S101 COULD INSPIRATORY PRESSURE SUPPORT (IPS) BE A USEFUL ADJUNCT IN PULMONARY REHABILITATION?

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A physiological training benefit from pulmonary rehabilitation is more probable if the exercise intensity exceeds the anaerobic threshold; a convenient marker of anaerobic metabolism being elevation of plasma lactate. Plasma lactataemia is buffered by bicarbonate with release of CO_2; in severe COPD this places an unsustainable load on the respiratory muscle pump. In COPD IPS ameliorates the loading experienced by the inspiratory muscles during treadmill exercise (Polkey et al *AJRCCM* 1996; *in press*). In the present study we sought to extend exercise induced lactataemia in patients with severe COPD using non-invasive inspiratory pressure support (IPS). 5 men with severe COPD (mean FEV_1 0.66l) performed 2 constant rate treadmill walks to a condition of severe dyspnoea; the second walk was supported by IPS delivered from a NIPPY ventilator (Friday Medical, London UK) and a full face mask. Plasma lactate was measured in arterialised blood drawn at baseline and at end exercise. A significant elevation in mean plasma lactate from baseline (1.83 mM/L) to end exercise of both the free (to 3.48 mM/L) and IPS assisted (to 2.82 mM/L) walks was observed ($p<0.05$). IPS resulted in a mean 136% increase in walking distance ($p<0.05$). We conclude that patients with severe COPD can prolong exercise induced lactataemia for longer if assisted with IPS. This technique warrants further study since it may prove to be a useful adjunct in pulmonary rehabilitation.

P1 GENERAL PRACTITIONER PRESCRIBING HABITS IN ASTHMA/COPD

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A study has been carried out in nine UK general practices to consider the prescribing costs in Asthma/COPD patients. Using the practices' computerised prescribing records, a search was carried out to identify all patients over 40 years of age, who had been prescribed a Beta-agonist during the previous six month period and who had a positive smoking history. The medical notes for these patients were reviewed and only those satisfying the following criteria were included in the study: consistently low lung function, sputum production and a history of chest infections. The age, sex, current diagnosis and prescribing history over the six months were manually recorded for the study group.

434 patients were identified, 224 female and 210 male, with an average age of 65 years. The diagnosis as recorded by the GP on the computer records was asthma in 52% and COPD (including emphysema and chronic bronchitis) in 45%; 3% of cases had no or other diagnoses.

Each prescription written for these patients during the six month period was costed. The total cost of treatment for all patients was £51,920. For bronchodilators, £16,730 was spent on Beta-agonists, £4295 on anticholinergics (23% of patients) and £1887 on combination preparations containing a beta-agonist and an anticholinergic (12% of patients).

351 patients (81%) were receiving steroid therapy at a cost of £29,008; an average cost of £82.65/patient. Assuming that the criteria for entry into this study actually identified patients with COPD and that only 10-15% of such patients may benefit from steroid therapy, it can be estimated that the treatment costs of steroids could potentially be reduced to £5380, a saving of £23,628.

This study demonstrates the economic implications of prescribing for asthma/COPD patients. Some of these resources may be better utilised by improving the accuracy of diagnosis and the appropriateness of treatment.

P2 OBSERVATIONS ON THE STRUCTURE, PROCESS AND CLINICAL OUTCOMES OF ASTHMA CARE IN GENERAL PRACTICE

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There is a need to establish whether the structure of asthma care in general practice is associated with measures of process and with primary and secondary care clinical outcomes. Debate about how to resource general practice asthma care is hampered by a lack of observational data from throughout the United Kingdom.

The National Asthma Management Study was designed to observe the present system of FHSA accreditation of asthma clinics based on measures of structure associated with measures of process or clinical outcome.

225 UK practitioners enrolled in a project and recorded details of how they organised asthma care and provided data from 6732 patients on general practitioner and nurse consultations, asthma attacks, symptom control, emergency treatments and hospital attendances covering a 12 month period.

FHSA approval for a Chronic Disease Management Asthma Clinic was associated with favourable patterns of structure and process but not clinical outcome. Practice audit and employment of a nurse with an asthma diploma were associated with favourable patterns of structure, process and clinical outcome.

Practices (n=143) who had recently audited asthma patient care (n=4259) compared to those who had not (82 practices, 2473 patients) had fewer patients who had attended an accident and emergency department in the past 12 months [121(3%):96(4%), Odds ratio 1.38, 95% Confidence Intervals 1.04-1.83] or hospital outpatients [247(6%):180(7%), 1.28,1.04-1.56] and fewer patients with respiratory symptoms on assessment [2400(56%):1465(59%),1.34,1.18-1.52] and days lost from work or school [375(9%):296(12%),1.48,1.25-1.74].

Findings from a large UK sample of practices are subject to participant bias and show association rather than causative links. The present FHSA asthma CDM accreditation system based on structure is not associated with favourable clinical outcomes. This opens the debate as to whether accreditation should be linked to recent experience of audit, which does appear to be associated with favourable clinical outcomes.

P3 THE PREVALENCE OF DIAGNOSED ASTHMA AND COPD IN A COMMUNITY POPULATION IN NOTTINGHAMSHIRE

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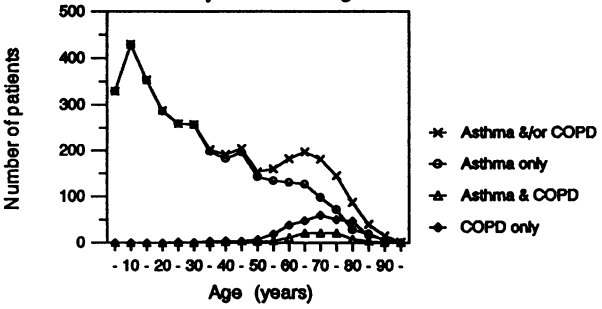
In a survey of five large general practices with fully computerised patient records for at least four years we have determined the prevalence of diagnosed asthma and COPD in patients over the age of four. Patients were identified from a computer search of practice records and individual records were then reviewed. From a total population of 38865 (52% F) 3692 patients (9.5%) had a diagnosis of asthma and/or COPD of whom 90% had received treatment within the past four years. The majority (3260; 8.4%) had a diagnosis of asthma alone, compared to 108 (0.3%) with asthma and COPD and 318 with COPD alone (0.8%). The age distribution of patients according to diagnosis is shown; a quarter were aged 5-16 years. Overall 53% of patients with asthma were female compared to 40% of patients with a diagnosis of COPD and 43% of patients under the age of 16. Amongst the 83% of patients over the age of 16 years with a smoking history recorded 22% were current smokers and 20% ex smokers in the asthma only group compared to 29 and 40% of patients with a label of COPD. Using computerised records obviates the problems of non-compliance seen in most community based surveys of asthma/COPD. The data emphasises the marked variation in diagnosed asthma in the community in relation to age.



P4 TREATMENT OF ASTHMA AND COPD IN A GENERAL PRACTICE POPULATION

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We have surveyed the use of asthma therapy over the last four years in five large general practices with computerised patient records covering a total population 38865 over the age of four. In the 3692 patients with a diagnosis of asthma and/or COPD 10% (363) had received no treatment in the four years, 27% (1007) had had ß agonist inhalers only (with 12% having ≥6 inhalers in the last year), 24% (876) had had intermittent inhaled steroids (ICS) and 33% (1223) regular ICS, mainly beclomethasone (81%). In the regular ICS group the proportion of adults taking ≥800, 500-750, 400 and <400mcg a day were 40%, 4%, 47% and 9% compared to 11%, 3%, 49% and 38% in patients under 17 years. In addition to regular ICS's 226 (6%) were taking three or more asthma medications, salmeterol most commonly (39%) followed by ipratropium (26%) and theophylline (19%). Oral steroids had been prescribed to 1062 patients (29%) on at least one occasion, to 218 (6%) on four or more occasions and were taken regularly by 1.3% (47, median prednisolone dose 7mg). A breakdown of treatment according to diagnosis is shown

Therapy received over previous 4 years		Asthma: n=3258 %	COPD+/-asthma n=426 %
No treatment		8	23
Bronchodilator only		28	22
Inhaled steroids:	intermittent	29	14
	regular	28	20
	regular + OAM	5	16
Oral steroids:	intermittent	29	34
	continuous	0.6	6

OAM = other asthma medication

In contrast to studies using FHSA data this approach allows us to look at details of treatment in patients with asthma and COPD separately.

P5 AN ANALYSIS OF THE DATA PRODUCED BY THE ASTHMA CHRONIC DISEASE MANAGEMENT PROGRAMME (CDMP), AND THE PRESCRIBING ANALYSIS AND COST (PACT) DATA IN SUFFOLK

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INTRODUCTION: The asthma Chronic disease management Programme is organised for the management of patients with asthma in primary care. Data is collected on patient numbers, age and sex, numbers on prophylactic medication, and hospital admissions. PACT data is an analysis of all prescriptions dispensed, and is distributed to general practitioners on a three monthly basis.

METHOD: 1994-5 CDMP data reported to Suffolk Heath was analysed and where appropriate compared with PACT data (for a three month period in 1995).

RESULTS:

1. CDMP asthma incidence

	Ages 0 - 14	All age groups
Mean reported incidence	10.3%	6.7%
Range	2.2% - 30.1%	1.6% - 14.7%

2. PACT Mean Bronchodilator prescribing/CDMP reported asthmatic = 1.7 items/3 months (range 0 - 6.87)
3. CDMP Mean % of asthmatics on prophylactic therapy = 60.25% (range 5.2% -120.7%)
4. PACT Mean prophylactic/Bronchodilator prescribing rate (as indication of percentage of asthmatics on prophylactic therapy) = 0.58 (range 0.34 - 1.3)
5. Mean Variation between CDMP % of asthmatics on prophylactic therapy and PACT prophylactic/Bronchodilator prescribing rate = 1.17 (range 0.06 - 2.91)
6. Mean hospital admissions = 6.9 (range 0 - 44).

DISCUSSION: In Suffolk general practices (1994-5):

Reported adult (1.6% - 14.7%) and paediatric (2.2% -30.1%) asthma diagnoses appear to show considerable variance between practices, that may not be accounted for by variance in asthma prevalence.

Reported (CDMP) and recorded (PACT) prescribing data of beta2 agonists and inhaled prophylactic medications, appear to show marked variance between practices within the health authority area.

No relationship was found between prophylactic prescribing and admissions

Reported prescribing practice does not appear, in general, to relate to recorded prescribing data.

P6 RELATIONSHIP BETWEEN HOSPITAL ADMISSIONS FOR ASTHMA AND PRESCRIBING IN GENERAL PRACTICE

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Aim: To investigate possible relationships between General Practice (GP) prescribing patterns and asthma hospital admissions.

Methods: All practices in Worcester District for which data were available were included. Data for hospital admissions in the year April 1993-March 1994 with a primary diagnosis of asthma were obtained from Worcester District Health Authority, recorded by age, sex, and GP, and an age sex standardised admission ratio (SAR) for each practice was calculated. Prescribing Analysis and Cost (PACT) data were provided by Hereford and Worcester FHSA . Prescribing rates were calculated as Defined Daily Doses (DDDs) per 1000 patients for each class of respiratory drug. The ratio of inhaled β agonists to inhaled steroids to was calculated. The Townsend Index of deprivation for each practice was calculated from the indices of the electoral wards of residence of patients in the practice.

Results: There were 199 admissions from 30 practices. SAR was significantly correlated with the inhaled β agonist : steroid ratio ($r = 0.44$, $p = 0.019$). After correcting for Townsend Index, the relationship remained significant ($p = 0.033$). There was no relationship between SAR and any other prescribing indicator.

Conclusion: GPs who prescribe relatively more inhaled steroids have fewer patients admitted to hospital for asthma. This may be a contributing factor to the relationship between deprivation and hospital admission rates.

P7 IMPACT OF AN ASTHMA NURSE SPECIALIST ON PATIENTS ADMITTED TO HOSPITAL WITH ACUTE SEVERE ASTHMA

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To evaluate the impact of an Asthma Nurse Specialist (ANS) on patients admitted to hospital with acute severe asthma, studies carried out at commencement of the post in 1993 [Thorax,1993;49:388P] were repeated two years later.

A questionnaire survey was prospectively performed on 50 consecutive admissions with acute severe asthma. Complete data from a postal survey at 1 month post discharge was received from 37 patients in 1995 (74%) and 41/50 (82%) in 1993. Patient characteristics were as follows: 1995 females 24 (65%), 1993 females 30 (73%). Mean age: 1995 42 (range 20-63), 1993 38 (range 18-67 years).

Results: Readmissions within 1 month of discharge: 1995 11/37 (30%), 1993 4/41 (10%). Patients taking oral steroids prior to admission 1995 13/37 (35%), 1993 16/41 (39%). Patients on BTS steps (3,4,5) one month post discharge: 1995 (32%,27%,41%,) 1993 (5%,54%,24%).

Management plan prior to admission: 1995 11/37 (30%), 1993 2/41 (5%). Management plan post discharge: 1995 29/37 (78%), 1993 18/41 (44%). Using a peak flow meter prior to admission: 1995 11/37 (30%), 1993 9/41 (22%). Using a peak flow meter 1 month post discharge 1995 30/37 (81%), 1993 31/41 (76%). Access to Practice Nurse run asthma clinic: 1995 31/37 (84%) 1993 26/41 (63%). Contact with Practice Nurse in last 12 months prior to admission 1995 8/37 (22%), 1993 9/41 (22%). Contact with ANS in 12 months prior to admission: 1995 10/37 (27%), 1993 12/41 (29%) Contact with practice nurse within one month of discharge: 1995 12/37 (32%), 1993 8/41 (20%). Contact with ANS within 1 month of discharge: 1995 11/37 (30%), 1993 3/41 (7%). Contact with GP within 1 month of discharge 1995 23/37 (62%), 1993 22/41 (54%).

Conclusion: Despite increased follow up of patients by asthma nurses and an increase in the number of patients recording peak flow rate and with self management plans, the re-admission rate has tripled. This may be a reflection of patients increased awareness of worsening asthma symptoms or that the 1995 cohort were more severe asthmatics. This may also be compounded by the national shortage of beds at the time of the 1995 study which may have resulted in premature discharge of patients.

P8 DO HOME NEBULISERS PREVENT READMISSION FOR ASTHMA

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Many doctors are aware of patients requesting nebulisers in the belief that it might prevent another admission. In view of the concern about regular bronchodilators we re-examined the audit data which covered 1666 adult patients (median age 41 range 16-94 yrs) admitted for acute severe asthma in 1990/91 to 36 hospitals. 214/1645 (13%) were readmitted within two months. Variables associated with readmission included being older, having greater PEF variability, being on inhaled or oral steroids prior to admission and the use of nebulisers. Readmission rates were: No regular nebulised treatment was used before or after 114/1311 (8.7%); If the nebuliser was stopped during the admission 9/73 (12.3%); If a nebuliser was begun during the admission 18/65 (27.7%); and for patients on regular nebulisers throughout 72/183 (39%). Patients on nebulisers were older (45 vs 40yrs) and included more females (68% vs 59%) but levels of PEF on admission and before discharge, prescription of inhaled steroids on discharge (only 80% with or without a nebuliser) were similar. 75% of nebulisers (185/247) were prescribed by chest physicians but the increased readmission rates (66/141 (46%) chest and 23/71 (32%) general) were independent of physician type. There was a weak correlation (p=0.05) for hospitals who prescribed the most nebulisers to also have the highest readmission rates. Patients on nebulised bronchodilators have more early readmissions for asthma. These data suggest it is unlikely to be just a reflection of disease severity. A prospective study is needed to ascertain whether regular nebulised treatment is appropriate in this situation.

P9 COMPLIANCE IN AN ASSESSMENT PROGRAMME FOR DOMICILIARY NEBULISED BRONCHODILATORS IN PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

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A placebo controlled single blind assessment programme is used routinely for the provision of domiciliary nebulised bronchodilators in our hospital. We have assessed compliance with the programme using a logging compressor (Medic-Aid datalogger and Sidestream nebuliser).

Seventeen patients were studied. The protocol consists of 6 days nebulised placebo, 150mM Na Cl (5 mls) plus Duovent 8 puffs qds via spacer 4 times daily, followed by 6 days of nebulised Salbutamol 2.5 mg and Ipratroprium Bromide 500 mcg (4.5mls) plus 8 puffs of placebo inhaler via spacer 4 times daily. Patients were not told of the logging ability of the machines. Adherence to prescription of nebulised medication, reported usage and actual usage and the time taken to deliver each individual dose were examined.

Reported drug intolerance resulted in 2 patients having a straight 6 day trial of nebulised bronchodilators. In these 2 patients the compliance with prescribed treatment was 10% and 100%. One patient failed to complete the protocol. Of the remaining 14 patients 1 took less than 50% of the doses of nebulised medication prescribed, 3 between 50 and 75% of doses and the remainder over 75% of prescribed doses. Patients reported usage was overestimated, mean actual usage was 88% of that reported (range 63 to 98). The time spent nebulising each individual dose was very variable. The mean time nebulising individual doses was 11.3 (SD 3.3) minutes with a range of 1 to 27 minutes.

These data show that a significant minority of patients fail to comply with the dosing regime and instructions. Consideration should be given to routine use of logging compressors in nebuliser assessment programmes, to ensure valid conclusions are reached.

P10 ANALYSIS OF ATTITUDES OF ADULT PATIENTS TOWARDS ASTHMA MANAGEMENT

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A recent survey amongst 401 GPs has suggested that many GPs consider inhaled asthma medication to be a special case, and less suited to generic prescribing than other areas of medicine (GP Cross Disease Generic Survey, Allen & Hanburys, Data on file, 1996).

In contrast the author has conducted a postal survey amongst 1096 UK adult asthma patients in 73 practices, to determine their attitudes towards asthma, their compliance and confidence with their inhaler devices and how this may be affected by a change, for example to generics.

Results

1. 81% of patients feel it is important to get the inhaler they are familiar with each time they get a new prescription, as they trust it and can rely on it to work.

2. One fifth of patients would have concerns if their inhaler were to change.

3. The majority of patients would feel uncomfortable if they were away from home without their reliever inhaler, and one fifth would panic.

4. 40% of patients said their reliever inhaler lasts no more than 4 weeks; and of the patients who do not take their preventer inhaler as often as prescribed, half say they forget, or only take it 'when their asthma is bad'.

5. Almost one third of patients (31%) feel that having asthma **does** make a difference to what they can achieve in life, and 44% say that being familiar with their inhaler makes them feel more confident about their asthma.

The results suggest that patients develop confidence and trust in their regularly prescribed medication. Compliance is a major issue in asthma management, and GPs should consider carefully the impact on patient compliance of changing to a generic medication.

P11 PROVISION OF PRIMARY CARE ASTHMA SERVICES IN IN THE UNITED KINGDOM

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This is a preliminary report from a prospective, longitudinal, parallel group study, evaluating the effect of educating 466 practice nurses enrolled on the NATC Diploma in Asthma Care Course during 1995/6. When complete, this study will provide information on changes in delivery and markers of asthma care, over 1 year, in about 500 UK general practices serving over 3 million people. **Baseline data: a) Delivery of care and level of asthma interest(questionnaires) in 466 practices:** 48% of other nurses (not currently enrolled on the course) in these practices had previous training in asthma care and 144(31%) had attained the NATC Diploma, suggesting that these practices continued to be keen to improve their quality of care. 28% of the practices employ at least 1 full time nurse and over 37% at least 2 part time nurses. 55% of practices provide formal asthma clinics, 37% organised their care ad hoc while 7.5% did not provide any organised asthma care. **b) Markers of asthma care:** i) The mean age of diagnosis in 4608 children born in 1987 was 4.4 years (95%ci 4.3-4.4) On average, 80.4%(95%ci 78.2-82.5) of these children were diagnosed within the practice and 62.9% (95%ci 62.4-63.3) were currently(during the previous year) prescribed inhaled steroids . This data confirms previous suggestions (Eur Resp J 1994;7(18):91s) that childhood asthma is being diagnosed earlier. ii) Prevalence of diagnosed asthma in 466 practices at the start of the study: 209,612 patients (6.9%) are diagnosed asthmatic: the table shows the distribution of mean prevalence of diagnosed asthma by sex and age: These figures are higher than those quoted nationally (Asthma,HMSO 1995, ISBN 0113218974) and may reflect the relatively high level of asthma interest in these practices.

	<5yrs	5-14yrs	15-44yrs	45-54 yrs	55-64yrs	>65yrs
m	6.8%	12.4%	5.6%	3.8%	4.9%	5.9%
f	4.4%	9.3%	5.9%	5.1%	5.9%	5.2%

The NATC network of trained asthma nurses will provide a unique primary care data set which has the potential to delineate changing patterns of asthma care within the UK.

P12 ACCESSIBILITY AND HEALTH SERVICE UTILISATION FOR ASTHMA IN NORFOLK, ENGLAND

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In the predominantly rural county of Norfolk, England, a confidential enquiry into asthma deaths found a recurrent issue is a poor understanding of the condition amongst sufferers, leading to delays in seeking care (Thorax 1993; 1117-20). Using the results of a questionnaire survey, we examined the relationship between accessibility and health service utilisation in a sample of young adults in Norfolk. The study was based on 9764 responses from the Norfolk Respiratory Health Survey. Amongst those, 591 reported having suffered an attack of asthma in the previous 12 months. Using logistic regression, the analysis concentrated on associations between the use of health services and their accessibility. Utilisation behaviour was found to be associated with respondents' smoking status, and the socio-economic characteristics of their neighbourhood. However, associations with measures of health service accessibility were also apparent. Respondents reporting asthma were less likely to have ever visited a GP if they lived outside a settlement containing a surgery (Odds ratio 3.07; p=0.03), and the likelihood of consultation declined with distance from a surgery (Odds ratio for a 1 kilometre increase in distance, 0.79; $p < 0.01$). Those living further from an acute hospital unit were also less likely to have consulted a hospital doctor in the previous 12 months (Odds ratio for a 1 kilometre increase in distance, 0.95; $p = 0.01$). Our finding of lower levels of health service utilisation amongst some self-reported asthmatics living further from health facilities suggests that the condition of certain individuals might be poorly treated, which could increase the risk of fatality.

P13 SOCIAL DEPRIVATION, CHILDHOOD ASTHMA AND HEALTH SERVICE UTILISATION

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It is uncertain whether social deprivation influences how and where children with asthma are managed. A group of 1504 children aged 1-15 with asthma or asthma like symptoms from 12 general practices were identified [Bryce FP et al Controlled trial of an audit facilitator in the diagnosis and treatment of asthma in general practice. BMJ 1995 310 838-844]. An index of deprivation based on 1991 census data was assigned to each child by home postcode. The identified cohort were divided into quartiles based on this index of deprivation and the patterns of care in general practice and hospital over a 4 year period were examined.

Between 1990 and 1994 there were progressively more children treated with inhaled steroids, (6.4%, 12.2%, 16.2% and 19.9% respectively in each year), but this was independent of their index of deprivation.

Children in the most favourable social quartiles attended their GPs more often for routine review of their asthma (725, 701, 557, 487 respectively in each quartile), although patient initiated consultations were similar in all quartiles (745, 804, 939, 743). Socially deprived children had a higher rate of attendance at hospital outpatient clinics (199, 100, 251, 216) and were admitted to hospital more often than their more affluent contemporaries (23, 22, 27, 52).

Social circumstances do not appear to affect the treatment step of children with asthma, but do have a bearing on patterns of health service utilisation. Children with adverse social circumstances may receive less preventative follow up care in general practice and a consequence of this may be more hospital admissions and outpatient attendances.

P14 CHARACTERISTICS OF THOSE ASTHMATICS WHO REPEATEDLY SELF-REFER TO THE ACCIDENT AND EMERGENCY (A&E) DEPARTMENT

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This study evaluated the characteristics of patients who self-presented to A&E at the Royal Liverpool University Hospital with a computer coded diagnosis of asthma between 1/1/95 and 31/7/95. Three hundred and sixty two patients had 417 consecutive asthma attendances, of which 42 attended more than once (average number of multiple attendances 2.3 [range 2-5]). The average age of the repeat attenders was 42 yrs (range 18-72), 31 were female (74%). Patients were grouped according to age: 18-30 yrs (17 patients), 31-49 yrs (12 patients), 50+ yrs (13 patients). Variables including disease severity at presentation (as judged by BTS treatment steps), outcome (admitted or discharged), and day and time of presentation were compared. In all groups females predominated (12/17, 10/12, and 9/13 respectively). Trend analysis revealed that the 18-30 yrs group was more likely to have mild/moderate asthma (BTS steps I - III) ($p<0.005$) and were less likely to be admitted ($p<0.007$), compared to the other 2 groups. The majority of the 18-30 yr group presented between 9am and 7pm on weekdays, a time when GP surgeries are open.
These results suggest that there is a cohort of younger, mainly female, mild/moderate asthmatics self-presenting to A&E who are subsequently not admitted to hospital. We believe that repeat attendances to the A&E department in this age group may be avoided by better liaison with the patients GP, an ideal role for an asthma nurse specialist.

P15 IMPROVING THE EMERGENCY CARE OF ASTHMA PATIENTS BY LONDON AMBULANCE SERVICE (LAS)

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Background: With continuing concern about unacceptably high mortality and morbidity amongst asthma sufferers, the LAS carried out an audit of the care given to asthma patients who have recently been trained in the administration of nebulised salbutamol.
Objectives: (1) To assess accuracy of diagnosis of crews and appropriateness of treatment (2) To assess adherence to protocol.
Methods: A&E cards and pre-hospital report forms were analysed for all patients who were given nebulised salbutamol by LAS crews or who were diagnosed with asthma after transportation to one of four participating A&E departments between January and March 1995.
Results: Of the 252 patients in the study, 15 who were nebulised pre-hospitally received diagnoses other than asthma in A&E. Of those patients diagnosed in A&E with asthma, 79 were not nebulised by the LAS. 37 of these lay outside current protocols; 16 were not recognised by the crew as suffering from an asthma attack. Peak flows, pulse rates and respiratory rates were recorded by LAS in 46%, 72% and 52% of cases respectively. Adherence to drug administration protocols was high (97%).
Discussion: Following this audit protocols are being reviewed. A new patient report form is being introduced and LAS trainers will stress the importance of taking and documenting objective measurements. In these ways we hope to improve the quality of care for asthma sufferers in an acute attack. We will reaudit in 1997 to evaluate the effects of changes made as a result of evidence from this audit.

Thorax 1996;**51**(Suppl 3)

P16 CURRENT MANAGEMENT OF ASTHMA IN PRIMARY AND SECONDARY SCHOOLS IN WOLVERHAMPTON

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Previous studies into the management of asthma in schools highlighted many deficiencies in knowledge, procedures and the handling of asthmatic medication in state schools. In order to improve the management of asthmatic children whilst at school and to provide an educational resource for teachers, the National Asthma Campaign (NAC) produced a comprehensive information pack for schools (1991).

Aim: To determine whether in state schools in Wolverhampton there was a consistent policy for the management of the asthmatic child.

Methods: A questionnaire was sent to the headteachers of 130 state schools (16 secondary) requesting information on asthma registers, training of staff, procedure for dealing with an asthma attack and staff responsible for asthmatic children. Data are given in the form (Nursery: Infant: Junior: Primary: Secondary).

Results: 80 schools (6: 14: 13: 34: 13) responded. Of the 22011 children registered, 2051 (9.3%) had asthma. Most schools had an asthma register (6: 11: 7: 22: 11) and a procedure to deal with an asthma attack (5: 13: 8: 24: 11). Information to classmates about asthma attacks and when to call staff was variable (0: 5: 6: 18: 6). Older children were generally allowed to carry their own asthma medication (0: 4: 5: 16: 13). In most schools staff had been given formal training (5: 10: 4: 19: 8), but many schools still wanted further information about asthma (5: 9: 9: 27: 8) and were interested in staff attending an asthma course (4: 7: 7: 18: 6:). The responsibility for a child who become ill at school was headteacher (26%), staff (33%), first-aider (16%), headteacher/first-aider (14%) and others (11%).

Conclusion: The overall management of asthma in state schools in Wolverhampton lacks consistency. Whilst the NAC guidelines may have contributed to an overall improvement in the management of asthma in schools in the UK since 1991, the need for more consistent policies in state schools within Wolverhampton is evident.

P17 A STUDY OF CULTURAL ISSUES RELATING TO ASTHMA AND IT'S MANAGEMENT AMONG ASIAN PATIENTS

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Introduction: The prevalence of asthma varies in different ethnic groups. We studied whether acceptability of the diagnosis, treatment recommendations and self-management plans were potentially influenced by the cultural practices and beliefs of the patient.

Method: 140 patients of 5 different Asian ethnic origins were identified as having asthma from GP diagnostic registers. A questionnaire relating to cultural, religious and medical beliefs which might affect asthma management in the individual was administered in the preferred language.

Results:

Preferred Adviser	Doctor	Nurse	Pharmacist	Hakim	Other
General advice	52%	11%	14%	10%	13%
Severe asthma	75%	6%	1%	1%	17%

60% had had minimal or no explanation of asthma from a doctor/nurse.
50% felt asthma treatment was ineffective or harmful if taken regularly.
67% felt that religious practice caused them to stop asthma medication.
21% of respondents and 22% of their families felt that asthma was a big problem, disaster or punishment.
14% (of whom 64% were female) believed asthma would affect marriage prospects, 8% the ability to have children and 34% family life.
The following precipitants of asthma (in addition to those commonly recognised) were identified - cooking smoke 27%, fizzy drinks 20%, "balance of forces" 13%, spicy foods 15%.
36% perceived asthma to be a "cold" and 11% a "hot" disease.
53% think a Hakim's (traditional doctor's) medicine as good as, or better than Western medicine. 8% made their own medication.
The preferred methods for therapy administration were: 36% inhaler, 19% tablets, 19% liquid, 16% injection and 7% other.

Discussion: These findings suggest that cultural issues may be important in asthma treatment and self-management. An understanding of these issues could help in planning treatment and health gain strategies.

P18 DO WHITE EUROPEAN AND INDIAN-SUBCONTINENT ASTHMATICS DIFFER IN THEIR QUALITY OF LIFE ?

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Although primarily designed as an evaluative instrument, the Asthma Quality of Life Questionnaire (AQLQ) [Juniper EF et al, Thorax 1992;47:76-83] also has discriminative properties and has previously been used to compare groups [Malo JL et al, J Allergy Clin Immunology 1993;91:1121-7]. We have prospectively applied the AQLQ to asthmatics with a wide range of lung function (mean FEV_1 % predicted 76 %, SD±20) from areas of high ethnicity and medium or high socio-economic deprivation (1991 National Jarman >40) inner City Birmingham (U.K.) in a community based asthma study (mean ±SD patient age 34.5 ±15 years, range 11 to 59) and presently report on (1) the cross-sectional findings in relating health quality measures to clinical and functional parameters, and (2) a comparison of the quality of life between White European (W/E) and Indian Subcontinent (ISC) (34% non-English speaking) groups. For the group as a whole (n=689), mean overall AQLQ scores correlated weakly but highly significantly with indices of obstruction including FEV_1 % predicted ($r=0.35$, $p<0.001$) and PEFR % predicted ($r=0.31$, $p<0.001$). Analysing groups separately, the correlations were comparatively stronger for the W/E (n=345) than ISC (n=344) groups, respectively FEV_1 % predicted $r=0.38$ versus $r=0.32$ and PEFR % predicted $r=0.44$ versus $r=0.22$, all $p<0.001$; individual domains (activity limitations, symptoms, emotional function and exposure to environmental stimuli) correlated in the same pattern with comparatively slightly higher values for the W/E group. Analysing unpaired data (Mann-Whitney U) the AQLQ (either overall score or individual domains) failed to discriminate significantly between the two groups; the biggest difference was with emotional function where the ISC were more problematic. The weak correlations between AQLQ overall scores and lung function are consistent with the original published data. The comparatively weaker correlations for the ISC may reflect on greater variability in perception of airway narrowing in this group and a lower threshold to the reporting of disease.The AQLQ is equally valid in ISC as compared to W/E but has not been able to discriminate cross-sectionally between the groups; this may be due to similar asthma control (activity limitation and symptoms), similar socio-economic backgrounds, more ISC now U.K. born (58.4%) and less prone to educational / language barriers, or changing attitudes amongst the ISC group to asthma as a disease.

P19 DIFFERENCES IN ASTHMA MANAGEMENT BETWEEN WHITE EUROPEAN AND INDIAN SUBCONTINENT GROUPS

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Against a background of similar prevalence rates and severity of acute asthma, reasons for the higher hospital admission rates observed in Asian (Indian Subcontinent, ISC) compared to White European (W/E) groups have been hypothesised to include cultural differences such as a reluctance in accepting the diagnosis of a chronic disease, reduced compliance with prophylaxis [Ormerod LP. Respir Med 1995;89:415-7], or may reflect on poor asthma education due to language problems [Ayres JG. Brit J Dis. Chest 1986;80:242-8]. We report on how educational factors may manifest as ethnic differences in management amongst 344 ISC and 345 W/E asthmatics, overall mean age 34.5 years (SD±15, range11-59), and mean FEV_1% predicted 76% (SD±20) from districts of high ethnicity and medium or high socio-economic deprivation (1991 National Jarman >40) in inner City Birmingham. 42% of the ISC were non U.K.born, 34% spoke no English, and 9% had never attended school. Comparing the two groups (figures as % in each group, respectively ISC versus W/E, analysis by χ^2), although the numbers reporting previous asthma education did not differ (65% vs 69%, NS), more of the W/E had been taught about the mechanisms of airway narrowing and symptom recognition (31% vs 52%, $p<0.001$), advised about triggers (42% vs 54%, $p<0.01$), and had peak flow meters (23% vs 35%, $p<0.001$). Education about medications (46% vs 50%, NS) and inhaler technique (60% vs 64%, NS) did not differ, and nor did the numbers prescribed anti-inflammatory medications (75% vs 79%, NS), but the number who actually understood the role of their medications (42% vs 57%, $p<0.001$), self reported full compliance (64% vs 74%, $p<0.02$), and had been advised on self management plans (12% vs 21%, $p<0.01$) varied significantly. Follow up rates at GP asthma clinics were not different (34% vs 33%, NS), but more of the ISC were also being followed up at hospital (13% vs 5%, $p<0.001$). Although more of the ISC had previous asthma related hospital admissions (33% vs 25%, $p<0.01$) attendances at A&E had not differed (15% vs 17%, NS). The management of both ethnic groups has centred on drug prescription and compliance rather than developing an understanding about the disease and self management; as this is more noticeable for the ISC group it probably reflects the differing educational and language skills which need to be addressed more appropriately.

P20 The Management of Pulmonary TB in England and Wales in 1993.

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The management of 925 cases of pulmonary TB reported to the 1993 National TB notification survey is analysed and audited against recommended standards. 447 (48%) were white, 337 (36%) were asian and 141 (15%) of other ethnic origin. 794/920 (86%) were treated by thoracic physicians, the other 121 (14%) by a variety of other clinicians. 411 (44.4%) were positive on sputum microscopy, culture confirmation was obtained in 591 cases. 869/920 (94.5%) were commenced on recommended drug combination initially, but only 677/920 (74%) overall received a recommended regimen, with thoracic physicians significantly more likely to use standard therapy (Chi2 14.9:1df:P< 0.0001). Non-standard durations of either initial and/or continuation phases were used in 303 patients. In 167 there were satisfactory reasons for these modifications. Definite or suspected drug toxicity was reported in 79 (8.6%) of patients and was significantly higher in non-standard regimens. 72 patients (7.8%) died before the survey was carried out 1 year after notification, TB n=15 non TB n= 57. Of the 815 cases remaining at treatment completion, 430 (52.7%) were discharged at the end of treatment. There were adequate reasons for follow up in the majority. Continued efforts need to be made to increase the proportion of patients being treated with evidence based regimens and durations, to avoid unnecessary follow up and to save resources.

P21 MANAGEMENT OF PULMONARY TUBERCULOSIS IN ADULTS NOTIFIED IN SCOTLAND IN 1993

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Notifying consultants were asked to complete survey forms relating to treatment of cases of notified tuberculosis (TB) in Scotland in 1993.Forms were returned for all 351 cases of pulmonary TB notified in patients over 14 years of age. Bacteriological confirmation was made by both smear and culture in 144 cases, by culture alone in 67 cases, and by smear alone in 28 cases.
172 cases (49%) received isoniazid (H), rifampicin (R) and pyrazinamide (Z) as initial treatment, then H and R as continuation treatment - regimen HRZ/HR; 31 (8.8%) received H,R, Z and ethambutol (E) initially, then H and R - HRZE/HR; 8 (2.3%) received H,R and E then H and R - HRE/HR; on 30 forms (8.6%) no treatment for TB was described; on 48 (13.7%) forms no continuation treatment was described after initial therapy with HRZ or HRZE; in 28 (8%) of cases ethambutol was prescribed in continuation; 34 (9.7%) cases received a different drug combination from those described. Among the 321 patients receiving initial therapy, H and R together comprised part of the treatment in 316 cases (98.4%).
Detailed information on treatment given was available for 165 patients given HRZ/HR, and 28 given HRZE/HR, as described below. Initial treatment lasted for more than nine weeks in 53 (32%) cases receiving HRZ/HR and in 15 (54%) cases receiving HRZE/HR. 5 patients prescribed HRZ/HR and one prescribed HRZE/HR were still taking continuation therapy one year after treatment began. Chemotherapy was completed as planned in 129 (78%) patients given HRZ/HR and in 20 (71%) patients receiving HRZE/HR. Treatment was modified because of drug toxicity in 7 cases completing HRZ/HR and in 3 cases completing HRZE/HR. Treatment modification due to toxicity was less common in patients completing HRZ/HR than among those completing drug combinations other than HRZ/HR, HRZE/HR or HRE/HR.
These results suggest that there is significant variation in the drug regimens prescribed for treatment of pulmonary TB in Scotland, and in the duration of treatment, often at variance with existing treatment guidelines. Greater uniformity in treatment in accordance with existing guidelines should improve the overall treatment of pulmonary TB in Scotland.

P22 Management of Lymph Node TB in England and Wales 1993

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The management of 219 cases of lymph node TB reported to the 1993 National Survey was analysed. The diagnosis was supported by histology in 151 (69%), by bacteriology in 197 (49%) and made just clinically in 40(18%) of cases. 193 (88%) were treated by thoracic physicians, the remaining 26 (12%) by a variety of clinicians. 81/219 (82.5%) were from ethnic minority groups. Drug resistance was reported in 9/107 cases (8.4%), all in ethnic minority patients, with no combined Rifampicin/Isoniazid resistance. 211/218 were commenced on a recommended drug combination, but only 176/218 overall received a recommended regimen, with thoracic physicians more likely to use standard therapy. (Chi2 6.99:1df:P = 0.008). Non-standard durations of either initial and/or continuation phases of treatment were used in 83 patients. In 49 there were satisfactory reasons for these modifications, but not in 34 (19%). Definite or suspected drug toxicity was reported in 22 (10.1%) of cases, and was significantly more likely with non-standard regimens. Of the 209 observed to treatment completion, 129 (62%) were discharged at completion of treatment. There were adequate reasons for follow up in the majority not discharged, but not in 32 (15%). Whilst the overall results were satisfactory, as with pulmonary TB, further efforts need to be made to increase the proportion treatment with recommended regimens and durations, to avoid unnecessary follow up, and save resources.

P23 Cutaneous TB - A 15 year prospective series 1981 - 95

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1065 cases of TB were notified in this district of 265000 between 1981 and 1995 inclusive. 47 (4.4%) had forms of cutaneous tuberculosis. 11 had post primary forms, 6 being classified as lupus vulgaris, 4 as metastatic TB and 1 as orifical TB. 10 cases had one of the tuberculides being classifed as papulo necrotic tuberculide (n=1), erythema induratum (n=5), migratory panniculitis (n=1), and erythema nodosum related to TB (n=3). Primary skin TB was thus seen in 21 patients, 2.0% of the total, all but one of the cases being of non-white ethnic origin. This difference (white 1/315 vs 20/750 non-white) was highly statistically significant (Chi2 17.78:P < 0.0001). 26 cases of skin tuberculosis had adjacent structural disease (scrofuloderma). All were confirmed by histology or by bacteriology (n=20). Skin involvement occurred in 13/198 (6.6%) with peripheral lymph nodes, in 9/63 (14.3%) with bone/joint disease, and in 2/38 (5.3%) with genito-urinary disease. Scrofuloderma was seen in 8/315 white and in 18/750 non-white cases, a difference which is not significant (Chi2 0.019).

Skin tuberculosis occurs in a small, but important proportion of patients in a district of the United Kingdom with over 70% of notifications from ethnic minority groups.

P24 HOW VALUABLE ARE ROUTINE BRONCHIAL WASHINGS FOR TB STUDIES?

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The value of examining bronchial washings for mycobacteria in every patient undergoing bronchoscopy is unclear.
The results of microscopy and culture for mycobacteria in bronchial washings from 1643 consecutive bronchoscopic examinations were evaluated retrospectively.
Overall, 19 specimens (1.2 %) were positive for mycobacteria by microscopy and/or culture. Of these, 16 (1% of all specimens) were considered to be genuine mycobacterial infections, and 3 were considered to be false positive results. The three false positive cases were each AFB smear positive, but culture negative, and were subsequently diagnosed as having lung cancer. Presumably the tumour displaced dead mycobacteria from old granulomas.
Analysis of the 16 true positive results showed that 9 of these patients (56 %) underwent bronchoscopy for suspected tuberculosis. Five (31%) were thought to have cancer on clinical grounds and the diagnosis of mycobacterial infection was unexpected. The remaining 2 (12 %) positive patients were bronchoscoped for ill defined upper zone abnormalities.
Nine out of 59 patients (15 %) in whom the indication for bronchoscopy was suspected or possible tuberculosis were actually positive. The indication for bronchoscopy in the majority of patients (1057) was suspected cancer. Of these, mycobacterial infection was diagnosed in 5 (0.5 %) of whom two had endobronchial lesions mimicking cancer.
In conclusion, the overall yield of mycobacteria from bronchial washings is low even in those with suspected tuberculosis. However, in view of the consequences of a missed diagnosis of tuberculosis, the examination of bronchial washings for mycobacteria is a valuable exercise, and should not be limited to those in whom tuberculosis is suspected on clinical grounds.

P26 A PROGRAMME OF DIRECTLY OBSERVED THERAPY FOR TUBERCULOSIS IN LONDON

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Directly Observed Therapy (DOT) is the process whereby the nurse or doctor observes the patient ingesting antituberculous medications. At St George's Hospital, a programme of DOT has been established within the Chest Clinic. Data was collected retrospectively on all patients who entered the DOT programme from 1/95 to 7/96: 37 patients were enrolled in total. 28/37 (77%) were male. Mean age at entry was 39 years (17-76 yrs). Reasons for inclusion are summarised below. At the time of data collection 15 patients had completed the programme, 17 patients were receiving DOT, 1 patient had died, 2 patients had left the UK permanently.

Reason for DOT	%	Reason for DOT	%
Previous treatment	35	Alcohol excess	14
Non-acceptance	16	Psychiatric disorder	11
of diagnosis		Social isolation	5
Resistance risk	16	Prior non-compliance	3

All patients remaining in the UK have either completed or currently receive DOT. The programme was implemented without additional funding. Medication is administered thrice weekly by specialist TB nurses, in a dedicated room.
Drugs are given singly. Biochemical and haematological monitoring are arranged by the nurse. Continuity of care allows ongoing patient education and support, and rapid detection of adverse effects of medications.

In conclusion, we have shown that it is possible to implement an effective programme of DOT for TB within a pre-existing NHS Chest Clinic.

P25 RAPID DETECTION OF MDR-TB IN CLINICAL SAMPLES

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Clinical management of infection with multi-drug resistant *M. tuberculosis* (MDR-TB) poses a serious problem for clinicians, not least since diagnosis by conventional microbiological techniques may take many weeks or months. This study reports the use of a rapid approach to making the diagnosis in the setting of suspected nosocomial spread of MDR-TB. Sputum and bronchoalveolar lavage (BAL) samples were examined from two immunocompromised patients who were contacts of the index case. Resistance to rifampicin was identified using the PCR based Inno-LipaRifTB kit and confirmed by automated sequencing. Strain typing was performed using the PCR method of spoligotyping. Sputum from one of the suspected patients was found to contain an identical strain of *M. tuberculosis* to the index case, and M. *tuberculosis* DNA in the sputum had a point mutation in the rpoB gene identical to that identified in the isolate from the index case, thus indicating rifampicin resistance and likely nosocomial spread. These results were reported to the clinicians within 48 hours of the time of sputum collection.
From the second suspected patient, sputum was unavailable and BAL was smear negative. However, the BAL was found to contain *M. tuberculosis* DNA without any mutations on the rpoB gene, indicating the presence of an unrelated organism with rifampicin sensitivity, and allowing the patient to be discharged from hospital on conventional triple therapy. This methodology appears to offer a rapid aid to diagnosis for the clinician faced with a patient with suspected MDR-TB.

Research supported by the British Lung Foundation

P27 DISTRIBUTION OF CASES IN A BOROUGH WITH A HIGH INCIDENCE OF TUBERCULOSIS

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Attention has recently focused on social and economic factors which might influence the differing rates of tuberculosis between districts in the UK. Doherty et al. (Thorax 1995;50 Suppl.2:A60) showed that in London boroughs, ethnicity and deprivation independently contributed to tuberculosis rates. Newham, in the East End of London, is one of the the most socially deprived boroughs in the UK. Ethnic minorities make up approximately 50% of the population. The incidence of tuberculosis is high: in 1995 there were 148 notified cases, a rate of 68 per 100,000 population. However, within Newham the rate of tuberculosis varies widely between wards. The purpose of the present study was to examine the relative effects of deprivation and ethnicity on the distribution of tuberculosis cases in Newham.

Tuberculosis notification rates for 1995 were evaluated for each ward in Newham. The Jarman deprivation index and the proportion of ethnic minorities for each ward was calculated from 1991 census data. The relative effects of ethnicity and deprivation on tuberculosis rates within wards was examined using stepwise multiple regression analysis. (Preliminary examination of the data did not reveal a correlation between ethnicity and deprivation). Ethnicity significantly contributed to the variance in tuberculosis between wards ($F = 16.7$, $p < 0.0001$), but deprivation did not. These results indicate that tuberculosis is more common in those wards in Newham where a higher proportion of subjects from ethnic minorities reside.

From the 1991 census data the Jarman indices for London *boroughs* show a median value of 25, and range of -12 to 73. The comparable figures for Newham *wards* confirm greater deprivation (higher scores), with less variability (median 41, with a range of 23 to 53). This more constant level of poverty seen throughout Newham may partly explain the apparent inability to demonstrate an association between tuberculosis rates and Jarman Index in the present study.

