PR) of ≥100 bpm. On arrival in the Accident and Emergency Department (ie before treatment) 25 ml venous blood was withdrawn for the estimation of ANF, plasma active renin (PAR), angiotensin-2 ($A_2$) and haematocrit (Hct). Arterial blood gases (ABG) were measured on air and peak expiratory flow rate (PEFR) recorded. Patients were treated as thought appropriate by the attending physician and all measurements (except ABG and PR) were repeated on days 2 and 5 after admission. These results indicate that despite significant hypoxia and bronchospasm, there is no significant elevation of plasma ANF in ASA.

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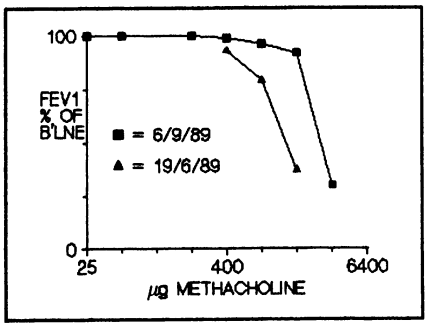
## An unusual response to methacholine

SC STENTON, JR BEACH, EH WALTERS, DJ HENDRICK *Chest Unit, Newcastle General Hospital, Newcastle upon Tyne, and University of Newcastle upon Tyne* A 22 year old, non-asthmatic male subject underwent a methacholine challenge test as part of a reproducibility study within an epidemiological survey of asthma. No asthmatic symptoms were recorded on a questionnaire and baseline $FEV_1$ was normal (5·6 l). A standard protocol (doubling cumulative doses of methacholine 3-6400 μg at 5 minute intervals) was used. Following the 3200 μg dose, the subject rapidly became breathless and wheezy. $FEV_1$ could only be measured with difficulty because of coughing and had fallen by 62% from the previous value to 1·7 l (30% of baseline). Following 200 μg salbutamol there was some immediate relief of symptoms and $FEV_1$ improved to 2·9 l (53% of baseline). $FEV_1$ was normal when remeasured at 2 hours and no symptomatic late reaction occurred. A very similar pattern of response had occurred to 1600 μg methacholine during the original test 3 months previously. Such marked bronchoconstriction at the higher dose levels of standardised methacholine challenge tests is extremely unusual in our experience. In the remainder of the study, the 1600 μg dose was administered 439 times. The mean fall in $FEV_1$ was 2·7% (SD 3·2) and the maximum fall 21%. The 3200 μg dose was administered 391 times. The mean fall was 2·6% (SD 3·3%, max fall 24%). It has been suggested that the dose-response curve to methacholine reaches a plateau in non-asthmatic subjects but this case illustrates that unusual and severe reactions do occasionally occur. These tests should be performed only under medical supervision with adequate facilities for urgent treatment.




## Failure to detect diurnal variation in airway responsiveness to methacholine

JR BEACH, SC STENTON, M DUDDRIDGE, EH WALTERS, DJ HENDRICK *Chest Unit, Newcastle General Hospital, Newcastle upon Tyne* It has been suggested that diurnal variation in airway responsiveness (AR) might underlie diurnal changes in ventilatory function in subjects with asthma, but it is also possible that refractoriness to repeated challenge with bronchoconstrictor agonists could have confounded the investigation of this problem. We consequently measured AR to methacholine in 24 subjects using a conventional dosimeter technique (doubling cumulative doses from 3–6400 μg at 5 minute intervals until $PD_{20}$.$FEV_1$ could be derived) at; 0800 on day 1, 0800, 1400, 2000 on day 2, and 2000 on day 3. We felt increasing values of $PD_{20}$ on day 2 could be explained either by diurnal change or by refractoriness, but that only diurnal change would duplicate the 0800 and 2000 hrs measurements of day 2 on days 1 and 3 respectively. As bronchoconstriction was reversed following each methacholine test using 200 μg inhaled salbutamol this dose was also administered 6 hours before the 2000 test on day 3, and approximately 8 hours before each 0800 test. Inhaled steroids were taken as usual. No subjects were taking oral beta agonists or theophyllines. Twenty subjects provided complete data, 17 of these had measurements performed on consecutive days. The results are shown in the table. The diurnal changes in $PD_{20}$.$FEV_1$ were small and not statistically significant (2 way analysis of variance, $F = 1·76$, $p < 0·1$). Diurnal variation is therefore unlikely to exert a major influence on the measurement of AR. The greatest difference in $PD_{20}$ was seen between the 0800 measurements on days 1 and 2 suggesting prolonged refractoriness to methacholine (>24 hours) may exert a more important effect.

| | Time/Day | | | | |
|---|---|---|---|---|---|
| | 0800/1 | 0800/2 | 1400/2 | 2000/2 | 2000/3 |
| Baseline $FEV_1$ | 2·73 l | 2·76 l | 2·93 l | 2·95 l | 2·93 l |
| Geom mean $PD_{20}$ | 61 μg | 81 μg | 87 μg | 95 μg | 84 μg |

## Effect of intranasal ipratropium bromide on curry induced rhinorrhoea

NB CHOUDRY, AJ HARRISON, RW FULLER *Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12 0NN and Boehringer Ingelheim, Bracknell, Berks RG12 4YS* Small studies have implied that rhinitis is caused by a pharyngeal-nasal reflex. We have studied this further in a group of 43 (27 (1) y, 15 F) normal volunteers ingesting a standard curry meal. The volunteers were selected for nasal symptoms following ingestion of curry. They first completed 7 visual analogue scales (VAS) related to nasal symptoms, cough and facial flushing. They then received a spray of either placebo or 40 μg ipratropium bromide (IPB) into each nostril. Thirty minutes later they all ingested the same amount of mutton nahrai over 10 minutes during which time they collected any paper tissues used for nasal clearance. Then at 60 minutes post-drug they again completed the 7 visual analogue scales. The scales for cough, sneeze, blocked and itchy nose and sweating were not changed by the curry. However, placebo VAS for runny nose, facial flushing and tissue use were significantly increased by the curry (Wilcoxon $p < 0·03$). IPB significantly inhibited the increase in the symptom of runny nose ($p < 0·05$) and halved the use of tissues but had no effect on facial flushing. The lack of effect of the curry on symptoms such as nasal itching and sneezing imply that the rhinorrhoea is due to a reflex and this was confirmed by the inhibition of ipratropium bromide on this symptom.