P28 Recent increases in tuberculosis notifications in Liverpool: the influence of immigration.

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Although other British cities exhibit a higher annual incidence of tuberculosis, no city's rates are currently rising faster than those of Liverpool (*CDR Review* 1995: 5; R29-R33). After reaching a low in 1987, notifications have gradually increased since. This study assesses the contribution of immigration to these rising tuberculosis rates.

Ethnic origin was assigned by name to all notified cases of tuberculosis in Liverpool retrospectively from 1974 to the present. In addition, average tuberculosis rates were calculated for each of the thirty-three council wards in Liverpool for 1981-85 and 1991-95. Multiple regression was used to determine the independent effects of various socio-economic and population measures from the 1981 and 1991 censuses in explaining these ward-based rates.

Since the mid 1970s, there has been a steady increase in the percentage of non-white cases of tuberculosis : from 8.7% in 1975-77, 15.1% in 1981-83, 17.5% in 1987-89 to 28.0% in 1993-95. The probable influence of immigration on tuberculosis in Liverpool was reinforced by the multiple regression analysis: in 1981 only unemployment showed a significant independent relationship with tuberculosis rates but in 1991 two indices of deprivation (overcrowding and elderly living alone) and ethnicity (proportion of households headed by a person born in the new commonwealth) significantly influenced tuberculosis rates.

The increasing proportion of non-white tuberculosis cases in Liverpool over the last 20 years, despite a decline in total cases before 1987 and increasing rates since, is not consistent with idea that immigration has influenced the recent increase. However, the fact that ethnicity now independently explains some of the council ward variations in tuberculosis rates but did not in the early 1980s, suggests that immigration does influence the distribution of disease within the city. It is possible that immigrants are more likely to live in the poorer areas of Liverpool.

P29 COMPARISON OF IS6110-RFLP AND SPOLIGOTYPING FOR THE ABILITY TO TYPE STRAINS OF *M. TUBERCULOSIS*.

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The ability to type strains of *M. tuberculosis* offers the potential to track the spread of infection and identify the location and patterns of behaviour promoting transmission. The main typing methodology of IS6110 restriction fragment length polymorphism (IS6110-RFLP) requires prior culture of the organism and results are available several months after sample collection. A new technique termed spoligotyping can be performed directly on sputum and results are available within a few days of sample collection. To compare these two methods, *M. tuberculosis* isolates from 167 patients attending three London hospitals were analysed by both IS6110-RFLP and spoligotyping. Isolates sharing DNA patterns with other isolates, which thus raise the possibility of clusters of cases, were found using IS6110-RFLP in 56 patients, using spoligotyping in 100 patients, and using both techniques in 32 patients. Conversely, unique DNA patterns were found in 111 patients by IS6110-RFLP, 67 by spoligotyping and 135 by combining both methods. These results indicate that IS6110-RFLP has a higher level of discrimination than spoligotyping. On the other hand spoligotyping was more useful for the analysis of isolates with few bands on IS6110-RFLP. The advantages in terms of speed of spoligotyping suggest that an optimal approach may involve spoligotyping with later confirmation by IS6110-RFLP.

Research supported by the British Lung Foundation

P30 A STUDY OF THE EPIDEMIOLOGY OF SPUTUM-POSITIVE PULMONARY TUBERCULOSIS IN HARARE, ZIMBABWE - ANALYSIS BY SPOLIGOTYPING

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There has been a 4-fold increase in cases of tuberculosis (TB) in Harare over the last 10 years. While HIV co-infection rates exceed 40%, it is uncertain which socio-economic factors contribute to this epidemic, and whether the increase is due to reactivation of latent disease or recent transmission. Ambulatory adults attending a chest clinic with clinical or radiological evidence of pulmonary TB and at least one smear positive sputum were enrolled over one month. Demographic, socio-economic, clinical and radiological data were gathered using a standardised proforma. Sputum was collected prior to commencement of anti-TB therapy and submitted for genetic fingerprinting by spoligotyping. Patients with identical spoligotype patterns were grouped into clusters. 61 patients were enrolled (median age 28 years; range 18-73; 61% males). The median time in Harare was 11 years (range 0-38), only 4 patients were normally resident outside Harare. 40% of the study population lived in crowded living conditions, exposing 216 children within their households. Using recent Central Statistical Office data, the socio-economic status of these sputum positive adults was indistinguishable from the general urban Harare population. 57% were married, 74% were either formally or informally employed. The median yearly household income was 737 $US (range 0-13,356). The median body mass index was 18.2 (range 13-27) but nutritional intake appeared adequate. Heavy alcohol intake was uncommon. Spoligotyping identified 20 different *Mycobacterium tuberculosis* strains from the sputum of 28 patients, 15 of whom fell into 7 clusters. Whilst these clusters were not closely related geographically within Harare, overcrowding was more common amongst patients in clusters (69% clustered vs 23% not clustered; $p = 0.026$). Interestingly, 2 clusters were found to be geographically related when the location of the patients' original rural family homes were analysed. In conclusion, while clustering of strains in association with overcrowding may be related to recent transmission, clustering within rural homes suggests reactivation of organisms acquired in the past.

P31 EPIDEMIOLOGY AND MOLECULAR ECOLOGY OF *MYCOBACTERIUM TUBERCULOSIS* FROM CLINICAL SOURCES: DNA FINGERPRINTING OF *M. TUBERCULOSIS* ISOLATES FROM CLINICAL SPECIMENS

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The continuing upsurgence of tuberculosis (TB) cases worldwide and the ever increasing numbers of immunocompromised individuals has led to an urgent need for investigations into the epidemiology of *Mycobacterium tuberculosis*, particularly as this organism is again emerging as a major infectious agent. Our investigation was initiated to correlate epidemiological data available to the Southern Health Board and strains of *M. tuberculosis* isolated from culture positive patients in the Cork and Kerry area using genetic fingerprinting technology. In addition, DNA fingerprinting may allow us to define and trace the main clonal lines within the species.
Previously, PCR based techniques have been utilised as a means of identifying *M. tuberculosis* species, however, the purpose of this study was to characterise *M. tuberculosis* isolates at the sub-species level in order to investigate endemic genetic variants within the species. We have adapted a rapid, sensitive and reproducible PCR based technique (AP-PCR) (Welsh and McClelland, *Nucleic Acids Research* 18;24, 1990) to generate informative genetic fingerprints of *M. tuberculosis* isolates maintained in the TB laboratory at St. Stephens Hospital, Sarsfield Court, Cork. AP-PCR (arbitrarily primed polymerase chain reaction) utilises a single, randomly chosen primer to produce a pattern of DNA fragments characteristic / unique to an individual strain, thus allowing differentiation of genetic variants within a species. AP-PCR has been utilised to fingerprint bacterial species such as *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Helicobacter pylori* and *Burkholderia cepacia*, however, this is the first report of its use to genetically fingerprint *M. tuberculosis* isolates. A pilot study was carried out whereby we successfully generated genomic fingerprints of *M. tuberculosis* strains isolated from patients over a two year period. Two distinct strains were identified (A & B) with clonal variants occurring within group A (A1, A2). Results were correlated with conventional epidemiological data. with no identifiable trends.

P32 DNA fingerprinting of Mycobacterium tuberculosis : a tool for prevention and control

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For the efficient prevention and control (and eventual elimination) of tuberculosis it is important that we identify the source of infection. Experience suggests that, in many districts, the source of infection for the majority of cases is unknown, despite a detailed epidemiological investigation at the time of diagnosis.

In areas with a low proportion of ethnic immigrants, such as Liverpool, the source of infection remains within the indigenous population. Increasing epidemiological evidence suggests that today the elderly are at most risk of developing tuberculosis as latent disease reactivates in later life. This group are therefore the largest potential source of transmission of tuberculosis in the community.

The use of DNA fingerprinting to identify identical organism strains allows a more accurate assessment of whether the mycobacterium present has a common origin. A pilot study in Liverpool during 1995 suggested that 3 clusters of infection had occurred in a small sample of just 16 patients. Two of these clusters confirmed a known epidemiological link but in the third no link could be determined. In the latter, 1 patient was known to be highly infectious, suggesting that the strain identification was accurate. These data suggest that that reactivation of latent disease may not be as significant as previously thought but that a community based source of infection is present. There is a strong need to identify this source of transmission and target the population who are at greatest risk for screening and protection.

P33 AN AUDIT OF A RESPIRATORY NURSE TUBERCULOSIS SERVICE

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A protocol for a new follow-up service for patients by hospital-based Respiratory Nurse Tuberculosis Specialists (RNTS) was drafted, based on BTS guidelines for the management of tuberculosis. This included giving patients a full verbal and written explanation of TB and its treatment, with diagrams of the tablet regime and a British Lung Foundation leaflet both in English and the patient's native language, if available. Home visits were arranged within three weeks of the start of treatment and at the two month stage, when pyrazinamide was due to be stopped. Additional visits were made if necessary. Compliance with treatment was assessed at each visit by a pill count.
In the first six months, 29 patients were followed by the RNTS service. 16 (55%) were fully compliant with treatment, while 11 (38%) were only partially compliant and 2 (7%) not at all. Eleven of the non-compliant patients (85%) were immigrants, compared with 6 (38%) fully compliant patients, suggesting that language/ethnic differences were the main cause.
The standard visiting regime was carried out in only 10 cases (34%), with extra visits required for the remainder to ensure compliance. 7 patients (24%) required up to 2 extra visits and 8 patients (28%) had to be visited even more frequently.
19 (66%) patients received standard treatment, while 6 (21%) had an extended period of treatment and 2 (7%) had treatment re-started. 4 patients required directly observed treatment.
There were few problems with GP prescriptions, resulting in only 2 patients being given the wrong/inadequate medication.
Seven patients (24%) failed to attend more than one out-patient appointment. Only one of these was fully compliant with his treatment. Of those patients who attended every appointment or failed to attend only once, 15 (68%)were fully compliant and 7 (32%) were partially compliant.The two patients who were not at all compliant failed to attend numerous appointments. However, the RNTS were unable to gain access on more than one occasion during home visits only 3 times.
In an era of increasing TB prevalence and multi-drug resistance, a service like the RNTS is essential for maintaining compliance and contact with patients, but is very time-consuming.

P34 AUDIT OF TUBERCULOSIS TREATMENT

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We have undertaken an audit of treatment of TB cases notified over a 6 month period (1/11/94 to 31/4/95). Aspects of treatment audited included: duration of treatment during the initial and continuation phases of treatment, drug dosages during the initial and continuation phases of treatment, whether liver function tests were checked before starting treatment, adequacy of treatment of patients with single drug resistance, and adequacy of precautions to avoid side-effects of ethambutol. The standards taken for correct treatment of tuberculosis were those stated by the Joint Tuberculosis Committee of the British Thoracic Society (Thorax 1990;45:403-8). The acceptable range for duration of standard chemotherapy was derived from a previous national audit (Respir Med 1991 ;85:319-23): initial phase of treatment 2 months with a range of 6 to 12 weeks, and a continuation phase of 4 months with a range of 13 to 21 weeks. Data were collected from the case-notes of 48 patients, of whom 40 were planned to receive a standard 6 month course of treatment.

Of the latter, in 37/40 (93%) the duration of treatment during the intial phase of treatment fell within the acceptable range, and in all 40 (100%) during continuation phase. Dosage in the initial phase of treatment was correct in 35/40 (88%), and in 38/40 (95%) in the continuation phase: deviations from the recommended dosage were minor. Thirty-eight out of 46 (83%) patients had liver function tests checked before starting treatment. Two cases with a proven isoniazid resistant organism received treatment for 36 and 52 weeks, and another case with suspected isoniazid resistance was treated for 27 weeks. Five cases were given ethambutol; in two patients this was started abroad. Of the remaining three cases visual acuity was not formally assessed before starting treatment, and in two cases there was no documentation in the case-notes that the patient had been warned about the possibility of visual deterioration. The clinical outcome by the end of treatment was good in all patients apart from one lost to follow-up.

This audit report has been circulated to doctors in Newham who supervise the treatment of tuberculosis, and the areas for improvement have been highlighted.

P35 UNDERSTANDING THE DIFFERENT INFLAMMATORY RESPONSES TO LIVE AND DEAD BCG: A PREREQUISITE FOR IMPROVED VACCINE DESIGN.

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Specific antituberculous resistance appears to be induced following inoculation of live but not dead BCG. This dependence on BCG viability may explain the diverse responses in terms of protective immunity in clinical trials of BCG conducted worldwide over the last thirty years.
In order to dissect out simple parameters which may differentiate a protective from a non-protective response, we have developed a murine *in vivo* model of experimental BCG infection to study the immune response in draining lymph nodes following footpad inoculation with either live or killed BCG preparations. In this model, live but not heat-killed BCG efficiently migrate to the draining lymph nodes and stimulate the early accumulation of mononuclear cells. In addition, live and heat-killed BCG stimulate different responses in terms of the level of expression of interferon-gamma, inducible nitric oxide (iNOS), as well as macrophage and dendritic cell markers in the draining lymph nodes.
This divergent *in vivo* response was reproduced *in vitro* when pure macrophage cultures were infected with BCG and responded differently to live and dead preparations, producing significant levels of TNF and reactive nitrogen intermediates only when infected with live BCG.
Taken together, these observations suggest that the differences encountered *in vivo* may be related to the ability of live BCG to migrate to local lymph node, where they cause the accumulation of cells expressing protective cytokines and therefore inducing an efficient immune response. These findings may have important implications for the design of new anti-tuberculosis vaccines.

P36 THE CORONARY LIGATED RABBIT AS A MODEL FOR PULMONARY HYPERTENSION SECONDARY TO HEART FAILURE: ROLE OF 5-HYDROXYTRYPTAMINE

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Pulmonary hypertension (PHT) is prevalent following chronic left heart failure. *In vitro*, human and animal pulmonary arterial responses to 5-hydroxytryptamine (5-HT) are potentiated in PHT (eg. Wanstall et al., 1990, Eur J Pharmacol., 176, 159-168). Here we evaluated the rabbit coronary ligation model of left heart failure as a putative model for PHT. We also studied the possible role of 5-HT. Experimental coronary artery ligated and sham-operated rabbits were prepared as described by Pye *et al.*, 1996, Cardiovasc Res, 31, 873-881. After 8 weeks, ejection fractions (EFs) were assessed by Doppler echocardiography. The rabbits were anaesthetised and their pulmonary arterial pressure (PAP) monitored via a specially designed cannula inserted via the right jugular vein, right atrium and ventricle. Positioning was confirmed using X-ray image intensification. 5-HT (1-400 μg/kg) was infused i.v.. After termination, the wet weight of the lungs (LW) were determined as well as the right ventricular weight (RVW).

EF was significantly decreased from 78.6±2.2% in shams (n=5) to 43±1.1% (n=4) in the heart failure (HF) group ($P<0.0001$, Students paired *t*-test). Mean PAP was increased from 11.7 ± 0.5mmHg to 16.9±1.0mm Hg ($P<0.01$) in the HF group. 5-HT (200 μg/kg) produced a greater maximum increase in PAP in the HF group (an increase of 8.6 ± 1.11mmHg cf. 3.53±1.2mmHg, $P<0.05$, n=4). 5-HT also produced a decrease in cardiac output measured by thermodilution. The lungs from the HF group were heavier (19.4 ± 4g cf. 11.9±0.3g, n=3) and the RVW was also increased in the HF group (0.69±0.05g/kg body weight cf. 0.42±0.02g/kg body weight, n=3).

These results suggest that this rabbit model of left heart failure is also one of secondary PHT. The hypersensitivity to 5-HT suggests that 5-HT may contribute to PHT secondary to left heart failure.

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P37 ANGIOTENSIN II CAUSES PROLIFERATION OF RAT PULMONARY MICROVASCULAR SMOOTH MUSCLE CELLS

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We have previously demonstrated that angiotensin converting enzyme (ACE) expression is increased in the walls of small pulmonary arteries of rats with hypoxia-induced pulmonary hypertension. Since ACE inhibitors are known to attenuate hypoxia-induced pulmonary vascular remodelling, we hypothesised that local production of angiotensin II (ANG II) by ACE might stimulate smooth muscle cell (SMC) hyperplasia in small pulmonary arteries. To address this question, SMC were isolated from peripheral pulmonary arteries of adult male Sprague-Dawley rats using a modification of a previously described technique (Am J Respir Cell Mol Biol 1994;10:604-12), involving infusion of iron oxide and agarose into the rat pulmonary circulation, partial collagenase digestion, and magnet separation of small vessels from surounding tissue. The SMC phenotype of isolated cells was confirmed by positive immunofluorescent staining for SMC specific alpha actin and myosin. Proliferation of SMC was assessed by growth curves and ^{3}H-thymidine incorporation in response to 0.1% calf serum (CS) and 10% CS, with and without the addition of 10^{-6}M ANG II. In the presence of 10% CS, 24 hour exposure to ANG II caused an 80% increase in ^{3}H-thymidine incorporation compared to 10% CS alone ($p<0.05$). In contrast, ANG II did not stimulate ^{3}H-thymidine incorporation by SMC under serum deprived conditions (0.1%CS). Growth curve studies over 7 days, conducted in the presence of 0.1%CS, showed that ANG II stimulated proliferation in SMC only when cells were primed by preincubation with 10%CS. No proliferation was observed in fully quiescent SMC. These preliminary studies indicate that ANG II functions as a progression factor in the proliferation of rat microvascular SMC. We speculate that local production of ANG II in the walls of small pulmonary arteries may contribute to the vascular remodelling observed in hypoxic pulmonary hypertension.

Supported by the British Heart Foundation.

P38 PEROXYNITRITE IS A VASODILATOR OF RAT PULMONARY ARTERIES AT CONCETRATIONS THAT DO NOT CAUSE ENDOTHELIAL DYSFUNCTION

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Under physiological conditions, the potent dilator gas, nitric oxide (NO) is continuously released by endothelial cells to maintain organ blood flow. Endothelial derived NO is catalysed by endothelial NO synthase (eNOS), which my virtue of its calcium dependency, forms discreet quanta of NO. Under inflammatory conditions, such as occur in septic shock, a calcium-independent isoform of NOS is expressed (iNOS) that produces copious amounts of NO, a process which is thought to contribute to the fall in blood pressure seen in clinical sepsis. In sepsis the presence of large amounts of activated leukocytes results in elevated levels of superoxide anions (O_2^-) which are known to react rapidly with NO to form the potent oxidant peroxynitrite ($ONOO^-$). Recent reports have described $ONOO^-$ as a toxic oxidant that could contribute to endothelium dysfunction in diseases such as septic shock. Since the pulmonary vasculature represents a prime site for oxidant formation, we have characterised the effects of authentic $ONOO^-$ on vascular tone in isolated rat pulmonary arteries. Pulmonary arteries were cut into rings and mounted in 2 ml organ baths containing warmed (37°C) and gassed (95%O_2:5%CO_2) Krebs' buffer. $ONOO^-$ ($1x10^{-6}$-$1x10^{-4}$M) had no effect on resting tone but caused concentration-dependent vasodilatation in vessels pre-contracted (1 g) with the thomboxane mimetic, U46619 ($1x10^{-6}$M). Similarly both acetylcholine (endothelium-dependant) and sodium nitroprusside (endothelium-independent) caused relaxation of pre-contracted pulmonary arteries. In separate experiments we found that pre-incubation of pulmonary arteries with $ONOO^-$, had no effect on subsequent responses to acetylcholine or sodium nitroprusside.

Thus, $ONOO^-$ is a vasodilator of rat pulmonary arteries at concentrations that do not cause vascular dysfunction. These observations detract from $ONOO^-$ being a toxic species in the pulmonary vasculature. $ONOO^-$ causes relaxation in the μM range whereas NO is active in the nM range. Thus, it is tempting to speculate that in conditions where NO is released in excess, $ONOO^-$ formation may quench NO and limit its dilator actions.

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P39 ROLE OF POLY-ADP RIBOSYLTRANSFERASE IN THE VASODILATOR ACTIONS OF PEROXYNITRITE

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The pulmonary vasculature is constantly exposed to oxygen species such as nitric oxide (NO) and superoxide anions which are usually metabolised by anti-oxidant enzymes. However, during inflammatory conditions, oxidants may be formed in excess leading to cellular damage or dysfunction. NO reacts rapidly with superoxide anions to form the putative toxic oxidant, peroxynitrite $ONOO^-$. $ONOO^-$ has been shown to activate poly-ADP ribosyltransferase (PARS) leading to a depletion NAD^+ and ATP, an event that is likely to greatly compromise energetic processes such as the maintenance of vascular tone. We have shown that $ONOO^-$ is a vasodilator of rat pulmonary arteries. Thus, we have investigated the possible contribution of PARS activation in the vasodilator properties of $ONOO^-$. Pulmonary arteries were cut into rings and mounted in 2 ml organ baths containing warmed (37°C) and gassed (95%O_2:5%CO_2) Krebs' buffer. Tone (0.5 g) was induced by the addition of U46619 ($1x10^{-6}$M). Under these conditions $ONOO^-$ ($1x10^{-6}$-$1x10^{-4}$M), acetylcholine ($1x10^{-8}$-$1x10^{-6}$M), and sodium nitroprusside ($1x10^{-8}$-$1x10^{-6}$M) caused concentration-dependent relaxation of pulmonary arteries. The NO synthase inhibitor, N^G-nitro-L-arginine methyl ester ($1x10^{-4}$M), inhibited the effects of acetylcholine but not $ONOO^-$ or sodium nitroprusside. Superoxide dismutase had no effect on any of the vasodilator agents. The PARS inhibitor 3-aminobenzamide ($1x10^{-2}$M) significantly inhibited the relaxation caused by $ONOO^-$ but did not effect that caused by acetylcholine or sodium nitroprusside.

Thus, $ONOO^-$ relaxes rat pulmonary artery directly, without causing the release of NO or superoxide. Moreover, $ONOO^-$, unlike endogenously released NO (by acetylcholine) or nitrovasodilators appears to cause relaxation by activation of PARS. We propose that $ONOO^-$ activates PARS resulting in the depletion of cellular ATP reducing active processes of vascular smooth muscle including vaso-constriction.

This work was support by grants from the British Lung Foundation and the British Heart Foundation.

P40 8-iso $PGF_{2\alpha}$ constricts and dilates rat pulmonary artery.

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8-isoprostaglandin (PG) $F_{2\alpha}$ is an isomer of a newly described group of PG-like compounds (isoprostanes), the majority of which are formed independently of the enzyme cyclo-oxygenase (COX) during conditions of oxidative stress. 8-iso $PGF_{2\alpha}$ contracts various smooth muscle preparations via activation of thromboxane (TP) receptors. However, the potential dilator actions of 8-iso $PGF_{2\alpha}$ have not been addressed. As isoprostanes are likely to be formed in the lung in diseases where oxidant stress is high, we have assessed the relative potency of 8-iso $PGF_{2\alpha}$ as a contractile (measured under basal tone) or a relaxant (measured after tone was induced in the PA) mediator in rat pulmonary arteries (PA). Moreover, we have investigated the role of endogenously released nitric oxide in the vaso-motor actions of 8-iso $PGF_{2\alpha}$. Rats were killed by cervical dislocation and the PAs removed. Tissues were mounted in 2 ml organ baths filled with Krebs buffer as previously described (Curzen et al., 1995).

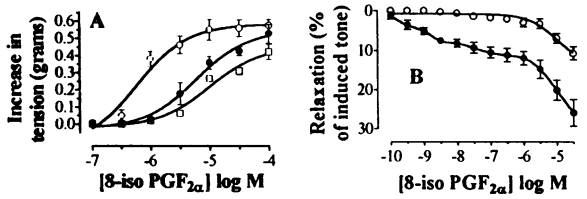

Figure 1. Effects of 8-iso $PGF_{2\alpha}$ on PA without (A) or with (B) pre-induced tone (using U46619; 1 μM). Closed circle, control; open circle, plus L-NAME; open square, plus indomethacin.

In the absence of added tone, 8-iso $PGF_{2\alpha}$ induced contraction of PA, however, once tone was introduced to the vessel a potent, nitric oxide dependent, vasodilator action of 8-iso $PGF_{2\alpha}$ was revealed. Thus 8-iso $PGF_{2\alpha}$ modulates PA tension causing vasodilatation at lower concentrations and vasoconstriction at higher concentrations. These observations may have important implications in understanding how pulmonary blood flow is regulated in diseases featuring oxidant stress.

P41 Differential release of 8-isoprostanes and prostaglandin (PG) E_2 by human pulmonary artery.

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Isoprostanes, including 8-iso $PGF_{2\alpha}$, are a newly described group of prostaglandin (PG)-like compounds which have biological actions. The majority of isoprostanes are thought to be formed independently of the cyclo-oxygenase (COX) pathway during conditions of high oxidant stress, although evidence exists for enzymatic production through the inducible COX (COX-2) pathway. As during inflammatory events the pulmonary vasculature is exposed to oxidants and cytokines known to induce COX-2, it is a likely site for isoprostane generation. Thus, we have measured the release of 8-iso $PGF_{2\alpha}$ (hatched columns) and PGE_2 (filled columns) from isolated segments (mean weight 32.78 mg) of human PA under different conditions over 24h in organ culture. Segments of human PA were treated with a mixture of cytokines (interleukin-1β (IL1β), tumour necrosis factor-α (TNFα), interferon-γ (IFNγ)) and lipopolysaccharide (LPS) in the presence or absence of the COX inhibitor, indomethacin (indometh) or the nitric oxide synthase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME). After incubation, conditioned medium was removed and assayed for 8-iso $PGF_{2\alpha}$ using an enzyme immuno assay kit and PGE_2 by radio-immunoassay.

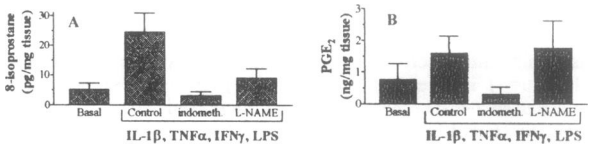

Figure 1. Total 8-isoprostane (A) and PGE_2 (B) release after 24 hrs of organ culture. Results are the mean ± SEM of 4 tissues from 2 donors.

Under basal conditions, human PA released 8-iso $PGF_{2\alpha}$ and PGE_2 in a ratio of approximately 1:100. The release of both eicosanoids was elevated or tended to be elevated by cytokine treatment and inhibited by indomethacin. However, the release of 8-iso $PGF_{2\alpha}$ but not PGE_2 was decreased by L-NAME. These observations suggest that although the release of both PGE_2 and 8-iso $PGF_{2\alpha}$ is catalysed by COX, nitric oxide mediates isoprostane but not prostaglandin formation.

P42 MECHANICAL AND CHEMICAL THROMBOLYSIS IN ACUTE MASSIVE PULMONARY EMBOLISM

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Massive pulmonary embolism remains one of the most challenging diagnoses in medicine. Obstruction of more than 50% of the pulmonary vascular bed leads to pressures of 40–50 mmHg, accompanied by ventilation-perfusion mismatch and shunting of venous blood. Rapid restoration of perfusion is essential to prevent death. Despite advances in diagnosis and treatment, 10% of cases are still fatal within the first hour.

Surgical embolectomy with cardiopulmonary bypass is associated with a mortality of 25-40%. Chemical thrombolysis alone has limited success. In our hospital, it has been combined with mechanical thrombolysis, either with the Amplatz device (a catheter-mounted cylinder containing a motorised propeller), which releases clot fragments of ≤200 μm diameter, or by dispersion with the tip of a Grolman pulmonary artery catheter. Ten patients with acute massive pulmonary embolism were treated between October 1995 and July 1996. There was radiological and (eventually) clinical improvement in every case, and no patient has died.

In one patient not given chemical thrombolysis immediately after the Amplatz procedure, many tiny fragments were dispersed distally, resulting in under-perfusion of the lungs, persisting ventilation-perfusion mismatch and hypoxia. In the light of this experience, we now use fibrinolytic therapy after mechanical thrombolysis whenever possible.

Further work is required, in order to define more clearly the indications for this technique; but we believe that it should be considered for any seriously ill patient with one or more large pulmonary emboli seen on angiography.

P43 A ROLE FOR NATRIURETIC PEPTIDES IN THE DIAGNOSIS OF PULMONARY THROMBOEMBOLISM

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Natriuretic peptides are secreted in response to changes in atrial and ventricular myocardial wall tension. We have hypothesised that levels of these peptides may be increased in patients with pulmonary thromboembolism (PE) and be of potential diagnostic value. Venous blood samples were obtained from an unselected group of 114 patients referred for ventilation-perfusion scintigraphy. Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and N-terminal pro-ANP (N-ANP) were measured by radioimmunoassay using commercially available kits. The scans were classified into three groups according to standard criteria (PIOPED); normal scan (n=20), low/intermediate probability of PE (n=77) and high probability of PE (n=17). The sensitivity and specificity of each assay for the detection of patients with high probability of PE were: BNP>8pmol/L - sensitivity 1.0, specificity 0.42; ANP>13pmol/L - sensitivity 1.0, specificity 0.32 and N-ANP>160pmol/L - sensitivity 0.94, specificity 0.30. In patients with high probability scans levels of natriuretic peptides were elevated in those who died (n=3) compared to survivors (n=14): BNP 168±84 pmol/L vs 28±7 pmol/L ($p<0.005$); ANP 53±26 vs 23±4 pmol/L ($p<0.05$) and N-ANP 709±154 vs 382±72 pmol/L ($p=0.07$), respectively. Thus, natriuretic peptides may be useful in screening patients with suspected pulmonary thromboembolism and reduce the demand for further investigation. In addition natriuretic peptides may be of value in identifying a high risk group who may benefit from more intensive therapy.

P44
A REDUCTION IN FUNCTIONAL ENDOGLIN LEADS TO PULMONARY ARTERIOVENOUS MALFORMATIONS IN HEREDITARY HAEMORRHAGIC TELANGIECTASIA

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Arteriovenous malformations in the pulmonary circulation (PAVMs) occur in approximately 20% of individuals with Hereditary Haemorrhagic Telangiectasia (HHT, Rendu-Osler-Weber syndrome). HHT is inherited as an autosomal dominant trait and most commonly presents with familial nose bleeds and mucocutaneous telangiectases. Not all families with HHT have defects in the same gene. Mutations in at least three genes result in HHT including endoglin on chromosome 9, and ALK1 on chromosome 12. Endoglin and ALK1 encode members of the transforming growth factor-β (TGF-β) receptor family, highly expressed in vascular endothelial cells.

A search for endoglin mutations in the families of patients with HHT-related PAVMs was undertaken. Over half of the detected mutations were due to deletions of genomic DNA. Two mutations, a C-T substitution in exon 4 which predicted the generation of a stop codon, and a large genomic deletion spanning seven exons and extending beyond the 3' border of the endoglin gene, did not produce a stable mRNA transcript. All other mutations produced an altered mRNA but should encode proteins that are shorter than wild-type endoglin.

This data indicates that at least two endoglin mutations generate null alleles, and support a model that the mutations inactivate the endoglin gene and thereby cause HHT by causing endoglin haploinsufficiency. Since endoglin has been shown to alter the effects of TGF-β1 signalling, dysregulated TGF-β responses are the most likely cause of the vascular lesions of HHT. As only a subset of vascular beds are affected, this suggests a temporal or spatial variation in the requirement for endoglin and highlights the restoration of appropriate endoglin control as a potential therapeutic route.

P46 β_2-ADRENOCEPTOR (β_2-AR) POLYMORPHISM DETERMINES SUSCEPTIBILITY TO BRONCHODILATOR DESENSITISATION IN ASTHMATICS

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In vitro studies have shown that the homozygous Gly 16 form of β_2-AR predisposes to and homozygous Glu 27 protects against desensitisation by β_2-agonist.We have performed a retrospective analysis of 3 studies in which asthmatic subjects received either placebo or inhaled formoterol 24μg bid for 3-4 weeks in double-blind, cross-over fashion.22 subjects mean age 38 years, FEV_1 63% predicted were evaluated.Most were on inhaled steroid, median dose 1000μg/day.Bronchodilator DRC to formoterol (6-108μg) was constructed at the end of each treatment.% subsensitivity was calculated as delta response (placebo)-delta response (formoterol)+delta response (placebo)×100: for maximal and 6 hour delta FEV_1 and FEF_{25-75} from the DRC.Analysis was by ANOVA.Subjects were divided into groups according to polymorphism at locus 16 and 27.There was a significant ($p<0.05$) difference between Arg 16 (n=4) and Gly 16 (n=10) homozygotes in % subsensitivity for max delta FEV_1(Arg 16 vs Gly 16):-8% vs 46% (95% CI for mean difference:15-92);and max delta FEF_{25-75}:-32% vs 74% (95% CI:49-164).6 hour delta FEF_{25-75} and FEV_1 were significantly different (Arg 16 vs Gly 16): 21% vs 104% (95% CI:38-130) and 30% vs 81% (95% CI:2-105) respectively. Values for heterozygote Arg 16/Gly 16 were intermediate.There was greater subsensitivity with Glu 27 (n=6) than with Gln 27 (n=5) for max delta FEF_{25-75} (Gln 27 vs Glu 27):-7% vs 68%(p=0.05);and 6 hour delta FEF_{25-75}:43% vs 93% (95% CI:5-94).However, all subjects with homozygous Glu 27 were also homozygous Gly 16.In conclusion, Gly 16 β_2-AR polymorphism determines susceptibility to bronchodilator desensitisation compared to Arg 16, with Gly 16 predominating over the protective effects of Glu 27.

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P45 COUGH SENSITIVITY TO NEBULISED CAPSAICIN AND LOW CHLORIDE SOLUTION IN LARYNGECTOMEES

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Inhaled tussive stimuli are used in the assessment of cough but the anatomical site of action of different agents is disputed. Our aim was to assess the importance of the larynx and oropharynx in the cough response to capsaicin, a selective stimulant of C-fibre afferents, and to solutions low in permeant ions which act predominantly via myelinated nerve fibres.

8 male total laryngectomees, mean age (range) 62 (43-73) yr and 8 non-respiratory patient controls mean age (range) 62 (54-73) yr were studied. All laryngectomees and 6 control patients were ex- or current smokers. Self reported cough was quantified using a visual analogue scale prior to cough challenge. Subjects inhaled increasing concentrations of capsaicin (0 to 500 μM) via a breath actuated dosimeter. The lowest concentrations provoking at least 2 (P_2) and at least 5 (P_5) coughs were recorded. Capsaicin was also delivered to the mouth of patients while breath holding at TLC. 4 isotonic solutions of decreasing chloride concentration (145 to 0 mM) were administered by tidal breathing from an ultrasonic nebuliser for 1 minute and coughs during administration counted. Oropharyngeal low chloride challenge was also performed in laryngectomees.

Laryngectomees reported more spontaneous cough but this was not statistically significant. Oropharyngeal capsaicin caused cough in 2 laryngectomees and in 3 control patients. Low chloride (LCl) by this route caused cough in 1 laryngectomee. This may have resulted from inhalation of residual tussogen mist in room air. Inhaled capsaicin sensitivity in laryngectomees (geometric mean P_2 7.2×10^{-6} M; P_5 2.9×10^{-5} M) did not significantly differ from controls (geometric mean P_2 6.0×10^{-6} M; P_5 2.2×10^{-5} M). A small excess of coughs in response to LCl among laryngectomees (mean coughs during 0 mM Cl^- administration in laryngectomees, 10 ; in controls, 2.4) did not reach not significance.

We conclude that the larynx is of limited importance in chemically provoked cough and that the oropharynx has no such role.

P47 β_2-ADRENOCEPTOR (AR) REGULATION AND FUNCTION IN FEMALE ASTHMATICS RECEIVING THE ORAL COMBINED CONTRACEPTIVE PILL

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We have previously shown that exogenous progesterone but not oestrogen up-regulates β_2-AR in healthy women (Tan et al.Br J Clin Pharmacol 1996;5:414-416).We have therefore gone on to study 11 asthmatic women, mean age 25 years, FEV_1 89% predicted whilst on (day20-21) and off (day5-7) the combined oral contraceptive pill (OCP) during a 28 day calender period.Baseline FEV_1 were 2.70L (on OCP) and 2.72L (off OCP).Lymphocyte β_2-AR parameters and bronchodilator dose-response curve (DRC) to salbutamol (100-1600μg) were measured at both periods.Results are summarised in the Table as mean (95% CI).

	On OCP	Off OCP
log B_{max}(fmol/10^6cells)	0.25 (0.18-0.33)	0.27 (0.19-0.34)
K_d(pmol/l)	14.0 (10.7-17.35)	13.6 (10.3-16.9)
E_{max}(pmol/10^6cells)	6.60 (4.05-9.15)	7.58 (5.03-10.14)
AUC FEV_1(L.h)	0.53 (0.45-0.62)	0.56 (0.48-0.65)
AUC FEF_{25-75}(L×10^3)	3.35 (2.41-4.32)	4.03 (3.06-4.97)
AUC K (mmol.h/L)	-0.50 (-0.65--0.35)	-0.44 (-0.59--0.29)
AUC tremor(log units.h)	0.72 (0.43-1.01)	0.89 (0.56-1.21)

Results showed no differences in β_2-AR regulation or DRC between the two periods.Thus, β_2-AR regulation and function in asthmatic women was unaltered by the OCP, in contrast to the previously observed facilitatory effect of progesterone in healthy women.

This study was supported by the National Asthma Campaign.

P48 REGULATION OF PULMONARY β2ADRENERGIC RECEPTOR EXPRESSION: CORRELATION BETWEEN RECEPTOR DENSITY, FUNCTION AND GENOTYPES

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We sought a relationship between polymorphisms in the coding block of the β2 adrenergic receptor (β2AR) gene and the pulmonary and systemic response to chronic dosing with an inhaled β2 agonist (salbutamol). We measured βAR expression (numbers) non-invasively by positron emission tomography (PET) with a radioligand beta antagonist ^{11}C- [S]- CGP12177 (Eur Respir J,1995, 8, 1001-1007) and bronchial function (bronchodilator sensitivity to acute salbutamol challenge) before and after two weeks β2 agonist dosing (salbutamol starting at 400mcg qds and increasing to 1200mcg qds during the second week). Systemic tachyphylaxis was measured by constructing dose response curves (DRC) for cardiovascular and metabolic indices. 12 male subjects (6 mild drug free asthmatics) were enrolled, each acting as his own control. The PET scan and DRCs post-therapy were performed 14 hrs after the last inhaled dose. Pulmonary β2AR (Bmax) after 2 weeks β agonist therapy varied from - 40% to + 7%. In 8 out of 12 subjects (5 normals and 3 asthmatics) with the non resistant genotype (gly/gly16, gly/arg16, and arg/arg16) there was a significant reduction in pulmonary Bmax by 15- 40% (mean -24%), [11.9 ±1.87 pmol.g^{-1} lung vs 9.05 ±1.49 , p<0.008], accompanied by a substantial bronchodilator and systemic tachyphylaxis to acute salbutamol challenge. The three way ANOVA gave a p value of 0.001 for sGAW, p=0.01 for systolic BP, p=0.001 for heart rate, p=0.001 for serum K+. There was no difference between normals and asthmatics. 4 subjects (3 asthmatics and 1 normal) who were homozygous for Glu27 polymorphism were resistant to down regulation in terms of both pulmonary β2AR numbers [9.8 ±2.1vs 9.7 ±2.48 p=NS] and bronchial and systemic tachyphylaxis p=NS. We conclude that the response to chronic administration of β2 agonist drugs in terms of β2AR expression and bronchial function is dominated by genetic polymorphisms of the β2AR gene.

P49 CULTURED HUMAN AIRWAY SMOOTH MUSCLE CELLS RELEASE PGE_2 IN RESPONSE TO BRADYKININ, GROWTH FACTORS AND ARACHIDONIC ACID

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Prostaglandin E_2 (PGE_2) is thought to play an important inhibitory role in the regulation of inflammatory processes in the airway. We have previously shown that bovine airway smooth muscle may be an important source of PGE_2. In this study PGE_2 synthesis by cultured human airway smooth muscle (ASM) cells after stimulation by proinflammatory mediator bradykinin, growth factors platelet derived growth factor (PDGF) and epidermal growth factor (EGF) and cyclooxygenase (COX) substrate arachidonic acid (AA) was studied, and its relation to the induction of two isoforms of COX enzyme was investigated. Under resting conditions, PGE_2 release was only 0.5-2.0 ng/mg protein. After 24 h incubation, bradykinin (10^{-8}~10^{-4} M) caused a concentration-dependent release of PGE_2 (140 ng/mg protein with 10^{-4} M bradykinin); EGF (25~400 ng/ml) also caused a modest increase in PGE_2 release in a concentration-dependent manner (8.47 ng/mg protein with 400 ng/ml EGF). However, PDGF-AA, PDGF-BB and PDGF-AB had no effect. Incubation with AA (10^{-6}~3×10^{-5} M) for 30 min caused large quantity of PGE_2 release (159 ng/mg protein with 3×10^{-5} M AA). Pre-treatment with COX inhibitor indomethacin completely blocked PGE_2 release by the above stimulants. Western blot analysis showed that no COX-2 was induced and COX-1 was responsible for the PGE_2 production under the experimental conditions used. The study shows that cultured human ASM cells release PGE_2 in response to various stimulants, implying that airway smooth muscle may be an important source of PGs in human airway.

Supported by the National Asthma Campaign.

P50 PROSTAGLANDIN E2 PRODUCTION BY OVINE TRACHEAL EPITHELIUM: CONTROL BY CYCLIC NUCLEOTIDES

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Prostaglandin E2 (PGE2) is an important product of arachadonic acid metabolism in the airway, and may have an inhibitory role in asthma by reducing inflammation. We mounted ovine tracheal mucosal strips in modified Ussing chambers and measured PGE2 production by radioimmunoassay. PGE2 was predominately secreted from the mucosal surface of the preparation (approximately 3-5 times greater than from the serosal surface). Removal of the epithelium reduced mucosal secretion to 1.5 times that of the serosal side. Incubation with the non-selective phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (IBMX) increased PGE2 production by both the mucosal (IBMX 81±9 pg/100µl, control 57±19 pg/100µl, n=8, p=0.02) and serosal surfaces (31±13 pg/100µl, control 18±13 pg/100µl, n=8, p=0.01). A similar increase was also observed with the cell permeable cAMP analogue dibutyryl cAMP (dbcAMP) in both mucosal (59±7 pg/100µl, control 33±8 pg/100µl, n=8, p=0.04) and serosal (31±3 pg/100µl, control 17±4 pg/100µl, n=8, p=0.01) secretion. 10^{-4}M sodium nitroprusside (SNP), an activator of soluble guanylyl cyclase, did not increase either mucosal (41±3 pg/100µl, control 40±4 pg/100µl, n=8, p=0.86) or serosal PGE2 production (11±3pg/100µl, control 13±1 pg/100µl, n=3, p=0.65), at concentrations of SNP that produced a marked elevation of cGMP levels in these cells. We conclude that in the ovine trachea PGE2 is secreted mucosally by the epithelial layer, and its production can be increased by cAMP but not cGMP.

P51 SYNTHESIS OF CYCLIC GUANOSINE MONOPHOSPHATE (cGMP) IN CULTURED HUMAN AIRWAY SMOOTH MUSCLE CELLS

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Increased cellular cGMP levels cause relaxation of airway smooth muscle cells (Suzuki et al., Clin. Exp. Pharmacol. Phys. 1986, 13: 39-46). cGMP is generated by the action of guanylyl cyclase which exists in two main forms; a soluble form activated by nitric oxide (NO), and a particulate form activated primarily by natriuretic peptides. Bronchodilatation has previously been demonstrated in vivo by activators of both soluble and particulate guanylyl cyclase. We have examined cGMP synthesis in cultured human tracheal smooth muscle cells following incubation with the NO donors sodium nitroprusside (SNP) an S-nitroso-N-acetyl-penicillamine (SNAP) in the presence of 10^{-3}M 3-isobutyl-1-methylxanthine (IBMX), a phosphodiesterase inhibitor. cGMP was measured by an ELISA assay (Amersham, UK) following acid extraction. Both SNP and SNAP increased cGMP levels in a dose dependent manner (both p<0.001). cGMP levels increased six-fold compared to baseline following SNP (10^{-3}M) incubation, and by twelve-fold following SNAP (10^{-3}M) incubation. These increases were inhibited by the addition of 5×10^{-3}M methylene blue (an inhibitor of guanylyl cyclase) and by 5×10^{-4}M haemoglobin (a scavenger of NO). Baseline production of cGMP was not altered by 10^{-3}M L-NAME or 10^{-4}M L-NMMA (both inhibitors of NO production) suggesting a lack of significant baseline NO production in this cell type. These results confirm the presence of soluble guanylyl cyclase in cultured human tracheal smooth muscle cells.

P52 INTERLEUKIN-1β CAUSES INDUCTION OF CYCLOOXYGENASE-2 IN CULTURED HUMAN AIRWAY SMOOTH MUSCLE CELLS

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The effect of interleukin-1β (IL-1β), together with tumour necrosis factor-α (TNFα) and interferon-γ (IFNγ), on prostaglandin E_2 (PGE_2) release and cyclooxygenase (COX) activity (reflected by PGE_2 synthesis from exogenous arachidonic acid) and its relation to the induction of two isoforms of COX in cultured human airway smooth muscle (ASM) cells was investigated. IL-1β (0.01-10.0 ng/ml), but not TNFα (6.25-100 ng/ml) or IFNγ (1-100 ng/ml), caused a time- and concentration-dependent enhancement in PGE_2 and other prostanoid (PGD_2, $PGF_2\alpha$ and TXB_2) production, with PGE_2 as the principal product (192 ng/mg protein after 24 h incubation with IL-1β 1.0 ng/ml). This stimulation was accompanied by a corresponding increase in COX activity (significant 2 h after stimulation with IL-1β 1.0 ng/ml). COX-2 protein measured by Western blot analysis was undetectable with untreated cells, but was increased in a time- and concentration-dependent manner by IL-1β, but not TNFα or IFNγ. In contrast, no variation in the expression of COX-1 protein was observed. Pre-treatment with the glucocorticosteroid dexamethasone (10^{-6} M) and protein synthesis inhibitors cycloheximide (10^{-6} M) and actinomycin D (10^{-5} M) not only markedly inhibited IL-1β stimulated PGE_2 release and COX activity but also suppressed IL-1β induced COX-2 induction. The study demonstrates that cultured human ASM cells release prostanoids in response to IL-1β stimulation and that the response is mostly mediated by the induction of COX-2 rather than COX-1 enzyme, implying that airway smooth muscle may be an important source of PGs in the airways and that COX-2 may play an important role in the regulation of the inflammatory process in asthma.

Supported by the National Asthma Campaign.

P53 EFFECT OF LORATADINE ON NITROGEN DIOXIDE (NO2)-INDUCED RELEASE OF PRO-INFLAMMATORY MEDIATORS FROM CULTURED HUMAN BRONCHIAL EPITHELIAL CELLS

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Recent studies have demonstrated that histamine can induce the release of inflammatory mediators from bronchial epithelial cells and that this effect can be attenuated by anti histamines. We have cultured human bronchial epithelial cells (HBEC) from surgical explants and investigated the effect of loratadine and its active metabolite (SCH 34117) on both constitutive and NO_2-induced release of IL-8, RANTES and sICAM-1 from these cells, following exposure for 6hours to either air or 400ppb NO_2. Exposure to NO_2 significantly increased the release of IL-8 (81.9pg/μg cellular protein; $p<0.05$), RANTES (62.3fg/μg cellular protein; $p<0.05$) and sICAM-1 (16.3pg/μg cellular protein; $p<0.05$), when compared with release of 52.5pg IL-8, 22.6fg RANTES and 7.7pg sICAM-1/μg cellular protein, respectively, in control cultures exposed to 5%CO2 in air. The NO_2-induced release of all three mediators was significantly attenuated by incubation of HBEC with 25μM loratadine and its active metabolite. Incubation of the cells with a lower concentration 2.5μM loratadine also significantly attenuated the NO_2-induced release of RANTES and sICAM-1, but not IL-8. In contrast, incubation of HBEC with 2.5μM metabolite did not attenuate the NO_2-induced release of any of these mediators. These results suggest that anti-histamines such as loratadine may be useful in the management of airway inflammation.

P54 NEDOCROMIL SODIUM ATTENUATES BRONCHIAL EPITHELIAL CELL-INDUCED EOSINOPHIL ADHESION AND RELEASE OF sICAM-1 FROM ENDOTHELIAL CELLS *IN VITRO*

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We have previously demonstrated that conditioned medium from cultured bronchial epithelial cells increases the adherence of eosinophils to endothelial cells **(Abdelaziz MM et al. Am J Respir Cell Mol Biol 1995: 13: 728-737)**. In the present study we have investigated the effect of nedocromil sodium on bronchial epithelial cell-induced adhesion of eosinophils to endothelial cells and the release of sICAM-1 from endothelial cells. Endothelial cell cultures were incubated with epithelial cell conditioned medium ± 10^{-7} to 10^{-5}M nedocromil sodium for 6 hours and subsequently assessed for eosinophil adherence. Release of sICAM-1 from the endothelial cells was investigated following incubation with conditioned medium ± 10^{-7} to 10^{-5}M nedocromil sodium for 24 hours. Conditioned medium significantly increased eosinophil adherence to endothelial cells from 9.3% (range 7.5-12.2%) to 23.2% (range 21.3-30.5%; $p<0.05$), an effect which was attenuated by nedocromil sodium in a dose dependent manner. Similarly, the release of sICAM-1 from endothelial cells was significantly increased by conditioned medium from bronchial epithelial cells from a baseline value of 11.5 pg ug^{-1} protein (range 8.1-15.4) to 67.65 pg ug^{-1} protein (range 55.6-73.5; $p<0.05$) and this was attenuated by treatment with nedocromil sodium in a dose-dependent manner. Both anti-TNF_α and anti-IL-1ß neutralising antibodies also significantly attenuated the conditioned medium-induced release of endothelial sICAM-1. These findings suggest that agents such as nedocromil sodium may influence epithelial cell-induced inflammation by modulating the expression of specific adhesion molecules.

P55 FLUTICASONE PROPIONATE (FP) AND BECLOMETHASONE DIPROPIONATE (BDP) ATTENUATE OZONE (O_3)-INDUCED RELEASE OF INFLAMMATORY CYTOKINES FROM NASAL EPITHELIAL CELLS (NEC) OF ATOPIC RHINITIC SUBJECTS

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Our studies of NEC of allergic rhinitics exposed to O_3 have demonstrated that this agent significantly increases the release of IL-8 and RANTES from these cells *in vitro* **(Calderon MA, et al. *J Allergy Clin Immunol* 1996; 97(1, pt3): 352)**. In this study we have investigated the effect of FP and BDP, two topical steroids widely used in the treatment of allergic rhinitis, on the release of these mediators following exposure to O_3. NEC were cultured from biopsies taken from 9 atopic rhinitics during the pollen season and exposed to either air or 50ppb O_3 for 6 hours in the absence or presence of varying concentrations of FP or BDP (10^{-8}M, 10^{-6}M and 10^{-4}M). IL-8 and RANTES released into the culture medium was measured by ELISA. FP at 10^{-4}M significantly ($p<0.05$) attenuated the release of IL-8 and RANTES after exposure to air, compared to controls (IL-8: 4.0 vs 9.2pg/ug protein, $p< 0.05$; and RANTES: 0.49 vs 1.05 pg/ug protein, $p<0.05$). 10^{-6}M FP significantly attenuated the O_3-induced release of IL-8 and RANTES, compared to controls (IL-8: 11.8 vs 14.7 pg/ug protein, $p<0.05$; and RANTES: 0.90 vs 1.38pg/ug protein, $p<0.05$). The attenuation of O_3-induced cytokine release was even greater with 10^{-4}M FP (IL-8: 8.0pg/ug protein; RANTES: 0.82pg/ug protein). 10^{-4}M BDP also significantly attenuated the release of IL-8 from NEC exposed to air compared with controls (5.0 vs 9.0pg/ug protein; $p<0.05$). O_3-induced release of IL-8 was not attenuated by BDP. Similarly BDP did not significant alter either the constitutive or O_3-induced release of RANTES, although there was a trend towards reduction. These results suggest that FP and BDP may modulate nasal airway inflammation by down-regulating the release of pro-inflammatory cytokines from nasal epithelial cells. Furthermore, FP appears to be more potent than BDP in this respect.

P56 EFFECT OF FLUTICASONE PROPIONATE AQUEOUS NASAL SPRAY ON ALLERGEN-INDUCED INFLAMMATORY CHANGES IN THE NASAL AIRWAYS OF ALLERGIC RHINITICS FOLLOWING EXPOSURE FOR SIX HOURS TO 400PPB NITROGEN DIOXIDE (NO_2)

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We have recently demonstrated that prior exposure for 6 hours to NO_2 significantly enhances the response of eosinophils in the nasal airways of allergic rhinitics to subsequent allergen provocation, during the early phase. In order to investigate whether treatment with fluticasone propionate aqueous nasal spray (FP) can alter the inflammatory response in the nasal airways under these conditions, 16 allergic rhinitic patients were randomised to receive either topical FP 200μg od or matched placebo for 4 weeks. At the end of treatment, all individuals underwent nasal lavage followed by a 6 hour exposure to 400ppb NO_2. Following exposure to NO_2, nasal allergen challenge was performed and nasal lavage repeated. After a 2 weeks' washout period, the individuals were given alternate treatment and tested as above. Analysis of eosinophil cationic protein (ECP) in lavage samples of these individuals, demonstrated that this was significantly increased 6.5-fold (from a median value of 2.3ng/ml(range= 1.0-7.1) to 15.1ng/ml(range= 1.5-40.0; p=0.001) following exposure to NO_2+allergen, when the individuals were treated with placebo. In contrast, there was a much smaller effect of exposure to NO_2+allergen challenge on ECP levels (1.5-fold increase from a median value of 3.3ng/ml(range= 0.2-9.2) to 5.1ng/ml(reange= 0.3-20.0; p=0.034), when these individuals were treated with FP. The difference in changes of ECP levels between placebo and FP treatments was significant (p=0.003). These results suggest that FP may down-grade NO_2+allergen-induced eosinophil activation in allergic rhinitics.

P57 FRUSEMIDE AND CYCLOSPORIN DO NOT INHIBIT EARLY ANTIGEN RESPONSE IN SENSITISED GUINEA PIG TRACHEAL TUBES

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Introduction: Frusemide inhibits allergen induced contraction in sensitised human bronchial rings through increased production of PGE_2. Cyclosporin may improve control in chronic asthma and increases PGE_2 production in other tissues. We used a sensitised guinea pig tracheal tube preparation to investigate the effect of these drugs on the early response to allergen and the dependence of their effects on prostaglandins.

Methods: Sensitised guinea pig tracheae were mounted in an organ bath allowing selective perfusion of mucosal and serosal surfaces. Change in whole airway cross sectional area (CSA) was measured by computer-linked video microscope. The mucosal surface was constantly perfused; drugs were added to perfusate (mucosa) or organ bath (serosa).

Results: When both drugs were applied simultaneously to the mucosal surface frusemide 10^{-4} M did not inhibit contraction to ovalbumin 10^{-4} or 10^{-2} mg/ml (97.5 and 97.8 % control respectively). When applied to the serosal surface cyclosporin 10^{-6} M but not 10^{-8} M increased resting tone of tracheae (96.5 ($p<0.05$) and 100.8 % control respectively). Cyclosporin 10^{-6} M increased ovalbumin 10^{-2} mg/ml induced contraction (from 95.4 to 89.4 % baseline CSA). Indomethacin inhibited the cyclosporin effect on resting tone and antigen response ($p<0.05$).

Discussion: We were unable to show protective effects of either frusemide or cyclosporin in this guinea pig model. Cyclosporin increased resting tone and antigen response which could be reversed by indomethacin suggesting that contractile prostaglandins were responsible. The differences in response to frusemide between guinea pig and human airways may reflect differences in the dominant cyclooxygenase products produced by airway tissues in the two species.

P58 ATTENUATION OF PROPRANOLOL-INDUCED BRONCHOCONSTRICTION BY NEBULISED FRUSEMIDE

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Inhaled propranolol causes bronchoconstriction in asthmatics by an indirect mechanism which remains unclear. Inhaled frusemide has been shown to inhibit several indirectly acting bronchoconstrictor stimuli. Our aim was to investigate whether frusemide protects against bronchial challenge with propranolol in mild stable asthma. 12 asthmatic subjects, 4 male, mean age (range) 30 (20-45) yr, mean (±SD) FEV_1 97 (±12) % predicted were studied on 3 separate days. At the first visit subjects inhaled increasing concentrations of propranolol (0.25-32 mg/ml) via a Ventstream nebuliser (Medic-Aid, Sussex, UK) breathing tidally for 1 min. The provocative concentration of propranolol causing a 20% reduction in FEV_1 (PC_{20}) was determined by interpolation from the concentration-response curve. At the following visits frusemide (4 ml x 10 mg/ml) or placebo (isotonic saline) was administered via a Ventstream nebuliser in randomised, double-blind, crossover fashion. FEV_1 was measured before and 5 min after drug. Each individual's PC_{20} propranolol was then given as a single dose. FEV_1 was recorded at 5 min intervals for 15 min. Residual bronchoconstriction was reversed with salbutamol 2.5 mg by nebuliser. Subjects were allowed to leave the laboratory when FEV_1 had returned to at least 90% baseline.

Mean baseline FEV_1 did not differ significantly on the two study drug days: 3.49 l on placebo day, 3.54 l on active drug day. Frusemide had no acute bronchodilator effect but reduced the maximum fall in FEV_1 due to propranolol: mean fall 18.2% after placebo and 11.8% after frusemide (p=0.02, Wilcoxon signed-rank test). We conclude that frusemide attenuates propranolol-induced bronchoconstriction, a property shared with sodium cromoglycate. Both drugs also block other indirect challenges. The present study lends further support to the suggestion that frusemide and cromoglycate share a similar mechanism of action in the airways.

P59 OCCUPATIONAL ASTHMA IN HEALTHCARE WORKERS; RESULTS FROM THE SHIELD SURVEILLANCE SCHEME IN THE WEST MIDLANDS, UK

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Shield is a voluntary reporting scheme for occupational asthma in the West Midlands. There are more than a hundred cases a year and healthcare worker is one of the most common occupations. Since 1989, fifty cases of health personnel, aged 24-73 years, have been reported to Shield (Incidence rate= 9.6 cases/100.000 workers/year). Only 18 % of them had a history of pre-existing asthma. Nearly half of the cases were nurses. There were 8 hospitals that had at least 2 cases, the most was 7 cases, per hospital. Glutaraldehyde was the most common causative agent (36 %). Latex (12 %), cleaning agents (12 %), and a variety of others were also a problem. Glutaraldehyde and latex are the 2 agents showing the great increase in incidence of all occupations between 1989-1996. The method of diagnosis were mainly by the history of asthma improving away from work and serial PEF reading. The mechanism of asthma in most of cases was considered to be due to allergy but more than one-third of the cases could not be given a definite mechanism. In spite of being health personnel, one-third of cases were still exposed to causative agents at the same job following diagnosis and few of them were notified to their department of occupational health.

P60 THE STUDY OF OCCUPATIONAL ASTHMA SURVEILLANCE IN HOSPITALS IN THE WEST MIDLANDS, UK

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Introduction: Employers have a duty to provide health surveillance to their employees who are exposed to respiratory sensitisers. Healthcare work is one of the high risk occupations in the development of occupational asthma in the West Midlands. The aims of the study were to assess the provision of respiratory surveillance in the hospitals in the West Midlands and identify contributing factors which affected the reported cases.
Method: 20 departments of occupational health in the West Midlands were listed from ANHOPS (Association of NHS Occupational Physicians). The representative of each department completed a postal questionnaire which included the number of hospitals covered, the number of previous reported cases and the provision of health surveillance.
Results: 18 departments covering 30 hospitals responded. Most of departments (88.9%) had provided advice on COSHH (Control of Substances Hazardous to Health Regulations) assessment and implemented the MS25 (the Medical Guideline for occupational asthma). 24 hospitals had undertaken occupational asthma surveillance. The agents under surveillance included glutaraldehyde (23/24), formaldehyde (10/24), methyl methacrylate (4/24) and latex (2/24). Most of hospitals (25/30) provided pre-employment screening for asthma with history taking (100%), physical examination (32%), and spirometry (76%). Periodic health surveillance was undertaken by history taking (23/30), physical examination (10/30), spirometry (22/30), chest x-ray (5/30), and allergy/sensitisation (6/30). There were 19 hospitals where at least one worker with occupational asthma had been reported. The hospitals which had a reported case had undertaken health surveillance more than the non-case hospitals. There were significant statistical differences ($p<0.05$) in terms of the provision of pre-employment screening and the exclusion of workers on health grounds at pre-employment stage between the hospitals with a reported case and the others.
Conclusion: Occupational health departments providing more surveillance identify more cases of occupational asthma.

P61 OUTCOME OF OCCUPATIONAL ASTHMA DUE TO PLATINUM SALTS

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Asthma due to platinum salts is an important cause of occupational asthma. We studied a group of 73 subjects from a platinum refinery 21months (2-42) after leaving employment.

There were 30 subjects who left because of sensitivity or allergy to platinum salts (the cases). The other 43 subjects left for non-medical reasons (the control group). Each subject was examined by modified MRC respiratory questionnaire, spirometry, skin prick test to platinum salts and common allergens and bronchial responsiveness to either cold air or exercise.

At leaving, 21 of the cases had a positive skin test to platinum salts. These cases were removed on average one month after the positive skin test. 19 cases (63%) left because of chest symptoms. One subject (3%) had nasal problems only and 8 (27%) had chest and either skin and/or nasal symptoms. Two subjects had been removed because of positive skin test but no symptoms.

At the time of follow-up cases reported productive cough, wheeze, chest tightness and breathlessness more often than non cases which reached significance for breathlessness ($p<0.001$). Only one subject had a positive skin test to platinum salts. 24% of the cases and 20% of non cases had more than 10% fall to either FEV_1 or PEF following cold air or exercise testing respectively. No significant difference was found in lung function or bronchial responsiveness to exercise or cold air between cases or non cases.

This prognosis is unsusually good for occupational asthma after leaving exposure. We suggest this may be due to early diagnosis and rapid removal of sensitised workers.

P62 REDUCING EXPOSURE TO CAT ALLERGEN IN HOSPITALS: THE EFFECT OF REGULAR VACUUM CLEANING ON Fel d 1 IN UPHOLSTERED CHAIRS

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We have previously demonstrated that upholstered chairs in 12 hospitals in the UK contain very high levels of cat allergen (Fel d 1) which may be of clinical significance in cat allergic asthmatic patients (Am J Respir Crit Care Med 1995; 151: A472). This study investigated the effects of regular vacuum cleaning of upholstered chairs on Fel d 1 levels. Fine dust samples were collected on four occasions, at four weekly intervals, from 36 fabric covered chairs in the outpatient area of a busy chest clinic by vacuuming each chair for two minutes. Samples were analysed for Fel d 1 using monoclonal antibody based ELISA. During the intervening weeks, 18 of the chairs (active group) were cleaned by vacuuming for 1 minute, three times per week, using a Nilfisk GM 210 vacuum cleaner with an inbuilt high efficiency particulate air (HEPA) filter. The results were expressed as Fel d 1 allergen recovered per gram of dust, as detailed in the table below.

	μg Fel d 1 / g dust: geometric mean (range)			
	Baseline Sample	4 Week Sample	8 Week Sample	12 Week Sample
Active	27.11 (15.60-82.00)	12.43 (5.36-48.00)	10.92 (4.40-21.00)	10.95 (4.00-22.00)
Control	25.48 (10.40-76.00)	35.80 (23.40-66.00)	41.85 (23.00-82.00)	50.00 (28.00-71.00)

At baseline there was no significant difference in Fel d 1 levels measured between the active and control groups ($p>0.1$). Following the repeated vacuuming, however, at 12 weeks the mean Fel d 1 antigen levels were almost five fold higher in the control group compared with the active group ($p<0.001$). These results demonstrate that regular vacuuming can reduce Fel d 1 allergen levels in upholstered chairs. We advise that fabric covered chairs in patient areas should be regularly vacuumed.

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P63 DISTRIBUTION AND AERODYNAMIC CHARACTERISTICS OF MAJOR CAT ALLERGEN Fel d 1

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Sensitisation to cat allergen is a significant cause of asthma. This study investigated the distribution, aerodynamic characteristics and particle size distribution of the major cat allergen, Fel d 1. Dust samples were collected in 40 homes with a cat and 50 homes without cats. Airborne Fel d 1 level was measured in 40 homes with cats and 40 homes without a cat. Air samples were collected in the absence of disturbance using a fixed location sampler sampling volumes of 3-4.3 m^3 of air (limit of detection 0.08 ng Fel d 1/m^3). Air sampling for particle size distribution was performed using an Andersen sampler over an 8 hour period/day on 5 separate days in a house with 4 cats. In the homes with cats, the highest levels of Fel d 1 were found in upholstered furniture (GM 464 μg/g, 95% CL 302-713), followed by the living room carpets (GM 270 μg/g, 95% CL 172-424). Bedrooms contained lower levels (carpet: GM 49 μg/g, 95% CL 23-105; mattress: GM 46 μg/g, 95% CL 23-97). Fel d 1 was readily detectable in homes without cats, but the levels were 10-100 fold lower than in houses with cats. The highest levels of Fel d 1 in homes without a cat were found in the upholstered furniture from the living room (GM 1.2 μg/g, 95% CL 0.7-1.9), followed by the living room carpet (GM 0.9 μg/g, 95% CL 0.6-1.4). Bedrooms contained significantly lower levels than living rooms (carpet: GM 0.24 μg/g, 95% CL 0.2-0.33; mattress: GM 0.25 μg/g, 95% CL 0.17-0.37). Airborne Fel d 1 was detected in all houses with cats, and the levels varied greatly between the homes (range 0.7-38 ng/m^3). Low concentrations of airborne Fel d 1 (range 0.24-1.78 ng/m^3) were found in 12/40 homes without a cat. Airborne Fel d 1 was mostly associated with large particles collected on the first stage of Andersen sampler (>9 μm), which averaged ~45% of the total allergen recovered. Small particles (<5 μm diameter) also carried Fel d 1 and these particles comprised ~25% of the total airborne allergen load. In conclusion, airborne Fel d 1 was detectable in undisturbed conditions in all homes with cats and in almost a third of the homes without cats. In houses with cats, a significant proportion (~25%) of airborne Fel d 1 was associated with small particles (<5 μm diameter). These particles would be expected to remain airborne for a long period of time and, when inhaled, could penetrate into the lower airways and initiate asthma attacks.

P64 CORRELATION BETWEEN LEVELS OF MAJOR CAT ALLERGEN Fel d 1 IN RESERVOIR AND SETTLING DUST IN HOMES WITH AND WITHOUT CATS

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Asthma is caused by sensitisation to indoor allergens. Exposure can be quantified using monoclonal antibody based ELISAs. This study investigated the relationship between levels of Fel d 1 in reservoir dust, from carpets, sofas and mattresses and levels of Fel d 1 in settling dust collected onto static petri dishes. Settling dust was collected on petri dishes, 150 mm diameter, placed 1-2 m above ground for 2 weeks in the living room (LR) and bedroom (BR) of 13 homes with and 13 homes without cats. Three dishes were left in each room, (total area = 1060cm^2) then extracted in 0.2% Bovine Serum Albumin and analysed. Results were expressed as Fel d 1 in ng/m^2/day. Reservoir dust was collected by vacuuming a 1 m^2 area of living room carpet (LF), sofa (S), bedroom carpet (BF) and mattress (M) for 2 minutes, then extracted and assayed; results were expressed as Fel d 1 µg/g fine dust. Fel d 1 was measured using a monoclonal antibody based ELISA. Results showed a log-normal distribution so geometric means (GM) and confidence limits (CL) were used in the analysis. Results are displayed in the table below.

		LF µg/g	S µg/g	BF µg/g	M µg/g	LR ng/m^2/day	BR ng/m^2/day
cats	GM	198.3	217	135.6	141.2	654	745
	CL	98-401	88-535	48-378	68-294	280-1529	334-1671
no cats	GM	1.46	4.95	0.83	0.96	4.99	4.25
	CL	0.56-3.8	1.6-12	0.27-2.5	0.3-2.9	2.27-11.3	1.98-8.5

Linear regressions were used to compare the data. There was a significant correlation between levels of Fel d 1 in settling dust in bedrooms and reservoir levels in bedroom carpets in homes with cats ($p<0.05$, $r= 0.6$) and in homes without cats ($p<0.001$, $r= 0.85$). There was a significant correlation between levels of Fel d 1 in settling dust in living rooms and reservoir levels in living room carpets ($p<0.05$, $r=0.56$) in homes without cats. Further studies of this simple technique should be performed to investigate the relationship between levels of Fel d 1 in settling dust, sensitisation and asthma symptoms.

P66 EXERCISE INDUCED BRONCHOSPASM IN GHANA:PREVALENCE IN URBAN AND RURAL CHILDREN

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Asthma is one of the few treatable conditions that have increased in prevalence in recent years in western societies. As more developing countries adopt a westernised style of living, increase in asthma prevalence can be expected to occur in these areas. The aim of this study was to establish the normal response to exercise in Ghanaian children, and then use these normal values to determine the prevalence of exercise-induced bronchospasm (EIB) in urban rich (UR), urban poor (UP) and rural (R) school children. Two hundred children without a previous history of respiratory symptoms aged 9-16 years were randomly selected and underwent free-running exercise testing. A normal response to exercise was defined as the group mean change in PEFR +/- 2 standard deviations. This value was used to identify the prevalence of EIB in UR, UP and R school-children. A total of 1095 children 9-16 years old from 3 different schools were exercised (UP=220, UR=599 and R=276). Using the results of exercise testing in asymptomatic children, the normal range was defined as <12.5 percent fall in PEFR after exercise. Thirty four children were classified as having EIB on the basis of the above definition, giving an overall prevalence of 3.1%. The prevalence of EIB was significantly higher in UR children than in both UP (4.7% vs 2.2%; $p<0.05$) and R children (4.7% vs 1.4%; $p<0.01$). However, the prevalence rates in the UP and R children were similar. In conclusion, the prevalence of EIB is higher in urban rich than in urban poor or rural children, suggesting that in addition to genetic predisposition, social and environmental factors (e.g. wealth, life-style and housing), are important determinants in the phenotypic expression of disease.

P65 HOUSE DUST MITE ALLERGEN ACCUMULATION ON SHEEPSKINS

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Exposure to high levels of the house dust mite allergen Der p 1 has been shown to be a risk factor for the development of asthma. Sheepskins have been widely used as infant bedding in New Zealand and have been shown to contain high numbers of house dust mites. This study assessed the rate of accumulation of Der p 1 in new sheepskins in the domestic environment. Six sheepskins were placed on mattresses occupied by adults, and six on the living room floors in six domestic dwellings. Dust was collected by vacuuming the whole sheepskin for two minutes at two weekly intervals and from adjacent areas, and analysed for Der p 1 concentrations by monoclonal antibody ELISA. After six weeks the sheepskins were warm washed and Der p 1 concentrations measured again. Results of Der p 1 concentrations are shown in the table as geometric means of µg/g fine dust with the range of values found.

Time	Bed sheepskins	Living room sheepskins	Mattress	Living room floor
Initial	1.2 (0.2-2.1)	0.5 (0.3-1.0)	6.7 (0.4-338)	17.2 (0.6-115)
2 wks	13.8 (1.8-154.4)	4.6(0.6-22.9)		
4 wks	19.4 (4.8-182.0)	9.0 (1.3-56.8)		
6 wks	29.4 (5.3-131.1)	8.9 (1.1-102.2)		
Post-wash	4.8 (2.4-20.4)	1.3 (0.1-9.3)		

There was a significant correlation between sheepskin Der p 1 levels at 6 weeks and the Der p 1 concentration in the adjacent areas ($r=0.78$ and $r=0.96$ respectively for bed and living room sites). This study has demonstrated a rapid accumulation of Der p 1 on sheepskins in the domestic environment governed by the site they are placed in. Sheepskins should not be used as bedding for infants at risk of sensitisation to house dust mites.

Supported by the Wellington Medical Research Foundation.

P67 Number preference in reading peak expiratory flow meters

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Number preference (NP) for tens digits 0 and 5 by subjects when reading the peak expiratory flow (PEF) from mechanical meters may reduce the diagnosis of asthma and especially occupational asthma from serial PEF records. The records of 274 subjects (set A) recorded using mini-Wright PEF meters and 35 subjects (set B) using electronic logging turbine spirometers (MIcroMedical) were examined for the ratio of tens digits 0 and 5 to the remaining tens digits (NP ratio; NPR). 24 records from set A and no records from set B were classified as having NP by visual inspection. No record from set B had a NPR >0.42 (mean 0.26, SD 0.08)). NPR for set B were positively skewed (mean 1.81, SD 12.33). Cut of 0.75 between no NP and possible NP and 1.0 between possible NP and definite NP were chosen. A further set (set C1) of records recorded on mini-Wright PEF meters was taken all with NPR <0.75. NP was induced in this records by rounding to the nearest 50 l/min (set C2). The mean diurnal variation (DV, amp. % pred) did not change (paired t-test, p=0.87). Maximum change in amplitude was 23.4L, DV 5.7% and % of a record with DV >15% was 47.6%. For OASYS-3 scored records the whole record score tended to decrease (paired t-test, $p<0.001$) but not for OASYS-NN scored records (paired t-test, p=0.93). Changes in classification of records are shown.

C1 \ C2 (OASYS-NN)	WE	?WE	No WE
WE	42	5	1
?WE	4	16	10
No WE	0	10	67

OASYS-3	
WE	No WE
29	4
5	112

WE: work effect, ?WE possible work effect

NP can cause records with a possible work effect to be erroneously classifies as having no work effect. DV is not greatly affected but large changes can occur in amplitude of variation and % of a record with DV >15%.

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P68 Comparison of mean daily diurnal variation in peak expiratory flow and FEV_1

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Historically serial PEF measurements have been used to assess variation in airway calibre over a period of time both in the monitoring and diagnosis of asthma and occupational asthma. Some have questioned whether the FEV_1 which is thought to better reflect the size of small airways would be a better indicator of changes in airway calibre. This study aims to compare the average daily diurnal variation (% predicted) in PEF and FEV_1 with both indices measured from the same exhalation manoeuvre. Subjects attending a specialist clinic for investigation of occupational asthma were asked to serially record their lung function using a MicroMedical Diarycard spirometer. This device records and stores PEF, FEV_1 and FVC by directly measuring flow and then calculating volume. Subjects were instructed to produce three maximum forced exhalations for at least two seconds following a maximal inhalation, every two hours from waking until going to sleep for at least 21 days. Following instruction each subject was observed performing ten practice manoeuvres in clinic before returning home. The records produced were only entered into the study if they were of the required length. Each reading was screened to ensure that the FVC exceeded the FEV_1 The best PEF and FEV_1 reading from each set of three were used in calculations as long as the next best reading was within 20 L/min for PEF and within 5% or 0.1 L for FEV_1 . If either the PEF or FEV_1 measurements in each set of three readings did not fulfil these repeatability criteria then the reading were omitted. The diurnal variation was calculated from each day of the record as amplitude % predicted. Days with less than four readings were excluded. The diurnal variation of each eligible day was used to produce an overall record average diurnal variation in PEF and FEV_1 . Record diurnal variations in PEF and FEV_1 were compared using a paired t-test The records of 31 individuals were used in the study. The mean (SD) number of days with more than three readings per day was 16.5 (6.3). The mean daily average diurnal variation in FEV_1 was 12.13% and 12.95% for PEF ($p=0.23$). 10 records had an average mean diurnal variation >15% PEF with one extra record having a diurnal variation >15% FEV_1 .There is no evidence that FEV_1 is more sensitive in measuring variation in airway calibre than PEF.

Dr Bright is supported by a grant from the National Asthma Campaign. UK

P69 THE EFFECTS OF CIGARETTE SMOKING AND DURATION OF WORK ON THE LUNG FUNCTION OF COAL MINERS

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We previously reported a positive relationship between duration of work and FEV1 in a group of miners aged over 70 applying for Industrial Injury Benefit for PD D12 - chronic bronchitis and emphysema (Thorax 52; 441P). We have now completed the analysis on 3850 miners. Their median age was 71 yr (range 39-94). All had spent at least 20 years underground (a requirement for the benefit) and the median duration of exposure was 37 yr (20-50). 23% were never-smokers, 53% ex-smokers, and 23% current-smokers. The median FEV1 was 1.79 L (72% of predicted) with a recorded range 5-143% of predicted. Stepwise multiple regression showed significant predictors of FEV1 to be age (-0.0041 L/yr: $p<0.0001$), height (+2.42 L/m: $p<0.0001$), smoking (ever v never -0.55L: $p<0.001$), amount smoked (-0.003 L/pack-year: $p<0.001$), cough (-0.135 L yes v no: $p<0.001$), sputum production (-0.08 L yes v no: $p<0.05$), age/year started work (+0.009 L/yr: $p<0.001$), and years worked underground (+0.011 L/yr: $p<0.0001$). Thus all the expected relationships with lung function were demonstrated except that as with the over-70 year olds, lung function improved with duration of mining. This relationship remained significant and of similar magnitude when subgroups of smokers, never smokers, and those starting work before and after 1940 were analysed. We regard a beneficial effect of underground mining as being implausible and believe the finding is most likely to represent an unidentified survival or selection bias. The data do not provide any evidence of an adverse effect of coal dust, but given that all subjects had at least 20 years underground exposure it is possible that an effect might have been missed by the regression analysis. Furthermore, there was a possible adverse effect from beginning underground work at an early age.

P70 THE ASSESSMENT OF SHORT AND LONG TERM MORBIDITY FOLLOWING SMOKE INHALATION INJURY

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All members of the BTS were asked to enrol patients presenting to the A & E Departments with smoke inhalation injuries into the above study. Details of the incident, the initial assessment of injury and treatment were obtained from a questionnaire. Those with significant morbidity were to be followed up over the next 12 months.

Sixteen patients were recruited from 6 hospitals in 18 months. 11/16 fires occurred in the house. Alcoholic intoxication was a predisposing factor in 4 cases. The commonest symptoms were tightness/chest pain (8), breathlessness (6) and irritation of nose and eyes (5). Oxygen was given more frequently than nebulised bronchodilators by the ambulance crew (8 vs 1 patient).

Initial assessment at the A & E Department included measurements of peak flow rates in 7 patients, Carboxyhaemoglobin levels in 9 patients and Oxygen saturation ($Sa\ 0_2$) in 11 patients.

Two patients with significant inhalation according to the study protocol were referred to the Respiratory Physician for follow-up. One was better after 2 weeks and discharged. The other had "recurrent bronchitis" and a significant decline in FEV1 over the next 12 months.

Long-term morbidity post smoke inhalation injury appears to occur but further work is required to estimate its incidence. Involvement of the A & E Specialists' Society may improve patient recruitment into subsequent studies.

P71 SEVERITY OF IMPAIRMENT IN LUNG FUNCTION TESTS - COMPARISON OF STANDARDISED RESIDUALS WITH PERCENT PREDICTED

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The use of the standardised residual (SR) to delineate normal from abnormal is becoming more common in lung function testing. Expression of results in this format is recommended by the BTS/ARTP, but no guidance is given in the use of SRs to assess the severity of impairment.

We identified 100 sets of lung function tests performed in our laboratory, 25 in each of the following categories: normal, mild, moderate or severe impairment. These categories were defined by percent predicted FEV1 according to commonly used criteria - normal (=or>80%), mild (60-79%), moderate (40-59%) and severe (<40%). We then calculated SRs for FEV1 in each of these groups, with the following results:

	Mean (SD) SR	Range
Normal	+0.33 (.63)	-1.36 to +1.49
Mild	-1.55 (.54)	-0.69 to -2.85
Moderate	-2.89 (.60)	-1.60 to -4.00
Severe	-3.89 (1.01)	-2.55 to -6.16

The mean SR for the mild group was greater than -1.64, implying that many of these patients would be classified as normal using SRs. There was considerable overlap between the groups, but we suggest the following severity scale for SRs:

Mild < 2.5
Moderate 2.5 to 3.5
Severe > 3.5.

P72 PREDICTED LUNG FUNCTION FOR ASIANS

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The forced expiratory volume in the first second (FEV1) and the forced vital capacity (FVC) of asians are said to be between 7% and 15% lower than the corresponding values for whites. We have previously shown that for a group of asians studied within the textile spinning industry in Lancashire, a number of predicted equations derived specifically for asians did not perform adequately (Thorax 1994;49:1057P). All lifelong non-smoking, asymptomatic asian workers aged 25 years or over, performing spirometry during three years of a longitudinal study of symptoms and lung function within the textile spinning industry have been studied. The difference between the FEV1 and FVC values of these workers and predicted values derived from whites equated to roughly 20% for both values which is higher than previously documented. Stringent quality control during the performance of spirometry was carried out in all cases. The data for 338 male and 90 female asian workers was therefore used to derive regression equations for this asian population. These are as follows

Males: FEV1=-1.11-(0.0237xage)+(0.0285xheight)
FVC =-2.22-(0.0226xage)+(0.0384xheight)
Female:FEV1=-0.51-(0.0197xage)+(0.0208xheight)
FVC =-1.04-(0.0214xage)+(0.0270xheight)

The residual standard deviation for FEV1 and FVC in males was 0.51 and 0.60 respectively, and for females was 0.36 and 0.41 respectively.

We suggest that these regression equations be used for all asian patients in hospital lung function laboratories at least locally in the North West.

P73 ACTUAL/BEST FUNCTION AS A PREDICTOR IN THE LONG TERM OUTCOME OF ASTHMA

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Actual/best function is used in clinical practice and suggested in guidelines as a spot measure of control. As function is variable in asthma, isolated measurements may be of limited value, although poor actual/best function is incompatible with good control at the time of observation. Actual/best peak flow (PEF) and best forced vital capacity (FVC) were recorded as explanatory variables in 1983 in 523 subjects (173 deaths) whose outcome was assessed in 1993/94, using three scales: death/regimen, death/change in best function, death/activity score. On univariate analysis, FVC was strongly associated with favourable outcome. The direct relationship between actual/best PEF and outcome was weaker and disappeared in most multivariate analyses. Relationships with actual/best PEF were explored further. When subjects with actual/best function of 100% were excluded, the relationship tended to be dichotomous, the cut-off point being between 85 and 90%, with those above the point having a good, and those below a poor prognosis. The analysis was repeated after entry of age and sex, with best function as a continuous variable, and actual/best as the three dummy variables, <85%, 85-99.5% and 100%. In addition to entry best function, the significant variables were: death/regimen (all subjects: actual/best, central heating; <55 at entry: actual best); death/activity score (all subjects: social class, atopy, current smoking; <55 at entry: as all subjects plus actual/best). When in the model, outcome was best when actual/best PEF was 85-99.5%. Only best function at entry stayed in the models for death/change in function. The results suggest that there is no advantage in a spot target of actual/best of more than 85-90%. Possible explanations for the poorer outcome in those in whom actual/best function was recorded at 100% are: inadequate assessment of best function; secondarily irreversible disease; appropriate use of long-acting bronchodilators; overtreatment reflecting adverse personality or leading to increased exposure to aggravating factors. The findings justify a target of 85-90% for actual/best function in guidelines for the management of asthma, but particular attention should be paid to those whose actual/best function is 100% at attendance.

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P74 ACUTE STEROID TRIALS IN COPD: LESSONS FROM THE ISOLDE TRIAL.

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Short term trials of oral prednisolone are traditionally used to separate patients with COPD into steroid responders and non-responders. The Isolde trial includes smokers and ex-smokers with an FEV_1 less than 85% predicted, an FEV_1/FVC less than 70% and a response to 400 mcgs of inhaled Salbutamol of $<10\%$ related to predicted value. After 8 weeks baseline measurements without any form of steroid therapy prednisolone 0.6 mgs per kilogram was given daily for 14 days, prior to randomisation to inhaled Fluticasone propionate or placebo for 3 years. The results of the first 574 patients are reported. In 38 steroids were contraindicated and were not started, in 64 the course was interrupted by side effects or exacerbations, and in 472, the course was completed as planned. The latter group were [mean (standard deviations)] 64 (7) years old; FEV_1 1.15 (0.45) and FVC 2.84 (0.79) litres.The mean (SD) post bronchodilator improvements following prednisolone were FEV_1 56 (251) and FVC 160 (58)ml significantly greater than those not receiving prednisolone (-50 and -60 mls respectively). The response was unimodally distributed, any division to responders and non-responders being arbitrary, 83 showed a >200 ml improvement in FEV_1 (? responders), 29 showed a >200 ml fall in FEV_1 (? steroid deteriorators). Both the steroid responders [319 (362)ml] and steroid deteriorators [224 (185ml)] showed more variation in post bronchodilator FEV_1 on 3 occasions before the steroid trial and those in the middle of the distribution [170 (117ml)]. These results suggest that steroid "responders" are those with inherently more variable FEV_1's rather than a group within inherently different responses to prednisolone.

P75 COPD GUIDELINES AND GENERAL PRACTICE - USE OF SPIROMETERS

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For the GP's in Asthma Group (GPIAG)

The BTS COPD Guidelines suggest the most appropriate way of assessing severity of COPD is by measuring FEV_1 and FVC. This survey examines current usage of spirometry in primary care.

A postal questionnaire was sent to the 548 members of the GPIAG (GP's with an asthma interest) and 2,000 randomly selected GP's. COPD Guidelines would be welcome by 93% of respondents. Spirometers were owned by 50% of GPIAG practices and 32% of the random group. The most common type used (61%) was the hand held electronic form. Only 25% of GP's with no spirometer would buy one. At present 11% of practices have the facility of open access spirometry. If given the choice 60% of respondents would opt for an open access service. 86% of spirometric measurements would be performed by Practice Nurses and 90% of GP's would be willing to send them on a training course.

The survey also examined the current state of performing reversibility tests for asthma and COPD. Bronchodilator reversibility is used by 97% of practices for asthma but only 78% of patients with COPD. Steroid trials are much less widely used and generally are ineffectively performed.

The survey shows a major need for spirometers, open access services in hospital plus an education programme for Practice Nurses. This will have considerable cost and manpower implications for primary and secondary care .

P76 AUDIT OF AN OPEN ACCESS LUNG FUNCTION LABORATORY SERVICE FOR GENERAL PRACTITIONERS (1991 - 1996)

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Between January 1991 and June 1996 a total of 1693 patients were referred by 120 GPs to the Lung Function Laboratory at Stafford. An average of 4.5 referrals per month from 26 GPs in 1991 has increased to an average of 37.2 referrals per month by 61 regular users in the first six months of 1996. This scheme offers GPs in Staffordshire access to computerised spirometry, oximetry, CO measurement, allergy skin tests, screening for the suitability for nebuliser and oxygen (LTOT) therapy and full tests for selected patients.

Of these referrals 984 were suspected of having asthma, 209 of having COPD and 70 of having emphysema. Testing for suspected asthma showed that 384 had completely normal tests and 403 supported the diagnosis of asthma. Thirty patients were referred for suitability for home nebulisers, of whom only 7 were found to be eligible. Out of 84 patients possibly requiring LTOT, 29 were found to fulfill the Department of Health guidelines.

More unusual findings were 8 cases of suspected pulmonary embolism. The technicians themselves identified 4 cases of possible sleep apnoea of whom 3 were confirmed by subsequent sleep studies. Two patients needed to be admitted to hospital, one for atrial fibrillation and one for severe hypoxia.

The increase in the number of referrals to the Open Access Scheme indicates that GPs in Staffordshire find lung function testing useful in the clinical diagnosis and treatment of their patients.

P77 MEASUREMENT OF SNIFF NASAL INSPIRATORY PRESSURE USING A PORTABLE MOUTH PRESSURE METER

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Sniff nasal inspiratory pressure (SNIP) has recently been proposed as a measure of inspiratory muscle strength which is easier for patients to perform than maximum inspiratory mouth pressure and is more reproducible (Thorax 1995;50:371-375). We have investigated whether a commercially available device designed for recording maximum mouth pressures can be used to measure SNIP.

One hundred sniffs with peak pressures in the range -10 to -100 cmH2O were recorded simultaneously using a pressure transducer (Validyne) connected to a chart recorder (Lectromed) and the "Pmax" monitor (PK Morgan). The digital display of the Pmax gives both a peak pressure and a one-second average, of which we used the former as an estimate of SNIP. The pressure transducers were connected to the Luer port on the barrel of a 10ml syringe, on the other end of which an Adams CPAP nasal pillow (Puritan Bennet) was placed to form the interface to the nose.

The mean (SD) difference in SNIP between the two measurement methods was 1.58 (2.03) cmH2O. When the peak pressure was more negative than -50 cmH2O, the Pmax device tended to underestimate SNIP slightly, but the maximum discrepancy was only 7 cmH2O.

The Pmax device can be adapted to measure SNIP, and is sufficiently accurate when SNIP is used as a screening test to detect inspiratory muscle weakness.

P78 DIAPHRAGM STRENGTH MEASURED USING MAGNETIC PHRENIC NERVE STIMULATION IN THE INTENSIVE CARE UNIT

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The catabolism of severe illness, drugs, electrolyte imbalance, and critical illness neuromyopathy can all cause muscle dysfunction. Although weakness of the respiratory muscles contributes to dependence on mechanical ventilation, measurement of respiratory muscle strength in the ICU is hampered by the difficulty in interpreting volitional tests of strength and technical limitations. We have used the new technique of magnetic phrenic nerve stimulation (Mills et al, Thorax 1995; 1162-72, AJRCCM 1995 A414) to assess diaphragm contractility in 12 mechanically ventilated patients (age range: 17-71) with prolonged or unexpected requirement for ventilation. Airway pressure and where possible trans-diaphragmatic pressure were recorded following unilateral or bilateral phrenic nerve stimulation. During phrenic nerve stimulation there was close agreement between airway and oesophageal pressure. In 2 patients technical difficulty precluded reliable measurements. Unilateral diaphragm weakness was demonstrated in 3 patients, probably attributable to recent thoracic surgery. Severe diaphragm weakness was seen in 6 patients: nemaline myopathy, glycogen storage disorder, MND, and critical illness neuromyopathy were later diagnosed in 4 of these cases, in 2 a specific diagnosis was not made. In 1 patient with severe peripheral weakness, phrenic nerve stimulation showed relative preservation of diaphragm function, also confirmed by diaphragm needle electromyography. We conclude that this new technique can be applied in the ICU and may be helpful in the diagnosis and management of ventilated patients.

P79 ABDOMINAL MUSCLE STRENGTH MEASURED BY GASTRIC PRESSURE DURING MAXIMAL COUGH

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Mouth pressure during a maximum static effort, PEmax, is dependent on patient motivation and interpretation of a low value might therefore be difficult. Cough is a natural manoeuvre and we hypothesised that it could be a useful additional tests for measuring abdominal muscle strength. We studied 20 normal subjects (10 M) and 74 patients (40M) referred for assessment of respiratory muscle strength. PEmax at TLC and gastric pressure (Pga) during single maximum coughs were measured until reproducible measurements were achieved. Mean PEmax (SD) for the normal subjects was 143 (40) cm H_2O for men and 110 (15) cm H_2O for women. Mean Cough Pga for men was 225 (25) cm H_2O and 164 (31) cm H_2O for women. Values greater than 80 cm H_2O for PEmax and 175 cm H_2O for Cough Pga in men and 60 cm H_2O and 100 cm H_2O in women were considered to exclude expiratory muscle weakness. In both the 20 normal subjects and the 74 patients Cough Pga was greater than PEmax with the exception of 1 normal subject and 1 patient. In 35 patients expiratory muscle weakness was diagnosed using PEmax alone, but by using Cough Pga in addition weakness could be excluded in 16 of these. We conclude that Cough Pga is a useful additional test of expiratory muscle strength.

P80 EFFECT OF SALBUTAMOL ON INPUT IMPEDANCE MEASUREMENTS IN LARYNGECTOMIZED SUBJECTS DURING TIDAL BREATHING.

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Respiratory function measurements in laryngectomized subjects are interesting because they avoid interference from (1) the larynx and (2) the pharynx and upper airway. We used a within-breath input impedance measurement technique to study bronchodilator responses in 11 laryngectomized subjects (mean[sd] age 61.7[9.6] yrs, 1 non-smoker, 10 ex-smokers). A 10 Hz, 0.7 ml amplitude oscillating flow signal was input at the airway opening via a plastic tracheostoma valve (Blom-Singer, California, USA) sealed to the peri-stomal region with silicone skin adhesive and double-sided adhesive tape (Blom-Singer, California, USA). In 5 subjects, a speech valve was present and sealed using an airtight plastic valve sizer. Total respiratory resistance (R10) and reactance (X10) were calculated in 3 modalities; (i) averaged during tidal breathing (denoted _av), (ii) gated to end-inspiration (denoted _ei) and (iii) gated to end-expiration (denoted _ee). 3 baseline tests and 3 tests at least 20 minutes post 400μcg of inhaled salbutamol (Volumatic) were made.