We wish to thank the chef at Chutney's, Drummond Street, London, for preparing the curry.

| | Placebo | IPB |
|---|---|---|
| VAS runny nose (mm) | 13 | 2* |
| VAS facial flushing (mm) | 18 | 13 |
| Number of tissues/person | 1 | 0·5 |

*$p < 0·05$
(median difference post − pre treatment).

## Quantitative features of acute respiratory failure

M STEVENS, M WILKINSON, GM ROCKER, DJ SHALE *City Hospital, Nottingham* The adult respiratory distress syndrome (ARDS) is becoming a less useful clinical description. It is likely that the currently defined state is the symptomatic and physiological manifestation of severe widespread lung injury. A variety of studies based on survival, inflam-

matory marker changes and prediction have suggested that there are no specific features to ARDS. We studied morphometric features in lungs of five patients dying in respiratory failure with risk factors for ARDS. The volume of interstitium and exudate were assessed by point counting. The proportions of cells, haemorrhage and cell free exudate were assessed. All patients required assisted ventilation. Transferrin accumulation was determined by the double isotope method. Results: The only significant quantitative difference was of a greater cellular content of the exudate in ARDS cases ($p < 0.01$). Four of the five sets of lungs showed a difference in the cellular content between right and left sides. Transferrin accumulation prior to death tended to relate to the volume of the interstitium. Conclusion: This study supports earlier studies with inflammatory markers and transferring accumulation in the lung, which demonstrated that ARDS was not a distinct pathophysiological entity.

### Arterial blood gases and lung spirometry in patients receiving long-term oxygen therapy (LTOT) for hypoxaemic chronic obstructive airways disease: changes over 2¼ years

MJ WALSHAW, C BLEASDALE, CC EVANS, CRK HIND *The Cardiothoracic Centre, Liverpool L14 3LB* Surveys from Durham (*Thorax* 1988;43:860) and Sheffield (*Thorax* 1990;45:195–8) have suggested that the $Pao_2$ whilst breathing air actually improves with time in those patients prescribed LTOT. Such changes were not seen in the original clinical trials (*Lancet* 1981;i:681–5; *Ann Intern Med* 1980;93:391–8). To study this question further, the 15 surviving LTOT patients with chronic obstructive airways disease in this district who were found on reassessment (whilst in a stable clinical state) in December 1987 to have a $Pao_2$ of < 7·3 kPa on breathing air were again reassessed in a stable clinical state in March 1990. The results are as shown in the table. The significant fall in haemoglobin levels suggests that patients were using LTOT appropriately. However, despite this evidence, there was no change in $Pao_2$ over 2¼ years in this group of carefully reassessed LTOT patients.

| | *Sept 1987* | *Mar 1990* | *p* |
|---|---|---|---|
| $Pao_2$ on air (kPa) [range] | 6·3 [5·1–7·2] | 6·4 [4·1–7·7] | NS |
| $Paco_2$ on air (kPa) [range] | 6·8 [4·7–8·7] | 6·9 [5·2–8·0] | NS |
| $FEV_1$ (litres) [range] | 0·56 [0·3–0·9] | 0·61 [0·3–1·2] | NS |
| FVC (litres) [range] | 1·31 [0·6–1·9] | 1·20 [0·7–2·0] | NS |
| Hb [range] | 16·1 [13·4–21·7] | 14·8 [12·2–18·9] | < 0·05 |

### Factors influencing survival on long term oxygen therapy (LTOT) for hypoxaemic chronic obstructive airways disease (COAD): a prospective study

MJ WALSHAW, C BLEASDALE, CC EVANS, CRK HIND *The Cardiothoracic Centre, Liverpool L14 3LB* Reassessment in December 1987 of the 55 patients with COAD in the Liverpool district prescribed an oxygen concentrator revealed that only 28 actually fulfilled the DSS criteria for LTOT (*Br Med J* 1988;297:1030–2). By March 1990, 11 of these 28 patients had died, one had received a heart-lung transplant, and one patient had moved to another district. The characteristics at December 1987 of the 15 survivors and 11 deceased patients were then compared, in order to determine what aspects of their disease or therapy might have influenced survival. We found that the deceased patients were significantly older and were less likely to use their supplementary oxygen at night ($chi^2 = 3.95$). No significant differences were found in daily oxygen use (as assessed by concentrator meter readings), $Pao_2$ on breathing air or supplementary oxygen, lung spirometry, or current smoking habits (table). These results suggest that patients with hypoxaemic COAD who use their LTOT at night are more likely to survive, and indicates the importance of encouraging nocturnal oxygen therapy in this group.

| | *Deceased* | *Survivors* | *p* |
|---|---|---|---|
| Age [range] | 70 [61–84] | 64 [56–75] | < 0·01 |
| Nocturnal $O_2$ | 7/11 | 15/15 | < 0·05 |
| Daily $O_2$ (h) [range] | 18 [10–24] | 15 [5·5–23] | NS |
| $Pao_2$ (air) (kPa) [range] | 6·1 [4·6–7·2] | 6·3 [5·1–7·2] | NS |
| $Pao_2$ ($O_2$) (kPa) [range] | 7·9 [6·3–9·7] | 7·5 [6·0–10·1] | NS |
| $FEV_1$ (litres) [range] | 0·45 [0·25–0·75] | 0·56 [0·30–0·90] | NS |
| FVC (litres) [range] | 1·2 [0·6–2·5] | 1·3 [0·6–1·9] | NS |
| Smoking habits | 2/11 | 5/15 | NS |

### Deaths and necropsies in a thoracic unit

DAR BOLDY, CH JONES, CW EDWARDS, H MATTHEWS *Departments of Respiratory Medicine, Histopathology and Thoracic Surgery, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST* Concern has been expressed by many pathologists about the decrease in post mortem (PM) examinations being performed over the last few years, because of the well documented inaccuracy of premortem clinical diagnosis (Cameron and McGoogan, *J Pathol* 1981;133:285). To examine our current practice, we studied prospectively all deaths under the care of 5 chest physicians and the 3 chest surgeons occurring between 1 April and 30 June 1989. There were 58 deaths (33 medical, 25 surgical): 13 were referred to the Coroner, 21 had a hospital PM requested and 24 had no request made for a PM. Of the 13 referred to the Coroner (2 trauma, 4 postop, 3 industrial, 4 unable to sign), 11 had a PM performed. Important unexpected findings were revealed in one patient (sudden death due to a myocardial infarction 10 days after a pneumonectomy). Twelve out of 21 (57%) requests for a hospital PM were granted: important unexpected findings were noted in 2 patients (lung abscesses due to multiple pulmonary emboli and sudden death due to acute left ventricular failure in a patient being treated for TB which was not confirmed by histology). Of the 24 patients in whom no PM was sought, 17 had proven carcinoma. One had presumed carcinomatosis and 6 medical cases had other pathology. Examination of the data revealed that PMs were not requested consistently on patients dying within the first month postoperatively, nor on acute medical patients dying within 2 days of admission from causes other than carcinoma. PM histology was taken in 20/23 cases and reports were available within 3 months in only 7 cases. In conclusion, the number of PMs requested was high (58·6%) and the rate of PMs performed was acceptable (39·7%). Important findings which could have affected outcome were noted in only 2/23 (9%) patients.

### Respiratory referral patterns within a major teaching hospital

SW WATKIN, JH CAMPBELL, F MORAN *Glasgow Royal Infirmary* Information relating to the spread of problems referred to respiratory specialists has implications for those involved in training for thoracic medicine as well as resource allocation. We prospectively recorded details of all referrals from other consultants to our unit over a 6 month period to quantify referral workload and analyse the pattern of referrals in terms of source, indication, disease group, level of specialist involvement required and impact on management. We analysed a total of 133 referrals all initially assesssed by a registrar from a bed complement of 850 total (220 general medical). Sixty nine (52%) of referrals were general medical patients, 9% general surgical, 18% medical specialties and 21% from surgical specialties. Some areas of the hospital with a high rate of respiratory problems, including intensive care, made fewer referral requests than expected. Forty one patients (31%) were referred specifically for practical procedures (37 bronchoscopy, 4 pleural biopsy). Thirty five per cent were referred primarily for help in diagnosis and 26% for advice on management of patients with known disorders. A further 4% in each case were referred for pre-operative assessment or for arrangements to be made for follow-up chest outpatient care. The 3 commonest diagnostic groups were bronchial carcinoma (20%), pneumonia (16%) and asthma (9%). The remainder fell into 15 respiratory diagnostic categories and 10 patients (8%) had a non-respiratory diagnosis. In 96/133 (72%) of cases alterations were made in diagnosis, management or chest x-ray interpretation as a result of the referral. These data reveal a significant influence of respiratory expertise on patient management. The study serves to emphasise such experience as an essential component in respiratory training.

### Microbial flora of the trachea during intubation in upper abdominal surgery

JP DILWORTH, RJ WHITE, EM BROWN *Department of Medicine and Department of Microbiology, Frenchay Hospital, Bristol* The lower respiratory tract is normally sterile in health. In the perioperative period reduced clearance of respiratory secretions produces ideal conditions for organisms aspirated from the oropharynx to cause infection. We have looked for

evidence of the transfer of pathogens from the oropharynx to the trachea during intubation. Twenty four patients undergoing upper abdominal surgery were studied. Using a protected brush, tracheal brushings were obtained immediately after intubation and at the end of operation, just prior to extubation. Patients were assessed postoperatively for the development of chest infection. In 15 patients there was significant growth of organisms (>10 colony forming units) from the post-intubation brush. In five of these *H influenzae* was isolated. There was a significant relationship between the growth of *H influenzae* and subsequent chest infection ($p < 0.05$). In only four patients were organisms isolated from the trachea in the pre-extubation brush and in two of these *H influenzae* was isolated. There was a significant relationship between the presence of *H influenzae* in the trachea prior to extubation and the development of infection ($p < 0.05$). All four patients with organisms isolated from both the postintubation and the pre-extubation brushes were current or previous heavy smokers. We have demonstrated the transfer of organisms from the oropharynx to the trachea during intubation. However, in the majority of patients this was transient and probably not of clinical significance. In those patients with *H influenzae* colonisation in the trachea there is a significant relationship to the development of chest infection.

### *Haemophilus parainfluenzae* as a respiratory pathogen

DA CAVAN, EG SMITH, JG AYRES *Departments of Respiratory Medicine and Microbiology, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST* The role of *H parainfluenzae* as a pathogen has been doubted, often being regarded as a commensal organism. To assess its pathogenicity the characteristics of all patients from whom *H parainfluenzae* was isolated were examined over a 10 month period (May 1989 to February 1990). Seventy seven isolates were obtained: 61 sputa, 9 eye, 2 ear, 3 nose, 1 throat and 1 wound swab. The 16 non-sputum isolates occurred predominantly in infants and children (median age 5 months, range 3 weeks to 32 years). All were penicillin-resistant and one was ampicillin-resistant (a $\beta$ lactamase producer). The 61 sputum isolates were obtained from an older population (median age 59 years, range 8 months–90 years; 37 male, 24 female). These represented 1·2% of the total sputa cultured (4901) in our laboratory during this period, 497 (10·1%) of which grew *H influenzae*. Twelve sputa were sent from outpatient or general practice. A respiratory illness was the reason for admission in 37/49 (73%) of inpatients; 6 (13%) were cardiology patients and the remainder orthopaedic, surgical and general medical patients. The mean $FEV_1/FVC$ ratio of inpatients was 54% of the predicted value and 37 (76%) were smokers. Six (11%) inpatient infections were hospital acquired. *H parainfluenzae* showed a heavy or moderate growth in 57 (93%) of sputum samples and was the sole isolate in 49 (80%). All isolates were penicillin-resistant. Ten (16%) were ampicillin resistant (8 $\beta$ lactamase producers). Resistance to cotrimoxazole, erythromycin and tetracycline occurred in 5 (8%), 3 (5%) and 10 (16%) respectively. Overall 18 (30%) showed resistance to two or more antibiotics. The seasonal distribution of cases showed peak incidences in February (12 cases) and August (8 cases) compared to a mean of 3 cases/month for the rest of the study period. *H parainfluenzae* is an important pathogen in respiratory tract infection and may have multiple antibiotic resistance. It should be reported routinely when isolated.