Gating had little effect on the intra-subject coefficient of variation of R10 over 3 baseline measurements in the 3 modalities (CV%=7.2 - 8.7, smokers and CV% = 1.5 - 3, non-smoker). Baseline resistance behaviour was biphasic in the non-smoker but rose with large monophasic, end-expiratory rises in smokers and large negative dips in reactance at end-expiration. Studying bronchodilator responses in the smokers only (excluding 1 using β-blockade) the following observations were made (R10 values in mean[sd] $kPa.l^{-1}.s$), SI indicates the Sensitivity Index (absolute change/baseline sd);

	Baseline R10	R10 Fall	%change	SI
R10_av	0.72[0.4]*	0.29[0.39]*	30.2[32.0]**	5.3[7.0]
R10_ei	0.38[0.1]*	0.10[0.08]*	23.7[18.6]*	5.0[6.1]
R10_ee	0.92[0.5]	0.46[0.49]	39.2 [32.3]	11.0[17.2]

paired t-test: * $P < 0.05$, ** $P < 0.001$ (differences from R10_ee)

These results illustrate how breathing-phase influences observable bronchodilator responses in smoking laryngectomized subjects.

P81 REGIONAL VENTILATION AND PERFUSION LUNG SCAN ABNORMALITIES IN ATOPIC ASTHMATICS FOLLOWING ALLERGEN CHALLENGE: COMPARISON WITH AIRWAY FUNCTION AND GAS EXCHANGE

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Abnormal lung ventilation and perfusion have been noted during acute bronchoconstriction, but the temporal course of regional changes is unclear. In a pilot study, planar ventilation (Xe-133) followed by planar and tomographic perfusion (Tc-99m) scans were performed on 7 non smoking male asthmatics (aged 30-64, predicted FEV_1 70-102%) 48h before, and 30min and 6h, after aerosolised allergen challenge (*D pteronyssius*/mixed grass pollen). Measurements of airflow obstruction (FEV_1), airway reactivity (PC_{20}histamine) and gas exchange (SaO_2, PaO_2 & $P_{A-a}O_2$) were made concomitantly. Inhalation and washout views of the ventilation scans and the posterior projections of the perfusion lung scans were analyzed using a previously reported method (Burton H *et al*, J Nucl Med 1984; 25:564-70) modified by normalising the scans to maximum uptake, instead of the total lung uptake. Early and late allergen induced bronchoconstrictor responses were variable (respective maximum falls in FEV_1 were 49% and 35%) as was the doubling dose shift in airway reactivity ($\Delta DDPC_{20}H$ 0.8-3.2). Hypoxaemia was most marked during early allergen-invoked bronchoconstriction ($\Delta Pa0_2$ 8-30%) but was still apparent at +6h in 5 subjects ($\Delta Pa0_2$ 5-18%). $P_{A-a}O_2$ was typically increased at +30 min (0.9-1.8 kPa). A variety of appearances were noted even on the baseline V/Q scans. Comparison of imaging analyses with physiological data showed some corresponding patterns, although there were instances of ventilation and perfusion abnormalites in patients with little change in physiological measurements. Lung scintigraphy generally showed greater perturbation than was indicated by the magnitude of airflow limitation and arterial hypoxaemia.

P82 MEASUREMENT OF INSPIRATORY MUSCLE PERFORMANCE USING INCREMENTAL THRESHOLD LOADING: A NORMAL RANGE

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Incremental Threshold Loading (ITL) has been proposed as a test of inspiratory muscle performance (IMP). It is more reproducible than measurement of maximum inspiratory mouth pressure (MIP), and since it measures IMP over a longer time period, more closely reflects the way in which respiratory muscles function. To date there has however been no normal range for an ITL test, with different investigators using a variety of different pressure increments.

We have developed an ITL test using a weighted plunger system which uses standard increments of pressure. In our protocol, subjects inspire through the weighted plunger generating an initial threshold opening pressure of 10 cmH_2O. This pressure is raised at two-minute intervals in increments of 5 cmH_2O until they fail to lift the plunger on two consecutive attempted breaths.

60 healthy volunteers (30 female) aged 20-80 years performed our ITL test. 12 subjects (6 female) performed the test twice to assess reproducibility. Using stepwise multiple linear regression, we regressed the number of completed stages (STAGE) against age, height and weight. STAGE was significantly related to age but neither height nor weight, the regression equations being as follows:

STAGE (males) = 19.7-(0.2 × age in years)

STAGE (females) = 17.7-(0.2 × age in years)

The within-subject standard deviation for those repeating the ITL test was 1.08 stages.

ITL is a simple technique with good reproducibility, which most subjects can use without difficulty. By using standard pressure increments we have established a normal range which should be applicable wherever similar pressure increments are used.

P83 REVERSIBILITY TO BRONCHODILATORS: ARE FORCED EXPIRATORY MANOEUVRES THE BEST?

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In patients with airflow obstruction, the relaxed vital capacity (RVC) often exceeds the forced vital capacity (FVC), the latter being limited by cough or dynamic airway collapse. In addition, patients tested for bronchodilator response sometimes report benefit despite no improvement in conventional forced expiratory indices. This suggests that the forced expiratory manoeuvre may be causing patients who do benefit from bronchodilators to be classified inappropriately as non-responders. We analysed 376 randomly selected records from patients who had been tested for bronchodilator reversibility at the Respiratory Function Laboratory within the past 3 years, to investigate if 1) there are a significant number of patients whose RVC is greater than their FVC and 2) if any of this subset of patients show reversibility in RVC but not in FEV_1.

Of the 376 records 198 showed RVC greater than FVC for the baseline values. Of these 198 records, 99 showed reversibility of FEV_1 (>160ml increase[1]) Of the 99 that did not show reversibility in FEV_1 , 20% showed reversibility in RVC and FVC (>330 mls increase[1]) and a further 7% showed reversibility in RVC only.

It can therefore be seen that 27% of patients who are assumed to be non-reversible by standard measurements are reversible judged by an improvement in RVC post bronchodilator.

In the 198 patients with RVC >= FVC, the change in FEV_1 with bronchodilators was unrelated to starting FEV_1 ($p=0.52$) whereas the change in RVC with bronchodilators was greatest in those with low FEV_1 (Pearson coefficient of correlation = -0.28, $p=0.00006$). This suggests that bronchodilator induced increase in RVC may be particularly useful in patients with severe obstruction.

This retrospective study of routinely acquired data has not addressed the reproducibility of RVC reversibility nor the correlation of this index with clinical or symptomatic benefit.

[1] Tweedale PM, Alexander F and McHardy GJR. Thorax 1987, 42:487-490

P84 LUNG FUNCTION IS GENERALLY PRESERVED FOLLOWING PERIPHERAL BLOOD STEM CELL TRANSPLANT.

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Abnormalities of pulmonary function are common in patients with haematological malignancies treated with bone marrow transplantation (BMT). In this study we have investigated 23 patients receiving peripheral blood stem cell (PBSC) transplants to determine the effects of this new method of transplantation on lung function. Mean age (range) was 49 (21-61) years and male:female ratio 1.5:1. Seventeen patients had lymphoma, 2 leukaemia and 4 multiple myeloma as their underlying diagnosis. Pulmonary function tests (PFT) were measured before transplant, at 3 months, 6 months, 9 months and one year post transplantation. Following PBSC transplant 8 out of 23 patients showed a reduction in FVC and TLCO of >20% at 6 weeks. Five of these 8 patients received BEAM chemotherapy, which includes carmustine and 3 received total body irradiation (TBI) as their conditioning regimen. Two of these patients were investigated and diagnosed for interstitial pneumonitis on the basis of a fall in TLCO. There was no change in lung function of 15 patients after PBSC transplant, although 4 received TBI while 11 received BEAM as their conditioning regimen, out of which 6 received bleomycin and/or busulphan in addition to their conditioning regimen. Four out of these 6 patients also received mantle radiotherapy prior to transplant. This compares favourably with earlier series on PFT abnormalities following allogenic BMT, suggesting that the PBSC are less toxic to the lungs. It also confirms that PFT gives early warning of development of pneumonitis.

P85 GASTROSTOMY FEEDING SIGNIFICANTLY IMPROVES LUNG FUNCTION IN CHILDREN WITH CYSTIC FIBROSIS

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The increased metabolic demands of cystic fibrosis (CF), and the relationship between pulmonary function, survival, and nutritional status, have led to the use of supplemental feeding regimes for CF patients failing to maintain adequate nutrition. Previous studies have produced conflicting reports on the effects of such regimes on lung function. We have reviewed the results of gastrostomy insertion in 18 consecutive paediatric CF patients over the last 7 years. Response has been analysed by changes in body mass using standard deviation (SD) scores for Log $Ht/Wt^{2.88}$(Rosenthal, M. et al. *Eur. J.Pediatr.* (1994) 153: 876-883), lung function, and serological parameters of nutritional status. Eight boys and 10 girls (median age 10.3 years; range 3-14) underwent gastrostomy insertion. Another 2 children are receiving regular overnight nasogastric feeding. All children were pancreatic insufficient, and 86% were taking regular calorie supplements prior to gastrostomy insertion. 4 children were known to have liver disease, and all were colonised with *Pseudomonas aeruginosa*. Mean (95% CI) SD score for $Ht/Wt^{2.88}$ at the time of insertion was -0.87 (-1.4;-0.36). Baseline lung function was markedly reduced, with a mean FEV_1 of 42%(33;51%) of predicted, and FVC of 63% (50;75%). All gastrostomy tubes were inserted under general anaesthesia, with no acute complications. Feeds used were tailored to individual children's requirements and provided between 22 and 60 kcal/kg (mean 42) by slow overnight infusion. After 6 months of supplemental feeding, there was a significant increase in body mass SD score of 0.77 (0.44;1.1), which after 1 year had increased to 0.88 (0.39;1.36). There was a significant improvement in FEV_1 of 25% of baseline (2;49%) and in FVC of 25% (-13;63%). No change was seen in levels of haemoglobin, albumin, cholesterol, or vitamins A and E, although in the majority of children these had been within the normal range at the time of commencing feeds. During the study period, 2 patients have died, 2 have required reinsertion of gastrostomy, and 1, who demonstrated a rapid weight gain has subsequently sustained this after removal of the tube.We conclude that in this moderately severe group of children with CF, gastrostomy feeding is well-tolerated, with a low risk of complications, and results not only in improved nutritional status but also in significantly improved lung function.

P86 NUTRITION, DIABETES, PANCREATIC FUNCTION AND SURVIVAL IN A BIRMINGHAM CYSTIC FIBROSIS CLINIC.

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Much of the improved survival in CF is attributed to improved nutrition. We have previously reported survival data on patients who enter our clinic from age 16. Median survival is reduced in males vs. females (32 vs37y), diabetics(DM) vs. non-diabetics (NDM, 27 vs 37y) and pancreatic insufficient (PI) vs. sufficienct (32 vs. 34y) though survival analysis may be unreliable on small numbers. We compared nutritional status at the end of years 1986, 1990 and 1994. Of 194 patients (55% male), 55 (67% male) had died and 21 had been transplanted, 96% were PI and 30% DM. Over the 8 year period the nutritional status of the clinic improved significantly. Height was unchanged but body mass index ($BMI=weight(Kg)/height(m)^2$) was increased from 19.0 to 20.3 ($p<0.05$) (British Dietetic Association acceptable BMI range 20-25). Males had better BMI than females and BMI increased with age in both sexes. Rates of change (measured for patients present at the beginning and end of the 4 year periods 1986-'90, '90-'94) was greater in men though there was no change in the rate between the 8 years. There were no differences in rates of decline of lung function with age between sexes or over the time periods. The sex distribution of PI vs. PS and DM vs NDM was equal. PS patients were taller and heavier than PI but did not have different BMI or lung function. DM patients were significantly shorter and lighter than NDM ($p<0.001$) and had worse absolute and %predicted lung function ($p<0.001$ except %FVC, $p<0.02$). The data support a general clinical improvement with time but not the apparent improved survival in women despite this being reflected in national UK CF Registry data. There is no apparent survival advantage in our clinic for patients with PS vs PI presumably due to the success of pancreatic and nutritional therapy whilst diabetics appear to be significantly disadvantaged in all parameters. There is a clear challange to improve the diagnosis and management of patients with CF related diabetes mellitus.

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P87 CYSTIC FIBROSIS RELATED DIABETES (CFRD): A RETROSPECTIVE SURVEY OF ADULT CYSTIC FIBROSIS (CF) PATIENTS OF ROYAL BROMPTON HOSPITAL (RBH) FROM 1966-1996

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With the increasing survival of patients with CF, it can be expected that the prevalence of CFRD will rise with clinical and cost implications to the health service. We undertook a retrospective survey of adult patients with CFRD that had attended the Adult CF Unit at RBH from 1966 to the end of March 1996. 158 patients with CFRD were identified. The case notes of 150 of these patients were available for review. We believe that this is the largest series of CFRD patients ever reported in the UK. A total of 503 adult CF patients were alive at the end of March 96 of which 74 had CFRD thus the prevalence of CFRD in our adult patient population was 14.7%. For the 74 CFRD patients who were alive at the end of March 96, there was a female predominance (male: 46% vs female: 54%) compared with a male predominance in the full CF population (male: 55% vs female 45%). The genotype of 296 of the 503 CF patients were available. There was a significantly higher proportion of CFRD patients who were homozygous for delta F508 compared with the full CF population (68% vs 52% respectively, $p = 0.03$).

Review of the case notes of all the 150 CFRD patients shows that the median age of diagnosis of CFRD was 22 years (range 10-57). The commonest methods of diagnosis of CFRD were raised random blood glucose (BG) confirmed with raised random or fasting BG (74%) and oral glucose tolerance test (11%). At least 27% of patients were asymptomatic of hyperglycaemia at diagnosis. 50 patients (33%) were treated with oral hypoglycaemic agents (OHAs) for a median duration of 11 months (range: 3 weeks to 108 months) until death or the end of March 96. Another 49 patients (33%) received OHAs for a median duration of 12 months (range: 2 weeks to 104 months) before commencing insulin. Only 29% of patients were treated with insulin when the diagnosis of CFRD was first made. There was no documented case of diabetic ketoacidosis. 2 patients had diabetic eye complications. Medical and nursing staff involved in the care of CF patients need to be aware of this increasingly common condition.

P88 THE USE OF RAISED RANDOM BLOOD GLUCOSE (RBG) ALONE IS UNRELIABLE IN THE DIAGNOSIS OF CYSTIC FIBROSIS RELATED DIABETES (CFRD)

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The diagnosis of non-cystic fibrosis related diabetes mellitus (DM) may be made if a single RBG estimation is over the diagnostic value of 11mmol/l (venous plasma), whether the patient is symptomatic of hyperglycaemia or not (1). CFRD differs in many aspects from non-CF related DM and abnormal glucose and insulin responses to an oral glucose load has been described. As part of a study to examine the pancreatic ß-cell responses following an oral glucose load in CF patients, 7 clinically stable adult CF patients not known to be diabetic (mean age 25) and 7 age and sex-matched non-CF controls underwent oral glucose tolerance tests (OGTTs). Each subject received 75g of Glucose BP. Blood samples were taken at intervals for glucose and insulin assays. All non-CF controls and 4 CF patients had normal glucose tolerance (NGT) and 3 CF patients had impaired glucose tolerance (IGT) as defined by the WHO criteria. 3 of the CF patients (2 in NGT group and 1 in IGT group) had BG values over 11 mmol/l at various time points* (see table) in contrast with none in the non-CF controls. **Blood glucose results following OGTTs in 7 CF subjects :**

Time (min)	Patient (P) 01	P02	P03	P04	P05	P06	P07
0	4.9	4.3	5.0	5.0	4.2	4.9	4.4
20	11.6*	7.1	4.8	6.1	8.4	7.4	8.8
30	12.8*	8.4	5.4	6.7	10.6	8.2	9.3
40	13.2*	10.9	6.7	7.6	12.1*	9.0	9.0
50	13.1*	12.5*	7.3	7.8	13.0*	8.5	9.7
60	9.3	13.7*	8.2	8.6	13.4*	9.4	8.5
75	6.3	13.9*	8.5	8.6	12.5*	9.0	6.8
90	5.0	12.8*	8.5	8.9	8.6	8.3	5.8
120	4.1 NGT	10.4 IGT	9.6 IGT	8.2 IGT	7.3 NGT	7.6 NGT	6.5 NGT

Provided that a large enough glucose load is taken by CF patients (e.g. a large meal) before a RBG is taken, their RBG may exceed the diabetic range even in CF patients with OGTT-defined NGTor IGT. Using RBG alone is unreliable in the diagnosis of CFRD and this method should be used in conjunction with other methods e.g. OGTT. Ref: 1. WHO Geneva 1985. Diabetes mellitus. Technical report series 727.

P89 SYMPTOMATIC HYPOMAGNESAEMIA IN CYSTIC FIBROSIS PRECIPITATED BY TREATMENT OF INFECTION

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Deficiency of magnesium, a predominantly intracellular cation occurs due to poor intake, malnutrition, malabsorption and pancreatic insufficiency. In cystic fibrosis, renal loss may be enhanced by aminoglycosides, diuretics and glycosuria yet hypomagnesaemia is rarely described. We describe 3 cases presenting with severe recurrent chest infection, all with hypercapnoeic respiratory failure and awaiting lung transplantation (Table 1). 2 were pancreatic insufficient, 2 diabetic and all were undernourished. All were receiving nebulised salbutamol and colomycin and 2 required maintenance oral prednisolone. Cases 1 and 2 presented with paraesthesiae, cramp and positive Trousseau's signs. In both, hypomagnesaemia was associated with hypokalaemia and hypocalcaemia and developed during treatment with intravenous antibiotics, including tobramycin, and prednisolone. Urinary Mg^{2+}, Ca^{2+} and K^{+} losses were elevated despite low serum levels. Correction of electrolyte abnormalities led to resolution of symptoms although case 1 had a grand mal epileptic fit. In case 3, asymptomatic hypomagnesaemia, not associated with Ca^{2+} or K^{+} deficiency, was detected before treatment and corrected before symptoms developed. The symptoms of Mg^{2+} deficiency in CF appear to be related to its severity and the association with reduced Ca^{2+} and K^{+} It is likely that poor nutritional status due to reduced intake and malabsorption contribute to whole body Mg^{2+} depletion. Renal loss induced by aminoglycosides and the effect of prednisolone and B_2 agonists leads to failure of homeostasis and the development of symptoms. The prevalence of hypomagenaesemia in CF is not known but we now include Mg^{2+} estimation as a routine measurement in all cases during hospital treatment.

Table 1: Normal range(mmol/l): Mg^{2+};0.7-1.0, Ca^{2+};2.05- 2.60, K^{+}3.5 -5.0.

No	age(sex)	Wt Kg(%)	FEV_1(%)	Mg^{2+}	$Ca^{2+}_{(corr)}$	K^{+}
1	29 (m)	58 (73%)	1.2 (26%)	0.16	1.56	2.2
2	25 (f)	44 (83%)	0.7 (27%)	0.28	1.86	2.7
3	31 (m)	41 (67%)	0.6 (16%)	0.37	2.11	4.1

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P90 PROGRESS IN TREATMENT IN A BIRMINGHAM ADULT CYSTIC FIBROSIS CLINIC SLOWS FUNCTIONAL DECLINE

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Survival in CF has increased to a median of 30 years. Survival analysis within clinics is difficult due to small numbers. Surrogate measures of clinic performance including age related lung function and weight and their rate of decline are easier to calculate and may eventually allow comparisons between clinics. We present data from 1986, 1990 and 1994 showing improvement in our clinic in 194 patients (55% male) including 55 deaths(67%m) and 21 transplants (11m). The proportion of males, diabetics (~30%), pancreatic sufficient patients(~4%) and the prevelence of ΔF508 (~71%) remained constant over the period. Mean ages at diagnosis, referral to the adult clinic and death were similar between sexes and between years (p=NS). Comparisons were made between sexes, age bands (<20, 20-24.9, 25-..,35-39.9yrs) and the years studied. Clinic size increased each year and the proportion of patients in older age groups increased despite the influx of new patients (% >30 years of age; 1986=6%, 1994=15%). Males were consistently taller, heavier ($p<0.001$) and had better absolute and percent predicted lung function than females ($p<0.05$). For both sexes body mass index (BMI=weight(Kg)/height(m)^2) was similar. Weight was greater in older age bands despite deteriorating lung function and improved signifcantly within bands across the years. The clinic mean BMI increased from 19.0 to 20.3 between 1986 and 1994 ($p<0.05$). Lung function deteriorated across age bands (ie with age) but comparison of age bands across the years showed increasing lung function between '86 and '94 though this did not reach statistical significance. Rates of decline in lung function were measured across the two 4 year periods '86-'90 and '90-'94. This was greater for females over both periods. Although the rate of decline slowed for both sexes over the two periods, these changes also did not reach statistical significance. The data suggest the clinic is healthier with more older patients who are declining less rapidly as a result of new therapy.

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P91 PHYSIOTHERAPY AND NEBULISED DRUG USE IN A BIRMINGHAM ADULT CYSTIC FIBROSIS UNIT: PATIENT PRACTICE, KNOWLEDGE AND ADHERENCE

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The lungs of people with cystic fibrosis are chronically colonised by bacteria from an early age. The principles of treatment include airway clearance by chest physiotherapy (CPT) following bronchodilation, and prophylaxis and treatment of infection by antibiotics. Despite regular review and tuition patients' practice, knowledge and adherence may be suboptimal. This was assessed by a self-administered anonymised questionnaire. 118 (61m) of 158 patients replied. 81% were prescribed bronchodilators, 80% nebulised antibiotics and 30% DNAse. 4% using bronchodilators, 6% using DNAse and 7% nebulising antibiotics were doing so at inappropriate times in relation to CPT. 18% were nebulising DNAse with an inappropriate air compressor. 85% reported performing CPT at least once daily with frequency and duration increasing during exacerbations but 3% never performed CPT. Techniques used alone or in combinations were the active cycle of breathing technique (ACBT, 32%), autogenic drainage (AD, 26%), postural drainage with percussion (23%), the Flutter device (23%) and the positive expiratory pressure (PEP) mask (11%). 75% of respondees performed regular exercise; the type, duration and frequency varied considerably according to individual capacity and preference. 93% had been assessed by a physiotherapist in the past year. Over 90% agreed their knowledge and techniques improved with regular advice. 71% felt encouraged by these reviews but less than 50% of respondees felt motivated to increase their exercise despite advice and encouragement. Patients expressed particular interest in the benefits of DNAse and alternative CPT techniques. The audit revealed that despite regular review and tuition, patients' knowledge and practices are less than ideal. There is a need for individually tailored CPT and exercise programmes supported by written guidelines on the timing of drug therapies in relation to CPT with improved outpatient support for patients who are well and at home.

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P92 THE ROLE OF E.L.I.S.A. IN THE EARLY DIAGNOSIS OF *PSEUDOMONAS AERUGINOSA* INFECTION IN CYSTIC FIBROSIS

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The role of serological tests in the early detection of *P.aeruginosa* infection in cystic fibrosis (CF) patients continues to be debated. We have used an enzyme linked immunosorbent assay (E.L.I.S.A.) based on the method described by Pedersen et al (1987)[1] to investigate changes in antibody levels associated with acquisition of *P.aeruginosa* infection. Initial studies on stored serum collected from CF children attending our Regional clinic demonstrated a significant difference in titre between non-colonised and chronically colonised patients ($p<0.05$). Further blind analysis was performed retrospectively on serial samples obtained at yearly intervals from 37 patients. 20 patients remained uncolonised with *P.aeruginosa* over the collection period; of these 17 (85%) patients had a low titre throughout, but 3 (15%) had a high titre on at least one occasion. 17 patients isolated *P.aeruginosa* for the first time during the study period; of these 6 (35%) demonstrated a rise in titre prior to microbiological diagnosis, however, 7 (41%) showed a rise in titre *after* microbiological diagnosis and in 4 patients (24%) there has been no rise in titre for up to 4.5 years. These findings demonstrate that this E.L.I.S.A. is unreliable in detecting early Pseudomonal infection. More sensitive and specific markers of early *P.aeruginosa* infection are required to guide management aimed at delaying the onset of chronic colonisation.

[1]Pedersen SS, Espersen F and Hoiby N (1987) J Clin Microbiol **25**(10):1830-1836.

P93 THE CLINICAL SIGNIFICANCE OF THE AUXOTROPHIC PHENOTYPE OF PSEUDOMONAS AERUGINOSA IN CYSTIC FIBROSIS

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Pseudomonas aeruginosa (PA) is the most important pulmonary pathogen in patients with cystic fibrosis (CF). It has previously been shown that a large proportion of PA isolates from CF patients are dependent upon specific amino acids for growth (the auxotrophic phenotype). The purpose of this investigation was to determine whether the previously observed association between the presence of auxotrophic PA and respiratory disease severity could be confirmed. Furthermore we questioned whether amino acid levels are higher during infective exacerbations than otherwise as this may contribute to the overgrowth of auxotrophs and hence the severity of exacerbations.

Sputum was obtained from adult CF patients colonised by PA at the onset of infective exacerbations and when well. Sputum samples were cultured for PA and for the auxotrophic phenotype by spreading serial dilutions on a minimal medium that supports only the growth of prototrophs, and a complete medium that supports both nutritional varieties. Total amino acids were determined by the ninhydrin technique.

126 sputum samples were obtained from 39 CF adults. In 30 subjects (73%) auxotrophs were identified; auxotrophs alone were present in 5(12.8%) (Group 1),and in 9(23%) only the prototrophic phenotype was identified (group 2). Comparing groups 1 and 2 the presence of auxotrophy was associated with disease severity as represented by FEV1 percent predicted (Group 1, mean FEV1 26% predicted (range 13% to 34%); group 2, mean FEV1 48% predicted (range 24% to 72%), $P< 0.05$*. There was a trend towards the proportion of auxotrophs and total amino acids increasing during exacerbations (ns). Weekly monitoring of sputum amino acids showed wide fluctuations that were not due to intra-sputum variability.

These data confirm the high prevalence of the auxotrophic PA and its association with disease severity in CF. This suggests that strategies to inhibit the growth of this phenotype by (for example) the use of methionine analogues may be worth investigating.

*Wilcoxon rank sum test for paired samples

P94 INFLAMMATORY MARKERS AND CLINICAL RESPONSE TO INTRAVENOUS ANTIBIOTICS IN ADULTS WITH CYSTIC FIBROSIS COLONISED WITH BURKHOLDERIA CEPACIA AND PSEUDOMONAS AERUGINOSA.

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Ten cystic fibrosis [CF] adults colonised with Burkholderia cepacia [BC] formed the study population [6M, 4F, mean age 21 yrs, mean body mass index [BMI] 19.9, mean % predicted FEV1 55.6]. Three patients were colonised with B cepacia alone and seven both with B cepacia and P aeruginosa [PA]. Thirty three controls were selected from CF patients colonised by Pseudomonas aeruginosa [21M, 12F, mean age 22 yrs, mean BMI 19.7, mean % predicted FEV1 60.4] and five patients who grew BC intermittently from their sputum formed a third study group [3M, 2F, mean age 27 yrs , mean BMI 19.4 ,mean % predicted FEV1 38.4]. At the onset of the first infective pulmonary exacerbation after recruitment, the patients were weighed and had their FEV1 measured with a dry bellows vitalograph. Blood was drawn for estimation of white cell count [WCC], neutrophil elastase-alpha 1 antitrypsin complexes [NE], and C reactive protein [CRP]. Patients were treated with two weeks of intravenous antibiotic therapy according to the in vitro sensitivity of the infecting organism. Within 48 hours of completion of intravenous antibiotics and six weeks later in a period of clinical stability the clinical [FEV1 % predicted , body mass] and laboratory measurements [WCC, NE, CRP] were repeated. For the whole CF population studied, the mean FEV1% predicted was significantly lower at the beginning of the exacerbation than at the end of the exacerbation or in stable state [$p<0.001$] and the mean WCC , NE and CRP were significantly higher at the beginning of the exacerbation than at the end of antibiotic therapy or in stable state [$p<0$ 001]. Identical trends were observed within each study group [BC, BCI, PA] , but there were no significant differences between the groups [$p>0.05$]. No difference in clinical response to intravenous antibiotics or generation of inflammatory markers has been demonstrated between the three groups of CF adults studied [BC, PA, BCI] in this cross sectional study of a single infective pulmonary exacerbation.

P95 IS FUSARIUM SPECIES A CAUSE OF FUNGAL ATOPY IN ADULT CYSTIC FIBROSIS ?- MC GRATH D S., SHORTT C., STACK M., KELLEHER N., AND BREDIN C P

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Fusarium (a common soil and plant pathogen), was identified in the past as a cause of allergic fungal sinusitis. However, only recently has it been associated with Allergic Bronchopulmonary Mycosis (Am J Respir Crit Care Med 1995). In an earlier study, at this centre, by Henry et al, atopy to a variety of fungal antigens was reported in an adult Cystic Fibrosis (CF) population. In addition, hypersensitivity skin testing was found to be a more sensitive method for diagnosing ABPM in CF than the Radioallergosorbent Test (RAST). Extending this study, it was planned to ascertain whether Fusarium was a further cause of fungal atopy in adult CF, and if so, to measure its prevalence. In addition, it was hoped to determine whether Fusarium atopy occurred in isolation or conjointly with other fungi. The final objective was to compare again the sensitivity of fungal antibody testing with that of hypersensitivity skin testing. Eighteen CF, eighteen asthmatic and eighteen control volunteers (matched for age and sex) were investigated. Immediate hypersensitivity skin testing to Aspergillus Fumigatus, Penecillium Notatum, Fusarium Moniliforme and Fusarium Vasinfectum was performed on each subject. Total serum IgE and fungus-specific RAST testing was also performed . A positive result for Fusarium was found in 33% of CF and 16.5% of asthmatic patients. Total serum IgE was significantly higher in CF ($p = 0.03$) and asthmatic ($p = 0.003$) patients when compared to controls. In addition, skin testing was twice as sensitive as serology for Fusarium in each group. Finally, in all cases positive for fusarium, mixed fungal atopy was illustrated.

P96 THE OUTCOME OF 72 PREGNANCIES IN 55 CF WOMEN: A UNITED KINGDOM SURVEY 1977-1995.

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55 women with CF who had 72 pregnancies were identified in 7 UK CF centres. The severity of maternal CF at the last menstrual period (LMP), outcome of pregnancy and effect on maternal health in the first postpartum year were noted. Median age at diagnosis was 1.5 years, 26 were homozygous and 15 heterozygous for ΔF508. 8 were pancreatic sufficient, 8 diabetic and 6 had early liver disease. 41 mothers had preconception counselling, 27 pregnancies were planned and 30 occurred within marriage. There were 47 live births (24 male), 26 carried to term (gestation ≥37weeks), 21 terminations (8 miscarriages) and 3 have yet to deliver. There were no still births or neonatal deaths and no child has CF but there were 3 foetal anomalies. Of the term (T) deliveries 14 had normal vaginal deliveries (NVD) and 4 caesarean sections (CS) with mean birth weight 3.22Kg and median Apgar scores 9,10. 5 abortions were performmed to protect maternal health, 1 for foetal anomaly and 5 for psychosocial reasons. Of 22 premature (P) deliveries had 6 NVD and 10 CS at mean 34(range 30-36)wks, with weight 2.28Kg , Apgars 8,10. Only 7T and 1P infants were breast fed. There was no difference in age, genotype, pancreatic status, liver disease or percent ideal body weight (%IBW, T=99.3%, P=97.8%; p=0.68) between P and T mothers. Mean $\%FEV_1$ (T=80%, P=60%;p=0.002) and, %FVC (T=92.5% P=79%; p=0.025) were significantly different. Both groups lost lung function ($\%FEV_1$; T= -7%, P= -16%, %FVC, T= -7%, P= -16%), but only group T regained it in the year post partum. During pregnancy T gained 8.8Kg, P 2.6Kg but both returned to their original weight. 10 mothers died with median survival with first child of T=11.9yrs, P=7.6yrs ($p<0.15$). We have previously proposed that pregnancy is least hazardous for mother and baby when $\%FEV_1>60\%$ predicted, but this data suggests that a higher $\%FEV_1$ is required for normal full term delivery and prolonged survival with child.

FPE is supported by the United Kingdom CF Trust.

P97 THE EFFECT OF PREGNANCY ON MATERNAL CYSTIC FIBROSIS vs NULIPAROUS SEVERITY MATCHED CONTROLS

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55 women with CF had 72 pregnancies in 7 United Kingdom CF centres. 44 mothers with 54 pregnancies were matched with nulliparous women with similar birth dates attending the same clinics with predicted $\%FEV_1$ ±10% at the age of the last menstrual period (LMP ±4years). No matches were found for 10 women who were excluded. The mean $\%FEV_1$ for cases (C) =72%, controls (nulliparous, N) =76% (p=0.8), age at LMP C=22.5, N=22.4 years, year of birth ranges C=Aug/57- Aug/77, N=May/59-Apr/78. There were no differences in age at diagnosis, genotype, pancreatic status or the number of diabetics. %FVC was C=88%, N=90% (p=0.6) and percentage ideal body weight (%IBW), C=98%, N=101% (p=0.24). The best values in the year post delivery were compared at an equivalent time for controls. $\%FEV_1$ C=69%, N=74%, (p=0.35) %FVC; C=91%, N=98.7 (p=0.42), %IBW; C=97%, N=103% (**p=0.01**). 43 completed pregnancies in 35 mothers were compared with controls. There was no difference in pre-pregnant $\%FEV_1$, %FVC or %IBW, and at one year no difference in lung function was seen but the cases had lost weight relative to controls %IBW, C= 97%, N=103%(**p=0.04**). Mothers delivering at term (T) showed no loss of lung function prior to delivery and no differences in any parameter in the year post delivery. During preterm (P) pregnancies (<37 weeks gestation) there was a trend to lose lung function $\%FEV_1$ CP=47%, NP=56% (p=0.18), %FVC Cp=64%, Np=73% (p=0.19), which was associated with poor weight gain; last %IBW, Cp=103%, Np=98%; (p=.34). At one year the trend to poorer lung function continued (but p=NS), but weight was reduced, %IBW; Cp=91%, Np=103% (p=0.01). This data suggests that healthy women who proceed to term do not lose lung function or body weight in the first postpartum year. Those delivering preterm lose lung function and gain less weight in pregnancy, and lose weight the following year. Premature delivery is a reflection of poor maternal health and women should be advised that their outcome of pregnancy and future health is likely to be impaired.

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P98 IS THE RISK OF FOETAL ANOMALIES GREATER IN MOTHERS WITH CYSTIC FIBROSIS?

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Pregnancy in cystic fibrosis (CF) is increasing with an estimated annual incidence of 3-4% of females age 17-34 since 1990 (USA CF Registry). Despite hundreds of documented deliveries no foetal anomalies have been reported. In 72 pregnancies in 55 women with CF in the UK we identified 3 cases of major birth defects. The 3 women became pregnant at ages 18.6-20.4. 1 had dF508/dF508, 2 dF508/unknown, all were pancreatic insufficient and at 86-111% predicted ideal body weight. Lung function was $\%FEV_1$ 71-98% predicted. All were using nebulised B_2-agonists and colomycin and took multivitamins, flucloxacillin and pancreatic enzyme supplements at the time of the last menstrual period. 1 mother who smoked 10 cigarettes a day, a diabetic with good glycaemic control received ciprofloxacin and intravenous (i.v.) azlocillin and gentamicin in the first trimester. Anomalies were detected on ultrasound scan and termination at 18 weeks revealed a congenital diaphragmatic hernia with pulmonary hypoplasia and polysplenia. The second mother who smoked 10 cigarettes a day received i.v. ceftazidime in the first trimester and delivered spontaneously at 36^+ wks. The infant had a large ventricular septal defect but surgery was avoided and the child is well at 2.7 years. The third became pregnant while using the oral contraceptive pill during a course of i.v. ceftazidime and colistin. Following repeated infections and considerable loss of lung function she was induced at 34^+ wks. The child has dextrocardia and unilateral renal cystic dysplasia but remains well at 2.2 years. In health the incidence of newborn anomalies in is 1-3% which is increased in diabetes, malnutrition, smoking and with certain drugs. Chronic sepsis, hypoxia, cor pulmonale and hepatobiliary disease increase the risk of growth retardation, prematurity and foetal death. The intrinsic risk in CF is unknown but the above factors are common in CF and may act to increase the risk of foetal anomalies.

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P99 INHIBITORY CONFORMATION OF THE REACTIVE LOOP OF α_1-ANTITRYPSIN

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α_1-antitrypsin is the most abundant circulating plasma proteinase inhibitor and the archetypal member of the serpin family of serine proteinase inhibitors. The common Z deficiency variant (342Glu→Lys) predisposes homozygotes to juvenile cirrhosis and early onset panlobular emphysema. Previously we have shown that Z antitrypsin deficiency results from a unique protein-protein interaction between the reactive centre loop of one molecule and a β pleated sheet of a second. These loop sheet polymers form under physiological conditions and tangle in the endoplasmic reticulum of hepatocytes. We have now determined the crystal structure of an antitrypsin mutant (51Phe→Leu) that stabilises the protein and prevents the process of polymerisation *in vitro* and *in vivo*. An engineered clone of antitrypsin containing the 51Phe→Leu mutation was expressed in *E.Coli* and purified to homogeneity. The resulting protein was 80% active as an inhibitor and had normal association and dissociation rate kinetics with human neutrophil elastase and bovine α-chymotrypsin. Crystals were grown as hanging drops in Tris/acetate buffer with 24% w/v PEG 4000 at 18°C. Diffraction data were collected from a frozen crystal to 2.9Å at 100°K using a rotating anode X-ray source. The protein structure showed good density for all regions apart from P11-P14 of the reactive loop and the model had an R factor of 21.8% and a free R factor of 28.8%. The structure showed a 5 membered A β–sheet, but instead of a helix, the reactive loop was held above the molecule as a β-pleated strand. This loop was anchored to the body of the protein by salt bridging of P5 glutamate to a well defined positively charged pocket of 3 lysine and 1 arginine residues at the pole of the molecule beneath the s3A-s4C junction. The facility of formation of a β-pleated conformation fits with the readiness of antitrypsin to form intermolecular loop-sheet linkages and favours our proposal that the interaction is between the reactive site loop of one molecule and the A β-sheet of another. The finding also explains the bonding of serpins to other β-sheet structures, notably the β-amyloid of Alzheimer's disease. The most profound implication however is for the mechanism of inhibition as the reactive centre loop, which is fixed in the canonical conformation, docks comfortably with the substrate binding pocket of both trypsin and chymotrypsin. This structure has major mechanistic implications for antitrypsin and the family of serine proteinase inhibitors.

P100 IDENTIFICATION OF A NOVEL CONFORMATION OF ALPHA$_1$-ANTICHYMOTRYPSIN: AN EXPLANATION FOR THE INACTIVE SPECIES FOUND IN LUNG LAVAGE FROM PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

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The pathogenesis of emphysema results from an imbalance between neutrophil proteolytic enzymes and their inhibitors. The most important inhibitors in the lung are the serine proteinase inhibitors or serpins typified by α_1-antitrypsin and α_1-antichymotrypsin. A previous report has suggested that α_1-antichymotrypsin from bronchoalveolar lavage fluid from patients with chronic bronchitis and emphysema is intact but inactive (J. Biol. Chem. 1986. 261: 4095-4099). We have used ammonium sulphate fractionation followed by Blue-Sepharose and DNA-Sepharose chromatography to isolate α_1-antichymotrypsin from the plasma of 20 healthy blood donors. Two species were obtained, one was the native fully active protein, and the other was inactive, monomeric and intact with a higher DNA-binding affinity and more anodal electrophoretic mobility. This inactive species was thermostable after heating at 100 °C for 2 hours and resistant to unfolding in 8 M urea and 7 M guanidine hydrochloride. Its reactive loop was resistant to proteolytic cleavage consistent with the incorporation of the loop into the main body of the protein. Unlike native active α_1-antichymotrypsin, this inactive species failed to accepted exogenous synthetic reactive-loop peptide. Together these findings suggest that this new conformation of α_1-antichymotrypsin is similar to the latent species of plasminogen activator inhibitor-1, α_1-antitrypsin and antithrombin. Preliminary data has confirmed the significant presence of this species in bronchoalveolar lavage from patients with chronic bronchitis and emphysema. The role of the conformational transition in the pathogenesis of chronic lung disease is the subject of further investigation.

P101

MATRIX METALLOPROTEINASES IN EMPHYSEMA

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While many studies have focused on neutrophil elastase (NE) as the major effector protease involved in matrix degradation in emphysema, the role of matrix metalloproteinases (MMPs), a group of potent matrix-degrading enzymes, has received little attention. The aim of this study was to assess bronchoalveolar lavage (BAL) levels of two major MMP types, collagenase and gelatinase B, in patients with emphysema and to determine if they reflect disease severity as assessed by pulmonary function and CT scan. BAL samples, obtained from 12 patients with CT-proven emphysema (all male, 5 smokers, 7 ex-smokers, age 60±11.3 y) and twelve matched controls (all male, 5 smokers, 7 nonsmokers, age 49 yrs ± 6.2) were analysed for collagenase and gelatinase B. Neutrophil elastase (NE) levels were also assessed. Collagenase activity was detected in BAL samples from all emphysematous patients but in only one smoking control ($p<0.001$). By comparison, gelatinase B was present in 7 of the 12 emphysematous patients and in two smoking controls ($p<0.01$) and NE was detected in 8 of the 12 emphysema patients and also in two smoking controls ($p<0.01$). No relationship between disease severity and either MMP or NE activity was observed. These results indicate that BAL collagenase is more useful in discriminating between emphysematous and control groups than either NE or gelatinase B and may be a better indicator of alveolar destruction than NE.

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P102 MATRIXMETALLOPROTEINASES EXPRESSION BY ALVEOLAR MACROPHAGES IN EMPHYSEMA

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Release of matrixmetalloproteinases (MMPs) by alveolar macrophages (AMs) has been implicated in the pathogenesis of emphysema. To date, however, the identity of these MMPs and whether or not their expression is directly up-regulated in emphysema has not been examined. The aim of this study was to assess MMP gene expression in AMs from emphysema patients. AMs isolated from bronchoalveolar lavage (BAL) specimens of 12 male emphysema patients (5 smokers; 7 ex-smokers) and 12 matched control subjects were analysed for interstitial collagenase, gelatinase A, gelatinase B and macrophage metalloelastase (MME) gene expression using semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR). A significant level of expression of interstitial collagenase was observed in AMs from all emphysema patients, but only in three of the control specimens, all of whom were smokers ($p<0.0001$). Similarly, gelatinase B mRNA levels were elevated in AMs from the emphysema group compared to the controls ($p<0.0001$). In the case of gelatinase A and MME, however, no significant differences in expression were noted between the patient and control groups. These results suggest that increased synthesis of interstitial collagenase and gelatinase B, but not gelatinase A or MME, by AMs may contribute to the alveolar matrix degradation which characterises emphysema.

This work was supported by the Health Research Board of Ireland.

P103 CIGARETTE SMOKE ENHANCES HOUSE DUST MITE ALLERGEN (DER P1)-INDUCED CHANGES IN PERMEABILITY OF HUMAN BRONCHIAL EPITHELIAL CELL CULTURES (HBEC)

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Although studies have suggested that exposure to cigarette smoke may be associated with the development of atopy, the underlying mechanisms are not clearly understood. It has been proposed that cigarette smoke impairs the barrier function of the airway epithelium leading to ready access of allergens such as Der p1, with subsequent sensitisation of the airways. In order to test this hypothesis we have cultured HBEC in cell culture inserts, as explant cultures from surgical tissue, and exposed these for 20 minutes to cigarette smoke in the absence or presence of 300ng/ml Der p1, over a period of 24hours. The cultures were assessed for changes in i) electrical resistance and ii) movement of ^{14}C-BSA and/or Der p1 across the epithelial cell culture. Exposure of HBEC for 20 minutes to cigarette smoke did not significantly alter either the electrical resistance or movement of ^{14}C-BSA across HBEC layer, when compared with exposure to air. In contrast, incubation of HBEC with Der p1 led to a significant decrease in electrical resistance over a period of 6 hours and an increase in the movement of ^{14}C-BSA over a period of 24 hours. Exposure of the cells for 20 min to cigarette smoke significantly enhanced these effects. The passage of Der p1 itself progressively increased with time during incubation. Movement of Der p1 was also increased by exposure to cigarette smoke.
These results suggest that although short term exposure to cigarette smoke does not increase non-specific epithelial permeability, it may render the epithelium more susceptible to adverse effects of allergens such as Der p1.

P104 EPITHELIAL PERMEABILITY *IN VIVO* AND *IN VITRO* AND TNFα IN NON-SMOKERS AND SMOKERS

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Airspace epithelial permeability is increased in smokers. Tumour necrosis factor (TNF) may increase epithelial permeability in lung inflammation. We studied the relationship between epithelial permeability and TNF in 15 smokers. All had ^{99m}Tc-DTPA lung scans after abstaining from smoking for 12 hrs (chronic smokers, C) or 1 hr after 2 cigarettes (acute smokers, A) and bronchoalveolar lavage (BAL) after either chronic or acute smoking. Seven non-smokers (NS) were also studied. Time to 50% lung clearance (t50) of ^{99m}Tc-DTPA was shorter in C (16.7±1.3 mins, mean±SE), indicating increased epithelial permeability, compared to NS (84.6±6.2, $p<0.001$) and was further reduced in A (14.8±1.0, $p<0.01$). TNF was not increased in BAL fluid from smokers but did increase in leucocyte conditioned medium (LCM) from acute smokers, after the cells were stimulated with LPS 100 ng ml^{-1} (NS 7.4±1.8, C 15.7±5.9, A 40.0±18.4, $p<0.05$). Type II alveolar epithelial cell monolayer permeability increased following incubation with acute smokers' LCM (LPS 10, C 3.44±0.18%, A 5.06±0.38, $p<0.05$; LPS 100, C 4.74±0.28, A 7.73±0.31, $p<0.05$). There was a weak correlation between t50 in smokers and TNF in LCM. Thus epithelial permeability in smokers is not related to the level of TNF in BALF nor to the ability of mixed BAL leucocytes to release TNF. Supported by the British Lung Foundation.

P105 MANGANESE SUPEROXIDE DISMUTASE (MnSOD) mRNA EXPRESSION IS DECREASED IN LPS-STIMULATED ALVEOLAR MACROPHAGES FROM CIGARETTE SMOKERS

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Both unstimulated and activated alveolar macrophages (AM) from cigarette smokers consistently release higher amounts of superoxide radicals (O_2^-) than cells from non-smokers. However, studies on anti-oxidant enzyme (AOE) activity in smokers' AM show conflicting results, as for MnSOD. In this study we evaluated the level of MnSOD gene expression in unstimulated and lipopolysaccharide (LPS, 10 mg/ml, 12 hrs)-treated AM obtained by bronchoalveolar lavage from 5 current smokers (8.46 ±2.28 packs/year) and 5 healthy non-smokers.
MnSOD mRNA levels (1 and 4 kb transcripts) were evaluated by Northern blot, using a DIG-labelled cDNA probe, chemiluminescent detection, and comparative quantification by densitometric volume analysis after normalisation against β-actin mRNA levels.
We found low levels of MnSOD mRNA in unstimulated cells for both groups (2.37 and 2.12 OD units in non-smokers, 1.31 and 0.89 OD units in smokers, for 1kb and 4kb transcripts, respectively). Interestingly, LPS stimulation of smokers' AM induced MnSOD mRNA to halved levels (11.52 and 12.42 OD units for 1kb and 4kb transcripts, respectively) of those observed in stimulated non-smokers AM (23.79 and 22.93 OD units for 1kb and 4kb transcripts, respectively).
These data suggest an inhibitory effect of cigarette smoking on MnSOD induction in LPS-stimulated AM perhaps acting through cytokine mediated mechanisms. Indeed, these cells are known to release less IL-1 and TNFa, inducers of MnSOD expression.
We hypothesise that the observed paradoxical low inducible levels of MnSOD mRNA in activated smokers' AM weaken the antioxidant defences in the lung with consequent local decreased antimicrobial potential and heightened susceptibility to infection.

P106 TRANSCRIPTIONAL INDUCTION OF Υ-GLUTAMYL-CYSTEINE SYNTHETASE BY OXIDANTS IS ASSOCIATED WITH AP-1 IN HUMAN ALVEOLAR EPITHELIAL CELLS.

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Glutathione (GSH) is an important antioxidant in the lungs. The rate-limiting step in GSH synthesis involves the enzyme Υ-glutamylcysteine synthetase (ΥGCS). Upregulation of ΥGCS gene expression in lung cells may be an important adaptive mechanism in response to oxidant stress. The ΥGCS heavy subunit (HS) gene promoter region consist of several putative redox-sensitive transcription factor binding sites such as AP-1 and the antioxidant responsive element (ARE). We studied the regulation of GSH synthesis and characterised the promoter region of ΥGCS-HS gene using the transient transfection of CAT constructs in human type II alveolar epithelial cells (A549) following oxidative stresses (H_2O_2 and menadione). Menadione (100 μM) depleted GSH at 1 hour (control 155±5, Menadione 122±3 nmoles/10^6 cells, $p<0.01$), followed by a 73% increase in GSH 24 hours after exposure, associated with increased ΥGCS activity (control 0.08±0.003, menadione 0.14±0.01, IU/mg protein, $p<0.001$) and a 158% increase in the expression of ΥGCS mRNA in epithelial cells. The ΥGCS 5'flanking region, which contains a putative ARE and various AP-1 like sites, linked to a chloramphenicol acetyl transferase (CAT) reporter gene were transiently transfected into A549 cells and the transfectants were treated with oxidants which increased CAT activity, measured by a CAT-ELISA assay. Analysis of the ΥGCS-HS promoter by the creation of deletion CAT constructs revealed that an ARE present in the proximal region of the promoter (-1050 to -818 bp), is not required for oxidant-mediated ΥGCS induction. These data suggest that oxidant stress induces GSH synthesis in lung epithelial cells by upregulation ΥGCS gene expression at the transcriptional level associated with the activation of AP-1/AP-1 like responsive elements, not ARE.
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P107 MODELLING THE INTERACTION BETWEEN OZONE (O_3) AND PULMONARY EPITHELIAL LINING FLUID (ELF) ANTIOXIDANTS

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Pulmonary ELF antioxidants; ascorbate (AH_2), urate (UA) and reduced glutathione (GSH) confer protection against O_3 by acting as preferential sacrificial substrates, preventing its reaction with more sensitive components within this compartment. In order to determine their individual importance in this respect, the following models of ELF were employed: Pure biochemical solutions of GSH/GSSG (412/17 μmol/L) AH_2 (200 μmol/L) and UA (200 μmol/L), composite mixtures of the above antioxidants, and composite antioxidant solutions containing 5 mg/mL human albumin. Each model was examined over the range 0-1500 ppb O_3 using a continually mixed interfacial exposure system, maintained at 37°C. All solutions were adjusted to pH 7.4 prior to exposure. The rate of consumption for each antioxidant was determined as the loss in concentration per unit time over a 720 min exposure period, under each of the ozone exposure concentrations. Consumption rates are expressed as mol L^{-1} s^{-1} ppb O_3^{-1}; (c. Table).

Antioxidant	Consumption rates (mol $L^{-1}s^{-1}ppb^{-1}$)		
	Pure antioxidant solutions	Composite antioxidant solutions	Composite antioxidant solutions + protein
AH_2	8.45±0.31 x 10^{-12}	5.39±1.04 x 10^{-12} '	3.12± 0.30 x 10^{-12} ''
UA	9.87±0.43 x 10^{-12}*	6.73±1.03 x 10^{-12} '*	6.30±0.20 x 10^{-12} '*
GSH	5.82±0.51 x 10^{-12}*	4.17±0.56 x 10^{-12} ''*	2.19±1.07 x 10^{-12} ''

Values represent mean ± SD (n=3). '†', significant difference from pure biochemical solution: '‡', significant difference between the composite solutions. For comparison of antioxidant consumption rates within each exposure model; '*' significance difference between UA and GSH vs. AH_2, and '¤' UA vs. GSH. In all cases significance was assumed when $P < 0.05$.

These data indicate, that in all models, UA represented the most reactive substrate toward O_3. Generally, as the model complexity increased, the consumption rate of each antioxidant examined decreased. This effect was less marked for UA than for either AH_2 or GSH, again suggesting it represented the most important antioxidant in the ELF for protection against O_3 *in-vivo*. Notably, GSH was significantly less reactive toward O_3 in the pure antioxidant solutions than either UA or AH_2, and did not appear to be an important substrate for O_3 in the composite models, despite being present at twice the concentration of the other antioxidants. It therefore seems unlikely that GSH represents an important direct scavenger of O_3 *in vivo*.

P108 PRO-INFLAMMATORY EFFECT OF PARTICULATE AIR POLLUTION (PM10) IN VIVO AND IN VITRO

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Numerous epidemiological studies have shown that particulate air pollution, especially small particles with an aerodiameter of ≤ 10mm (PM10) is associated with increased morbidity and mortality from airways diseases. We hypothesised that PM10 has oxidant properties leading to airway inflammation and increased epithelial permeability which accounts for its adverse effects. PM10 obtained from sampling filters produced 24.6 fold neutrophil influx in rat lungs 6 hours after intratracheal instillation compared with control animals associated with increased alveolar epithelial permeability measured as protein levels in bronchoalveolar lavage (BAL) fluid (control 0.31±0.02, PM10 0.62±0.01 mg/ml, p<0.001). BAL leukocytes 6 hours after PM10 instillation produced greater amounts of TNF and nitric oxide in culture (p<0.001 and p<0.05 respectively). Furthermore, intratracheal instillation of PM10 lowered glutathione levels in BAL fluid (control 0.42±0.03, PM10 0.25±0.01 nmol/ml, p<0.05). PM10 induced free radical-mediated damage to plasmid DNA, which was inhibitable by mannitol, and increased A549 epithelial cell permeability in vitro. To support our hypotheses that the size, but not the composition of PM10 is an important feature of its pathogenicity, we compared fine (200-500nm in diameter) and ultrafine (20nm) carbon black particles (CB). Ultrafine CB caused a 72 fold increase in neutrophils in rat BAL 6 hours after instillation compared with control, whereas fine CB only induced a 2.8 fold neutrophil influx. Similarly, greater enhancement of rat lung epithelial permeability resulted from instillation of ultrafine CB compared with fine CB (control 0.31± 0.03, fine CB 0.48±0.03 mg/ml protein in BAL fluid, p<0.05, ultrafine CB 0.78±0.14 mg/ml, P<0.01). This study provides evidence that PM10 has free radical activity and causes an inflammatory response and lung epithelial injury.

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P109 PRO-OXIDANT HYPOXANTHINE AND XANTHINE IN THE PLASMA OF PATIENTS WITH ARDS.

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Xanthine oxidase (XOD) has been implicated as a source of reactive oxygen species (ROS) in vivo, and may contribute to oxidative damage associated with some disease states including ARDS. It is formed from the dehydrogenase form of the enzyme (XDH) by a variety of causes including ischaemia/reperfusion and hypoxia. XOD utilises its substrates hypoxanthine and xanthine to produce uric acid, superoxide and hydrogen peroxide. These ROS whilst not particularly damaging themselves, are capable of forming more aggressive species such as peroxynitrite and the hydroxyl radical. It has been reported that hypoxanthine levels are increased in the plasma of ARDS patients compared to normal controls, and also in critically ill patients, possibly because of impaired ATP metabolism due to hypoxia. We have measured plasma hypoxanthine and xanthine levels by hplc in 14 surviving (N =118) and 14 non-surviving (N = 114) patients with ARDS. Xanthine levels were not found to be significantly different between the two groups, although levels were significantly increased compared to normal healthy controls. However, hypoxanthine levels were found to be highly significantly increased ($p < 0.0001$) in ARDS non-survivors (36.06 ± 3.094 μmols) compared to survivors (17.99 ± 2.26 μmols). Additionally when hypoxanthine levels were compared with plasma protein thiol levels (a possible marker of oxidative damage in ARDS patients) a significant negative correlation was found ($p < 0.05$). These results suggest an involvement of XOD in the morbidity of ARDS, and may indicate that hypoxia is an important contributing factor to the severe oxidative stress.

Research supported by the British Lung Foundation

P110 AN *IN VITRO* MODEL OF NEUTROPHIL MIGRATION ACROSS HUMAN PULMONARY ARTERY ENDOTHELIAL MONOLAYERS

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To date *in vitro* studies of transendothelial neutrophil (PMN) migration have used the umbilical vein as a source of human endothelial cells (HUVEC). Evidence of variations in endothelial cell characteristics depending on vascular origin (Sage *et al*, Arteriosclerosis 1(6),p427-442, 1981) suggests that endothelial cells of pulmonary origin would be more representative than HUVEC in *in vitro* studies of pulmonary inflammation.

The aim of this study was to establish a model of PMN migration across monolayers of human pulmonary artery endothelial cells (HPAEC). HPAEC were grown on microporous membrane filter inserts coated with human type IV collagen. After 4 days the presence of an intact monolayer of HPAEC was confirmed by Scanning Electron Microscopy. Migration of PMNs (isolated from human venous blood) across the monolayer in response to n-formylmethionylleucyl-phenylalanine (fMLP) was assessed following a 3h incubation at 37°C. Results (Table) indicated that, while ~40% of PMN in control assays adhered to HPAEC monolayers, migration through the monolayer was minimal. On stimulation with fMLP, migration of up to 74% of added PMN was observed at the optimal fMLP concentration of 10^{-8}M.

Table: Effect of fMLP on PMN migration across HPAEC monolayers

	Number of PMN (% of total)		
	Non-adherent	Adherent	Migrated
Control	57.49 ± 8.14	42.50 ± 8.15	0.05 ± 0.10
fMLP (10^{8}M)	8.09 ± 6.95*	18.06 ±10.35*	73.82 ±14.71*

(n=4, *Mann-Whitney two-tailed p value < 0.05)

The model described here provides an improved system for *in vitro* studies of pulmonary inflammation.

This work was funded by the Health Research Board, Ireland

P111 INTERLEUKIN 1-β INDUCES NEUTROPHIL ADHESION TO HUMAN PULMONARY ARTERY ENDOTHELIAL CELLS

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Adhesion of polymorphonuclear leucocytes (PMNs) to pulmonary endothelium is an initial step in the inflammatory process characteristic of the Adult Respiratory Distress Syndrome (ARDS). Inhibition of the adhesion process has potential clinical applications in relation to inflammatory pulmonary disease. To date most studies examining PMN adhesion to endothelial cells have used human umbilical vein endothelial cells (HUVECs). Previous work (Davern S *et al*, Am J Resp Crit Care Med 1996, 153 (4):A617) has shown that LPS stimulated PMN do not adhere to human pulmonary artery endothelial cells, as they do to HUVECs. The aim of this study was to determine whether PMNs adhere to IL-1β stimulated HPAECs, as has been observed with HUVECs. Confluent HPAECs were pre-incubated with IL-1β, the cytokine washed off, PMNs added and adhesion calculated by measuring myeloperoxidase (MPO) content in adhered and non-adhered samples and expressing this as a % of total MPO. Significant adhesion (**p<0.01) of PMNs to HPAECs occurred even at the lowest concentration of IL-1β used (Table).

Table	Control	IL-1β 2.5 U/ml	IL-1β 5 U/ml	IL-1β 10 U/ml	IL-1β 20 U/ml
Mean	28.15	52.84**	54.38*	58.5**	59.85**
SEM	8.96	3.97	3.63	3.85	7.34

(Student Newman Keuls multiple comparisons test, n=5)

These results suggest that upregulation of adhesion molecules on endothelial cells rather then on PMN may be of more significance in PMN adhesion to endothelial cells of pulmonary origin than to those of umbilical vein origin.

This work was sponsored by the Health Research Board Ireland.

P112 CROSS-DESENSITISATION OF NEUTROPHIL IL-8 RECEPTORS INVOLVES DIFFERENTIAL RECEPTOR SUBTYPE REGULATION

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Human neutrophil IL-8 receptors (IL-8R) undergo rapid homologous desensitisation following repeated stimulation with IL-8. It has also been demonstrated that cross-desensitisation of IL-8R may occur after stimulation with C5a or fMLP (Richardson et al; J.Biol.Chem:270:27829). We investigated the underlying mechanisms of this cross-desensitisation response to IL-8 induced by pretreatment with fMLP or C5a. We used a combination of ^{125}I-IL-8 binding studies and flow cytometry with specific anti-IL-8R subtype antibodies to measure IL-8R surface expression. We found the cross-desensitisation induced by fMLP or C5a was associated with a subsequent reduction in IL-8R on the surface of neutrophils. The reduction in IL-8R number following cross-desensitisation was not reversed on removal of the C5a or fMLP stimulus. FACS analysis showed that this heterologous desensitisation resulted from a pronounced and sustained downregulation of IL-8RB only. Calcium mobilisation studies using melanoma growth stimulatory activity (MGSA) and IL-8 suggests that a sustained loss of IL-8RB may play a part in maintaining fMLP-induced IL-8R cross-desensitisation. In vivo, C5a is generated in the first phase of an inflammatory reaction, followed by a later phase of IL-8 generation, mostly from neutrophils (Collins et al; J.Immunol:146:677). Therefore chemoattractant-induced neutrophil cross-desensitisation may be of importance in regulating neutrophil accumulation during the inflammatory response in vivo, and may be mediated predominantly by IL-8RB.

P113 EPITHELIAL CELLS ARE A SOURCE FOR MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) - POTENTIAL ROLE IN ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

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MIF is an important modulator of the inflammatory and immune response. We have recently isolated this pro-inflammatory mediator within the alveolar airspace in ARDS patients (Am J Respir & Crit Care Med 1996;153:A594). In this study we have investigated whether the human alveolar type II epithelial cell line (A549) is a source for MIF.

A549 cells were obtained from European Collection of Animal Cell Cultures (ECACC) and cultured under standard conditions. MIF was assayed in collected 24 hour supernatants via standard ELISA and Western Blot techniques. Immunohistochemical analysis for cellular MIF was performed using optimal diluted rabbit polyclonal anti-MIF antibody. Detection was performed using standard ABC immunoperoxidase technique.

We found that both TNFα and Lipopolysaccharide (LPS) induce MIF release from our A549 epithelial cell line (see below). Results are expressed as a mean (± SD) of three experiments. Immunohistochemical analysis performed on ARDS lung tisssue, showed not only macrophages, but also type II pneumocytes staining positive for significant quantities of MIF.

	Control	LPS	TNFα
MIF (pg/ml)	164 (± 25)	560 (± 266)	682 (±325)

In this study we describe for the first time, an epithelial cell line, A549, as a source for MIF. In addition our immunohistochemical findings suggest that epithelial cells are an important source for alveolar MIF found in ARDS. These results highlight the importance of MIF as a pro-inflammatory mediator in ARDS and inflammatory disease in general.

P114 DIESEL EXHAUST PARTICULATES (DEP) ENHANCE THE RELEASE OF PRO-INFLAMMATORY MEDIATORS FROM HUMAN BRONCHIAL EPITHELIAL CELLS, *IN VITRO*

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Although epidemiological studies have suggested that DEP may be linked to exacerbations of respiratory diseases, the underlying mechanisms are not clear. We have cultured human bronchial epithelial cells (HBEC) and investigated the effects of 10-100 ug/ml DEP and a filtered 50ug/ml DEP solution on, i) ciliary beat frequency (CBF), ii) membrane integrity, and iii) release of inflammatory mediators. DEP significantly attenuated the CBF of HBEC, in a dose- and time dependent-manner, compared to control cultures. 100μg/ml DEP caused the greatest attenuation in CBF, which was significantly decreased by 36.1% (from a mean value of 7.2Hz to 4.6Hz; $p<0.01$) after 2hours incubation, and by 72.5% (from a mean value of 6.9Hz to 1.9Hz; $p<0.001$) after 24hours' incubation. Similarly the filtered DEP solution significantly decreased the CBF of the HBEC. In contrast, 10-100 ug/ml DEP and 50 ug/ml solution of filtered DEP significantly increased the electrical resistance of HBEC. Analysis of inflammatory mediators released into the culture medium showed that IL-8, GM-CSF and sICAM-1, but not RANTES, were increased by incubation of HBEC with DEP after 24 hours. 50μg/ml DEP was found to be optimally active and significantly increased the release of IL-8, GMCSF and sICAM-1 from median values of 12.9pg, 32.5fg and 7.2pg/ug cellular protein in control cultures, to 41.63pg ($p<0.01$), 55.5fg ($p<0.03$) and 12.5pg/ug cellular protein ($p<0.01$), respectively. The filtered DEP solution had a similar effect on the release of IL-8 and sICAM-1. These results suggest that DEP may play a role in the development of respiratory diseases by modulating the activity of epithelial cells.

P115 A PHASE II STUDY OF AN INTENSIVE MODIFIED 'ICE' REGIMEN IN PATIENTS WITH GOOD PROGNOSIS SMALL CELL LUNG CANCER

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Phase II studies have recognised that the ICE regimen produces high response rates in patients with good prognosis small cell lung cancer (SCLC) but causes severe myelotoxicity. A phase II study was conducted in 30 patients with good prognosis SCLC, to assess whether the high response rate could be maintained but myelotoxicity reduced using 6 cycles of a modified ICE chemotherapy regimen (carboplatin 6x(GFR+25)mg , ifosfamide 3g/m^2 + mesna 3g/m^2, mesna 1.8g/m^2 bolus, and 50mg oral etoposide twice daily for seven days), given every four weeks.

30 patients were recruited between Dec 1994 and Sept 1995. 14 had a WHO performance status of 0, 15 of 1 and 1 of 2. 27 patients had limited, and 3 extensive, disease. Patients had a median age of 60 years (range 39-77 years).

83% (25/30) of patients (95% CI (70-97%)), experienced a partial or complete response at some stage in their treatment, 15/25 (60%) after the first cycle of treatment. 20/25 (80%) of patients maintained their maximum response throughout treatment.

Nadir blood counts showed that 19 patients (63%, 95% CI (46-81%)) had WHO grade 3 or 4 thrombocytopenia, and 24 (86%, 95% CI (73-99%)) had grade 3 or 4 neutropenia at some point in their treatment.

Modified ICE was shown to produce a high response rate but myelotoxicity, although reduced from rates observed using full dose ICE, was still unacceptably high, resulting in dose delays and modifications. A randomised study is now underway within the YCTRU to determine whether administration of amifostine will further attenuate the myelotoxicity of the modified ICE regimen.

P116 ENHANCED SURVIVAL IN SMALL CELL LUNG CANCER WITH DOSE MODIFICATION ACCORDING TO RENAL FUNCTION

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Survival is prolonged in small cell lung cancer (SCLC) patients treated with ifosfamide, carboplatin and etoposide (Thatcher N et al, Br J Cancer (1989) 60 98-107). The influence of renal function upon carboplatin pharmacokinetics was described by Calvert AH et al (J Clin Oncol (1989) 7 1748-56) but dose calculation by surface area remains more usual. A retrospective case note study was made of 50 patients with SCLC presenting here for treatment with ifosfamide 4g iv, (and mesna), carboplatin 300mg/m^2 iv and etoposide 50mg oral twice daily for five days, repeated every 4 weeks.The minimum follow up period was 24 months, median survival 12.4. Enhanced survival, significant by t-test was found with;- •Disease limited to one hemi-thorax on presentation, (median survival 15.0 month, 95% confidence interval 13.3-19.5, n = 28)

- Consolidation radiotherapy, (16.7, 13.6 - 22.6, n = 14)
- Carboplatin (CPt) dose within 50mg of the dose calculated by modified Calvert formula below (16.8,14.5 -22.0, n=18)

CPt dose in milligram = 6 x (GFR + 25),
where GFR = K x (140-age) x weight(Kg)/SCL, when K = 1.23 for males and 1.05 for females; GFR = glomerular filtration rate in mL/min;and SCL = serum creatinine level in micromol per litre)

•Both limited disease and 'Calvert' modified CPt dose as above (22.7, 17.7 - 26.1, n=12). Two year survival was 41.7%

Other workers have shown it necessary to observe a maximum carboplatin dose - however, this renal calculation appears to confer a survival advantage.

P117 NAVELBINE (NVB) IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER (NSCLC)

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The standard treatment for stage IV NSCLC has traditionally been supportive care (SC) alone and the role of chemotherapy has been questioned. Statistically significant effects on survival have been seen in 5 randomised trials of platinum-based chemotherapy, one of which had a control arm of SC alone. Several agents appear interesting on the basis of reported response rates (RR) in phase II trials, however, RR are notoriously variable in this disease, and correlate poorly with survival. Phase II studies have demonstrated that NVB alone or in combination with CDDP has promising activity against NSCLC. As a single agent, NVB has demonstrated a survival advantage over other regimens in randomised trials. On the basis of these preliminary trials, a phase III study was designed to compare intravenous NVB (30 mg/m2 weekly) plus CDDP (120 mg/m2 on day 1 and day 29 and then every 6 weeks) with vindesine (3 mg/m2 weekly for 6 weeks and then every 2 weeks) plus CDDP and to evaluate whether the best of these regimens afforded a survival benefit compared with intravenous NVB alone. 612 pts were enrolled in this trial. An adjusted log rank test demonstrated a significant advantage for NVB plus CDDP when compared with vindesine plus CDDP (Median survival : 40 w vs 32 w respectively: p=0.04) and with NVB alone (p=0.02). The incidence of granulocytopenia was significantly higher in the NVB plus CDDP arm compared with the other two treatment groups without clinical consequences, neurotoxicity was significantly more frequent in the vindesine plus CDDP group.These results indicate that the combination of NVB +CDDP is a viable treatment option for pts with NSCLC and may provide advantages compared with other commonly used regimens and it should be considered as a reference regimen. These data were recently confirmed by a SWOG study (ASCO 1996). NVB development in this indication continues in several areas to offer an alternative in pts who cannot receive a CDDP containing regimen : NVB+Ifosfamide in different doses and schedules can give RR in the range since 25% to 60%.(Median survival: 40 w; range: 28-47 w). Also NVB + Mitomycin C produces a good response rate with acceptable toxicity. The activity of NVB has definitively been demonstrated in randomised trials and in several phase II studies in combination with other active drugs. Both the higher response rate and the longer survival observed with NVB-containing regimens indicate that it should be considered as a reference regimen in pts with advanced NSCLC. In addition, based on the demonstrated activity of NVB in advanced NSCLC, NVB is included in various therapeutic strategies. The treatment of unresectable locally advanced NSCLC relies on combination modalities in which NVB has a role to play either as an induction chemotherapy partner or as a radiosensitising molecule. Resected early stages might as well benefit from CDDP based adjuvant chemotherapy according to recent metaanalysis. In this setting NVB is currently being evaluated in randomised trials to define a possible improvement on overall survival.

P118 A PHASE II OF CISPLATIN (CDDP), IFOSFAMIDE (IFM) AND INCREASING DOSAGE OF NAVELBINE (NVB) IN UNRESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC)

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CDDP, IFM and NVB are the most active drugs in NSCLC. When given as single agent. NVB has shown an increased survival rate in randomised trials. In particular, one such trial showed that the combination of NVB and cisplatin result in statistically superior survival compared with standard therapy (JCO 1994), This was recently confirmed by the SWOG study comparing NVB+CDDP vs CDDP (ASCO 1966). Preliminary results with NVB+CDDP+IFM are very encouraging. Based on this data, between 12/92 and 02/94 a clinical trial was performed in patients(pts) with unresectable stage III (IIIA N2, IIIB) NSCLC using 3 different schedules : Group A : CDDP (75mg/m² D1)+IFM (3g/m² D1)+NVB (25mg/m² on D1) ; Group B : CDDP (75mg/m² D1)+IFM (3g/m² D1)+NVB (25mg/m² on D1 & 8) ; Group C : CDDP (75mg/m² D1)+IFM (3g/m² D1)+NVB (25mg/m² on days 1 & 15 and 12.5mg/m² on day 8) every 21 days. The purpose was to assess the response rate (RR), survival and tolerance. A first assessment, according to WHO criteria was performed after 3 cycles. After this, stage III patients received standard radiotherapy (60Gy over 6 weeks) and responding stage IV pts received 3 cycles more.

85 pts were included (A: 35 pts; B: 28 pts; C24 pts): median age 59 y. (range 36-73) males 74 pts, stage III 37 pts; stage IV 48 pts. 32 pts suffered from adenocarcinoma, 37 from squamous cell and 16 from undifferentiated cell.

Dose intensity (according to Hryniuk method) was the same for the 3 groups concerning CDDP and IFM. For NVB dose density was 8.1mg/m²/w, 14.7mg/m²/w and 16.9mg/m²/w for A,B,C groups respectively. Haematological toxicity was the main toxicity observed, especially in the group B.

5 pts achieved complete response (CR), 36 pts partial response (PR) after 3 cycles but 14 CR and 17 PR at the end of treatment. The overall median survival(MS) was40 wks. The RR observed by group was 31.5% (30 wks MS), 44.5% (40 wks MS), 66.6% ((55 wks MS) for group A,B and C respectively.

This study confirms that increased dose intensity with NVB is feasible and improves response rate and survival without excessive haematological toxicity.

P119

HIGH DOSE-RATE INTRALUMINAL RADIOTHERAPY FOR TRACHEAL CARCINOMA

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Of a total of 770 patients treated with high dose-rate intraluminal radiotherapy (ILT) at the Christie Hospital from 1988 to 1994,41 had tracheal tumours.Data was available on 37 patients.22 patients had tumours with tracheal and main bronchus involvement.Of these 16 had squamous cell carcinoma (11 primary bronchial carcinomas with tracheal extension, 5 recurrent bronchial carcinomas following previous tumour resection), 2 small cell,1 adenocarcinoma,1 renal cell carcinoma metastasis and 2 unknown histology (both affecting trachea and a main bronchus).

The remaining 15 patients fell into two main categories.3 were due to direct infiltration from adjacent organs (glottic,oesophageal and thyroid). 11 had 'primary' tracheal tumours (5 squamous cell carcinoma,4 adenoid cystic,1 carcinoid,1 adenocarcinoma).The remaining patient had an apparent primary tracheal neoplasm of unknown histology with an associated right midzone mass on chest x-ray.

35 of the 37 patients were symptomatic;symptoms included dyspnoea,cough, haemoptysis,chest pain,weight loss and stridor.18 patients had received previous XRT,9 patients received concurrent radiotherapy(XRT) ,4 patients had additional laser photo-resection and 2 went on to have further XRT. 22 patients had a good/partial response following ILT,5 had no significant symptomatic change and no data could be obtained in 8 patients.

Mean survival in 27 patients was 6 months (range 1 week to 45 months), 5 patients were alive at 7,6,14,19months and 5 years respectively following treatment and 5 were lost to follow up.

The series confirms the rarity of true tracheal tumours.ILT is capable of achieving good symptom control and occasionally long survival.ILT is useful in patients who have had previous external beam radiotherapy and may be used with other treatment modalities.

P120 QUALITY OF LIFE (QOL) IN PATIENTS WITH LUNG CANCER: DOES THE TREATMENT MATTER?

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A prospective study of QOL in patients with lung cancer was carried out between Jan. 1995 and Apr. 1996. QOL was measured pre-treatment (baseline) and three months after diagnosis (follow-up), using the Nottingham Health Profile (NHP) and the EORTC QLQ-C30 and QLQ-LC13.

At baseline, 129 lung cancer patients participated in the study. At follow-up 96 patients were alive. Of these, 82 patients agreed to be reviewed, of whom 60 had had active treatment. Analysis was restricted to those for whom both baseline and follow-up data were available.

1. General health (NHP): except for slight improvement with sleep difficulties on all other measures patients reported increased health problems. Of these, deterioration in energy, social isolation, and physical mobility were significant ($p = 0.004$, 0.02, and 0.0008 respectively).
2. Functioning and global quality of life (EORTC QLQ-C30): in all areas the patients' functioning and global quality of life decreased. These reductions in patients' physical, role, and cognitive functioning were significant ($p = 0.0003$, 0.0004, and 0.04 respectively).

Overall, the results were unchanged when the analysis was restricted to cell type, extent of disease, and different treatments.

These findings raise important issues for those involved in caring for lung cancer patients.

P121 HISTOLOGICAL CONFIRMATION RATES AND SURVIVAL IN LUNG CANCER IN YORKSHIRE

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Recent discussion papers suggest that cancer patients benefit from a proactive approach to management. Histological confirmation rate (HCR) is suggested as an appropriate outcome measure of this activity and its audit. The Yorkshire Cancer Organisation receives reports of all cases of lung cancer within the former NHS Region. The HCR was calculated for each of the 17 districts for each of the ten years 1983-1992 (170 district-years). Survival curves were constructed by quartile of HCR. The data was available from 27,824 subjects. The HCR for district-year ranged from 32-75% (interquartile intervals: 50%, 57%, 64%), the median rising from 55 to 64% over the period. Survival improved with each successive quartile ($p < 0.01$). Median survival was 62 days in the 1st and 84 days in the 4th quartile, with maximum separation at 120 days. Survival curves for the 3rd and 4th quartiles were superimposed after one year. Calendar year was entered into the model to allow for the consistent increase in HCR over the period. This did not alter the relationships. **Conclusions:** Survival was more closely associated with HCR in those of poor prognosis. The higher HCR may reflect more appropriate palliation which, by enhancing mood, increases survival. As there was no difference after one year in survival of the 3rd and 4th quartiles, further curable patients are unlikely to be revealed at HCRs above 60%. As there is an association between survival and HCRs up to nearly 80%, this might be an appropriate audit standard.

P122 IMMUNE CELL INFILTRATES AND PROGNOSIS IN PRIMARY LUNG CANCER

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Aim : To investigate the significance of pattern and phenotype of immune cell infiltrates in resected primary lung cancer.

Material and Methods : From a series of 750 fully reviewed and followed-up cases of resected primary lung cancer for which scores (low/absent, moderate or high) for overall immune cell infiltrate had been estimated at histology review, 95 cases were selected from all three categories for more detailed characterisation of the immune cell infiltrate using immunohistochemical and image analysis techniques. Lymphocytes expressing markers CD3, CD8, CD57 or, CD79a, CD68+ve macrophages and S100+ve Langerhans cells were measured in overall density in the tumour and the degree to which each cell type infiltrated directly amongst tumour cells (intratumoural) as opposed to being present around tumour cell aggregates (peritumoural) in the tumour stroma.

Results : For the 750 cases there was no difference in post-operative survival between the three groups. The degree of overall infiltration by each individual cell type was also unassociated with patient survival although patients with high levels of CD57 +ve lymphocytes (NK cells) did appear to do better, though not significantly ($P = 0.07$, Kaplan Meier, Log rank test).

However high levels of intratumoural infiltration by CD3 +ve and S100 +ve cells were associated with longer post operative survival ($P = 0.02$, $P = 0.045$ respectively, Kaplan Meier, log rank test). CD57 +ve cells showed a similar trend but again, did not reach significance ($P = 0.056$). Infiltration by CD8, CD79a and CD 68 +ve cells made no difference.

Conclusion : Overall assessment of lymphoid/macrophage infiltration as assessed on an H + E stained tumour section does not give useful prognostic information in primary lung cancer. Measured high density of CD3 +ve, S100 +ve and perhaps CD57 +ve lymphoid cells may confer survival gain but this adds little to the effect of tumour status/stage to overall prognosis.

P123 RISING INCIDENCE OF PRIMARY LUNG ADENOCARCINOMA IN NORTH EAST SCOTLAND

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There is a reported rising incidence of adenocarcinoma in the United States and in one regional study, based on cancer registry data, in Yorkshire, England.

Most patients who have a histological diagnosis of lung adenocarcinoma registered have that diagnosis made on sputum, fine needle aspiration or bronchoscopically derived material. There is known inherent inaccuracy of typing, particularly adenocarcinoma, on such material.

We have reviewed the histological material from a series of 841 patients who had primary lung cancer resected between 1980-1994 in Aberdeen. Adenocarcinoma has risen as a proportion of all tumours resected from 31% (19/61) in 1980 to 48% (24/51) in 1994. Data from the local Cancer Registry shows that in 1980, only 5% of cancers were actually registered as adenocarcinoma while by 1994 this had risen to 14%. The Lobectomy/wedge : Pneumonectomy ratio during this period has remained unchanged at 60:40. The proportion of female patients having lung cancer resection shows considerable variation year to year but has risen from 23% in the first four years of study to 31% in the last four years.

Although inevitably a small and selected group, resected lung cancer is a more robust source of data on tumour cell type than that from cancer registration. Our data supports the belief that adenocarcinoma is increasing in incidence.

P124 LUNG CANCER: LOCAL REVIEW OF SERVICES

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Ealing, Hammersmith & Hounslow HA covers a population of 640,000 in West London. A review of the services for lung cancer took place steered by a large multidisciplinary group representing local professional, lay and purchaser interests, serviced by the HA. The process was informed by a detailed analysis of hospital activity for one year (1994/5) using the contract minimum data set for patients with a lung cancer diagnosis.

Problems highlighted included: dispersal of lung cancer patients under many consultants from many disciplines (151 individual consultants admitting 447 lung cancer patients in 854 episodes in the year); the majority of inpatient admissions being classed as emergencies (73% of the non-daycases); relatively few elderly patients admitted under oncologists, respiratory physicians or thoracic surgeons (44% of the >75s compared with 66% of the <65s); low overall surgery rates (5% receiving resections); greater use of and spend on specialist oncology for younger patients and those living near the Cancer Centre.

The resulting proposals for improvements in local services were largely based on the BTS (draft) guidelines and included the involvement of respiratory physicians in the management of all patients, irrespective of patient age. Clinical audit and greater use of nurse specialists were also advocated. Each local hospital was recognised to need to have "Cancer Unit" capacity for lung cancer.

The full report of this review is available on request, and could be useful to other districts also attempting "Calman" reviews.

P126 A NAMED NURSE PROGRAMME FOR THE CARE OF PATIENTS WITH LUNG CANCER

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All patients with a diagnosis of lung cancer attending the Southern General Chest Clinic are provided with a named nurse who is present when bad news is broken, reviews the patient on every clinic attendance and is available, via a mobile phone, during the working week. The nurses undergo continuous training in patient communication and palliative care but also have a full range of usual nursing duties. The work of three nurses was audited over a 6 month period during which they cared for 75 patients. There were 590 consultations, 61% via the telephone, 86% of patients using the mobile phone facility (median number of calls per patient 2, range 1-37). Patients required information and advice on symptoms in 58% of consultations, information on treatment plans in 24%, assistance sorting out hospital appointments or transport in 21%, advice on medication in 17%, advice on finance in 13% and in 65% of consultations some emotional support was required. The additional workload was considerable. Forty-three per cent of consultations lasted 20 minutes or more and 51% required further phonecalls to other departments to solve particular problems. Sixty-four per cent of resulting paperwork had to be done out of hours. Nurses needed to be relieved of their duties for 51% of consultations.

The audit revealed a considerable demand for help which could not be met by usual clinic services. The advantages of the programme compared with a dedicated specialist nurse service were identified and included availability to patients, mutual staff support, staff development and job satisfaction. Providing such a service is demanding of nursing time, requires flexibility within a unit and has considerable resource implications.

P125 LUNG CANCER SERVICE PROVISION IN A LARGE TEACHING HOSPITAL

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Liverpool has one of the highest incidences of lung cancer in Europe and around 300 new cases are seen yearly at our unit. As part of the ongoing audit of the provision of lung cancer services we studied prospectively all patients who entered the investigation cascade for lung cancer during a three month period. Patients were included at attendance for fibreoptic bronchoscopy and were followed through their subsequent investigations to identify any delays within the system (n=112). Standards of care were defined for acceptable times between their first hospital contact and bronchoscopy and from CT scan request to receipt of the CT report (14 and 21 days respectively). Standard times between the GP letter being written and referral for either surgery or consideration for onco/radiotherapy were also defined (6 weeks for both). The median time from first hospital contact to bronchoscopy was 7 days (n=112) and from CT request to CT report receipt was 15 days (n=63). Despite these values falling within our defined standards, a significant number of patients lay outside these standards (23% for bronchoscopy and 44% for CT scanning). The median time from the GP referral letter to surgical referral (n=17) and to surgical resection (n=7) was 40 days and to referral for onco/radiotherapy (n=29) was 30 days. Significant numbers lay outside the defined standard for all three groups. Outliers in all groups were more likely to be out-patients as opposed to in-patients.
This data demonstrates that when auditing lung cancer services all patients should fall within defined standards of care.

P127 *PSEUDOMONAS AERUGINOSA* ADHERENCE TO CYSTIC FIBROSIS RESPIRATORY EPITHELIUM IS REDUCED BY ANTI-ASIALO GM1 ANTIBODY AND NEURAMINIDASE INHIBITION

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Pseudomonas aeruginosa (*P. aer*), the bacterial pathogen responsible for most of the lung damage in cystic fibrosis (CF), adheres in greater numbers to cells of CF origin than to non-CF cells, which in part may explain the close relationship between this infection and CF. We have previously shown that this increased adherence results from the absence of normal CFTR, in that *P. aer* binding is reduced after *in vitro* liposome-mediated *CFTR* gene transfer. Previous studies have demonstrated that *P. aer* binds to asialylated glycolipids which are present in increased numbers on the surface of CF cells, and that neuraminidase, an exo-product of P. aer, by cleaving sialic acid from glycolipids, can increase the availability of such binding sites. Mechanisms to reduce the adherence of *P. aer* to CF cells, thought to be the initial step in the process of infection, could potentially delay or prevent pulmonary colonisation and the deterioration in lung function which ensues. We have studied the possibility of reducing binding to asialo GM1 receptors, both by blocking with anti-asialo GM1 antibody, and with the inhibitor, 2,3-dehydo-2-deoxy-N-acetylneuraminic acid (DANA), to prevent neuraminidase-mediated increase in asialylated glycolipids. Nasal epithelial cells from 9 CF subjects were divided into 3 aliquots: each was exposed to a fixed concentration of a non-mucoid laboratory strain of *P. aer* (strain K), one aliquot after 1 hour incubation with a polyclonal rabbit anti-asialo GM1 antibody, and another in the presence of 50 μM DANA. A further 3 samples were used to study the affect of a control polyclonal anti-mouse antibody. Bacterial adherence to the apical surface of ciliated epithelial cells was quantified in a blinded fashion by direct visualisation using scanning electron microscopy. Pre-treatment with anti-asialo GM1 antibody resulted in a reduction in bacterial binding to every sample, with a mean reduction of 50% (mean binding /10 cells: baseline 9.7; anti-asialo GM1 treated 4.5; p=0.001). The control antibody did not affect adherence. Incubation of the cells with the bacteria in the presence of DANA resulted in a 27% mean reduction in *P. aer* adherence (baseline 10.4 /10 cells; DANA 6.8; p=0.08). These data confirm that adherence of *P. aer* to CF epithelium is in part related to asialo GM1 receptors. The use of agents to either block or prevent the uncovering of binding sites may therefore be a therapeutic option worth exploring in CF.

P128 DYSREGULATION OF CALCIUM METABOLISM IN HUMAN NEUTROPHILS EXPOSED TO THE *PSEUDOMONAS AERUGINOSA* PIGMENT 1-HYDROXYPHENAZINE

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We have previously reported that the *P. aeruginosa*-derived pigment, 1-hydroxyphenazine (1-HP), potentiates the release of primary granule enzymes from activated human neutrophils *in vitro* (J Infect Dis 1990;162:178-185; J Infect Dis 1992;166:568-573). In the present study we have investigated the effects of 1-HP, at concentrations (0.4-12.5 μM) which potentiate neutrophil degranulation, on calcium fluxes in these cells following activation with FMLP (1 μM). Intracellular Ca^{2+} transients were monitored by fluorescence spectrophotometry using FURA-2 as the Ca^{2+}-sensitive indicator, and radiometrically by measurement of efflux and influx of ^{45}Ca. The intensity of the immediate peak fluorescence response of FMLP-activated, FURA-2-loaded neutrophils was unaffected by 1-HP, indicating the absence of effects of the pigment on release of Ca^{2+} from intracellular stores. However, in neutrophils exposed to 1-HP, a dose-related prolongation of FURA-2 fluorescence was observed, indicating sustained increases in cytoplasmic Ca^{2+} in these cells. These results were confirmed by the radiometric procedure, which demonstrated reduced efflux of ^{45}Ca from FMLP-activated neutrophils in the presence of 1-HP. Dysregulation of cellular Ca^{2+} metabolism may explain the potentially harmful, pro-inflammatory interactions of 1-HP with human neutrophils.

P129 RESPONSIVENESS OF CIRCULATING NEUTROPHILS FROM ACUTELY INFECTED AND STABLE CYSTIC FIBROSIS PATIENTS TO STIMULATION

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Neutrophil migration is a multistep process involving the sequential rolling of the neutrophil along the endothelium (using L-selectin) and firm adhesion to the endothelium (mediated by Mac-1). Stimulation of the neutrophil triggers the shedding of L-selectin and upregulation of the Mac-1 complex (CD18/CD11b). Recent studies suggest that circulating neutrophils in patients with acute lung disease may be hyperresponsive to activation stimuli (Laurent, T. *et al*, Am J Respir Crit Care Med 1994; 149: 1534-8). The aim of this study was to investigate whether circulating neutrophils from acutely infected cystic fibrosis (CF) patients were similarly hyperresponsive when stimulated with neutrophil agonists. Blood samples (n=13) from 11 acutely infected CF patients (6F, 5M), 16 chronically infected CF patients (8F, 8M) and 15 matched, non-infected controls (8M, 7F) were analysed for surface expression of L-selectin and Mac-1. While no significant difference in the basal levels of adhesion molecules on circulating neutrophils was observed between the three groups, upon stimulation with interleukin-8 (Il-8) and n-formylmethionylleucylphenylalanine (fMLP), acutely infected CF patients shed significantly less L-selectin than both chronically infected CF patients ($p<0.05$) and normal controls ($p<0.01$). L-selectin was also shed to a significantly lesser degree from the surface of neutrophils from stable CF patients compared to normal controls ($p<0.05$). This difference in L-selectin shedding indicates that circulating neutrophils in CF patients have a "dampened" response to stimulation with respect to L-selectin, and are less likely to shed this adhesion molecule from their surface upon stimulation. This effect is most noticeable during acute infections.

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P130 NEUTROPHIL RESPONSIVENESS IN CYSTIC FIBROSIS PATIENTS IS AFFECTED BY CLINICAL STATE

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Neutrophils produce a variety of substances to defend the host. These include superoxide and granule products which can damage host tissues, such as the lungs. Superoxide generation and elastase release in response to fMLP was determined for neutrophils from 12 patients with cystic fibrosis (CF) and from 12 non-CF subjects. Neutrophils were isolated from patients at the start of an exacerbation, after antibiotic treatment and while clinically stable. Each patient was matched to a control subject. Superoxide generation was measured by the reduction of cytochrome C (nmol of cytochrome C reduced /10^6neutrophils/20min.). Elastase release was determined in the supernatant by ELISA (ng/10^6neutrophils/20min.). Superoxide generation and elastase release was consistently less in patients than controls at all fMLP doses (10^{-9} to $3x10^{-7}$M). This reduction was greater at the start of an exacerbation than after treatment. Analysis of log transformed data of the maximal response to fMLP revealed that superoxide generation by neutrophils from patients with CF was reduced compared with control values to 62% when in exacerbation ($p=0.0003$), 82% after treatment, and 72% whilst clinically stable ($p=0.04$). Corresponding values for elastase release were 74% ($p=0.04$), 96% and 75% ($p=0.09$). Circulating C-reactive protein and neutrophil elastase α_1-antiproteinase complex in the patients were greater at the start of an exacerbation, fell after treatment, and rose again when stable. It is likely that prior exposure of neutrophils to one or more of these agents resulted in this downregulatory effect.

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P131 PROTEASE CONTENT OF CIRCULATING NEUTROPHILS FROM PATIENTS WITH CYSTIC FIBROSIS

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Chronic pulmonary inflammation, characterised by a massive influx of neutrophils from the bloodstream, is now regarded as the immediate cause of lung destruction and disease in cystic fibrosis (CF). It is recognised that *in vivo* 'priming' of neutrophils may contribute to the destructive potential in disease states including CF. Several studies indicate that, during infection, inflammatory mediators can promote the production of more 'potent' neutrophils (containing higher quantities of elastase) during maturation in the bone marrow (Burnett *et al*, Lancet Nov. 1987, pp 1043-1047). The objective of this study was to assess the potency of circulating CF neutrophils with respect to levels of neutrophil elastase (NE), neutrophil collagenase (NC) and myeloperoxidase (MPO). n=19 CF patients with stable disease and n=19 age and sex matched non-CF controls were recruited to the study. Neutrophils were isolated from patient and control venous blood and resuspended at a concentration of 3 X 10^6 PMN/ml. Results (mean ±SEM) are shown in the following table:

		Controls	CF Patients
NE activity (mU)	n=18	0.012±0.002	0.019±0.002 *
NC activity (U/ml)	n=19	2.097±0.427	1.178±0.147
MPO activity (mU)	n=19	0.015±0.003	0.008±0.002

Levels of active NE were significantly elevated in CF neutrophils compared to controls (*$p=0.0325$) whereas no significant difference was seen in either NC or MPO levels. This study suggests that CF neutrophils are primed *in vivo* to produce elevated levels of active NE but not of NC or MPO.