### Observations on inflammatory markers in bacteraemic and non-bacteraemic pneumococcal pneumonia

P VENKATESAN, DJ SHALE, J MACFARLANE *Respiratory Medicine Unit, City Hospital, Nottingham* Fourteen patients with pneumococcal pneumonia were studied prospectively to follow the course of temperature, white cell count (WCC), C reactive protein (CRP), lactoferrin and tumour necrosis factor (TNF). There were 10 males aged between 28 and 85 years (median 62 yrs). *Streptococcus pneumoniae* was cultured from blood in 6 patients and from sputum in 1 patient. All patients had pneumococcal capsular antigen in sputum, serum or urine. Seven patients were antigenaemic and this group included the 6 bacteraemic patients. One patient, who was bacteraemic, died. One patient failed to raise oral temperature above 37°C and another 5 did not raise it above 37·5°C. All but 2 patients were apyrexial by 7 days. All patients developed a leucocytosis with a WCC $>11 \times 10^9/l$ at some stage. The neutrophil count paralleled changes in the WCC. By 7 days the WCC was almost normal in 10 patients. In the remaining 4 the WCC rose, rather than fell, subsequent to admission. These 4 patients were antigenaemic. Two of them had asthma and received courses of steroids. In the other 2 the rise in WCC coincided with a deterioration in clinical state. CRP was elevated in all patients and was recorded $>300$ $\mu$g/ml in 10. Levels fell rapidly subsequent to admission. Lactoferrin, released principally by neutrophils, was elevated, but less than twice normal, in 4 patients, and elevated greater than this in another one. Four out of these 5 patients were antigenaemic. TNF, released principally by macrophages, was elevated in 5 non-antigenaemic patients during the early part of admission, then returning to normal, and was elevated in 5 antigenaemic patients later, from day 4. In this series we did not find any significant differences between antigenaemic and non-antigenaemic patients with respect to average levels of CRP, lactoferrin and TNF. However antigenaemic patients (median age 72 yrs) were older than non-antigenaemic patients (median age 36 yrs).

### Psittacosis: a clinical review

BA CROSSE, PJ STANLEY *Infectious Diseases Unit, Seacroft Hospital, Leeds* Psittacosis/ornithosis continues to be a significant human disease; the incidence seems to be increasing (Public Health Laboratory Service etc. *Br Med J* 1981;**283**:1411). Pneumonia after exposure to birds may be readily recognised but other presentations may not be. Cases of psittacosis diagnosed in the West Yorkshire region between 1965 and 1989 were reviewed. Infection was defined by a four-fold rise or fall in antibody to Chlamydia group B. Two hundred and nineteen cases were identified. Seventy six per cent of cases were aged 20 to 70. Infection in children was rare. The ratio of male to female cases was 1·9:1. Fifty five cases were patients in the Infectious Diseases unit and detailed data was available. The commonest presentation was of a respiratory tract infection with constitutional symptoms. Neurological and gastrointestinal features were prominent. Unusual presentations were myocardial infarction, encephalitis, relapse of polymositis and hepatitis. Radiological consolidation was present in 81% of cases; x-ray findings frequently exceeded clinical signs. A normal white blood cell count was noted in 72%. Hyponatraemia was noted in 40%. Sixty two per cent of cases had been in contact with birds, notably budgerigars, parrots, pigeons or mixtures of exotic species. Half of these birds had been ill or had died, or had been newly acquired. Most were household pets or housed in garden aviaries. Three case clusters were identified, all related to an avian source. Cases without avian contact may have been due to *Chlamydia pneumoniae* (Grayston JT, *et al. N Engl Med J* 1986;**315**:161–8). Knowledge of avian contact may prompt a critical change in antibiotic treatment, and clinicians should consider the diagnosis. We share concern regarding the importation of exotic birds and the rising incidence of psittacosis. (Wreghitt TC, *et al. Lancet* 1988;**2**:743). Statutory notification of the infection might clarify the risks.

### Changing patterns of tuberculosis in Edinburgh

MB ALLEN, CD SELBY, AG LEITCH *Royal Victoria Dispensary, Edinburgh* Notifications of tuberculosis have been falling in Britain for several years. To determine if this has been associated with a change in the nature of the disease we have examined the patterns of TB over the last 25 years. In Edinburgh, a static population of 500 000, details of each notification have been recorded on cards since 1960. From a review of these cards, details on demography, presentation, bacteriology and radiographic changes were obtained. To avoid undue bias, two consecutive years were examined at five year intervals from 1960–1 through until 1985–6. Notification gradually declined, falling from 290 in 1960–1 to 74 in 1985–6, with those aged over 65 years making a relatively greater contribution (11% to 35%). Sex incidence (M:F 60:40) was unchanged but the number who were smear positive increased from 24% in 1975–6 to 36% in 1985–6. The number of cases identified by contact tracing remained constant throughout the period at 12%. There was a trend for the chest x-ray to show more minimal disease (24% to 46%) with less cavities being identified (28% to 1·4%). The number and patterns of extrapulmonary disease were unaltered during the 25 years. In the year 1985–6 there was a rise in after death notifications.

### Infection control procedures in UK respiratory laboratories

AH KENDRICK, EC SMITH *Respiratory Department, Bristol Royal Infirmary, Bristol* There is a theoretical risk of cross-infection of patients via lung function equipment which has not been proven. At present there are no guidelines for infection control procedures. To determine the current state of practice, a survey of UK laboratories was undertaken, with specific reference to infection control

procedures for spirometery, gas transfer, lung volumes and general laboratory housekeeping. Eighty nine laboratories replied. Ninety six per cent of respondents believed there was a risk of infecting patients but only 37% of these had a written policy which had been formulated with help from infection control officers (69%), manufacturers (46%) or from literature (30%). Worksurfaces in laboratories were cleaned every day (55%) or weekly (24%) and waste bins emptied daily (90%). Filters (vapour or bacterial) were used by 22% on spirometers and 19% on gas transfer and helium dilution lung volumes. Most (59%) laboratories did not clean inside spirometers or transfer factor equipment. Rubber/plastic mouthpieces were generally washed in hot soapy water followed by soaking in a chlorine releasing agent (32·9%), glutaraldehyde (27·4%) or chlorhexidine (15·1%). Breathing circuits for spirometry and helium dilution lung volumes were changed or cleaned between patients (8·1%), daily (23·3%), weekly (27·1%) or on leaking (10·5%). Where cleaned, they were washed and then soaked in a chlorine releasing agent (23%), glutaraldehyde (24%) or chlorhexidine (12%). There was confusion about the safety of glutaraldehyde and it had been withdrawn from use in 8/89 laboratories. National guidelines were requested by 24% of respondents. We conclude that infection control procedures in respiratory function laboratories needs to be evaluated, and a set of national guidelines would be an asset.