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P132 CIRCULATING IMMUNOREACTIVE INTERLEUKIN-6 (IL-6) IN CYSTIC FIBROSIS

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Cytokine networks are important in infectious lung conditions. Previous studies have demonstrated circulating levels of neutrophil elastase-α_1-anti-proteinase complex (NEAPC) and C-reactive protein (CRP) as markers of inflammatory activity in cystic fibrosis (CF). In this study Interleukin-6 (IL-6) and Tumour necrosis-α (TNFα) levels were compared to NEAPC and CRP. Twelve patients with CF and chronically infected with *P.aeruginosa* were studied at the start of an exacerbation, after antibiotic treatment, and while clinically stable; 12 healthy non-CF subjects were matched at each time point. Venous blood was obtained for serum (IL-6 and CRP) and EDTA plasma (NEAPC and TNFα). Aliquots were stored at -70°C until assayed by ELISA. Lung function was determined at the same time. IL-6, NEAPC, CRP and peripheral blood absolute neutrophil count were all reduced ($p<0.01$) after antibiotic treatment. Levels of all these were greater in the stable group than at the end of an exacerbation; IL-6 ($p=0.007$) and CRP ($p=0.01$). IL-6 correlated ($r=0.836; p<0.0001$) with CRP, and both were significantly greater than in controls ($p<0.001$) at all study times. FEV_1 and FVC improved with antibiotic treatment ($p<0.01$) but remained less than control values at all time points. IL-6 was related to other inflammatory markers, although the results for TNFα were less clear. CRP probably represents a down-stream indicator of IL-6, and therefore IL-6 may be an earlier indicator of inflammatory activity. The separation between patients and healthy subjects, the marked drop of IL-6 following antibiotic treatment and its close correlation with CRP supports the use of IL-6 as a circulating marker of inflammation in CF.

Supported by the Cystic Fibrosis Trust (U.K.) and the Astra Foundation (UK)

P133 FREE RADICAL ACTIVITY AND ANTIOXIDANT LEVELS IN SERUM OF DIABETIC AND NON-DIABETIC CYSTIC FIBROSIS PATIENTS

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INTRODUCTION. High free radical activity (FRA) from a combination of neutrophils, increased intracellular metabolism and infecting bacteria occurs in cystic fibrosis (CF). These patients are also at risk of dietary deficiency of anti-oxidant vitamins. High markers of FRA including malondialdehyde (MDA) have also been reported in non-CF diabetics. This study compares a serum marker of FRA and antioxidant levels in diabetic and non-diabetic CF patients and controls.
METHODS. The subjects were 10 non-diabetic CF, 10 diabetic CF, 9 diabetic controls and 8 normal controls. FEV1 was measured in the CF group as a guide to disease severity. Serum malondialdehyde (MDA) Vitamins A, C and E, ESR, CRP and HbA1c% were measured. Comparison between groups was by Mann-Whitney U test and results given as means (SEM).
RESULTS. There was no difference in FEV 1 between CF groups. ESR and CRP were higher ($p<0.05$) than controls in both CF groups. MDA levels tended to be higher in the diabetic CF group compared to controls (5.3(0.5) vs 4.0(0.4) umol/L; $p=0.08$) but no different from the non-diabetic CF group(4.3(0.4) $p=0.2$) Vitamin A levels were significantly lower in both CF groups compared to controls (1.6(0.2) and 1.5(0.2) vs 3.4(0.3) umol/L; $p<0.001$). Vitamin E levels were at the low end of normal in both CF groups. Vit C levels were lower in the diabetic CF group compared to normals (0.8(0.1) vs 1.3(0.1)mg/100 mls;$p<0.05$) but little different from the non-diabetic group(0.9(0.1);$p=0.06$). HbA1c% was highest in the non-CF diabetic group. There was no difference in MDA and antioxidant levels between the control and non-CF diabetic group.
CONCLUSIONS. **1**.These data do not suggest that this group of diabetic CF patients are at greater risk of FRA than the non-diabetic CF group. **2.** Lower antioxidant Vitamin A and C levels in both CF groups may make them more susceptible to FRA than normal controls.

P134 THE EFFECT OF INTRAVENOUS ANTIBIOTIC THERAPY ON MARKERS OF OXIDATIVE STRESS IN CYSTIC FIBROSIS

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Patients with cystic fibrosis (CF) are subject to increased levels of oxidative stress due to the production of reactive oxygen species by neutrophils and macrophages in response to chronic pulmonary sepsis, and reduced antioxidant intake due to pancreatic malabsorption. This may be one cause of the chronic lung destruction seen in CF patients. We investigated the effect of intravenous antibiotic therapy (median duration 14 days), prescribed for pulmonary exacerbations, on plasma levels of antioxidants and markers of oxidative damage in 14 (7 male, median age 25) pseudomonas colonised CF patients. Increases were observed in plasma levels of ascorbic acid (pre 26.7, post 35.9μM, $p=0.048$) and retinol (pre 2.1, post 3.1μM, $p=0.039$), possibly reflecting improved nutrition as patients' clinical status improved. No significant change occurred in plasma levels of α-tocopherol (pre19.5, post 25.7μM, $p=0.101$) or total reduced thiols (pre 412, post 399μM, $p=0.551$). Plasma uric acid concentration decreased following treatment (pre 292, post 260μM, $p=0.005$), which may be explained by a reduction in metabolic turnover. Protein carbonyls (a marker of protein oxidation) increased (pre 0.9, post 1.0 nmole/mg protein, $p=0.039$) suggesting increased clearance of these oxidation products from the lung. No change in the plasma levels of malondialdehyde (pre 7.1, post 7.8 pmole/mg prot, $p=0.875$) a marker of lipid peroxidation were seen. Pulmonary exacerbations and their treatment may therefore alter oxidant/antioxidant balance in CF patients.

P135 SHORT TERM EFFECT OF NEBULISED HUMAN RECOMBINANT DNASE (rhDNAse) ON NEUTROPHIL INFLAMMATORY PRODUCTS IN CYSTIC FIBROSIS

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Pulmonary secretions in cystic fibrosis contain large quantities of neutrophils. Neutrophil elastase (NE) released by these neutrophils may overwhelm pulmonary α_1 protease inhibitor and contribute to the pulmonary destruction seen in CF. The highly cationic NE binds to and is inactivated by polyanionic molecules such as DNA, which is present in large quantities in CF pulmonary secretions due to neutrophil degeneration. Improved removal of pulmonary secretions may therefore increase or decrease the NE burden in the CF lung. We have measured serum NE-α_1 protease complex, serum lactoferrin, plasma C-reactive protein, and pulmonary function in 10 CF patients (6 male, median age 25) prior to and following 3 weeks of nebulised rhDNAse therapy. Mean FEV_1 increased from 1.07l to 1.17l ($p=0.04$), a result comparable to large trials of rhDNAse therapy. No significant difference was observed in median serum concentration of NE-α_1 protease complex (pre: 930 ng/ml, post: 1195 ng/ml, $p= 0.59$), median serum lactoferrin concentration (pre: 7.17 nM, post: 7.68 nM, $p= 0.96$), or median plasma C-reactive protein concentration (pre: 17 mg/l, post: 22 mg/l, $p=0.72$) following rhDNAse therapy. Short term rhDNAse therapy does not therefore dramatically alter the levels of these markers of neutrophil inflammation despite causing significant bronchodilatation.

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P136 EFFECT OF CYCLIC GUANOSINE MONOPHOSPHATE (cGMP) ON OVINE AIRWAY EPITHELIAL TRANSPORT

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Transepithelial ion transport is responsible for maintaining the correct electrolyte and water composition of airway lining fluid, which is crucial for the efficient function of epithelial and other cells lining the airway. cGMP is important in controlling this process across renal and intestinal epithelia, and has been shown to activate CFTR via a protein kinase A mechanism. Using ovine tracheal epithelia mounted in modified Ussing chambers we have investigated the effect on short-circuit current (Isc) of activators of soluble and particulate guanylyl cyclase, alone and in the presence of 3-isobutyl-1-methylxanthine [IBMX] (a non-specific phosphodiesterase inhibitor). Ovine tracheal epithelia (n=41) had a mean baseline transepithelial potential difference (PD) of 5.8mV and a mean Isc of 49.5μAcm^{-2}. Sodium nitroprusside (10^{-4}M), atrial natriuretic peptide (10^{-7}M), brain natriuretic peptide (10^{-7}M), and C-type natriuretic peptide (10^{-7}M) all had no effect on Isc measurements when added both the serosal and mucosal surface. 10^{-4}M IBMX when added to the mucosal surface resulted in a mean reduction in Isc of 4.2μAcm^{-2} [8.9% 0f baseline] (n=14) indicating a reduction in sodium absorption. SNP and the natriuretic peptides in addition to IBMX did not alter Isc compared to IBMX alone. We conclude that manipulating cGMP levels does not significantly alter ion transport across ovine tracheal epithelium.

P137 IN VIVO ASSESSMENT OF POTENTIAL NOVEL PHARMACOLOGICAL AGENTS TO ACTIVATE CFTR IN CYSTIC FIBROSIS

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Pharmacological activation of chloride secretion may usefully supplement attempts at gene therapy. We have assessed *in vivo* examples from 4 different drug categories, suggested in *in vitro* studies to activate the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Agents were assessed for their effect on the bioelectric properties of the G551D CF mouse model, and where possible, in CF subjects. Drugs were administered in the presence of amiloride (100 μM) and a low chloride bathing solution. Genistein (50 μM), a tyrosine kinase inhibitor, shown to activate CFTR in transfected NIH 3T3 fibroblasts through a non-cAMP mechanism, did not induce secretion in any animal (n=4). NS004 (20μM), a substituted benzimidazolone with a putative direct action on CFTR stimulated chloride secretion in the CF mice (2.8 mV (SEM 0.5), n=5). Sodium nitroprusside (SNP, 100 μM), shown to phosphorylate CFTR via a protein kinase G-dependent mechanism, induced small variable responses at 100 μM (Δ PD 0.7 mV (0.2), n=4). SNP was additionally assessed on the nasal epithelium of CF subjects without significant effect (-1.1 mV (0.7) n=4. Type III phosphodiesterase inhibition has been shown to induce chloride secretion in CF tissues in vitro. Neither of the type III phosphodiesterase inhibitors ORG 9935 (30 μM) or milrinone (MIL, 100 μM) induced significant secretion in CF mice or CF subjects, although topical MIL could initiate chloride secretion in non-CF subjects. We conclude that the majority of these agents either produce levels of CFTR activation below the level of detection of our assays or that the in vitro studies do not extrapolate to the in vivo setting. Direct channel activators such as NS004 may hold promise for CF.

P138 α_1-ANTITRYPSIN MUTATIONS AND THE SEVERITY OF CYSTIC FIBROSIS (CF) LUNG DISEASE

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An imbalance between proteinases and their inhibitors, most notably α_1-antitrypsin (α_1-AT) is thought to be an important factor in the progression of cystic fibrosis lung disease. We have evaluated the effect of the common S and Z deficiency alleles and the Taq-1 polymorphism in the 3' non-coding region of the α_1-AT gene on the severity of CF lung disease. 157 patients were recruited from two regional CF centres in the UK. Lung disease was assessed by FEV1%, the 'Northern' CXR score and age at onset of colonisation with *Pseudomonas aeruginosa(PA)*. A mutivariate analysis was performed using the covariates; age, sex, treatment centre, colonisation with *PA*, colonisation with *B. cepacia,* liver cirrhosis, pancreatic status, smoking and CF genotype. 20/150 unrelated patients had antitrypsin deficiency phenotypes (16 MS, 1 SS and 3 MZ) which were associated with less severe lung disease as assessed by FEV1%; adjusted means 62.6% and 50.9% for the normal group;p = 0.042. There was no effect on CXR scores (p=0.127), or age at onset of colonisation with *PA* (p=0.899) and no interaction was found with CF genotype. Patients with the MS phenotype also had a higher FEV1%, (adjusted means 63.7% vs 51.7%) however, this effect just missed significance; p=0.06. The Taq-1 polymorphism was identified in 21/150 (14%) unrelated patients and in 19/135 (14.1%) of healthy blood donors; p > 0.2. The polymorphism had no effect on the severity of lung disease as assessed by FEV1%, CXR score or age at onset of colonisation with *PA*; p values 0.365, 0.813 and 0.146 repectively. As expected the MS phenotype significantly reduced the plasma level of antitrypsin during the inflammatory response (p< 0.001) but this was unaffected by the Taq-1 polymorphism (p=0.551). These data show that the deficiency alleles of α_1-AT are surprisingly associated with less severe lung disease in CF.

P139 THE EFFECT OF INHALED BETA AGONISTS AND ANTICHOLINERGIC AGENTS UPON HEART RATE VARIABILITY

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Beta agonists, particularly Fenoterol (F), have been implicated as a possible cause of the rising mortality from asthma, possibly by increasing the risk of fatal cardiac arrhythmias (Crane et al *Thorax* 1995;50(suppl):s5-s10). Autonomic instability is associated with an increased risk of the development of ventricular arrhythmias and sudden death and can be assessed by measurement of heart rate variability (HRV) (van Ravenswaaij-Arts et al *Ann Int Med* 1993;118:436-447). Drugs may affect HRV. Oral beta blockers have been shown to enhance HRV in normal subjects and in patients with coronary artery disease and this may contribute to their protective effect (Niemala et al *Am J Cardiol* 1994;23:1370-1377). Similarly intravenous atropine has been shown to reduce heart rate variability. These changes are apparent immediately. The aim of this study was to establish whether low doses of inhaled beta agonists and anticholinergics have a measurable effect upon HRV in normal subjects and whether there is any difference between F and a shorter acting beta agonist, Salbutamol (S). **Methods** 19 normal subjects (age 26 $\pm$3.4 years) underwent 24 hour ECG monitoring and took, in random order 4 puffs of placebo (PL), S, Atrovent (A) or F during the 24 hour period. The normalised low frequency (nLF) and high frequency (nHF), expressed in ms, power spectra were determined over a five minute period before and after each inhalation. **Results** There was no difference in nLF (PL 0.72 $\pm$0.143, S 0.72 $\pm$0.15, A 0.76 $\pm$0.14 or F 0.72 $\pm$0.11, AOVO F= 0.3 P= 0.8) or nHF (PL 0.21 $\pm$0.11, S 0.2 $\pm$0.14, A 0.19 $\pm$0.12, F 0.22 $\pm$0.94, AOVO, F=0.16 P=0.9) at baseline. By contrast in the first hour F (0.65 $\pm$0.18, P=0.009) reduced, and S (0.8 $\pm$0.13, P= 0.01) increased, nLF compared with PL (0.72 $\pm$0.1). A (0.74 $\pm$0.14 P=0.7) had no effect. F (0.29 $\pm$0.18, P=0.01) increased nHF, compared to PL (0.17 $\pm$0.06) whereas S (0.17 $\pm$0.9) and A (0.22 $\pm$0.15) had no effect, P=NS. **Conclusion** 4 puffs of A did not have a significant effect upon HRV. S increased sympathetic tone as evidenced by the increase in nLF whereas paradoxically F increased parasympathetic and reduced sympathetic tone, which should protect against cardiac arrhythmias. These findings warrant further investigation.

P140 EXPERIENCE WITH LONG-TERM METHOTREXATE IN STEROID-DEPENDENT ASTHMA OVER SIX YEARS

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The addition of methotrexate (MTX) -7.5-15mg/week-to the treatment regimen of 36 steroid-dependent asthmatics was prospectively evaluated over a mean period of 34.9 months (SD 19.5, range 6-72). Prior to MTX therapy they had been taking a mean prednisone dose of 16.7mg (SD 8.7) for at least a year in addition to inhaled beclomethasone/budesonide/fluticasone (mean daily dose 1287 mcg (SD 423) mcg) and bronchodilators. The patients attended monthly with symptom and Peak Flow diary cards and the physician would reduce the daily prednisone dose by 2.5mg if the diary card variables and measurement of lung function were unchanged or improved. All the other treatment remained unchanged. Twenty patients were weaned from all regular systemic steroid therapy, a 50% or more reduction was achieved in 8 and a less than 50% reduction in 8 patients. There was no significant change in the diary card parameters, chest X-ray or lung function (expiratory flow rates, lung volumes and transfer factor for carbon monoxide). Abnormal liver function tests were noted in 7 of the 21 patients which resolved despite continuation of therapy in 6. However, a five-fold rise in serum transaminases were noted in one patient. Thrombocytopaenia was noted in another patient. In both patients, cessation of MTX resulted in speedy resolution. Gastrointestinal side effects were reported in 7 but resolved in 6 with intramuscular MTX. There were no pulmonary complications. Liver biopsies in 9 patients who had received more than 2500 mg of MTX and were all within normal limits. Long-term MTX therapy, appears to be both safe and efficaceous as a steroid-sparing agent in the majority of steroid-dependent asthmatics.

P142 COMPARISON OF A DESKTOP AND A LABORATORY THEOPHYLLINE ASSAY SYSTEM IN CLINICAL PRACTICE

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The side effect profile of theophyllines and the relationship with serum drug levels indicate an important role for monitoring drug levels in clinical practice. We compared a desktop theophylline assay system suitable for ward and out-patient department use (the Biotrack 516, Ciba Corning Diagnostics Corp., Medfield, MA 02052, USA) with a laboratory assay system (the Abbott TDx automated fluorescence polarisation analyser system, Abbott laboratories, Irving, Tx, USA). Paired clinical samples for estimation of theophylline levels were collected in 60 patients receiving treatment in this centre and were assayed by both methods. There was a highly significant ($p < 0.001$) correlation between the two assay methods ($r = 0.98$) across the whole range (2 - 37 μg/ml) and within the therapeutic range of 5 - 15 μg/ml ($r = 0.95$). The limits of agreement for the data by the Bland and Altman method indicated a ± 2 μg/ml limit for the 5 - 15 μg/ml range and a ± 2.7 μg/ml limit for the total range studied. The Biotrack 516 requires minimal training in its operation and maintenance and is relatively rapid in processing a sample (4 minutes). It is sufficiently accurate in the clinically important range of 5 - 15 μg/ml to make it of practical use for management of patients requiring theophylline therapy when a more sophisticated laboratory assay system is not readily available.

P141 THE MEASUREMENT OF SERUM PREDNISOLONE AND CORTISOL IN PATIENTS WITH SEVERE ASTHMA

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Assessing compliance with oral steroids in severe asthma is difficult as direct measurement of serum prednisolone is not possible with most available immunoassays. Indirect assessment by detecting suppressed serum cortisol has been recommended, particularly in the diagnosis of steroid resistant asthma. We have developed and validated a high performance liquid chromatographic (HPLC) method that assays prednisone, prednisolone, cortisol and cortisone in plasma. We have assayed serum from 16 adult outpatients with severe asthma (median age 34yrs, 8 male); 13 had been prescribed daily oral prednisolone (mean 23.9mg range 4-40mg/day), one IV hydrocortisone 100mg bd and two no systemic steroids at the time of the assay. The median interval from dose to venesection was 2.5 hours (range 0.75-15.5hrs). Three distinct groups of results were evident when a scatter plot of serum cortisol and prednisolone concentrations was constructed. The first (n=4) had no or nearly no detectable prednisolone with normal concentrations of cortisol (269-409nmol/l) and included the two subjects taking no systemic steroid, the subject using hydrocortisone and one subject (known to be poorly compliant) who claimed to have taken 40mg prednisolone 90 minutes earlier. The second group (n=8) had appropriately suppressed levels of cortisol (mean 58.6nmol/l, range 51-72nmol/l) with prednisolone levels ranging from 256 to 874nmol/l; all of these subjects reported taking between 2.5 and 40mg of prednisolone in the preceding 8 hours. The third group (n=4) had similarly low serum cortisols (56-83nmol/l) but no or nearly no detectable prednisolone; one subject reported taking 4mg of prednisolone 15.5hrs earlier and this interval probably accounts for the low level of prednisolone detected. The other 3 subjects claimed to have taken 20, 30 and 40mg of prednisolone in the preceding 2.5 hours. These subjects could be intermittently poorly compliant or have markedly abnormal prednisolone absorption or metabolism. They would have been incorrectly classified as compliant if their serum cortisol concentrations alone had been interpreted. The HPLC method allows objective assessment of compliance with oral prednisolone and may also be valuable when investigating other aspects of steroid metabolism in asthma.

P143 RANDOMISED CONTROLLED ASSESSMENT OF A 'WINDMILL TRAINER' DEVICE IN THE MEASUREMENT OF PEF IN CHILDREN

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The reproducibility of Peak Expiratory Flow (PEF) measurements in young children is often poor. For this reason diagnosis of respiratory disease in this age group is based primarily on clinical symptoms rather than quantitative measures of PEF. The 'Windmill Trainer' is a plastic Windmill which clips on the barrel of the Windmill. If air is vented through the slot of the PFM it spins the Windmill. The further the Windmill is placed away from the mouthpiece the larger the flow required to spin it. We tested the hypotheses that the 'Windmill Trainer' in conjunction with a low-range Mini-Wright AFS Peak Flow Meter (PFM) improves PEF reproducibility. The study was designed as a group comparison, one group randomised to PEF measurement aided by the Windmill and one without (Control). All children were assessed by the same asthma nurse and provided the same instruction. Each child was allowed two training blows and then three measured blows. The surrogate reproducibility measure for each child was defined as the SD of the measured blows. Training ability was scored using an analogue scale (0= bad - 5=excellent).

RESULTS: A total of 79 school children aged 4.5-7 years, without a history of asthma were assessed. Study results are displayed in the table below.

PEF Assessment	N	% Pred. PEF	Reproducibility Mean (95% CI)	Training Score Mean (95% CI)
WINDMILL				
All	41	95.0%	13.45 (10.91 to 15.99)	3.20 (2.93 to 3.47)
4.5 - 6.5 yr	28	95.5%	14.35 (11.13 to 17.56)	3.11 (2.76 to 3.46)
6.5 - <8.0 yr	13	94.1%	11.52 (7.59 to 15.45)	3.36 (2.96 to 3.76)
CONTROL				
All	38	87.8%	16.15 (14.02 to 18.27)	3.23 (2.99 to 3.47)
4.5 - 6.5 yr	26	89.4%	16.38 (11.13 to 21.63)	3.25 (3.05 to 3.45)
6.5 - <8.0 yr	12	84.9%	15.67 (11.13 to 20.22)	3.24 (2.85 to 3.63)

These data suggest that children assessed with the Windmill Trainer achieve PEF measures closer to those predicted and have an improved PEF reproducibility (17%).

P144 NORTHAMPTON ASTHMA SURVEY: RESULTS OF A POSTAL QUESTIONNAIRE

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Anonymised postal questionnaires were sent to 1176 (~1% of the total list size of participating practices) randomly selected adults (age 18-60) in Northampton diagnosed as having asthma. The questionnaire included a previously validated asthma symptom score (ASS), other health indicators and questions on specific asthma services. 706 responses (60%) were received (45% male, mean age 37.6: 55% female, mean age 37.8). Symptoms were frequently reported (e.g. 14.4% had disturbed sleep on most or every night in the last month). The ASS positively correlated with depression score (r=0.49) and limits to energy (0.54) and physical function (0.61) scores. Women had significantly higher ASS than men (34.3 vs. 30.7 : p=0.03) Despite large variations in check-up rates, peak flow meter provision and smoking status between patients from different practices there was no significant difference in the average ASS.
81% were prescribed inhaled steroids. 23.5% claimed that they rarely or never took this prescribed medication but these individuals had a lower average ASS (NS) than those who did. More women than men had a peak flow meter at home (62%F:53%M; p=0.03) and women were more likely to alter medication in response to Peak Flow Rate (53% of F with meters: 41% of M). Daily and ex-daily smokers had significantly higher ASS than never or ex-occasional smokers (p<0.05).
32.7% had at least 1 emergency consultation within the last year. There was a strong association between number of emergency consultations and ASS. 53.6% of the total sample believed that they had had an asthma check-up within the last 6 months.
In conclusion, this random sample of adults with asthma demonstrates significant correlation of symptoms with other health measures, current or previous regular smoking and emergency consultations. Patients admitting to not taking prescribed preventers did not suffer worse asthma symptoms than those who claimed to take them. Differences between patterns of care provided by GP practices was not shown to influence overall symptoms.

P145 A STUDY TO ASSESS THE NEED FOR A REFERRAL BOOK FOR PATIENTS WITH ASTHMA

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Objective- To assess a need for a referral mechanism for asthmatic patients between Hospitals and all Primary Health Care Team (PHCT) members.
Design- 1 year pilot study involving the use of a referral book from October 1994 October 1995. Retrospective study. The General Practice notes of 79 people reviewed attending a Community Hospital between January 1995 and December 1995 with acute asthma.
Aim- To improve the present asthma referral system following attendance at Acute or Community Hospitals after acute asthma attacks.
Participants - Staff on a chest ward at local Acute Hospital, staff at one Minor Injuries Unit at a local Community Hospital and a local two centred general practice setting and all (PHCT) members within the General Practice.
Main Outcome Measures - The attendance numbers, reasons for acute asthma exacerbations at Acute and Community Hospitals and referrals to the General Practice. The follow up referral rates, reasons for and outcomes of referrals between all PHCT members .
Results - The number of patients referred following an acute attack between Community Hospital and General Practice was 19 with a follow up rate of 18(95%). Training of the Community Pharmacist resulted in 4 referrals during this time but none in the 10 months prior to the training. The remainder of the PHCT made or received 4 referrals over the 12 month period. The referral numbers dropped significantly after 5 months into the scheme when a decision was made to stop prompting them.Majority of referrals within the PHCT was between General Practitioners (G.P's)and Practice Nurses (PNs) at 137(97%).
Conclusion - The use of a referral book involving the whole of the PHCT was not acceptable unless prompted and added to heavy paper loads. A revised version for use between Community Hospital and General Practice is felt worthwhile and could provide an effective mechanism to ensure follow up.

P146 ONE YEARS ASTHMA ADMISSIONS IN CORNWALL - STILL DEFICIENCIES IN BASIC CARE

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As a result of the recommendations of the Cornwall Asthma Taskforce *("All together now - collaboration to improve the care of people with asthma". McKenzie I : Journal of Interprofessional Care, vol 9,3,1995;245 - 250)* there has been an Asthma Liaison Team in operation in Cornwall since February 1995.
Five Asthma Liaison Nurses (ALN's) aim to review all acute admissions at home in the weeks immediately following the hospital stay.
In the year April 1995 - March 1996, 521 patients were assessed following admission. This represents 86% of all admissions of Cornish residents with acute asthma (*personal communication : Director of Public Health, Cornwall & Isles of Scilly Health Authority*).
Data about these patients was collected using an assessment tool designed by the ALN's.
Of these admissions ; 72 % had a diagnosis of asthma prior to their admission in the study period, 42 % were < 5 years of age and 53 % were males.
50 % of patients were non-compliant with their prescribed preventer therapy prior to their admission to hospital. Only 46 % of > 65 year olds were non-compliant with prophylaxis compared with 75 % of those aged between 15-19 years. 43 % of patients had unsatisfactory inhaler technique with their prescribed device. Only 38 % of 15-19 year olds had poor inhaler technique compared with 60 % of those aged > 65 years. Compliance was less good in smoking households. 94 % of patients had no written self management plan.
Our data reveals that, in a large group of asthmatics sufficiently severe to require hospital admission, there were deficiencies of care in three basic areas. Compliance with treatment was unsatisfactory and tended to be worse in smoking households. Poor inhaler technique is a continuing problem and very few patients have any kind of self management plan.
An admission for acute asthma is an opportunity to address these issues, which is being actively pursued in Cornwall.

P147 DEFINING THE ROLE OF THE RESPIRATORY NURSE SPECIALIST IN THE SOUTH WEST REGION

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The post of Respiratory Nurse Specialist (RNS) is relatively new and there has been a recent growth in the number of these posts in the South West Region. Since we are aware of the differences in the duties of these nurses, we carried out an audit to assess their role. At present, there are 24 adult RNS posts in the region, spread throughout 13 Trusts. Twentyfour questionnaires were mailed and 23 responded. Of the nurses who answered the questionnaire, 22 had been in their post for < 5 years.

The survey showed that there are a wide range of duties undertaken by RNS. The percentage of nurses dealing with different areas are as follows:
Asthma 100%, COPD 100%, nebuliser service 100%, lung function tests 91%, LTOT 87%, cystic fibrosis 65%, TB 65%, bronchoscopy 60%, home ventilation 56%, AIDS 52%, rehabilitation 4%. These nurses were graded from E-H grades, with the higher grades (G & H) tending to be involved in the more specialised areas such as home ventilation. The nurses had a variety of qualifications, with 56% holding a teaching qualification and 73% holding a specialised respiratory qualification.

The survey examined the methods by which RNS communicate within the hospital and community setting. All the nurses received referrals from both general and respiratory hospital physicians, 82% received community referrals - all of these from GPs and 73% from practice nurses.

Our results demonstrate the wide variety of duties undertaken by the RNS and we feel that this information may be useful to others who are undertaking this role. This survey has helped to further define the role of the RNS, and now further research is needed to examine how effective the role is.

P148 THE COMBINED ROLE OF THE RESPIRATORY HEALTH PRACTITIONER AND THE PHYSIOTHERAPIST IN REDUCING BED OCCUPANCY IN PATIENTS WITH CHRONIC RESPIRATORY DISEASE

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Chronic respiratory disease is associated with numerous hospital admissions and subsequent readmissions. Studies suggest these are largely due to poor compliance with treatment and incorrect drug regimens.

At this hospital, a programme of home care led by Respiratory Health Practitioners and a Physiotherapist has been established. The programme includes follow-up physiotherapy and indivualised exercise plan, education of patient and carers, review of medications, along with regular domestic visitation to promote compliance and to offer support.

We retrospectively analysed the bed occupancy rates of 14 patients with chronic respiratory disease over a 12 month period - 6 months prior to entry and 6 months post entry into the home care programme. Hospital bed occupancy was reduced from a mean of 16 days per patient in the first 6 months to a mean of 3 days following entry into the home care programme.

These findings suggest that a multidisciplinary home care programme for patients with chronic respiratory disease may reduce rates of readmission to hospital.

P149 UNRECOGNISED NEEDS OF PATIENTS WITH END STAGE PULMONARY DISEASE MAY BE IDENTIFIED BY THE RESPIRATORY NURSE PRACTITIONER IN THE PRIMARY SETTING

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Patients with end stage chronic obstructive pulmonary disease (ECOPD) have a multitude of needs which often go undetected. The ability of such patients to perform activities of daily living can be enhanced by referral to allied health care professionals (ACHP) - District Nurses (DN), Occupational Therapists (OT), Physiotherapists (PT), Social Workers (SW).

We retrospectively analysed the effectiveness of the Respiratory Health Practitioner (RHP) in identifying the needs of patients with ECOPD in the primary setting (home) which had not been identified in the secondary setting (hospital inpatient and outpatient episodes). Records of 59 patients (27 female, mean age 71 years) referred from secondary sources to RHPs were reviewed.

	Pre-assessment by RHP	Post-assessment by RHP	Total
DN	5(8%)	19(32%)	24(40%)
OT	2(3%)	37(62%)	39(65%)
PT	0(0%)	39(66%)	39(66%)
SW	4(6%)	18(30%)	22(36%)

All patients were referred to at least 1 AHCP. A patient survey demonstrated that patients appreciate the care given by the RHP and prefer home visitation to frequent outpatient attendances.

In conclusion, through visiting patients with ECOPD at home, RHPs are able to identify needs that had previously been undetected in the secondary setting, thus enabling appropriate referrals to AHCP to be made.

P150 SURVEY OF HEALTH MONITORING DATA AT EUROPEAN LEVEL FOR ASTHMA

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In recognition that some public health objectives may be best achieved through action at European level, the Maastricht Treaty gave the European Union (EU) new powers and responsibilities. The EU public health programme recognises there is a need for collection, collation and publication of objective health data and that asthma is a disease that may warrant surveillance. The European Commission commissioned a report to evaluate the quantity and quality of health data about asthma currently available.
Mortality data are available from the World Health Organisation (WHO), which does not disaggregate asthma from other airway diseases, the Avoidable Mortality Atlas, which provides useful but delayed information, and from the European Statistical Office (Eurostat) which provides absolute numbers of deaths from several respiratory diseases aggregated. Age-standardised mortality rates for age 5-44 vary from 0.08/100 000/year in Greece to 1.00/100 000/year in England and Wales (Avoidable Mortality Atlas, in press). Information about prevalence of asthma is available from research projects or state health interview surveys but is collected using a variety of procedures, though two recent collaborative studies have used standardised methods. The prevalence of wheeze with shortness of breath in the last year in 20 to 44 year old Europeans varies from 1.4% to 16.3% (European Community Respiratory Health Survey, 1996). Hospital utilisation data are collected in many countries and published by the Organisation for Economic Cooperation and Development (OECD), though there are no standardised methods of data collection. The data available suggest that there is wide variation in discharge rates and length of stay for asthma. There is very little collection of primary care utilisation data in member states and none at EU level. Asthma medication use is collated and published by the OECD as Defined Daily Doses/1000 population, a presentation method recommended by the WHO, but data are only available for the Scandinavian countries.
At present there is no system in place for the collection and collation of accurate and timely data collected using consistent methods for asthma monitoring in the EU.

P151 ASSESSING THE QUALITY OF LIFE OF ASTHMA IN FAMILY PRACTICE

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A random sample of 180 adult asthmatic patients was identified from the computerized batabase of a large family medicine group practice. Individuals were mailed a general questionaire to collect baseline demographics along with asthma management. This was validated by a retrospective chart review. In addition they were asked to complete a Quality of Life (QOL) questionaire. The SF-36 (Medical Outcome Study, MOS, short-form general health). Its 36 questions are selected to represent nine health concepts (physical and social functioning, role limitations for physical or emotional problems, mental health, energy of fatigue, pain and health perception). Results were compared against a matched group of the US general population.

Of 180 surveys, 125(70%) were returned from initial mailing. 32.9% of respondants were female the mean age was 54, sd 20 years. 8.6% were smokers. 20% required prn *B*-agonists alone, 35% required low dose inhaled corticosteroids (<1000 mcg beclomethasone or equivalent), 44 % required high dose inhaled corticosteroid, 1% required continuous oral corticosteroids. Only 5% were on theophylline preparations. 18 % had however been given oral corticosteroids for their asthma within the last two years. 5% had had an emergency visit for asthma and 2% had been hospitalized for asthma over the previous two years.

All nine QOL categories were correlated with the severity of asthma and there were very significant differences from the US general population normals, particularly in the domains of physical functioning (61vs74), general health (60vs72)and role limitations (56vs71) $p<0.01$.

It is important to address measures of QOL in common conditions in family practice. QOL assessment in asthmatic patients has been neglected apart from a few patients with severe disease attending specialist clinics. Information from studies of QOL in family practice maybe helpful as a first step towards asthma continuous quality improvement projects.

P152 THE IMPACT OF SEVERE ASTHMA ON THE LIVES OF WOMEN

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Quality of life is affected markedly in women known to be suffering from severe asthma. This preliminary study has shown that women perceived that they had problems related, in particular, to lack of energy, physical mobility and social isolation.

Twenty five women, aged between 15 and 55 years (mean (SD): 38yr.(11.5)) known to be suffering from severe asthma (duration of asthma 1-50 (median 18) years: number of hospital admissions 1-7 (median 2)) were recruited from patients attending a chest clinic. Each patient completed the Nottingham Health Profile (NHP) and the Asthma Quality of Life Questionnaire (AQLQ) on two occasions (summer; winter).

There were marked differences between the responses obtained from the participants and those from age - matched healthy females of similar social class: for example (study v. NHP norms (summer interview), respectively), lack of energy 47 v 23; physical mobility 26 v 5; social isolation 33 v 7; pain 38 v 8 (35-49 year age group). Results obtained at the second (winter) interview were similar. The perceived deficiencies in quality of life could be translated into problems related to activities of daily living such as looking after the home, hobbies and holidays. Responses to the AQLQ confirmed that all the patients had severe asthma.

The importance of quality of life issues in women with severe asthma has been highlighted. Further studies are indicated .

P153 THE PREVALENCE OF ANXIETY AND DEPRESSION IN PATIENTS WITH CHRONIC NON-PRODUCTIVE COUGH

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There is evidence to suggest that chronic cough is associated with certain psychological dimensions such as anxiety and depression. We present preliminary findings from an ongoing study exploring the psychological profile of patients with chronic non - productive cough (CNPC). 33 patients (22 female, median age 53, [range 26-77 years]) attended the chest clinic , Belfast City Hospital. All patients were non smokers with no previous history of respiratory disease. The median duration of cough was 48 months [range 6-240 months]. Spirometry was normal in all cases. All patients completed the Hospital Anxiety and Depression (HAD) Scale and the Spielberger State-Trait Anxiety Inventory (STAI) during their initial consultation. A significant correlation was found between the different scales on the HAD and the STAI validating the reliability of these as a measure of anxiety and depression. The mean anxiety and depression scores on the HAD for the whole group were 6.5 (SD 3.75) and 3.84 (SD 3.204) respectively. HAD scores indicated a significant level of anxiety in 3 patients and a borderline level in 10 patients. Although there was no evidence of a significant level of depression 6 patients did reach a borderline score.There was no significant difference between male and female patients. The level of anxiety and depression did not correlate with patients age or duration of cough. Patients with CNPC do not appear to have a higher level of anxiety and depression than the general population. Further work is required to characterise the psychological functioning of subgroups of patients with chronic cough, in particular those with no clear aetiology, or who fail to respond to diagnosis specific therapy.

P154 CAN SHORT TERM EFFECTS OF COUGH REMEDIES BE MEASURED ?

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Cough is a common symptom that is difficult to quantitate. Cough sensitivity to inhaling increasing concentrations of capsaicin (from a dosimeter in 9 doubling dilutions from 1.9 to 500 µM) is reproducible in healthy subjects and differs with different disease states (Eur Respir J 1992;5:296-300). This study assesses the ability to detect changes in cough sensitivity before and thirty minutes after taking nothing, 10 mls Benylin expectorant and 10 mls pholcodeine elixir. A fourth arm involved sips of water, taken immediately prior to each incremented dose of the second test on that day. Each pair of tests was performed on separate days, in random order. We recorded up to a limit of five coughs post inhalation(C5) and found most people reached a limit at 25 µM. We report the data up to 25 µM . Results were plotted as the number of coughs at each concentration and the area under the curves compared (arbitrary units).

	Nil	Benylin	Water	Pholcodeine
Pre	1.54 + 0.27	1.39 + 0.3	1.40 + 0.29	1.5 + 0.28
Post	1.26 + 0.27	0.93 + 0.28	0.82 + 0.24	0.9 + 0.27
p value	Not Sig.	0.02	0.01	<0.01

There were no between day or order effect in baseline values. There was a non significant trend towards tachyphylaxis on the control day. After each active treatment the cough sensitivity was significantly reduced both compared with the pre value and with the control day. 15 of the 16 subjects showed improvement after pholcodeine. The capsaicin cough test may be a useful tool to evaluate the effectiveness of cough treatments. This may be the first evidence that the "speakers glass of water" has a genuine therapeutic effect.

P155 AIRWAYS INFLAMMATION IN CHRONIC NON-PRODUCTIVE COUGH

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The pathophysiology of chronic non-productive cough (CNPC) in non-asthmatics is not clear. However raised metachromatic cell and eosinophil numbers have been reported in bronchoalveolar lavage (BAL) and sputum respectively, suggested airways inflammation may be involved.
We performed BAL (180 ml, right middle lobe) on 14 non-asthmatic subjects with CNPC (mean duration of cough 96±23m) and compared the cellular characteristics and inflammatory mediator concentrations (histamine, tryptase and eosinophilic cationic protein [ECP]) to normal subjects (n=7). All subjects were non-smokers, had normal spirometry and PC20 histamine > 8mg/ml.
Lavage return was significantly less in CNPC compared to normal subjects ($p<0.01$). There was no difference in total cell count, however mast cell numbers were elevated in CNPC ($p< 0.05$). Tryptase (CNPC 1.97±0.09 ng/ml, normal 1.75±0.09 ng/ml), and histamine (CNPC 0.62±0.23 ng/ml, normal 0.16±0.05 ng/ml) levels were significantly elevated in CNPC compared to normal subjects ($p<0.05$). ECP was detected in BAL from 3 of 14 subjects with CNPC.
These finding demonstrate an increase in mast cell numbers and mast cell derived mediators in CNPC and suggest increased airway mast cell activation. In addition, some subjects with CNPC but without bronchial hyperresponsiveness, have increased eosinophil derived mediators in lavage fluid. These subjects, although not fulfilling current diagnostic criteria, may have cough variant asthma.

P156 TIME SERIES ANALYSIS OF FEV_1 IN PATIENTS WITH EXACERBATIONS OF COPD

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Deterioration in lung function is found when patients present with exacerbations of COPD but little is known of changes before and after onset of symptoms.

Between October 1995 and March 1996, a group of 25 COPD patients from East London (22M, 3F; mean(SD) age 66.1(9.1) yrs, FEV_1 1120 (440) ml, FVC 2460(640) ml, P_aO_2 8.79(1.23) kPa) recorded on diary cards, daily morning FEV_1 and FVC (Micro Medical Ltd spirometers), peak flow rate and changes in respiratory symptoms. Eighteen patients had 30 exacerbations (E); range 1-4/patient. Diagnosis was made by one physician using criteria based on Anthonisen et al (Ann Intern Med. 1987:106; 196-204). For each E the regression coefficient of FEV_1 or FVC on time prior to E was calculated. Significance of these from zero was tested by Wilcoxon signed-rank test. Three different intervals were examined. For days 14 to 8 prior to E, FEV_1 and FVC did not fall significantly, median slope -2.5 ml/d (P=0.308) and -0.5 ml/d (P=0.422) respectively, and were taken as baseline. Over days 7 to 1 prior to E, FEV_1 fell moderately, median slope -4 ml/d (P=0.042) but not FVC, median slope 1.5 ml/d (P=0.989). On days 1 to 0, both fell markedly, median slope FEV_1 -50 ml/min/d (P=0.004) and FVC -130 ml/d (p<0.001). Recovery, defined as the time at which the 3 day moving average of each parameter exceeded or was nearest baseline, took for FEV_1 9.3 (7.1) days and for FVC 9.4(7.1) days.

The increased airflow obstruction prior to the onset of E suggests the involvement of viral and other environmental factors in the pathogenesis of exacerbations.

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P157 PATTERNS OF SYMPTOM CHANGE DURING AN EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Improvement during a COPD exacerbation is best monitored symptomatically. The rate of change of symptoms and which are most likely to improve is not established. We studied 31 patients, median age 69 years, 29 with complete data, during a COPD exacerbation and recorded dyspnoea, cough, wheeze, sputum production, mobility and general wellbeing in a daily diary card until discharge. Total scores were obtained by summing the components and were compared to a VAS scale of change in wellbeing on discharge. Total scores improved significantly from day 1 to day 2 of admission (p<0.001), did not change from days 2 to 5, but showed a further significant improvement from day 2 to the day of discharge (p<0.001).

symptom	mean admission score	mean discharge score	mean difference in score (admission-discharge)
sleep quality	4.1	2.6	1.5*
breathlessness	4.3	3.0	1.3*
cough	3.6	3.1	0.5**
mobility	4.3	3.5	0.8*
wheeze	3.4	2.9	0.5
sputum	2.9	2.8	0.1
wellbeing	4.1	3.2	0.9**

*p<0.001; **p<0.005

Improvement in breathlessness was paralleled by improvements in sleep quality and mobility and reflected by improvement in general wellbeing, whereas changes in cough, wheeze and sputum production were less marked. There was no relationship between improvements in daily symptom scores or VAS on discharge and changes in prebronchodilator FEV1. In this group of patients, changes in breathlessness, mobility and sleep quality were the best guides to recovery from a COPD exacerbation.

P158 THE SEVERITY OF COPD, AUTONOMIC NERVE FUNCTION, CARDIAC ARRHYTHMIAS AND MORTALITY.

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Prolonged QTc interval is associated with a twofold risk of sudden death (Algra et al Circulation 1991; 83:1888). Patients with hypoxaemic COPD have a subclinical autonomic neuropathy and a prolonged QTc and they are at a greater risk of death (Stewart et al Resp Med 1995; 89:79).

We followed-up for 3 years a group of 49 COPD patients (29 M, 20 F) with a wide range of severity of airways obstruction as shown by FEV_1 (range 18 - 85 % of predicted). All these patients underwent respiratory function tests, blood gases, autonomic nerve function tests and 24 hr ECG recording at initial visit. 16 patients died during the follow-up (observation period 3 - 38 months). Patients who died had more severe airways obstruction [FEV_1(L) 0.71 ± 0.26 compared to 1.01 ± 0.59 ; p < 0.05] and were more hypoxaemic [Pa02 (kPa) 7.2 ± 1.2 compared to 8.2 ± 1.9, p < 0.05]. However they had less frequent, although statistically insignificant, ventricular ectopics / per hour (3.9 ± 8.3 compared to 41.7 ± 134.4) and a similar frequency of supraventricular ectopics / per hour (23 ± 29 compared to 29 ± 83 in the group who were alive). The total autonomic neuropathy score was slightly, although statistically insignificantly, worse in the group of patients who died (4.7 ± 2.0 compared to 4.3 ± 1.8). The QTc interval measured at rest was similar in both groups (0.414 ± 0.034 ms compared to 0.419 ± 0.048 ms).

Thus the severity of COPD, not cardiac arrhythmias or autonomic nerve dysfunction abnormalities had prognostic significance in our group of patients.

P159 EVALUATION OF DOMICILIARY LONG-TERM OXYGEN THERAPY WITH OXYGEN CONCENTRATORS

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Domiciliary long-term oxygen therapy (LTOT) in Israel, is usually supplied by means of oxygen concentrators (OCs). Various factors that determine the efficacy of such a treatment were evaluated. Sixty three patients, with cardiopulmonary disease, arbitrarily selected from lists of health care providers, were visited at home by a biomedical engineer and a pulmonary function technician. The evaluation consisted of i) responses to a directed questionnaire, ii) assessment of OC output characteristics, and iii) measurement of the patient's oxygen saturation (SaO_2) at rest with and without oxygen supplement. Only 33% of patients received oxygen treatment for the recommended 12-24 hours/day and 5% of patients waited the recommended 10 minutes of OC warm-up before connection. Filters were cleaned weekly by only 30% of patients and the concentrator was serviced 3-4 times a year in 25% of cases. The OC was thought to be unduly noisy by 24% of patients and connecting tubing of less than 6 metres was fitted to 90% of OCs (thereby limiting patient mobility). Most of OCs did not yield the recommended oxygen concentration and the flow rate meters on them tended to under read. Therefore, only 22% of patients received the prescribed oxygen supplement. Whilst breathing room air, a substantial proportion of patients had an SaO_2 >90%. Improvements are clearly required in terms of more strict adherence to medical guidelines for LTOT, patient education and supervision, supply and maintenance of concentrators and related equipment. The establishment of a supervisory non-commercial body should be considered.

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P160 PATIENT ACCEPTABILITY OF A COMBINED OXYGEN CONCENTRATOR AND NEBULISER UNIT

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Long Term Oxygen Therapy (LTOT) and inhaled bronchodilators are established treatments for Chronic Airflow Limitation (CAL), with around one third of patients requiring both modes of treatment. Until now separate machines were needed to deliver these therapies. The Oxyneb is an oxygen concentrator with an additional outlet port linked to the concentrator's compressor allowing simultaneous or separate delivery of oxygen and nebulised drugs using compressed air. This study assessed patient acceptability of the new machine.

Prototype machines were installed in the homes of 23 patients (17M, 6F; mean age 64 years; mean % predicted FEV1 30% (range 11-52 %) known to use LTOT and nebulised bronchodilators. Details regarding age, supply and servicing of existing compressors were documented and the time taken to administer the usual dose of bronchodilator using their existing machine was recorded. At a second visit the time taken to administer the same drug and dosage via the Oxyneb was recorded. An investigator administered questionnaire was used to record each subject's opinions and attitudes towards the machine.

All subjects felt the Onyneb was quieter. 18 (77%) felt they gained more bronchodilator effect from the Oxyneb. 5 (23%) perceived no difference but none felt that it was less effective than their original compressor. Mean nebulisation time was faster with Oxyneb (12 minutes $\pm$ SD 5.7) than subject's existing machine (16 minutes $\pm$ SD 7.7) $p = 0.003$ (Student's t-test). None of the subjects wanted their old concentrator back, but only 3 (13%) would be happy with the Oxyneb alone. The rest (87%) felt that the Oxyneb plus their original nebuliser for use outside the home or in case of breakdown was their preferred option.

A previous study identified noise and nebulisation time as specific problems for subjects using oxygen concentrators and compressors. This study has shown the Oxyneb addresses both these problems and is well received by patients.

P161 INHALER USE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Twenty patients with COPD and moderate airflow obstruction entered a trial of the ease of use of seven inhaler devices (accuhaler, aerohaler, autohaler, diskhaler, eformoterol inhaler device, metered dose inhaler (MDI), turbohaler,) tested in random order. Most patients used metered dose inhalers routinely. A twelve point scoring system was developed for each device. Devices were demonstrated in a standard fashion and use was tested immediately and one hour later. Scoring on inhaler technique was done by two independent observers. Patients ranked the seven inhalers for ease of use and for preference.

Scoring was reproducible between observers, mean difference of 0.36 on 12 point scale, 3.6% of scores varying by more than 1 point. Analysis of variance showed significant differences in scoring between devices with accuhaler scoring highest and diskhaler least. There were significant differences in patient ranking with accuhaler first for ease of use and preference. The MDI was ranked second by patients with turbohaler third while inhaler technique ranked turbohaler second and MDI fifth. There was a significant decline in ability to use devices over one hour after instruction ($t=2.21$, $p=0.014$). Only MDI and autohaler scores did not drop although changes for individual devices were not significant.

In this study of patients with COPD using devices commonly used for delivery of inhaled drugs there were significant differences in patient preferences and in ability to use devices with significant decline in ability over the first hour after instruction.

P162

SMOKING AND QUALITY OF LIFE AMONG ADULT PATIENTS PRESCRIBED BRONCHODILATORS.

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We surveyed 1463 adults (aged 16 -50 years) in Grampian general practices who had recently been prescribed a bronchodilator. 1139 (78%) completed a postal questionnaire which included the SF-36 generic Quality of Life (QOL) questionnaire (Ware JE et al. Medical Care 1992: 31(3):247-263), a question on current smoking status and questions on day wheeze and night disturbance caused by cough or breathlessness. GP records showed that 80% of respondents had a diagnosis of asthma, 19% had no stated diagnosis in their records and 1% had a bronchitis/COPD diagnosis. Twenty six per cent were current smokers, 24% were former smokers and 50% had never smoked. Respondents were grouped into 3 symptom frequency groups - Group 1 : Wheeze every day (23%) had 39% current smokers. Group 2: Wheeze weekly (26%) had 27% current smokers. Group 3: Wheeze less than weekly (52%) had 19% current smokers ($\chi^2=46.0$, $df=6$, $p<0.001$). The current smokers had significantly worse quality of life, independent of their level of symptoms, age, gender or social deprivation category (Carstairs score). The strongest negative relationships to current smoking were for Health Perception ($F=49.3$, $p<0.001$) Energy and Vitality ($F=20.9$, $p<0.001$) and Mental Health ($F=20.1$, $p<0.001$). Current smokers were more likely to make a visit to their GP in the past year than non smokers (36% vs 30%, $p<0.05$) but were less likely to attend asthma clinic checkups when invited (45% vs 55%, $p<0.05$).

Smoking is a significant contributor to poor quality of life among patients with asthma and smokers appear less willing to participate in preventive management of asthma.

P163 LYMPHANGIOLEIOMYOMATOSIS: A UK SURVEY

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Introduction: Lymphangioleiomyomatosis (LAM) is a rare lung disease of unknown aetiology which affects only women and generally presents before the menopause. It is characterised by progressive dyspnoea, haemoptysis, pneumothorax and chylous pleural effusions and runs a variable course although death has usually resulted from respiratory failure within ten years of symptoms in reported series.

Methods: We contacted all chest physicians in the UK asking for details of patients seen within five years. Consent was obtained from physicians and patients to study hospital notes. Patients with LAM diagnosed by lung biopsy or CT with a compatible history were included.

Results: 44 patients were identified, 35 have been studied of which 30 met diagnostic criteria. Major presenting symptom (1 allowed only) was pneumothorax 12, dyspnoea 8, chylous effusion 6, haemoptysis 1, weight loss 1, other 2. Two patients had died. In survivors mean duration of disease from first symptom was 9 years (range 3.4-18). In 1990 we identified 23 patients with LAM in the UK; at least 19 of the 23 are still alive (2 have died, 2 lost to follow up). Of the 30 patients 16 had been treated with progesterone alone, 3 with progesterone, tamoxifen and buserelin, 1 with tamoxifen and oophrectomy and 1 with tamoxifen alone. Over half (17) were taking an inhaled β agonist and of 14 patients tested 11 had a greater than 10% rise in FEV_1 after a β agonist. Three patients had received a lung or heart-lung transplant (2 alive, 1 dead). Renal angiomyolipomas were found in 4 of the 11 patients screened.

Conclusions: Using similar methods to the 1990 study we have already identified 30 patients with 10 left to screen. Survival appears to be better than in previous series. β agonists may improve lung function in LAM but the long term effects of β agonists and progesterone have not been determined. Randomised controlled trials would probably require international co-operation.

Study supported by a grant from the Mason Medical Foundation

P164 THE TUBEROUS SCLEROSIS 2 GENE PRODUCT TUBERIN IS CONSTITUTIVELY EXPRESSED IN HUMAN AIRWAY SMOOTH MUSCLE AND UPREGULATED BY SERUM

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Background: Loss of heterozygosity of the Tuberous Sclerosis (TSC) 2 gene occurs in hamartomas of TSC and sporadic angiomyolipmas. Pathological similarities between lymphangioleiomyomatosis and pulmonary TSC suggest the same underlying defect may be responsible. We therefore studied the TSC2 gene product tuberin in normal airway smooth muscle. Tuberin shares sequence homology with the catalytic domain of rap1GAP. The rap proteins are GTPase activating proteins which regulate ras by hydrolysis of ras GTP to inactive ras GDP. Ras can activate transcription factors and kinases.

Methods: Airway smooth muscle cells were cultured from human trachealis muscle obtained at post mortem. Cells were grown to confluence and growth arrested for 24 hours or treated with 10% foetal bovine serum. Cells were harvested and RNA extracted. The TSC2 transcript has 3 isoforms, primers were synthesised spanning the 2 splice sites. Reverse transcriptase polymerase chain reactions (RT-PCR) were performed using primers to tuberin and GADPH controls.

Results: A PCR product of approximately 990 base pairs was obtained, this corresponds to tuberin isoform 2 (995 bases) or 3 (992 bases). This was expressed in growth arrested cells and upregulated by treatment with 10% foetal bovine serum.

Conclusion: Tuberin is constitutively expressed in cultured human airway smooth muscle cells and is upregulated by serum. Its sequence homology with rap1GAP suggests it could regulate airway smooth muscle growth by inactivating ras. Loss of tuberin in may be important in the smooth muscle proliferation seen in lymphangioleiomyomatosis and pulmonary TSC.

P165 LOCAL ANAESTHETIC INFILTRATION PRIOR TO ARTERIAL PUNCTURE; SURVEY OF CURRENT PRACTICE AND A RANDOMISED DOUBLE BLIND PLACEBO CONTROLLED TRIAL

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Preinfiltration with local anaesthetic (LA) is recommended for arterial puncture (AP) for blood gas analysis (The BTS and ARTP. Respir Med 1994;88:165-194.). By means of a telephone survey of 100 junior hospital doctors we established that 84% never used LA. We therefore undertook a randomised double blind placebo controlled trial to establish whether the recommendation above is justified. Patients undergoing AP were randomised to one of three groups prior to arterial stab. A: Pre infiltration with 2% lignocaine (n=33), B: Pre infiltration with normal saline (n=34), C: No pre infiltration (n=34). Patient and doctor then rated the discomfort of the procedure. **Results** are presented as mean (SD) and comparisons were made using Kruskal Wallis and Mann Whitney U tests. Both patients (AvBvC H=13.64 p=0.001, AvB 1.5 (0.8) v 2.2 (0.9) p=0.0008, AvC 1.5 (0.8) v 2.1 (0.7) p=0.0005, BvC 2.2 (0.9) v 2.1 (0.7) p=0.7) and doctors (AvBvC H= 7.46 p=0.024, AvB 2.0 (0.8) v 2.5 (0.8) p=0.036, AvC 2.0 (0.8) v 2.6 (0.8) p=0.011, BvC 2.5 (0.8) v 2.6 (0.8), p=0.6) rated the pain of AP less when LA was used. Infiltration with LA was no more painful than placebo (Mann Whitney U AvB 1.8 (0.8) v 2.0 (0.8) p=0.25). The procedure was no more difficult following LA as assessed by passes made (AvBvC 2.5 (2.7) v 1.9 (2.2) v 1.7 (1.7) p=0.74), times skin broken (AvBvC 1.4 (0.7) v 1.3 (0.7) v 1.3 (0.7) p=0.8) and the doctors rating of the procedure (AvBvC 1.2 (0.5) v 1.1 (0.4) v 1.1 (0.3) p=0.6). **Conclusion** Most junior doctors do not routinely use LA during AP. This study supports the BTS/ARTP recommendation by showing that the use of LA reduces pain during AP without making the procedure more difficult and is no more painful than infiltration with placebo.

P166 THE SYSTEMIC FIBRINOLYTIC ACTIVITY OF INTRA-PLEURAL STREPTOKINASE IN HUMANS

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A recent controlled trial has shown that intra-pleural streptokinase improves the tube drainage of infected pleural fluid (AJRCCM 1996:153(4): A462). Studies of crude indices of coagulation suggest this benefit is accompanied by little systemic fibrinolysis. To improve the estimation of the risks of intra-pleural streptokinase in humans, this study examines its systemic fibrinolytic activity in detail.

Eight patients (5M 3F, age 38, range 19-76) receiving 250,000 i.u. intra-pleural streptokinase to aid drainage of a loculated or infected pleural effusion were studied. In all subjects pleural drainage was via a 14 French catheter flushed four times daily to maintain catheter patency and otherwise kept on -20 cmH_2O suction. Streptokinase was introduced dissolved in 30 mls 0.9% saline and retained in the pleural cavity for two hours. Blood was taken before streptokinase administration for fibrinogen (FIB) and D-dimers due to fibrin degradation (DD), prothrombin (INR), activated partial thromboplastin (APTT) and thrombin (TT) ratios. These end points were remeasured at 5 and 24 hours after the administration of streptokinase.

There were no changes of either statistical or physiological significance in any end point at 5 or 24 hours post-streptokinase (paired t-test). The baseline and averaged results (5 and 24 hour samples averaged together) are presented in the table.

	Baseline (SD)	Mean (SD) after SK	diff. (SD)	paired t-test significance
INR	1.24(0.11)	1.22(0.21)	-0.02(0.25)	p >0.8
APTT	1.01(0.18)	0.99(0.10)	-0.02(0.13)	p >0.6
TT	1.00(0.07)	0.88(0.31)	-0.12(0.30)	p >0.3
FIB gl^{-1}	3.57(0.77)	3.86(0.68)	0.31(0.61)	p >0.15
DD mcg ml^{-1}	<0.6(0)	<0.6(0)	0.00(0.00)	p >0.9

250,000 i.u. of intra-pleural streptokinase produces no detectable systemic fibrinolysis in humans.

P167 *CHLAMYDIA PNEUMONIAE* ANTIBODY TITRES ARE SIGNIFICANTLY ASSOCIATED WITH AFRO-CARIBBEAN AND ASIAN ORIGIN

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Chlamydia pneumoniae **antibodies were measured by micro-immunofluorescence in 1,840 adult in-patients, admitted with acute exacerbation of COPD in 10·8% and acute asthma in 6·7%. A control group of 82·5% consisted of patients admitted with non-pulmonary, non-cardiovascular disorders. 71·1% of patients were Caucasian, 18·7% Asian and 10·2% Afro-Caribbean. 55·5% were male. A Townsend deprivation score was assigned by linking postcode sectors to census enumeration districts. Multi-factorial analysis was performed, stratified by age, sex, race, Townsend score, smoking habit and steroid medication.**

Among the controls, antibody titres indicating acute *C. pneumoniae* infection were found in 4·8% of Caucasians, 6·6% of Asians and 10·2% of Afro-Caribbeans. Titres indicating chronic infection were found in 11·2% of Caucasians, 13·4% of Asians and 21·0% of Afro-Caribbeans. For Afro-Caribbeans *versus* Caucasians, the odds ratio (OR) for acute infection was 2·99 (95% CI 1·39, 6·41); and for chronic infection, 2·11 (95% CI 1·10, 4·05). For Asians *versus* Caucasians, OR were 2·08 (95% CI 1·04, 4·17) for acute and 1·35 (95% CI 0·74, 2·45) for chronic infection. Among patients admitted with acute exacerbation of COPD or asthma, OR did not differ significantly between ethnic groups. The Townsend score had no effect on the probability of infection.

We infer that Afro-Caribbean and Asian patients with respiratory disease may be at a higher risk of *C. pneumoniae* infection than Caucasians. The difference appears to be independent of social deprivation. This observation deserves further investigation.

P168 KNOWLEDGE AND COMPLIANCE WITH RESPIRATORY PHYSIOTHERAPY TECHNIQUES IN ADULTS WITH BRONCHIECTASIS

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Chest physiotherapy is widely accepted as an important treatment modality for patients with bronchiectasis. We reviewed the knowledge and compliance with chest clearance techniques in patients with bronchiectasis attending the Lung Defence Clinic at Papworth Hospital.

Patients were assessed on their knowledge of previously taught physiotherapy techniques and on their current practice. When patients where unaware of Active Cycle of Breathing Techniques (ACBT) and postural drainage (PD) these were taught and related to their CT findings.

76 consecutive patients referred to the Lung Defence Clinic were reviewed : 43 had been seen in the last 2 years (group A), 17 had been seen over 2 years ago (group B) and 16 had never been seen by a physiotherapist before for their chest condition (group C).

46% (20) of group A were using correct techniques, of these 17 were using ACBT and PD, 3 only needed ACBT. 42% (18) of group A required some modification to their techniques, of these 6 knew about ACBT and PD, 7 only knew about PD and 3 only knew about ACBT. 12% (5) of group A were not practising any physiotherapy, but 2 knew about ACBT and 1 knew about PD.

12% (2) of group B were using correct techniques of ACBT together with PD. 41% (7) required some modification to their techniques, of these 6 only knew about PD and 1 only knew about ACBT. 47% (8) of group B were not practising any physiotherapy, but 1 knew about ACBT and PD, and 2 knew about PD.

We conclude that patients seen by a physiotherapist more recently had a better knowledge and compliance with physiotherapy techniques than those seen over 2 years ago. Further work is needed to investigate whether compliance is maintained with regular physiotherapy reviews.

P170 FINGER CLUBBING IN MALIGNANT PLEURAL MESOTHELIOMA

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Malignant mesothelioma is occasionally cited as a cause of finger clubbing although in fact the incidence of clubbing in this relatively rare condition is not well described. In addition, for the exact incidence to be determined the confounding effects of asbestosis must be excluded. We have investigated the occurence of clubbing in 77 dockyard workers with malignant mesothelioma proven either by histology or cytology and a control group of 654 patients with either benign pleural plaque or diffuse pleural fibrosis (DPF) diagnosed radiologically. Cases with possible asbestosis suggested either by clinical, radiological, or pulmonary function abnormalities were excluded. The patients were examined by one observer (CMcG), who was not blind to the diagnosis; finger clubbing was considered to be present when there was fluctuation of the nail bed to palpation.

	MESOTHELIOMA	DPF	PLAQUE	TOTALS
CLUBBED	23	18	66	
NOT CLUBBED	54	90	480	
TOTALS	77	108	546	731

We found a highly significant difference between the frequency of finger clubbing in cases of malignant mesothelioma and in benign pleural disease (chi-square = 16.0, $p < 0.0001$). There was no significant difference between the frequency of clubbing in DPF and pleural plaque. We conclude that the increased incidence of clubbing in cases of mesothelioma as compared to pleural plaque suggests that finger clubbing can be attributed to the disease itself, rather than the presence of sub-clinical asbestosis. The significantly higher incidence justifies the inclusion of malignant pleural mesothelioma as a cause of finger clubbing.

P169 CLINICAL FEATURES AND EPIDEMIOLOGY OF MALIGNANT PLEURAL MESOTHELIOMA IN GLASGOW 1987-92

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INTRODUCTION. Malignant mesothelioma is common in the west of Glasgow due to asbestos exposure in the Clyde shipyards. Clinical features and rise in incidence in this area have been reported previously.(Hulks et al. Thorax 1989;44: p496). National epidemiological studies suggest that the incidence may not peak until 2020 (Peto et al. Lancet 1995; 345:535-9.) The objective of this study was to determine, from case record examination, if there had been a change in the clinical features of the disease in our population and whether the national rise in incidence was reflected locally.

METHODS. Case records were identified from coded morbidity returns and the local cancer registry.

RESULTS. 167 records were studied of which 144 new cases were identified as definite or probable pleural mesothelioma. Yearly incidence did not change significantly over this period (See table). Mean age at diagnosis was 67 years and the most common symptoms were dyspnoea(66%), pain(51%) and weight loss (33%). 64% of patients had definite asbestos exposure and 51% were recorded as definite shipyard workers. Only 6% had not worked in shipyards or engineering works. 24 patients(17%) were diagnosed without histological confirmation of which only 2 did not have asbestos exposure. Median survival, at 30 weeks, was similar to previous studies. Age and mode of presentation did not correlate with survival time.

Yearly Incidence	
1987	22
1988	26
1989	21
1990	27
1991	23
1992	25

CONCLUSION. The incidence of disease has risen in this area compared to 1980-86 (Hulks et al.) but the clinical features and survival are unchanged. However we did not find a rise in incidence during the period studied. These findings suggest that the peak in incidence of mesothelioma may have been reached in a population exposed to asbestos mainly in shipyards.

P171 ACUTE SEVERE ALVEOLAR HAEMORRHAGE SYNDROME : A SINGLE CENTRE EXPERIENCE

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Acute severe alveolar haemorrhage syndrome (AHS) is a rare heterogenous entity of haemoptysis, bilateral airspace shadowing, respiratory failure and anaemia. The outcome of 9 patients presenting over a 5 year period was reviewed retrospectively. 7 patients were male, mean age 51 (range 29-72), 8 were ex-smokers. Six patients (pts) had Wegeners Granulomatosis / microscopic polyangiitis. Two patients had isolated pulmonary haemorrhage, (1 homogenous anti-nuclear antibody positive, 1 peri-nuclear ANCA positive). One patient had anti glomerular basement disease. AHS was the de-novo presenting feature in 5 patients. All 7 pts with multisystem disease had renal involvement. All received methylprednisolone, cyclophosphamide (6 iv, 2 orally), 7 underwent plasma exchange, 1 received OKT3 and 4 received immunoglobulin therapy following plasma exchange. Respiratory support included 100% high flow oxygen (3 pts), CPAP (2 pts), mechanical ventilation (3 pts). Four patients died: neutropenic sepsis, sepsis, ventilatory failure and cardiovascular instability respectively. All 3 pts requiring mechanical ventilation died. Two survivors are maintained on plasma exchange and pulsed cyclophosphamide (1 has recurrent haemoptysis). Following OKT3, one survivor has no symptoms. The remaining survivor has no symptoms following pulsed cyclophosphamide. All survivors received plasma exchange. Acute severe AHS is most often associated with small vessel vasculitis, it is uncommon and carries a poor prognosis if ventilatory support is required.

P172

OUT-PATIENT MANAGEMENT OF α-1 ANTITRYPSIN DEFICIENCY-CURRENT PRACTICE IN THE WEST MIDLANDS 1996

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There are currently no published UK guidelines for the management of patients with chronic obstructive airways disease (COAD) or α-1antitrypsin deficiency (α-1AT). We carried out a doctor delivered questionnaire to 20 respiratory physicians throughout the West Midlands, evaluating current practice for the investigation and management of COAD (ages 40 and 70), homozygous (PiZ) and heterozygous α-1AT.

The reported investigation and management was similar for all groups with the exceptions noted in Table 1. Treatment with long term inhaled steroids for all groups is used empirically by 25% of physicians, the rest using inhaled steroids only if patients are found to be steroid responsive (80% would carry out an oral steroid trial). All physicians advise routine influenza vaccination and 55-60% advise pneumovax. 25% of physicians have smoking cessation programs for patients and 15% have some form of pulmonary rehabilitation.

The physicians current screening practice for α-1AT is as follows: all screen young (<50y/o) patients with emphysema/COAD, 20% older emphysema/COAD, 15% bronchiectatics, and 5% screen asthmatics. Most treat patients with heterozygous α-1AT as they would COAD without deficiency although 20% treat them as PiZ. 45% actively follow up heterozygotes and 45% screen heterozygotes relatives for α-1AT. To date α-1AT patients are investigated and treated similiarly to COAD patients without deficiency with the exception of screening, closer follow up and monitoring of lung function ($p<0.05$).

Table 1: % investigations in COAD (ages 40 and 70) and in PiZ patients

Investigations	COAD-70y	COAD-40y	PiZ
Peak flow chart	15%	85%*	50-65%
Annual full pulmonary function tests	15%	30%	70%*
α-1AT measurement	25%	100%*	
Baseline arterial blood gases	0%	5%	15%
High resolution CT chest	10%	60%*	65%
Long term follow up	5%	40%*	95%*
Screening family members	0%	15%	100%*

* $p<0.05$ (comparing COAD (ages 70 with 40) and COAD (age 40) with PiZ)

P173 COMPARISON OF A MODIFIED BICARBONATE BUFFER AND EUROCOLLINS SOLUTION FOR HYPOTHERMIC STORAGE OF RAT LUNGS: EFFECT ON LUNG FUNCTION

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Lung transplantation is an accepted therapy for end-stage pulmonary disease but limited safe periods for tissue storage currently restrict transplant programs. To develop improved methods of lung storage we have established an isolated, ventilated and perfused rat lung preparation to study the effects of long-term preservation on lung function. In the present study hypothermic storage in EuroCollins (EC) solution, commonly used in human lung transplant surgery, was compared with storage in a standard perfusion solution. Lungs from adult male Wistar rats were excised, placed in a chamber and perfused at 37°C via the pulmonary artery (constant flow rate:15 ml/min) with bicarbonate buffer (BB) containing 2% bovine serum albumin. Vascular resistance (VR) was assessed by a pressure transducer attached to the perfusion circuit. Lungs were ventilated by positive pressure (tidal volume:1.6-1.8 ml, 80 breaths/min) and the ratio of tidal volume:tracheal pressure (TV:TP) provided a measure of airways compliance. After a control perfusion period (20 min), lungs were flushed with cold (4°C) storage solution (BB or EC) and then immersed in the same solution for varying periods of 4°C storage (0, 0.5, 2, 4, 6 h). After storage, lung function was assessed at the end of a 20 min 37°C reperfusion period. TV:TP (ml/cm H_2O) and VR (ml/min/cmH_2O) at the end of the control and reperfusion periods for lungs stored for 6 h in either solution are shown in the table. Similar data for unstored lungs are shown for comparison.

	TV:TP		VR	
Storage	Control	Reperfusion	Control	Reperfusion
0 h (n=7)	0.043(0.002)	0.036(0.003)	1.92(0.33)	2.02(0.30)
6 h BB (n=6)	0.051(0.007)	0.017(0.002)*	2.15(0.50)	2.90(0.50)
6 h EC (n=6)	0.054(0.004)	0.013(0.002)*	2.04(0.08)	4.66(0.57)*

Values are mean (±SE).* = $p<0.05$ when compared to unstored lungs.

After 6 h storage, significant and similar deteriorations in lung compliance were seen for both solutions. EC also caused a significant increase in VR. We conclude that flushing and storage for 6h in EC solution offers no improvement from hypothermic storage in standard perfusate.

P174 A RE-AUDIT OF PULMONARY FUNCTION LABORATORIES IN THE WEST MIDLANDS

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In 1991 the West Midlands Pulmonary Function Audit Group examined the consistency between pulmonary function laboratories in the West Midlands. Three healthy subjects visited each centre and performed a standard set of pulmonary function tests and were given predicted values based on their age and measured height and weight. Demographic data on nine hypothetical subjects was also supplied for the laboratories to produce predicted values. Equipment was checked for accuracy using standard methods.

The 1991 audit revealed significant inter laboratory variability. Sources of error were identified and after consultation, recommendations were made to improve consistency.

In 1995 the audit was repeated using the same three subjects. Significant differences continued for all predicted results except for residual volume (RV) and forced vital capacity (VC) and for all actual results except for functional residual capacity (FRC) ($p<0.05$). However improvements in the coefficient of variation was seen compared with 1991 for predicted forced expiratory volume (FEV1), total lung capacity (TLC), gas transfer (TLCO), FVC, FRC and RV. Similar improvements were seen actual results for FEV1 and FVC. Increased variation was seen for predicted corrected transfer factor and actual RV. Analysis of the hypothetical data continued to show unacceptable variation suggesting continuing computer algorithm inconsistency. Some encouragement can be taken from the improvements seen but further work needs to be done.

P175 A REVIEW OF THE IMPACT PULMONARY FUNCTION TESTING HAS IN A LARGE TEACHING HOSPITAL IN BIRMINGHAM

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We reviewed the workload of the lung function service and pulmonary function test (PFT) results for a 2 month period (OCT-NOV 1995). The patients notes were obtained in order to determine a) the interval from request to testing and testing to results reaching notes, b) the type of results obtained and c) what effect the PFT result had on clinical decision making.

In the 2 months studied 250 patients had spirometry in the Asthma Clinics; all results were incorporated in the notes and appropriate action taken at that clinic visit. 165 patients had full pulmonary function testing. 87% were OPD referrals and 13% inpatients. 60% were new patients. Waiting time for OPD was 90% within 20 days and for inpatients 90% within 3 days. 90(55%) of 165 patients had notes reviewed. 95% of PFT were abnormal; obstructive pattern found in 82 patients (33 were severe), restrictive in 63 (15 were severe). 15% of severe abnormalities were at first presentation to the lung function service.

Where case notes (90) were reviewed, 88% had commented on the PFT. 51% were commented between 1-10 days. 12% between 11-20 days, 25% over 20 days and no comment in 12%. 95% of those commented; management was reviewed in 40%, diagnosis confirmed in 21%, management changed in 19%, condition excluded in 15% and no management action taken in 5%.

This study generally confirmed the clinical usefulness of pulmonary lung function testing at our department and a large proportion of testing were abnormal. Majority (88%) of results were acknowledged by the clinician.

P176 URINARY NEOPTERIN EXCRETION AS A MARKER OF ACTIVITY IN SARCOIDOSIS

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Serum angiotensin converting enzyme (ACE) has been used to monitor disease activity in sarcoidosis but has been shown to have low sensitivity of 69% (Studdy 1989). Neopterin is specifically released from human monocytes/ macrophages and its production is closely associated with activation of the cellular immune system. Patients with active sarcoidosis have higher urinary neopterin levels than those with inactive disease (Lacronique 1986).

We have compared urinary neopterin levels and serum ACE on 179 occasions in 97 patients with sarcoidosis. There was a significant positive correlation between urinary neopterin levels and serum ACE activities (r= 0.59, p= 0.0001). Urinary neopterin was raised on 87(49%) occasions whereas serum ACE was raised on only 62(35%) occasions. In 114(64%) occasions, the two measurements agreed (in 72 both results were normal; in 42 both results were high). In the remainder 65(36%) occasions, urinary neopterin levels were raised on 45 occasions and serum ACE activities on 20 occasions.

Our results suggest that measuring urinary neopterin is useful in monitoring disease activity in patients with sarcoidosis and may be more sensitive than serum ACE.

P178 BRONCHOSCOPY SOFTWARE DEVELOPMENT: COSTS AND BENEFITS

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Between January 1991 and 1996 software was developed to record and analyse bronchoscopy episodes with active data collection on 1700 episodes in 1589 patients between May 1992 and August 1996. Specific design features of the software include a facility for direct download of patient demography from the hospital Patient Master Index, a network based version allowing access from any part of the Trust's network and remote print facility. The total outlay on the project has been just under £61,000, £55,000 on programming and hardware, but exclusive of any medical / technician time involved in the development. Linked to the bronchoscopy system are additional data fields, allowing audit of many areas of routine clinical practice. The software has been used in a City wide audit, and to plan for the effects of the Calman initiatives on medical manpower and cancer services. For example 1) analysis of 1665 episodes by referring consultant group showed that 88% of patients were referred by a physician, (78% of this group under a chest consultant), 6.2% by Infectious Diseases, 2.7% by the Elderly and the remainder from various groups. 2) analysis of the appropriateness of referral to the local cancer centre for 78 patients (complete data in 72), identified as having small cell cancer from bronchial biopsies, revealed 13 had not been referred for the following, 5 patient / relative refusal, 3 no reason, 2 metastases, 3 for varied reasons including lost to follow up! Additional benefits have been seen in saving of administrative and secretarial time. This project illustrates the benefits of a computerised system, but the high costs of developing and supporting new software must be carefully considered.

P177 THIN-SECTION SPIRAL VOLUMETRIC CT FOR THE ASSESSMENT OF LOBAR AND SEGMENTAL BRONCHIAL STENOSIS

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Spiral volumetric CT has been used for assessment of stenoses of the trachea and main bronchi (Quint L.E. et al Radiology 1995; 194: 871-877) and high resolution CT has demonstrated bronchial wall thickening in segmental bronchi in patients with a variety of diseases including sarcoidosis (Lenique F. et al, Radiology 1995; 194: 419-423). However, to our knowledge no attempt has yet been made to demonstrate and assess stenoses of lobar and segmental bronchi with thin-section volumetric CT.

We used this technique to scan selected volumes of lung in 5 patients with known or suspected lobar and segmental bronchial stenoses. Four, 3 men, had sarcoid (aged 46-49 years; duration 5-18 years; FEV_1 42-62% predicted; FER 41-53%; PEF 42-69% predicted). Two had bronchograms 10 and 11 years earlier. One woman aged 61 had had endobronchial amyloid for 21 years (FEV_1 58% predicted, FER 36%, PEF 36% predicted).

Volumes of lung between 5.8cm and 7.2cm in craniocaudal extent were scanned. 2mm or 3mm slices were obtained and reconstructed at 1mm or 2mm intervals. The scans clearly demonstrated stenoses in all patients. Distortion of bronchi and bronchiectasis distal to stenoses were other features seen in the sarcoid group.

Of the 20 lobar bronchi scanned in the sarcoid group 2 were stenosed and 9 distorted. Two of the 3 lobar bronchi scanned in the amyloid patient were stenosed. Thirty of the 60 segmental bronchi scanned in the sarcoid group were judged to be stenotic. All of the segmental bronchi in the amyloid patient were stenosed or occluded. Distortion was seen in 20 segmental bronchi in the sarcoid group but was not a feature in the amyloid patient. Two of the sarcoid patients had bronchiectasis. Comparison of the CT scans with the old bronchogrmas in the patients with previous bronchograms showed good correlation and little interval change.

Bronchography is no longer performed. Bronchoscopy cannot determine the length of a stenosis. With the development of new techniques in bronchial dilatation and stenting, and for monitoring stenoses with an easily repeatable non-invasive test, an investigation such as thin-section spiral volumetric CT appears very attractive. On the basis of this limited study we feel that it will be a valuable tool in the assessment of lobar and segmental bronchial stenoses.

P179 COMPARISON OF OXIMETRY AND TRANSCUTANEOUS CARBON DIOXIDE ($TcPCO_2$) LEVELS IN PATIENTS UNDERGOING FIBREOPTIC BRONCHOSCOPY (FOB)

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Twenty-two consecutive patients undergoing routine FOB, 15 male, mean age 62.3yrs (range 45-82yrs), mean (SD) FEV_1 of 61.8 (20.1)% and FVC 74.1 (23.1)% predicted, were studied using oximetry (OXImeter, Radiometer) and $tcPCO_2$ monitoring (TINA, Radiometer). Atropine (mean dose 0.59mg; range 0.30-0.60mg) and Omnopon (mean dose 9.43mg; range 2.50-10.0mg) were given IM 30min before the FOB with Diazemuls (mean dose 7.60mg; range 2.50-20.0mg) given IV at onset of procdure to induce light sedation. Supplemental oxygen (2L/min) via nasal cannulae was administered to all patients, increased according to clinical need and to maintain oxygen saturation (SaO_2) over 90%. Monitoring began 1hr prior to FOB for 4hrs. No patients required reversal of sedation. Results(Values expressed as means with standard deviation in parenthesis.)

stable, pre-bronchoscopy, SaO_2	93.6 (3.0)%
stable, pre-bronchoscopy, $tcPCO_2$	43.7 (6.3)mmHg
time to reduction, from baseline, in SaO_2	319.1 (327.8)sec
time to elevation, from baseline, in $tcPCO_2$	170.6 (372.4)sec
maximum $tcPCO_2$ during bronchoscopy	53.5 (7.6)mmHg
increase in $tcPCO_2$ during bronchoscopy*	9.9 (5.0)mmHg
time for $tcPCO_2$ to return to baseline	1297.7 (1168.9)sec
duration of bronchoscopy	639.6sec

Time zero is taken as the time of administration of IV Diazemuls. The mean increase in $tcPCO_2$ during FOB* differs significantly ($p<0.001$; Students paired t test) from pre-FOB values, and the $tcPCO_2$ deteriorated more rapidly from baseline than corresponding oxygen saturations in 19 cases. $TcPCO_2$ monitoring during FOB provided evidence of hypoventilation with significantly elevated levels of $tcPCO_2$. This method of monitoring also provided an earlier indication of respiratory depression during FOB compared with pulse oximetry.

P180 CRYPTOGENIC FIBROSING ALVEOLITIS - A COMPARISON OF PRESENTATION, RESPIRATORY LUNG FUNCTION AND OUTCOME BETWEEN CAUCASIANS AND ASIANS

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The clinical course of cryptogenic fibrosing alveolitis (CFA) is better known in Caucasians than in those from the Indian subcontinent (ISC). We have reviewed the case notes from all patients with CFA presenting after 1985, to identify ethnic differences. The diagnosis of CFA was established using clinical, lung function, radiological evidence and where available from histology.

There were 35 Caucasians (21 male) and 27 Asians (11 male). The Asians presented younger (ISC 56.6 yrs 2SD 9.7 vs. Cauc. 64.0 yrs 2SD 10.7 $p < 0.01$) and this was similar for both sexes. Duration of symptoms prior to presentation were similar (Cauc. 10.4 months 2SD 11.7 vs. ISC 12.1 2SD 13.0). Asian females had significantly worse restrictive spirometry at presentation, but no differences in TLC or diffusion when corrected for ethnicity. ISC female FEVI % predicted 55.8% 2SD 19.2% vs. Cauc. 71.3% 2SD 19.8% $p < 0.05$. ISC FVC % predicted 54.6% 2SD 15.6% vs. Cauc. 68.5% 2SD 15.2% $p = 0.02$. ISC TLC 72.9% 2SD 16.4% vs. Cauc. 68.0% 2SD 24.0% NS. ISC DLCO 40.2% 2SD 14.0% vs. Cauc. 39.0% 2SD 17.4% NS. Asian males presented only with a significantly worse % predicted FEVI than Caucasian males (54.0% 2SD 15.4% vs. Cauc. 68% 2SD 20% $p < 0.05$).

A smaller proportion of Asians were tried on immunosuppressives (excluding steroids); 26% vs. 40%, but this was not significant by Chi square testing.

Survival to death was similar in both groups (Cauc. n = 16; 31 months 2SD 29 vs. ISC n = 11; 39 months 2SD 22). In both groups over 90% died within 5 years of onset of symptoms.

P181 ANTIBODY LEVELS IN SALIVA OF PATIENTS WITH PIGEON FANCIERS LUNG

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Avian antigen specific and total IgM, IgG and IgA (IgA1 & IgA2) levels were measured in saliva and serum from 87 symptomatic Pigeon Fanciers. Albumin levels were used as a protein reference and smoking status was monitored by cotinine levels. Antibody activity to pigeon serum was present in all the isotypes examined with relatively higher levels of IgG antibody present in serum and relatively greater levels of IgA antibody in saliva. A significant correlation ($r = 0.522$, $p<0.001$) was shown between serum and salivary IgG antibody activity.

It appeared that a proportion of this salivary IgG was synthesised locally when serum and transuded salivary albumin levels were considered. As is well recognised, cigarette smoking caused depression of antibody production in all isotypes.

Saliva sampling may offer a further convenient, accurate and non-invasive approach to assist in the assessment of immunological sensitisation in Pigeon Fancier's Lung.

P182
INHALER TECHNIQUE AMONG ADULT PATIENTS PRESCRIBED BRONCHODILATORS.

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As part of a larger study of asthma care we carried out home interviews with a random sample of 346 adults (aged 16 -50 years) in 50 general practices in Grampian, who had recently been prescribed a bronchodilator. The home interview assessed quality of life and attitudes to asthma review and included an assessment of inhaler technique. 84% of interviewees had a standard metered dose inhaler. 8% had a turbohaler, 5% had rotohaler or diskhaler, 3% had an autohaler. Inhaler technique was scored out of a maximum of 5 points, covering preparation of inhaler (1), prior exhalation (1) co-ordination (2) and final breath hold (1). . Of the 4 subscales, co-ordination best predicted total score. 37% of interviewees scored 5, 31% scored 4 and 32% scored 3 or lower. Younger interviewees (less than 36 years) scored significantly better than those aged 36 to 50 years (4.0 vs 3.7, p=0.02). 18% of patients said that no doctor nurse or pharmacist had ever shown them how to use their inhaler. These patients did not differ in inhaler technique score. 91 patients who had attended an asthma clinic in general practice in the previous year did not differ in inhaler technique score from 100 who had been invited but did not attend. Inhaler type was significantly related to technique score. Only 64% of patients using metered dose inhalers scored the maximum of 2 for coordination, compared to 95% of patients using other types of inhaler.

P183 SYSTEMIC EFFECTS OF HIGH DOSE INHALED STEROIDS (BUDESONIDE, BECLOMETHASONE AND FLUTICASONE) TAKEN VIA LARGE VOLUME SPACER

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High dose inhaled steroids (>1.5 mg per day) may have systemic effects. We have used a single high dose of inhaled steroid taken at 11 pm to study the systemic effects of budesonide (BUD), Beclomethasone dipropionate (BDP) and Fluticasone (FLU) on 9 am serum cortisol. 16 healthy volunteers took 2 mg or 4 mg of each drug from a large volume spacer (Volumatic or Nebuhaler) in a double blind study. Each subject also took two inhaled placebo treatments. The mean serum cortisol after 32 placebo tests was 652 n mol/L. For each treatment we report the mean percent change from placebo with 95% CI. Statistical analysis was by Wilcoxon signed rank test.

TREATMENT GIVEN	% change in Cortisol V Placebo	95%CI	p value V Placebo	p value V 4 mg BUD
2 mg BUD	25% fall	3-47%	0.035	0.32
4 mg BUD	43% fall	22-64%	0.0001	-
4 mg BDP	66% fall	49-82%	0.0008	0.049
2 mg FLU	72% fall	59-85%	0.0005	0.013
4 mg FLU	86% fall	82-91%	0.0005	0.002

We conclude that this model system is useful for comparing the systemic effects of different inhaled steroids. Using this system, our results are in agreement with previous studies that have found the systemic potency of Fluticasone to be at least twice that of Budesonide with intermediate results for Beclomethasone . (Barnes PJ, Respir Med 1996; 90: 379-84). This study provides no information about the relative therapeutic potency of each inhaled steroid.

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P184 SYSTEMIC EFFECTS OF HIGH DOSE BUDESONIDE (4 mg) TAKEN BY FOUR INHALER SYSTEMS AND ORALLY

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High dose inhaled steroids (>1.5 mg per day) may have systemic effects. We have used a single 4 mg dose of budesonide (BUD) taken at 11 pm to compare the effect of four different inhaler systems on the 9 am serum cortisol level of 16 healthy volunteers in a double blind study. **MDI** = Metered Dose Inhaler, **DPI** = Dry Powder Inhaler (Turbohaler). Each subject also took two inhaled placebo treatments and 4 mg oral budesonide (to assess GI absorption). The mean cortisol level from 32 placebo tests was 652 n mol/L.

For each treatment, we report the mean % change from placebo with 95% CI. **P V Placebo** = Wilcoxon signed rank test; p value compared with placebo. **P V Nebuhaler**= Wilcoxon p value compared with change in cortisol level after 4 mg BUD via Nebuhaler spacer. * =<0.05, ** =<0.01, *** =<0.001

TREATMENT (Budesonide 4 mg via.....)	% change in Cortisol V Placebo	95%CI	p value V Placebo	p value V Nebu-haler
Nebuliser	8% rise	+28 to-13	ns	**
Oral Budesonide	14% fall	+ 6 to-34	ns	*
Nebuhaler	43% fall	-22 to -64	***	-
DPI (Turbohaler)	72% fall	-58 to-85	***	*
MDI - No spacer	73% fall	-57 to-90	***	*

We conclude that this model system is useful for comparing the systemic effects of different inhaler devices. Using this system, we found that the use of a large volume spacer reduced the systemic absorption of budesonide compared with MDI alone and DPI. Oral budesonide had only slight systemic effect (due to first pass metabolism in the liver) and nebulised budesonide appeared to have no effect on cortisol levels in these tests.. This study provides no information about the therapeutic potency of each system.

P185 ADRENAL SUPPRESSION WITH INHALED FLUTICASONE PROPIONATE (FP) AND TRIAMCINOLONE ACETONIDE (TAA) IN NORMAL SUBJECTS

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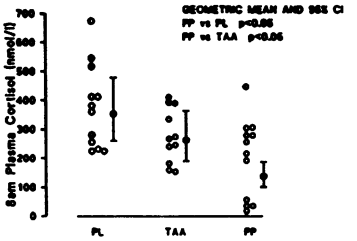
Twelve normal subjects mean age 27.5 years were studied in a single (investigator) blind crossover design comparing a total dose of 1625µg FP (MDI), 1600µg TAA (Oral Inhaler) or placebo (PL); given in two divided doses at 8am/10pm over a 24 hour period, each treatment separated by a 1 week washout. Measurements were made of overnight urinary cortisol and creatinine excretion and 8am plasma cortisol (10 hours after the 2nd dose).

For 8am plasma cortisol (geometric mean, nmol/l) compared with PL (353.1) FP (137.7) produced significant suppression (2.57-fold difference: 95% CI 1.50 to 4.39), whereas TAA (262.8) did not (1.34-fold difference: 95% CI 0.77 to 2.34). FP produced 1.91-fold greater adrenal suppression ($p<0.05$) than TAA (95% CI 1.10 to 3.33). Values < 150nmol/l: TAA (n=0), FP (n=4) $p<0.05$. Overnight urinary cortisol/creatinine ratio (geometric mean, nmol/mmol) did not show any difference between FP (1.48) and TAA(1.60), with both producing suppression versus PL (4.01).

Thus FP (MDI) produced approximately two-fold greater adrenal suppression than TAA (Oral Inhaler) when given on a microgram equivalent basis in normal subjects



P186 A PHASE III OPEN PARALLEL GROUP STUDY TO COMPARE THE EFFECTS OF INHALED FLUTICASONE PROPRIONATE(FP)(500MCG BD) AND BUDESONIDE(BUD) (800MCG BD) ON BONE DENSITY MEASUREMENTS(BMD) OVER 1 YEAR IN STABLE CHRONIC ASTHMATICS

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59 patients with stable chronic asthma, previously taking between 1500-2000mcg Beclomethasone diproprionate or 1200-1600mcg BUD were randomised to receive either FP 500mcg bd (30 patients) Group A, or BUD 800mcg bd (29 patients) Group B, both given via MDI and large spacer. Patients who had previously received maintenance oral steroids, or who had received 1 short course of oral steroids in the preceding 3 months or more, or 3 short courses in the last year, were excluded.

Spinal bone mineral density(BMD) and bone markers were measured at baseline,6 and 12 months.

All patients had normal T and Z scores at baseline. Spinal BMD increased in both groups after 12 months. Group A 0.5%,Group B 1.6%,P = 0.36.

Serum osteocalcin levels increased significantly from baseline in both groups. Group A 16.9% (P=0.02) and 14.3% in Group B (P=0.04). Procollagen 1c-terminal Peptide(PICP) did not differ significantly from baseline after 12 months in either group. Markers of bone reabsorption showed large variability between patients but with no statistical difference between the two groups.

Conclusion - High dose inhaled BUD and FP have no adverse effect on bone markers or bone turnover in the long term.

P187 COMPARISON OF THE SYSTEMIC EFFECTS OF SALBUTAMOL AND TERBUTALINE WHEN INHALED FROM A METERED DOSE INHALER OR AS A DRY POWDER IN HEALTHY VOLUNTEERS

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β_2 agonists are usually administered by inhalation either from a metered dose inhaler (MDI) or as a dry powder. The latter devices are easier to use, but more expensive and there is some controversy regarding the bioequivalent effects of these methods of delivery. This study assessed the dose equivalence of salbutamol (S) administered from an MDI (SM) and a Diskhaler (SD) and terbutaline (T) administered from a Turbohaler (TT). Twelve healthy volunteers were given incremental doses of S (200µg, 200µg, 400µg, 400µg, 400µg - total dose 1600µg) or T (500µg, 500µg, 1000µg, 1000µg - total dose 4000µg) at 15 min intervals on 3 occasions. Heart rate (HR), the QT interval (QTc) and T wave height were measured from the ECG and plasma potassium (K) and blood lactate were measured at baseline and 5 min after each inhalation. Treatments were assigned using a randomised, double-blind, double-dummy, cross-over design. The mean ± SD results after the second and final doses are shown.