### *Mycobacterium chelonei* isolation during bronchoscopic procedures and the practical implications for bronchoscopic sterilisation

DK CHADHA, K NYE, PB ILES, D HONEYBOURNE, P HODGKIN, R WISE, S BALDWIN *Dudley Road Hospital, Birmingham* Over a six month period from January to June 1989, 157 fibreoptic bronchoscopies were carried out during which bronchial washings were obtained in 58 cases. *Mycobacterium chelonei* was isolated from the washings on 8 occasions. Two patients were initiated on anti-tubercular therapy which was discontinued when contamination was suspected. A search for the source of contamination led to isolation of *M chelonei* from the tap water supply as well as freshly reconstituted detergent. No organisms were grown from alkaline glutaraldehyde. Rinsing the bronchoscopes with sterile water after routine cleaning and sterilisation (as recommended by the BTS Research Committee Working Party, 1989) failed to eliminate the problem. *M chelonei* was isolated from washings even from two previously unused bronchoscopes. Further investigations revealed the reservoir of infection in a contaminated detergent dispenser which was routinely rinsed with tap water before refilling. We no longer use any detergent dispenser but pour detergent directly from its original container into sterile washing bowls. We recommend that sterile water should be used not only for rinsing of the bronchoscopes but also for rinsing of all containers and dispensers as well as for reconstituting detergent.

### Q fever—acute chest radiographic appearances in 55 cases

DL SMITH, R WELLINGS, C WALKER, JG AYRES, PS BUDGE *Department of Respiratory Medicine and Department of Radiology, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST* We have reviewed chest x-rays taken within 20 days of onset of symptoms in 55 cases of Q fever diagnosed by standard serological methods. Fifty one of these films were PA radiographs, 4 were AP. In addition 30 lateral films were available and were used to assist in localisation of shadowing. All the cases formed part of the large Q fever outbreak seen in the West Midlands in 1989. Films were viewed and scored separately by 2 observers (RW and CW). There was agreement on 88·2% of observations. Where opinions differed, the films were jointly reviewed and a consensus agreed. The mean interval (SD) between date of onset of symptoms and date of film was 5·9 (4·3) days (range 0–20). There were 6 normal films. Shadowing was unilateral in 45 (92%) films, and bilateral in 4 (8%). In the majority of films shadowing was peripheral (49%); segmental shadowing was seen in 29%, perihilar shadowing in 17% and lobar shadowing in 5%. The nature of shadowing was homogeneous in 72%, rounded in 11·2%, nodular in 7·4% and reticular in 6·5%. Linear atelectasis was seen in 2·8%. There was no cavitation. A single zone (of six) was affected in 31 (63%) films, 2 zones in 16 (33%) and 3 zones in 2 (4%). The shadowing was uniformly ill-defined. Left sided shadowing was more common than right in a ratio of 3:2. Lower zone shadowing was commonest, middle zone next commonest and upper zone shadowing least common (ratio 5:3:2). Air bronchograms were present in 18 (37%) films and a small pleural effusion was seen in one film. We conclude that the appearances of acute chest x-rays in Q fever are varied. Shadowing has a predilection for the lower zones, occurs more commonly on the left, is ill-defined, largely homogeneous and tends to be peripheral. Appearances may be normal in the first 20 days of illness.

### Bronchiectasis: a forgotten association of rheumatoid disease

T SOLANKI, E NEVILLE *Department of Respiratory Medicine, St Mary's Hospital, Milton Road, Portsmouth PO3 6AD* Rheumatoid disease has a number of well recognised pleuro-pulmonary associations. Patients with rheumatoid disease are more susceptible to a variety of infections and previous reports have argued that tuberculosis was commoner in rheumatoid patients thus leading to bronchiectasis in these patients. In order to establish whether bronchiectasis is a real association of rheumatoid disease, we performed a retrospective review of 77 patients with bronchiectasis and 86 patients with pulmonary fibrosis attending the department of respiratory medicine. Six of 77 (7·8%) bronchiectasis patients and seven of 86 (8·1%) patients with pulmonary fibrosis were found to have rheumatoid disease. Five of the six bronchiectasis patients were female and their ages ranged from 48 to 83 years. Five developed respiratory symptoms between one and 34 years before the onset of the rheumatoid disease. The remaining patient developed respiratory symptoms two years after presenting with rheumatoid arthritis and the diagnosis of bronchiectasis was made seven years later. No patient had a history of pneumonia or tuberculosis at the onset of the respiratory disease and the radiographic abnormalities were bilateral and basal in all cases. One patient with bronchiectasis and three patients with pulmonary fibrosis had a positive rheumatoid factor but no clinical evidence of arthritis, while all the remainder had active arthritis and positive serology. Although the cause for an association between rheumatoid disease and bronchiectasis is obscure, we suggest that it is a real rather than a spurious association occurring at least as frequently as pulmonary fibrosis.

### Two cases of chronic pulmonary disease associated with the hyperimmunoglobulin E syndrome

S MAXWELL, DS KUMARARATNE, PE ILES, D HONEYBOURNE *Departments of Thoracic Medicine and Clinical Immunology, Dudley Road Hospital, Birmingham* Hyperimmunoglobulin E syndrome consists of recurrent bacterial infections of the skin and sinopulmonary tract, chronic eczema and a serum IgE above 2000 kU/l. Other features include asthma, coarse facies, mucocutaneous candidiasis, defective neutrophil chemotaxis, recurrent subcutaneous abscesses and strong type I reactions. Sweat tests are normal. Case 1 is a 33 year old woman who presented with multiple staphylococcal lung abscesses. In the next 2 years recurrent skin abscesses and staphylococcal pneumonia developed. She had suffered with chronic asthma and eczema. Levels of complement, total and specific immunoglobulins were all normal, but impaired neutrophil phagocytic activity and an IgE level of 12 440 kU/l were found. Ranitidine therapy then resulted in a reduction in the frequency of infections (Thompson RA. *Lancet* 1989;i:630). Case 2 is a 20 year old man who developed recurrent ear and chest infections as a child and had multiple strong type I skin tests. He had recurrent hospitalisations with staphylococcal pneumonia. He developed asthma, chronic dermatitis and mucocutaneous candidiasis. In teenage years repeated chest infections continued with Haemophilus and Pneumococcal species and the eventual development of severe cystic bronchiectasis. A markedly elevated IgE level of 25 000 kU/l was found along with normal neutrophil function and total immunoglobulin levels. Low levels of specific antibody against several capsulated bacteria including Pneumococci and Haemophilus were found. Ranitidine therapy and regular IV gammaglobulins have resulted in a decrease in infections. This rare syndrome may be helped by treatment with $H_2$ antagonists and specific antibody deficiencies may be helped by intravenous gammaglobulin.

### Plasma neutrophil granule products in bronchiectasis

MS WISEMAN, DJ SHALE *Respiratory Medicine Unit, City Hospital, Hucknall Road, Nottingham NG5 1PB* In bronchiectasis there is a vicious cycle of infection, inflammation and lung injury. The neutrophil is a major effector cell, recruitment into the lung requires intravascular activation. We monitored plasma levels of neutrophil elastase alpha-1-antiproteinase complex (NEAC) and lactoferrin (Lf) by ELISA as an index of inflammatory activity in 11 bronchiectatic patients, five with cystic fibrosis, during a symptomatic deterioration of their bron-

chiectasis when *Haemophilus influenzae* was cultured from their sputum. All were treated in an open fashion with Distaclor 500 mg tid for 14 days. Blood samples and spirometry were obtained at the onset of treatment and 14 and 28 days later. Laboratory determinations were performed blind of the protocol. Lung function did not improve, but both neutrophil granule products were significantly reduced 14 and 28 days after commencing treatment. In patients with severe airways disease where objective monitoring of the progress of infection is not possible determination of plasma neutrophil granule proteins may be a useful alternative.

| | *Pre treatment* | *Post treatment* | *Post +14 days* |
|---|---|---|---|
| Lf (nmol/l) | 2·50 (1·68) | 1·86 (1·04)* | 1·26 (0·42)* |
| NEAC ($\mu$g/ml) | 0·48 (0·16) | 0·35 (0·09)* | 0·26 (0·08)* |
| $FEV_1$ (l) | 1·06 (0·41) | 1·09 (0·41) | 1·10 (0·40) |

*$p < 0·05$ compared with pretreatment.

## Spontaneous pneumothorax—new method for predicting successful manual aspiration?

K YOGANATHAN, D SEATON, R BARKER, TJ COADY *Ipswich Hospital, Ipswich* It is customary to treat spontaneous pneumothorax actively on grounds of size or if there is underlying lung disease. Whereas the usual approach has been to use an intercostal tube with an under-water seal, simple manual aspiration has re-emerged as an alternative procedure that spares the patient discomfort and is easier to perform. A disadvantage of aspiration is that it is impossible to predict accurately which patients will recollapse the lung within the next 24 hours as a result of a small persistent pleural leak. Such patients would require further treatment, with delay in their successful management and discharge. We have previously described a technique by which chlorofluorocarbons (CFCs) present in a metered dose inhaler (MDI) may be detected in a gas sample (Coady TJ, *Lancet* 1988;2:1286) and have adapted this technique in order to demonstrate the presence of a pleural leak at the time of manual aspiration. The technique has so far been applied to 13 patients with 16 episodes of pneumothorax. Using a two-way valve, each patient inspired from a 150 l Douglas bag containing air and 5 puffs from a placebo MDI. Manual aspiration was carried out in standard manner, the aspirated gas being sampled by a flame ioniser. The detection of CFCs in the pneumothorax gas implied the presence of a pleural leak. No leak was found in 6 cases of pneumothorax. Further collapse did not occur in any of these cases and tube drainage was avoided. A leak was found in 10 cases and although the post-aspiration pneumothorax was radiographically smaller in 5, subsequent enlargement occurred and tube drainage was needed in 8. Our findings imply that the absence of CFCs in the aspirate will be followed by resolution of the pneumothorax, whereas the presence of CFCs will be associated with the need for tube drainage in 80% of cases.

## High resolution computed tomography assessment of disease activity in the fibrosing alveolitis of systemic sclerosis: a histological correlation

AU WELLS, DM HANSELL, K HARRISON, C BLACK, RM DU BOIS, B CORRIN *Departments of Thoracic Medicine, Radiology, Pathology, Royal Brompton and National Heart Hospital, Fulham Road, London and Department of Rheumatology, Royal Free Hospital, London* High Resolution Computed Tomography (HRCT) has an established role in the assessment of diffuse lung disease. We evaluated the accuracy of HRCT in predicting the histological appearances of open-lung biopsies taken from 23 lobes in 12 scleroderma patients with fibrosing alveolitis. Biopsies were graded on a five point scale from inflammation alone through to fibrotic change alone. A similar scale was used to score the HRCT appearances of the lobe from which the biopsy was taken, from parenchymal opacification alone (taken to reflect increased cellularity) through to a reticular pattern alone (representing fibrosis). The most frequent histological appearance was "predominant fibrosis with some inflammation" (14/23). This grade was accurately predicted by HRCT (sensitivity 86%, specificity 92%). In only one of remaining nine biopsies did HRCT incorrectly identify predominant fibrosis. The accuracy of CT scanning was only 33% in this group of nine biopsies. This discrepancy was due in part to regional variation of disease activity within lobes. We conclude that HRCT correlates extremely well with histological appearance in those cases in which fibrosis predominates.

## Alveolar targeting of particulate $^{99m}$Tc-DTPA using a new delivery system—the APE nebuliser

RF MILLER, PH JARRITT, D LUI, J KIDERY, R DE JONG, PJ ELL, SJG SEMPLE *Department of Medicine and Institute of Nuclear Medicine, UCMSM, Middlesex Hospital, London and Mallinckrodt Diagnostica, Holland* Alveolar targeting is important for the delivery of inhaled drugs such as pentamidine. Existing delivery systems (ultrasonic and jet nebulisers) are hampered by poor mass output and may also produce inappropriately large aerosol droplets. We have developed a new delivery system which generates a particulate aerosol by pressurising air to 3 atmospheres, this is then vented through the outer channel of a concentric double needle at the same time as an aqueous solution of the drug to be nebulised (plus a small quantity of absolute alcohol) is injected through the centre needle, this produces a fine mist at the needle tip. At this point the alcohol and water vapour evaporate leaving a particulate aerosol which rapidly loses momentum and is collected in a fully collapsible 35 l bag. Patients inhale from the 35 l bag through a conventional breathing circuit. We studied 18 subjects—Group One, 11 healthy men with normal spirometry, Group Two, 7 men with AIDS receiving secondary prophylaxis with inhaled pentamidine, spirometry [mean (SEM)] $FEV_1$ 3·08 (0·26), FVC 4·83 (0·29). An equilibrium $^{133}$Xenon scan was performed; using planar imaging 20% contour was taken to provide a lung outline. Subjects then inhaled from 300 MBq $^{99m}$Tc-DTPA from the APE and central, peripheral, apical, and extrapulmonary deposition of the $^{99m}$Tc-DTPA was recorded and a penetration index (PI) was derived. Output characteristics of the nebuliser were mass median aerodynamic diameter = 2·0 $\mu$m, span = 1·4, mass output = 82%. Inhalation took [mean (SEM)] 4·7 (0·18) min. The PI and apical/peripheral deposition were Group One, 0·97 (0·08), 0·69 (0·16) and Group Two 0·93 (0·09), 0·67 (0·16) [mean (SEM)]. There was virtually no oropharyngeal/tracheal deposition. SPET images confirmed homogenous intrapulmonary deposition. The APE has a ready application for delivery of inhaled pentamidine as treatment and prophylaxis of *Pneumocystis carinii* pneumonia. In view of its excellent intrapulmonary deposition it may provide an alternative to conventional ventilation studies with radioactive gases.

## Measurement of pulmonary endothelial permeability to transferrin following lung transplantation

DN HUNTER, R LAWRENCE, M YACOUB, CJ MORGAN, TW EVANS *Brompton Hospital, London; Harefield Hospital, Middlesex* A wide variety of pulmonary insults may lead to changes in vascular endothelial integrity, the extreme example of which is the adult respiratory distress syndrome (ARDS). The accumulation of 113m In-transferrin in the lung interstitium has been successfully used as an index (protein accumulation index, PAI) of endothelial permeability in ARDS (Rocker GM, *et al. Clin Sci* 1988;75:47–52). Furthermore, an increase in regional PAI following re-expansion and re-perfusion of collapsed lung has been demonstrated (Keegan J, *et al. Nucl Med Commun* 1989;**10**:871–8). It is possible that similar changes occur following the re-perfusion of a transplanted lung, reflecting damage sustained during the extracorporeal period. Using new solid-state caesium iodide (CsI) mini scintillation counters (Oakfield Instruments, Oxford, UK), we therefore measured PAI in 16 transplanted lungs (9 patients) in the 48 hours following reimplantation. The mean (SEM) PAI $\times 10^{-3}$/min measured in 22 normal lungs (11 subjects) was 0·18 (0·09) and in 11 lungs with ARDS (7 patients) was 2·77 (0·5), ($p < 0·001$). PAI in transplanted lungs was 1·17 (0·48) ($p < 0·05$ cf normals, $p < 0·01$ cf ARDS). We conclude that pulmonary endothelial integrity is compromised in the 48 hours following lung transplantation, although not as severely as in those patients fulfilling the criteria for ARDS.

Work supported by the Eleanor Peel Trust and the National Heart and Chest Hospitals.

## Measurement of epithelial lining fluid volume employing a new technique—"microlavage"

DR BALDWIN, R WISE, JM ANDREWS, D HONEYBOURNE *Departments of Thoracic Medicine and Medical Microbiology, Dudley Road Hospital, Birmingham* The volume of epithelial lining fluid (ELF) recovered by bronchoalveolar lavage (BAL) has been estimated using the urea concentration of lavage fluid as an endogenous marker. However, this results in an overestimate of ELF volume because urea diffuses into lavage fluid during conventional BAL. It was recommended therefore,

that lavage be completed within 1 minute when employing the urea dilution method (Marcy TW, *et al. Am Rev Respir Dis* 1987;135:1276–80), but this is impossible whilst using the large volumes of instilled saline necessary to sample distal airways. A method is described which may circumvent these problems. In initial studies in post mortem lung, a standard 1·7 mm bronchial brush tube was wedged into a distal lung subsegment. It was found that only 20 ml of saline was required to lavage distal airways. The procedure was then performed in 28 patients undergoing fibreoptic bronchoscopy for diagnostic purposes. After "microlavage", a standard 200 ml BAL was performed in a different lung subsegment, ensuring that dwell time was less than 4 minutes. Specimens were centrifuged and the total protein and urea levels used to calculate the ELF volume recovered by microlavage. From this, the total protein concentration of the ELF was calculated and used to determine ELF volume recovered by conventional BAL. The differential cell counts of both samples were compared. The technique of microlavage yielded a median aspirated volume of 3·4 ml. BAL differential counts were similar to microlavage (r = 0·85 to 0·92). The volume of ELF recovered by conventional BAL based on microlavage was a median of 1·17% (range 0·18–3·33) of the recovered volume, compared with 1·51% (0·53–4·06) using the standard urea dilution method (96·5% confidence interval for difference 0·5 to 1·07). Microlavage confirmed the overestimate of ELF volume by the urea method and may be useful for quantification of ELF volume.

## Immediate reactions to a doctor's postal advice to quit smoking in men with high risk to develop lung cancer and obstructive lung disease recruited through a population survey

S HUMERFELT, B MEIDELL, E GRIEG, LE ARRØ, G KVAALE, A GULSVIK *Department of Thoracic Medicine, Section for Medical Informatics and Statistics, Department of Social Psychology and Institute of Hygiene and Social Medicine, University of Bergen, Norway* A population survey has been done among all men aged 30–44 years (22896) living in 34 municipalities on the south west coast of Norway. Information on smoking habits and occupational exposure to asbestos have been obtained via self-administered questionnaires while $FEV_1$ was recorded using dry-wedge Vitalograph S-model spirometers. A group of 2612 men has been identified as current smokers with either known asbestos exposure (n = 1187), an age- and height-adjusted $FEV_1$ in the lowest quartile (n = 1015) or both (n = 410). They were included in a randomised intervention trial in January 1990 where 1301 men received a personal letter through the post with a doctor's advice to quit smoking as well as a brochure on different smoking cessation techniques. The additional 1311 men did not receive any information and will be used as a control group for later comparison. The immediate reactions following the postal advice were assessed through a self-administered questionnaire sent 2 weeks later to a random half (n = 657) of those who received the letter and brochure. The response rate was 61% (n = 401) after the first reminder letter: 65·3% wanted to, while 22·7% tried to and 7·4% managed to stop after they received the postal advice to quit. A higher proportion (37%) among smokers with both asbestos exposure and a low $FEV_1$ tried to stop compared to those who tried to stop among smokers with asbestos exposure alone (22%) and those smokers with a low $FEV_1$ alone (19%). When asked to foresee their future smoking habits, 33·9% reported that they probably will not smoke and 15·2% reported that they certainly will not smoke 12 months ahead. In conclusion: 7·4% reported to have stopped smoking after a postal advice to quit.

## Grampian Smokebusters—an innovative smoking prevention programme for children

YVONNE STEVENSON-ROBB, JAMES FRIEND *Grampian Action on Smoking and Health, PO Box 245, Aberdeen* In October 1987 a unique smoking prevention programme for young people aged 10–13 was launched with 18 000 children in the target age group. Innovative in style, the Grampian Smokebusters campaign attracted 14 000 subscribing members in the first two years. The campaign operates as a club for non-smokers with a variety of incentives being offered to those who remain non-smokers. One of those incentives is a membership card resembling a credit card, which entitles members to substantial cash discounts on goods and services from around 200 local shops, sport centres etc. As well as proving attractive to children, the club has also made an impact in schools, within families and within the general community as a positive force for non-smoking. Activities undertaken by child members have included sponsored events for charity, petitions, boys v girls football matches, creation of "SFZFKs" (Smoke Free Zone For Kids), helping friends and relatives to give up, competitions, Smokebuster of the Year Awards, holiday competitions, a summer hotline (ideas for things to do locally during school holidays), National No Smoking Day events. Grampian Smokebusters also organised the first conference on Tobacco and Young People, where 250 Smokebusters from Scotland decided on the agenda, discussed issues and called for change as well as accepting a motion for a "Scottish Children's Charter on Smoking". An independent evaluation of Grampian Smokebusters has been conducted and will be separately reported. Grampian Smokebusters is supported financially by the Chest, Heart and Stroke Association (Scotland) and Grampian Area Health Board.

## An evaluation of the short term effects of Grampian Smokebusters—a club to encourage non-smoking in 10–13 year old children

E VAN TEIJLINGEN, J OLDMAN, JAR FRIEND *Department of Thoracic Medicine and Sociology, University of Aberdeen, Scotland* In October 1987 a Smokebusters Club was established in Grampian, Scotland (population 500 000) for non-smoking children aged 10–13. An independent evaluation to examine the short-term impact of the Club and its effect on smoking behaviour was undertaken, using a questionnaire survey of a one in ten sample of the 18 000 children in the target group. The survey was conducted at the start of the Project and repeated in the same children approximately 20 months later. In addition to questions related to smoking habits and awareness of the Smokebusters Club, information on the use of disposable income, and on musical and leisure interests was sought. In 2 years following the start of the Club 14 000 children became members. Of the 1785 who answered the original questionnaire, 71% completed the second. Of these, 98% knew about the Smokebusters Club. At the Second Survey, smoking levels in Grampian among girls were lower than those in the Office of Population, Censuses and Surveys (OPCS) 1986 Scottish survey and than the OPCS 1988 English survey, but among boys the percentages smoking were similar to both the OPCS surveys. The period between the two surveys, non members and ex members of Smokebusters were two and a half times more likely to start smoking than current members, although this may not be causal. Smoking was associated with particular activities and musical tastes and with perceived "adult images".

The evaluation was supported by the Cancer Research Campaign (UK).

## Smoking cessation in hospital patients given repeated advice plus nicotine (N) or placebo (P) chewing gum

IA CAMPBELL, RJ PRESCOTT, S TJEDER-BURTON *Sully Hospital, Penarth, S Glamorgan, CF6 2YA Department of Medical Stastitics, University of Edinburgh, EH8 9AG* Two hundred and nineteen hospital in-patients with smoking related diseases were advised by their physicians to give up smoking. Before they left hospital a Research Assistant gave the patients packages of identical appearance containing, randomly, either nicotine (2 mg) or placebo gum. The patients were instructed on the use of the gum and the stop smoking advice was reinforced. Advice was repeated at 2, 3, 5 weeks, 3 months and 6 months and the patients were finally reviewed at 12 months. A stronger gum (4 mg N or P) was offered up to three months to those who continued smoking. Claims of abstinence were verified by measurement of expired air CO. Success was defined as claimed non-smoking at 6 and 12 months with claimed non-smoking between these times, with claims at 6 and/or 12 months being verified. Seven patients were not evaluable at 12 months because of emigration, death or the development of terminal cancer. Success rates were the same in the N and the P groups, ie 20%. Of these, 86% claimed to have abstained from the time of initial advice. Of the failures, 71% restarted smoking within 2 weeks of discharge from hospital. Patients with heart disease did better (32% success) than those with lung disease (13% success) and other diseases (6% success). No relationship was found between outcome and sex. Smokers of 16–25/day did better than those who smoked more or less. Those aged 50–59 years had a higher success rate (32%) than younger or older groups. We conclude that reinforcing the physician's initial advice with chewing gum and with further advice repeated at intervals during the ensuing six months improves success rates in comparison with other studies of patients with smoking related diseases, but in this notoriously difficult group no difference emerged between nicotine and placebo gums.