Dose µg	ΔHR b/min	ΔQTc ms	ΔT mm	ΔK mmol/L	ΔLactate mmol/L
SM 400	4.5 ± 5.4	18.2 ±19.3	-1.1 ± 0.5	-0.24 ± 0.36	0.18 ± 0.28
1600	15.7 ± 11.9	52.2 ±35.3	-1.9 ± 0.9	-0.63 ± 0.55	0.67 ± 0.46
SD 400	1.8 ± 5.4	23.0 ± 24.0	-0.7 ± 0.8	-0.03 ± 0.22	-0.11 ± 0.14
1600	13.9 ± 10.7	63.1 ± 43.9	-2.0 ± 0.8	-0.62 ± 0.40	0.57 ± 0.33
TT1000	-0.3 ± 2.8	13.0 ± 19.3	-0.5 ± 0.7	-0.01 ± 0.30	0.16 ± 0.41
4000	11.9 ± 12.0	51.1 ± 36.4	-1.7 ± 0.9	-0.58 ± 0.44	0.75 ± 0.63

There were no differences between the drugs at any time point. Using this methodology, S is equally potent when given by MDI or as a dry powder. The equivalent dose ratio by weight for S and T is 1:2.5

P188 IMPROVED DELIVERY BECLOMETHASONE DIPROPIONATE (BDP) 400 MCG DAILY ACHIEVES EQUIVALENT ASTHMA SYMPTOM CONTROL AS 800 MCG BDP FROM CONVENTIONAL CFC INHALER

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A finer particle size of BDP from an aerosol solution formulated with CFC-free propellant HFA-134a improves airways delivery of BDP. This study evaluated whether asthma symptom control could be achieved with lower total daily doses of HFA-BDP from the new metered dose inhaler (MDI). 347 moderate symptomatic asthmatics, using inhaled bronchodilators alone or with inhaled steroid ≤ 400 mcg/day, had symptoms improved (over run-in) to a new baseline by administration of a short course of 30 mg oral prednisone. Patients were then randomized to 12 weeks of treatment with CFC-BDP at a dose of 800 mcg daily, HFA-BDP 400 mcg, or HFA placebo.

Adjusted Mean ± SE Percentage of Nights Without Sleep Disturbance Due to Asthma Symptoms

Treatment/day	Run-in	Oral steroid	10-12 weeks
HFA-BDP 400 mcg	43.5 ± 4.0	72.4 ± 4.1	74.3 ± 4.0*
CFC-BDP 800mcg	42.1 ± 3.9	77.1 ± 4.0	72.2 ± 3.9*
HFA placebo	46.2 ± 4.0	74.5 ± 4.1	47.5 ± 4.1

*Mean change from oral steroid less than HFA placebo ($p<0.001$).

After 12 weeks treatment, percentage of nights without sleep disturbances for HFA-BDP 400 mcg and CFC-BDP 800 mcg were equivalent, similar to the response seen with oral steroid and significantly better than placebo. Daily symptom scores and beta-agonist use showed a similar pattern. There were no differences in adverse events between the HFA and CFC formulations. In moderate asthmatics HFA-BDP 400 mcg and CFC-BDP 800 mcg gave equivalent symptom control over 12 weeks.

P189 BRICANYL™ TURBOHALER™, SEREVENT™ ACCUHALER™ & FORADIL™ AEROLIZER™: COMPARATIVE DRUG DELIVERY

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Drug delivery from two recently available pre-metered dry powder inhalers (DPIs), Foradil (FA, eformoterol fumarate 12μg), a simple capsule system and Serevent Accuhaler (SA, salmeterol 60 x 50μg) a multi-dose blister system, have been compared with the established self-metering reservoir DPI, Bricanyl Turbohaler (BTH, terbutaline sulphate 100 x 500μg). Single dose emission (ED) was determined for 3 DPIs from 3 batches per product at clinically pertinent flow rates. 10 dose sequences were similarly collected into the Astra-Draco 5-stage liquid impinger (5 SLI) to assess particle cloud quality in terms of fine particle deposition (FPD, Stages 3, 4, 5) and mass median aerodynamic diameter (MMAD). Each multi-dose DPI was sampled "through-life". Mean results, as percent label claim for ED & FPD are shown in the Table.

ED variation for FA & SA is similar and half that for BTH. Decreasing flow rate by 50% to values potentially achievable by children reduced ED for BTH to 63% but had little effect on FA (85%) or SA (88%). Particle cloud quality ranking was BTH>FA>SA. However the difference in FPD between BTH (41%) & FA (31%) is exaggerated by the 5 SLI cut values of 6.8 & 5.3μm at 60 & 100 L/min respectively.

DPI Flow Rate	FA 100 L/min	SA 80 L/min	BTH 60 L/min
ED±sd (%) (n)	84.5±9.6[1] (90)	93.1±10.1 (265)	75.8±19.0 (280)
FPD[2]±sd (%) (n)	30.9±4.3 (15)	21.4±1.9 (27)	40.6±8.1 (27)
MMAD±sd (μm)	3.6±0.1	3.9±0.2	2.9±0.2

[1]90 L/min: [2]FA≤5.3μm, SA≤5.8μm, BTH≤6.8μm

P190 COMPARISON OF THE EFFECT OF NON-CHLOROFLUORO-CARBON-CONTAINING (NON-CFC) SALBUTAMOL AND CONVENTIONAL CHLOROFLUOROCARBON (CFC) SALBUTAMOL IN ASTHMATIC CHILDREN

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In this study, 44 asthmatic children were randomly allocated to receive either Non-CFC salbutamol or CFC salbutamol. Recruited patients suffered from mild to moderate asthma, could reliably perform a spirometry and had a FEV1 <85% at the time of the study. FEV1 and vital capacity (VC) were performed before and 10 min after inhaling 200 μg Non-CFC salbutamol (Airomir®) (A) or 200 μg CFC salbutamol (Ventolin®) (V). Medication was administered using a randomised double-blinded design using a spacer device (Volumatic®, Glaxo). Mean age was 11.2 years (5.8-16.8) in group A and 10.6 years (5.4-17.6) in group V. At the start of the study VC (± SD) was 81.3% of predicted (±14.1) and 83.9% (±14.9) in resp group A and group V; FEV1 was 71.1% (±12.0) and 74.4% (±10.2) in resp group A and group V. Both parameters did not differ significantly. After inhalation of A, VC and FEV1 increased to resp 87.1 (±13.4) and 83.5% (±12.9). After inhalation of V, VC and FEV1 increased to resp 88.9% (±12.6) and 84.0% (±9.7). All changes of VC and FEV1 were significant in both groups and no differences were shown between group A and group V. We conclude that 200 μg Airomir® or Non-CFC salbutamol and 200 μg Ventolin® or CFC salbutamol have similar bronchodilating effects in asthmatic children.

P191 MODERATELY SEVERE ASTHMA CONTROLLED AT A SIGNIFICANTLY LOWER DOSE FROM A NEW CFC-FREE STEROID INHALER

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To improve airway delivery, a new hydrofluoroalkane (HFA) solution aerosol was developed featuring finer particles than current available products. Symptomatic asthmatics (n=233) taking 400 to 800 mcg beclomethasone dipropionate (CFC-BDP) were enrolled to assess asthma control at 800 mcg HFA-BDP compared with an increased dose of the conventional CFC-BDP formulation. All patients received a short course of oral steroids (30 mg daily for 7-14 days) to ensure steroid responsiveness [defined as ≥ 15% morning peak expiratory flow (AM PEF)]and to provide "optimal" baseline data. Patients were randomized to 12 weeks of treatment with 3 puffs 250 mcg CFC-BDP bid (n=117) or 4 puffs 100 mcg HFA-BDP bid (n=112) in a double-dummy design. Patients collected AM and PM PEF data daily.

Adjusted Mean ± SE for AM and PM PEF

Treatment†	Run-in	Oral steroid	Weeks 10-12
AM PEF			
HFA BDP 800 mcg	349.1 ± 7.4	423.0 ± 8.5	401.4 ± 9.5‡
CFC BDP 1500 mcg	344.9 ± 7.0	417.1 ± 8.0	395.1 ± 9.0
PM PEF			
HFA BDP 800 mcg	373.6 ± 7.9	426.3 ± 8.6	413.6 ± 9.6‡
CFC BDP 1500 mcg	376.0 ± 7.4	431.5 ± 8.1	409.4 ± 9.0

‡Adjusted mean change from oral steroid equivalent to CFC-BDP at $p<0.001$.

Over 12 weeks, 800 mcg of improved delivery HFA BDP and 1500 mcg of CFC BDP gave equivalent asthma control, in terms of AM and PM PEF.

P192 COMPARISON OF pMDI* PLUS NEBUHALER® AND TURBOHALER® IN ASTHMATIC PATIENTS WITH DYSPHONIA

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Seventy-two inhaled steroid dependent patients with chronic dysphonia entered a 12 week, open, parallel group comparison of budesonide pMDI + Nebuhaler® (N) and Turbohaler® (T). This study investigated fixed and equal doses of budesonide pMDI + Nebuhaler® and budesonide Turbohaler® (800-2400 ug) in an open design. 51 completed the study per protocol. N = 26 (21 female, mean age 57 [22 - 77], mean FEV_1 1.6 [0.2 - 3.4]L). T = 25 (18 female, mean age 58 [21 - 81], mean FEV_1 1.8 [0.5 - 5.0]L). A dysphonia diary card was completed weekly. Voice laboratory assessments and laryngoscopy were performed on entry and at 12 weeks.

T patients scored their voice status as better at 4 weeks ($p<0.02$), (T 40% v N 8% [$p<0.02$]) but there was no significant difference at 12 weeks (T 52% v N 23% [$p=0.08$]). There were no differences in voice laboratory and diary data between the two groups at 12 weeks. 13 (52%) of T and 12 (46%) of N had laryngoscopic evidence of disordered glottic closure at study entry and 14 (56%) T and 13 (50%) of N had visible abnormalities after 12 weeks. Glottic closure changed in 4 T and 5 N patients, but there was no correlation with voice symptoms.

The trend of symptomatic improvement of voice status in the T-group did not correlate with voice laboratory assessments and laryngoscopic evidence of disordered glottic closure. These methods appear to be of little value in the assessment of the asthmatic patient with chronic dysphonia.

(* = pressurised metered dose inhaler)

P193 PHARMACOKINETICS OF BECLOMETHASONE DIPROPIONATE FROM CFC-FREE ULTRAFINE AEROSOL AND CONVENTIONAL CFC INHALERS IN ASTHMATICS

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Reformulation of beclomethasone dipropionate (BDP) as a solution in the CFC-free propellant HFA-134a (HFA-BDP) has produced an MDI delivering BDP with a finer particle size distribution compared with CFC-BDP. Deposition studies demonstrate that more fine particles are delivered to the lungs, with less swallowed, which could affect absorption of BDP. A clinical study was performed to determine serum levels of the total amount of beclomethasone-derived material obtained by hydrolysis of the sample (TOTAL) following HFA-BDP and CFC-BDP. 23 mild asthmatics received BDP in a 3-period crossover. Serum samples were analyzed by mass spectrometry. The mass of the fine particles (<4.7 microns) was determined by the Andersen cascade impactor.

RESULTS:

Treatment	Fine Particle Mass (mcg)	Cmax (pg/mL)	AUC pgxh/mL)	Tmax (h)
HFA-BDP 200mcg	93	590	2339	0.6
HFA-BDP 400mcg	186	1191	4962	0.8
CFC-BDP 400mcg	102	410	2092	2

The rate and extent of absorption of TOTAL after HFA-BDP were significantly greater than after CFC-BDP. The two doses of HFA-BDP were proportional for Cmax and AUC. Pharmacokinetic results agreed with fine ("respirable") particle mass predictions.

CONCLUSIONS:
The absorption profile, due to improved delivery to the lung, demonstrates that HFA-BDP ultrafine aerosol achieves similar TOTAL serum levels with half the dose compared with current CFC-BDP. Therapeutic efficacy of HFA-BDP at half the dose of CFC-BDP is being compared in clinical studies.

P194 THE IN VITRO DEPOSITION OF LACTOSE CARRIER FROM DRY POWDER INHALER FORMULATIONS

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Many commercially available dry powder inhaler formulations comprise drug mixed with a diluent such as lactose in order to provide reproducible dose delivery. The particle size of lactose is usually 5-90 μm. The aim of the current studies was to determine the amount of lactose deposited in the lower stage of a twin stage impinger (TSI) as indicated respirable fraction. The dry powder inhaler formulations contained salbutamol sulphate 400 μg and lactose 27 mg (the same drug:diluent ratio as Ventolin Rotacaps®400 μg). Different size ranges of lactose were used to produce three formulations (Table). Particle distribution was determined by laser diffraction. Dry powder blends were filled into capsules and evaluated using the TSI operated at 60 L min^{-1} for 10 s. A commercially available dry powder device, the Cyclohaler®, was employed to deliver the formulation into the airstream. High performance liquid chromatography was employed as an analytical method which used a refractive index detector to analyse the lactose carrier. In the three formulations including Rotacaps®, lactose was found to penetrate to the lower stage. Lactose could not be detected when 63-90 μm powder was used (Table).

Table Lactose deposition from different formulations in the TSI

	Lactose deposition (SD) n=6			
Carrier Lactose	Formula 1 63-90 μm	Formula 2 Lactochem®	Formula 3 micronised	Formula 4 Rotacaps
upper stage (mg)	20.02 (1.00)	19.27 (1.62)	20.86 (1.25)	18.57 (0.89)
lower stage (μg)	not detected	992 (77)	3504 (187)	432 (44)

Increasing the amount of fine lactose in a powder blend is one possible strategy for improving the respirable fraction of the drug. This study shows that the amount of lactose likely to reach the lower respiratory tract also increases. Such powder may induce cough and wheezing and its implications for lactose intolerant individuals should be considered.

P195 IMPROVING THE DELIVERY EFFICIENCY OF DRY POWDER INHALERS (DPIs) BY ADDING FINE CARRIER PARTICLES TO POWDER FORMULATIONS

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Most DPIs can only deliver about 10% of the administered drug to the lower airways. The majority of DPIs consist of an inhaler device and powder formulation, the latter being composed of drug and carrier particles. The carrier, which is frequently lactose, is added to aid the flowability and dispersion of drug particles. A small amount of fine particles of magnesium stearate have been used to improve drug delivery of DPIs but this is not practical due to possible side effects of the ternary material. Thus, the present study investigated the possibility of employing fine particles of carrier to increase the delivery efficiency of DPIs.

Salbutamol sulphate (6.4 μm) was blended with fine (4.96 μm) and coarse (63-90 μm) lactose particles in a ratio of 1:67.5 in a Turbomixer following the mixing processes shown in Table. Fine lactose particles amounted to 6.0% of the coarse particles. Drug deposition was determined by a twin stage liquid impinger at a flow rate of 60 l min^{-1} through a Rotahaler®. Fine particle fraction (FPF), defined as the portion of drug particles collected in the lower stage of the impinger, was considered to be respirable. Addition of fine carrier particles to the powder formulation increased FPF of salbutamol sulphate (Table). Drug deposition was also affected by mixing process. Powder formulations prepared by first blending fine lactose with coarse lactose then mixing with the drug (Formulation d) produced a significantly higher (ANOVA; $p<0.05$) FPF of salbutamol sulphate than those of powders prepared by other procedures as used to prepare formulations b and c (Table).

Table Effects of lactose fine particles on FPF of salbutamol sulphate

	Formulations	FPF (mean ± sd, n=3)
a)	coarse lactose only	6.8 ± 1.0%
b)	drug + coarse lactose→ + fine lactose	9.1 ± 0.5%
c)	drug + fine lactose→ + coarse lactose	10.7 ± 0.6%
d)	coarse lactose + fine lactose → + drug	14.7 ± 1.1%

P196

WITHDRAWN

P197 THE NON-CFC SALBUTAMOL METERED DOSE INHALER PERFORMANCE WITH A SPACER DEVICE

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The first non-CFC, pressurised metered dose inhaler, (MDI), containing Salbutamol sulphate, (Airomir™) became available in U.K. during March 1995. Recently there was some interest in its performance in conjunction with a spacer device.[1] Therefore, we have carried out an in-vitro evaluation of the fine particle deposition of the delivered dose of drug from the Airomir™ Inhaler with and without the Aerochamber™ spacer device, using the USP Andersen Sampler and test method. The data were analysed for: (A) 'Respirable mass' (RM), µg/shot, the mass of sprayed drug particles less than 4.7 µm. (B) Mass median aerodynamic diameter, MMAD, (µm) of the sprayed dose. (C) Geometric standard deviation, (GSD), %. (D) Respirable fraction, % (RF) = RM/dose from adapter x 100. The data are tabulated below:-

Inhaler Batch No.	Without Spacer				With Spacer			
	RM (µg)	MMAD (µm)	GSD (%)	RF (%)	RM (µg)	MMAD (µm)	GSD (%)	RF (%)
14/94K01	46	2.4	1.5	48	50	2.5	1.5	52
17/94L02	45	2.3	1.5	48	51	2.4	1.5	53
7534	56	2.4	1.4	57	57	2.5	1.5	56

The data demonstrate that the spacer device has no significant effect on the fine particle fraction of drug delivered from the inhaler. Therefore, it is concluded that the Aerochamber spacer device may successfully be used with the Airomir Inhaler.

Reference (1)
"The use of the Chlorofluorocarbon Free Salbutamol Preparation, Airomir, with Different Spacer Devices." P.W. Barry and C. O'Callaghan; Thorax 1995: 50 (suppl.2), A78, P112.

P198 PEAK INSPIRATORY FLOW THROUGH TURBUHALER® IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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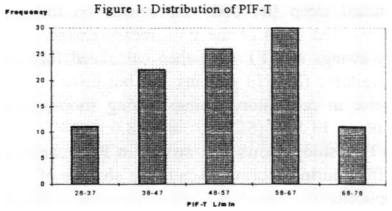
Many patients with chronic obstructive pulmonary disease (COPD) receive therapy by the inhaled route. This study was performed to assess whether patients with severe COPD could generate sufficient peak inspiratory flow (PIF) to operate Turbuhaler® effectively.

A hundred patients [45 male, 55 female, mean age 69.1 years] with COPD [mean (SD) duration 17.7 years (16.3)] and PEF ≤ 200 L/min or FEV_1 ≤ 1L were studied. A series of randomly assigned inspiratory and expiratory lung function tests were contiguously performed, using portable spirometers, within 48 hours of the screening visit. Patients did not receive any study medication and their normal medication was not restricted. Sixty-six were previous smokers, 8 occasional smokers, 19 habitual smokers and 7 had never smoked.

Mean (SD) FEV_1 was 0.7 (0.2)L and PEF was 182 (68)L/min. 37 patients were in hospital following an acute exacerbation. All patients were able to generate PIF through Turbuhaler® (PIF-T) of 28L/min. 83% generated PIF-T of 40L/min (mean 53; range 28-78L/min). The distribution of PIF-T is shown graphically in Figure 1. PIF-T correlated with PIF without Turbuhaler® (r = 0.35), PEF (r = 0.3), FEV1 (r = 0.2) and FVC (r = 0.23) although the relationships were too weak to be used to predict PIF-T.

The results suggest that patients with severely limited lung function caused by COPD can operate Turbuhaler® effectively.

Figure 1: Distribution of PIF-T



P199 TURBOHALER: OBJECTIVE ASSESSMENT OF PATIENT GENERATED FLOW

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Pulmonary drug deposition from the Turbohaler (TM) is determined by the patient generated flow, a velocity of greater than 60 l min-1 being considered to give optimum effect (Newman et al. Terbutaline sulphate Turbuhaler: Effect of inhaled flow rate on drug deposition and efficacy. Int J Pharmaceuticals 1991;74:209-213). Gray et al showed wide inter and intra observer variation with respect to assessment of patient generated flow when using an inhaler device. (Gray et al. Assessment of interrater and intrarater reliability in the evaluation of metered dose inhaler technique. Chest 1994 105;1994:710-714). A commercially available teaching device consisting of a flow meter / Turbohaler combination (Astra pharmaceuticals) which measures inspiratory flow through the Turbohaler has been incorporated into our routine inhaler assessment / education programme to assess patient flow generation. This device categorises inspiratory flow into four ranges < 30, 30-40, >40 < 60 > 60 $lmin^{-1}$. The results of 132 patient episodes are reported. In a subgroup of fifteen patients routinely using Turbohaler delivered drugs, the maximum recorded flow rates were < 30 $lmin^{-1}$ n=4 (27%), ≥30 - <40 $lmin^{-1}$ n=3 (20%), ≥40 - < 60 $lmin^{-1}$ n= 5 (33%), and ≥60 $lmin^{-1}$ n=3 (20%) respectively. Measurement of flow rate made in the 117 patients who were Turbohaler naive, after they had received appropriate training in it's use, were as follows: <30 $lmin^{-1}$ n= 28 (24%), ≥30 - <40 $lmin^{-1}$ n=32 (27%), ≥40 - <60 $lmin^{-1}$ n=45 (38%), ≥60 $lmin^{-1}$ n=12 (10%). These data show that a significant proportion of patients requiring inhaler therapy are not able to generate optimum flow through the turbohaler. The flow monitor provides a useful objective measure of patient ability to generate adequate flow especially as this device does not provide a satisfactory auditory cue as occurs with breath activated metered dose inhalers. We believe that the use of this device and other electronic devices eg Vitalograph aerosol inhalation monitor are essential in patient assessment and education, providing uniformity across units.

P200 RELATIONSHIP BETWEEN AUTONOMIC AROUSALS, EEG AROUSALS, RESPIRATORY EVENTS AND SUBJECTIVE SLEEPINESS IN PATIENTS UNDERGOING INVESTIGATION FOR OBSTRUCTIVE SLEEP APNOEA

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Daytime hypersomnolence is an important symptom of the sleep apnoea/hypopnoea syndrome and the most compelling reason for treatment. Measuring sleep fragmentation is thus critical in a respiratory sleep study. Sleep fragmentation can be estimated from respiratory events (apnoeas, hypopnoeas, dips in oxygen saturation), EEG arousals, and autonomic changes (heart rate and blood pressure rises). We have compared these different approaches in 40 patients having polysomnography for possible sleep apnoea, as well as their correlation with subjective sleepiness (Epworth Sleepiness Score, ESS). Respiratory signals were scored for apnoeas / hypopnoeas (AHI) and dips in arterial oxygen saturation of >4% (Dip rate); EEG was scored by the American Sleep Disorders Association criteria for 3 second arousals (ASDA); autonomic measures were heart rate rises of > 10 bpm (HR) and indirect blood pressure rises (pulse transit time, PTT, Clin Sci 1994;87:269). The number of events/hour was used to calculate the correlation between each of these and their correlation with ESS ($P < 0.05$ for all correlations displayed). Data analysis is not yet complete, $n > 21$ for all correlations.

	HR	ASDA	AHI	Dip rate	ESS
PTT	r = 0.87	r = 0.91	r = 0.72	r = 0.87	r = 0.38
HR		r = 0.73	r = 0.53	r = 0.80	
ASDA			r = 0.92	r = 0.92	r = 0.39
AHI				r = 0.88	
Dip rate					r = 0.49

Respiratory events, EEG arousals and autonomic arousals are closely correlated. Dip rate is the best predictor of ESS. PTT measured blood pressure rises may provide a useful automated alternative to manual scoring of EEG arousals as an index of sleep fragmentation.

P202 DETECTION OF CORTICAL EEG AROUSALS FROM A NEURAL NETWORK (NN) ANALYSIS

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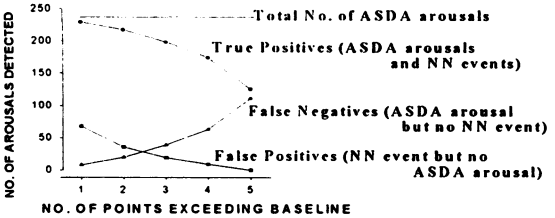
Traditionally EEG sleep fragmentation is scored according to simple arbitrary thresholds which ignore large amounts of EEG information. Computer based analyses may improve this situation. To begin assessing this approach we used a neural network system that provides a second by second output of sleep 'depth' (Questar, Oxford Medical, UK) to attempt to identify ASDA EEG arousals.

8 men with severe obstructive sleep apnoea were studied. EEG from 20 minutes of continuous OSA with obvious EEG arousal was analysed with the neural network system and then computer processed for arousal detection. By trial and error, we devised an algorithm looking for changes above a baseline. The baseline was defined as the second highest value of a 10 second moving rank filter against which we compared the next 5 one-second data points of EEG. Events were scored 5 times depending on whether 1, 2, 3, 4, or 5 of these points exceeded the baseline (X axis). We compared neural network events with ASDA arousals identifying events as true positive, false positive or false negative. ASDA EEG arousals were consensus scored by 2 scorers.



When 1 prospective observation exceeded the baseline our algorithm detected 229 of 237 (97%) ASDA arousals with 68 false positives. When 3 prospective points exceeded the filter threshold it detected 198 of 237(84%) ASDA arousals with 19 false positives.

Neural network EEG analysis can be post processed to detect some ASDA arousals. It also detects other events which may represent arousal from sleep not detected using the ASDA criteria.

P201 INTER-OBSERVER VARIABILITY IN THE ASSESSMENT OF EEG AROUSAL

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Chronic sleep deprivation leads to excessive daytime sleepiness and impaired performance. Recently, it has become apparent that recurrent sleep disruption can have equally serious consequences. However, traditional sleep assessment criteria have inadequate resolution to document reliably these transient disturbances or arousals. Accordingly, the American Sleep Disorders Association (ASDA) recently proposed detailed criteria to *specifically and reliably identify the occurrence of transient arousals.* The aim of this study was to investigate inter-observer variability in the assessment of EEG arousal.

Polysomnographic data were recorded from ten subjects being investigated for suspected obstructive sleep apnoea. From each, nine 40 s epochs were identified. Epochs were equally distributed by base sleep stage **i.** light (I/II), **ii.** deep (III/IV) and **iii.** REM, and as those which (by our judgement) **a.** contained EEG arousal, **b.** did not contain EEG arousal, and **c.** could not be readily categorised.

The order of the 90 epochs was randomised. Copies were distributed to 20 expert observers who assessed each epoch for arousal according to the ASDA guidelines, indicating the arousal duration where appropriate. Agreement was quantified using the Kappa (κ) statistic.

To date, results have been collated from 11 centres. For 40 epochs, the consensus (6+ observers) rated the epoch 'arousal', for 50 epochs, 'no arousal'. Good agreement (9+ observers concur) was reached for 58 epochs, with moderate overall agreement ($\kappa = 0.47$). Degree of agreement was not related to arousal duration, but was dependent on base sleep stage ($p < 0.05$), being best for deep sleep ($\kappa = 0.59$), moderate for REM ($\kappa = 0.50$) and poor for light sleep ($\kappa = 0.30$).

We conclude that variability exists in the interpretation of the ASDA criteria, particularly for arousals occurring during light sleep.

P203 EFFECT OF SNORING ON RESPIRATORY EFFORT MEASURED INDIRECTLY BY BEAT TO BEAT BLOOD PRESSURE

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The size of the respiratory swings in blood pressure (pulsus paradoxus) correlate well with the degree of inspiratory effort measured with an oesophageal balloon. To take advantage of this phenomenon to estimate changes in inspiratory effort requires a measure of beat to beat blood pressure. In a respiratory sleep study to identify obstructive sleep apnoea (OSA) and its variants, such measurements are useful to indicate increased inspiratory effort following upper airway narrowing. Our unit has shown that two non-invasive devices, the photoplethysmographic volume clamp (Finapres, Ohmeda) and pulse transit time (RM50, Parametric Recorders) can provide this information. Pulse transit time (PTT) measures BP indirectly because the pulse wave propagation time (eg from heart to finger) is inversely related to arterial wall tension, which in turn depends on blood pressure. This report on snorers, taking part in another study on oral appliances, was done to verify that indirect measurements of PTT could detect the increases in inspiratory effort that usually accompany snoring. In 14 snorers (with no evidence of significant OSA on their diagnostic study) snoring (using a throat microphone), posture, oxygen saturation, thoracic excursions, and indirect blood pressure (PTT) were measured during overnight studies at home. Where available, paired ten minute periods each of continuous regular snoring, and of no snoring, were selected when there was no evidence of accompanying apnoeas, desaturations or hypopnoeas. These periods were during assumed sleep (no body movements on the thoracic excursion tracings) and selected blind of the PTT measurements. The mean size of the respiratory swings in PTT were then calculated for each of the 18 paired data sets available from 13 patients. All but three of the paired data sets showed a rise in respiratory swings during snoring periods, with the means swings being 13.5ms (SD10.5) and 18.6 (SD8.7) silence and snoring respectively. This study shows that swings in PTT can detect the increased inspiratory effort during snoring, even in the absence of any associated apnoeas and hypopnoeas.

P204 DEVELOPMENT OF A VALIDATED SNORING QUESTIONNAIRE: REPEATABILITY OF QUESTIONS

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Background A properly validated questionnaire of snoring would be useful in the clinical evaluation of patients and for epidemiological studies. **Aims** To determine the repeatability of questions in a new snoring questionnaire consisting of a patient and a partner version. **Methods** Questions were selected following interviews with patients, their partners and interested medical and nursing staff. Patient and partner questionnaires containing 39 and 55 questions respectively, covering "severity", "impact" and "description" were developed. 100 patients presenting to a Sleep Clinic with snoring or suspected obstructive sleep apnoea were asked to participate in the study. Each couple was asked to fill in their questionnaires independently and return them by post. Two weeks after the return of these questionnaires a second set was sent. 3 months was given to return the second questionnaires. Repeatability was assessed using the kappa statistic - a measure of agreement. A kappa < 0.4 indicates only "fair" agreement (DG Altman 1991 Practical Statistics for Medical Research) and such questions were deemed poorly repeatable. **Results** The response rate for the first questionnaire was 77% for patient and partner and 79% (n=56) and 80% (n=57) respectively for the second. Patient kappa values had a mean of 0.58 (95% CL+/-0.05) and 4/39 (10%) questions were poorly repeatable. Partner kappa values had a mean of 0.55 (95%CL+/-0.05) and 8/55 (15%) questions were poorly repeatable. Poorly repeatable questions included 'How likely are you to fall asleep during the day?' and 'How often does your partner stop breathing during sleep?'. **Conclusion** Patients and their partners can repeatably answer questions about snoring. However a small proportion of questions were poorly repeatable and these included some which are often asked in routine clinical practice.

P205 COMPARISON OF A BEHAVIOURAL TEST TO ASSESS DAYTIME SLEEPINESS WITH THE TRADITIONAL MWT.

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Standard objective tests of daytime sleepiness include the MSLT and maintenance of wakefulness test (MWT). These require continual EEG monitoring and are cumbersome and expensive. We have devised a simple test of 'wakefulness' based on a behavioural response to an intermittently illuminating light emitting diode (LED). This study reports this tests ability to discriminate subjects with severe symptomatic OSA from normals and compares this result with the traditional EEG based MWT.

10 subjects (7M 3F) with severe OSA (>4% SaO_2 dip rate 33.5 (SD 19.7)) and symptoms of daytime sleepiness (Epworth Sleepiness Score (ESS)17 (5.1)) and 10 normal subjects (4M 6F, ESS 4.4(2.5)) were studied. The EEG MWT and the behavioural LED test were performed on each subject in random order on 2 separate days. Both tests included 4x40 minute sleep resistance challenges at 2 hourly intervals. Tests were performed under the same conditions while sound isolated in a darkened room. During the behavioural test, instead of EEG monitoring, subjects were asked to press a switch in response to a LED regularly illuminating for 1 second in 3. When there was no response for 21 seconds the test was terminated.

Both tests effectively discriminated the normals from the sleepy OSA subjects. The mean sleep latency during the behavioural test was longer than for the EEG MWT and this difference was significant in the OSA group but not in the normal group (see below). Retrospective analysis showed there was no difference in these results if sleep onset was defined as no response for 15 seconds instead of 21.

	Mean Sleep latency in minutes (SD)		*Difference between EEG MWT and behavioural test*	
	EEG MWT	*LED test*	*Mean(SD)*	*Paired t test*
Normal subjects	38.1 (2.8)	39.8 (0.6)	1.7 (3.0)	$p > 0.1$
OSA patients	7.3 (3.7)	10.5 (3.9)	3.2 (4.2)	$p < 0.05$

The behavioural test discriminated normal subjects from sleepy patients as well as the MWT and was simpler to administer. It has the advantage that sleep onset is defined objectively as a failure to respond rather than from subjective EEG interpretation. This technique may provide a simple method of objectively quantifying daytime sleepiness.

P206 REFERRAL SOURCES AND OUTCOMES FROM 1 YEARS HOME OXIMETRY STUDIES IN PATIENTS WITH SUSPECTED SLEEP APNOEA (OSA)

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We have analysed referral sources and outcomes for referrals for home oximetry (Minolta Pulsox-5) between 1st April, 1995 and 31st March, 1996. The Desaturation Index (DI) was obtained from the Aequitron SleepLab as the number of 4% hypoxic dips/hour. Data are mean (range).
Group: 176 patients (142 Male) were included. Age was 47.7 (8 - 75) yr, DI 12.4 (0 - 84.3) hr^{-1}, Body Mass Index 28.8 (14.6 - 48.1) $kg.m^{-2}$ and Epworth score 10.5 (0 - 24).
Referral Sources: Patients were referred directly from GP's (31%), ENT surgeons (57%) and other sources including tertiary referrals (12%).
Outcomes: These are shown in the table. Most patients in group 1 had an Epworth > 10 (17/24) and a DI < 10 hr^{-1} (23/24). There was no significant difference between groups 1 and 2 in the Epworth scores, but both groups had significantly higher values than groups 3 and 4 ($p < 0.05$).

	n	DI	Epworth
1. Polysomnography	24	3.2 (0 - 16.2)	11.0 (2 - 21)
2. CPAP Trial	55	27.9 (0.6 - 84.3)	12.2 (0 - 24)
3. Palatal Surgery	39	3.4 (0 - 12.3)	8.7 (1 - 20)
4. Other Action	58	7.3 (0 - 73.0)	9.2 (1 - 21)

Group 4 included patients who were discharged with no further action (60%), who were advised to loose weight loss (21%) or whose outcome is unknown. There was no significant difference ($X^2 = 7.6$) between the number of patients referred by GPs and ENT surgeons, who had polysomnography (8:10), a CPAP trial (23:29), palatal surgery (7:32) or other action (17:30).
Conclusion: We conclude that one in seven patients (14%) required full polysomnography, whilst about half (55%) required no further action by the sleep unit. The high percentage of referrals from the ENT surgeons reflects the close links established between the two groups, including a monthly joint outpatient clinic.

P207 AUTOMATIC NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE TITRATION IN THE LABORATORY, PATIENT OUTCOMES

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Manual titration of nasal continuous positive airway pressure (NCPAP) treatment for obstructive sleep apnoea (OSA) is time consuming and expensive. There are now 'intelligent' NCPAP machines that try to find the ideal pressure for a patient by monitoring some combination of apnoeas, hypopnoeas, inspiratory flow limitation and snoring. Although these machines usually find similar pressures to skilled technicians, it is not clear if their use in the sleep laboratory influences subsequent acceptance by patients. 122 patients with OSA undergoing a trial of NCPAP were randomly allocated to either manual or automatic (Horizon, DeVilbiss) titration of pressure during their first night on NCPAP in a hospital sleep laboratory. The primary outcome (available on 112 patients) was the acceptance of NCPAP or otherwise, six weeks following the initial titration night. Baseline indicators of severity were compared in the groups, as were the pressures selected and the patients' subsequent improvement in sleepiness. Initial OSA severity was not significantly different in the two groups. The mean NCPAP pressures (cmH_2O) in the two groups were similar (manual 8.7 SD2.5, automatic 8.2 SD2.1). The % of patients successfully established on CPAP at six weeks was 64% and 73% for the manual and automatic groups respectively: 13% versus 2% had given up completely (manual and automatic respectively, $P<0.05$) and there were about equal numbers (23% versus 25%) in each group who were still undecided. The improvement in the Epworth sleepiness score was similar in the two groups. The substitution of automatic NCPAP titration instead of a manual titration during the first night of NCPAP in patients with OSA does not reduce the numbers accepting the treatment at six weeks, and may slightly improve it. This has important cost saving potential.

P208 DO CPAP TITRATION STUDIES PREDICT SUBSEQUENT CPAP USAGE OR EFFECTIVENESS?

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In overnight CPAP titration studies, we attempt to minimise the frequency of apnoeas, hypopnoeas and EEG arousals by adjustment of the CPAP pressure. However, our clinical impression is that there is little relation between our ability to abolish completely these events and the patient's subsequent progress on CPAP.

We have, therefore, examined the relationship between the frequency of these events at optimal CPAP pressure during the CPAP titration study and a range of measures of CPAP effectiveness. We studied 105 patients representative of our clinic population who use CPAP therapy for the Sleep Apnoea/Hypopnoea Syndrome. The correlations (Spearmans rank correlation coefficients, *r*) were:-

	Apnoeas+Hypopnoeas per hour on CPAP	EEG arousals per hour on CPAP
Objective CPAP usage (hours per night)	$r = -0.02$ NS	$r = 0.09$ NS
Epworth Sleepiness Score (ESS) on CPAP therapy	$r = -0.04$ NS	$r = 0.03$ NS
Change in ESS since starting CPAP therapy	$r = -0.02$ NS	$r = 0.17$ NS
No. of changes in CPAP pressure since titration study	$r = -0.01$ NS	$r = 0.02$ NS

We have also reviewed the CPAP titration studies of 50 randomly selected patients who have discontinued CPAP therapy. There is no significant difference between the results of their CPAP trials and those of patients continuing CPAP (Apnoeas+hypopnoeas/hour 7.8 vs 7.9, EEG arousals/ hour 19.4 vs 19.6).

This study demonstrates no relationship beween patient outcome and apnoea/hypopnoea or arousal frequencies on CPAP titration studies, and indicates that patients with continued abnormality on CPAP titration can do well on CPAP without further intervention.

P209 RESPONSE OF BED-PARTNERS AND PATIENTS TO NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NCPAP) FOR OBSTRUCTIVE SLEEP APNOEA (OSA)

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NCPAP is highly effective in treating OSA but its impact on the bed-partners of patients has been poorly documented. We assessed the impact of NCPAP on sleep quality and daytime symptoms in bed-partners and patients with established OSA by a questionnaire study. Ninety one patients who were between 2 and 12 months of commencing NCPAP therapy were included, and 85 replies (93% of sample population) were received. 71 patients continued to use NCPAP and formed the study population. These were divided into "responders" and "non-responders" according to the patient's replies. Forty five responders and 10 non-responders had bed-partners. Bed-partners answered a questionnaire assessing improvements in sleep quality, daytime alertness, mood and quality of life, for themselves (Q1-4) and for the patient (Q5-8). Possible scores ranged from -1 to +3. Results are listed in the table. The data demonstrate that only bed-partners of responders experience significant subjective benefits from NCPAP therapy to the patient. However, bed-partners in both groups note improvements in patient symptoms with NCPAP.

	Responders			Non-Responders			
	n=45 median	Lower Quartile	Upper Quartile	n=10 median	Lower Quartile	Upper Quartile	p
Q1	3	2	3	0	-1	1	<0.0005
Q2	1	0	2	0	0	0.5	<0.05
Q3	2	0	2	0	0	1	<0.05
Q4	2	1	3	1	0	1.5	<0.05
Q5	3	2	3	2	0	3	<0.01
Q6	3	2	3	2	1	2	<0.005
Q7	2	1	3	2	0	2	n.s.
Q8	3	2	3	2	1	2	<0.01

P210 DENTAL IMPLICATIONS OF OBSTRUCTIVE SLEEP APNOEA (OSA)

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This paper emphasises the importance of dental expertise as part of the team approach to diagnosis and treatment of OSA. Mandibular advancement splints (MAS) may be a therapeutic option but few guidelines exist to indicate who may benefit and which type of appliance may be most effective.

Cephalometric radiography has revealed that the entire facial complex is retrusive and the mandibular body is 5.9 mms shorter ($p=0.002$) when compared with normal controls. Narrowest oropharyngeal dimensions are reduced (post-palatal by 3.9 mm and post-lingual by 1.5 mms). The cross-sectional area of the soft palate is 20% greater whilst the space available for the tongue is reduced by 10% (Battagel and L'Estrange 1996).

The patterns of adaptive behaviour of oral and oropharyngeal structures in response to mandibular advancement can be revealed by fluoroscopy (L'Estrange at al 1996). A comparison with predictions from cephalograms has suggested that a single film may predict those subjects likely to respond positively to mandibular advancement splints. Favourable features include a small lower facial height, a normal position of the lower jaw, a high position of hyoid and only moderate oropharyngeal airway restriction.

Fluoroscopy emphasises the need to minimise the degree of jaw opening associated with mandibular advancement in order to secure maximum airway enhancement.

The extent to which the jaw may be advanced comfortably in the first instance is restricted by patient tolerance, the capsule of the mandibular joint and associated musculature. The provision of incremental advancement with associated soft tissue adaptation permits an optimal result for each individual.

P211 HLA-TYPING IN PATIENTS WITH SLEEP APNOEA-HYPOPNOEA SYNDROME

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Background: Yoshizawa et al have described a significant increase in HLA-A2 and HLA-B39 antigens in patients with sleep apnoea-hypopnoea syndrome (SAHS) compared with normal controls and the Japanese population (*Internal Medicine* 1993;32:94-97) suggesting genetic predisposition and linkage. Mathur and Douglas have shown a strong familial component of SAHS in a case control study of 51 first degree relatives of thin patients with SAHS which may relate to differences in facial structure (*Ann Intern Med* 1995;122:174-178).

Aim: To determine whether HLA-linkage is important in the genetics of SAHS.

Methods: HLA-typing (A,B and DR antigens) was performed in a) 39 unrelated patients (all male, mean age 54.5 years) with SAHS (mean apnoea/hyponoea index (AHI) 40.8) and b) 9 index patients (all male, mean age 58 years, mean AHI 53.2) with SAHS and 20 of their first degree relatives (9 male, 8 with AHI >15 on polysomnography) and the results of both groups were compared with those from a previously published regional control group of 264 healthy adults (*Tissue Antigens* 1987;29:115-119). We chose patients with SAHS with BMIs <30 kg/m^2 to avoid studying genetic markers of obesity. Statistical analysis was by χ^2 test as adapted by Haldane and the p values were corrected for the number of antigens tested (26) using the Bonferoni inequality method.

Results: There was no significant increase or decrease in any of the 26 HLA-A,B and DR antigens tested in either group compared with the control group.

Conclusions: 1. Our study does not confirm an HLA haplotype association with SAHS as suggested in a paper from Japan. 2. The familial tendency of SAHS described by Mathur and Douglas is not HLA linked and further investigations into the genetics of SAHS are required.

P212 THE EFFECT OF REGRESSION DILUTION BIAS ON THE NOCTURNAL HYPOXAEMIA V BLOOD PRESSURE RELATIONSHIP

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Nocturnal hypoxaemia is inaccurately assessed by one night's sleep study which will artifactually reduce its relationship with blood pressure through regression dilution bias. This study aims to quantify this effect.

Two data sets were analysed. 893 normal men aged 35-60, studied during a survey of OSA and mean blood pressure (MBP) (BMJ:1990:300:75) and 204 subjects (162M, 42F, Age 49SD10.8, >4%SaO_2 diprate 14SD20.3) referred with possible sleep apnoea to centre 2. The normal subjects received one night of arterial pulse oximetry (Biox 3700) at home, and the sleep clinic group two nights (Pulsox 5). The severity of nocturnal hypoxaemia was quantified as the number of >4% falls in SaO_2 per recording hour (>4% diprate).

To describe how regression to the mean affects nocturnal hypoxaemia, the $\log_{10}$>4% diprate on the first night's oximetry in the 204 sleep clinic patients was sorted into ascending order and divided into 12, 0.25 range cells with the first two cells collapsed. For the resulting 11 cells, the difference between the average $\log_{10}$>4% diprates on the first and second nights was calculated. Above $\log_{10}$>4% diprate of 1.2 (=16hr^{-1}) regression to the mean is minor as nocturnal hypoxaemia is reproducible. Below this threshold regression to the mean changes in an approximately linear way:

diff $\log_{10}$diprate = -0.29 x mean first night $\log_{10}$diprate +0.12(r^2=0.81)

Since only 4 of the 893 (<0.5%) normal subjects had a >4% diprate >16 hr^{-1} this equation was used to correct the normal data for regression dilution bias. These 893 subjects were sorted into ascending $\log_{10}$>4% diprate and grouped into 9, 0.20 range cells with the first two cells collapsed. The cell average MBP was plotted against the cell average $\log_{10}$>4% diprate and the corrected cell average $\log_{10}$>4% diprate and their linear relationships described:

MBP = 5.4 x $\log_{10}$>4%diprate+103.6 (r^2=0.75)

MBP = 7.0 x corrected $\log_{10}$>4%diprate+102.8 (r^2=0.83)

Correction for regression dilution bias strengthens the relationship between MBP and nocturnal hypoxaemia severity. This previously unconsidered effect may have distorted apparent relationships between OSA, MBP and obesity in community studies.

P213 AUDIT OF A SLEEP STUDY SERVICE 1993-1995

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A sleep study service was established without Health Authority funding in late 1993. During 1993-1995, 94 sleep studies, on the indication of snoring, were performed. Patients were evaluated after an over-night stay. OSAS was defined as apnoea index >5.

Thirty-five patients (37%) had OSAS (29 men and 6 women) and 59 were simple snorers (non-OSAS). In the OSAS group mean age for men was 53 years (33-74) and for women 60 years (26-70) . In the non-OSAS group the mean ages were 49 for men (26-75) and 48 (35-65) for women. In the OSAS group 77% had an increased BMI and 40% were on treatment for hypertension. In the non-OSAS group 44% were overweight and 15% had anti-hypertensive treatment.

Surgical treatment with UPPP (uvulopalatopharyngoplasty) on its own (5) or before (4) or after CPAP (1) was given to 10 patients in the OSAS group. CPAP was given to 12 patients. Thirteen patients had no treatment; 4 were awaiting treatment and 3 declined CPAP. In the non-OSAS group 13 patients had UPPP and 4 had CPAP. 42 patients had no treatment; two patients were awaiting UPPP and 5 were offered surgery but refused.

A questionnaire was sent to all patients to evaluate their subjective effects of treatment. 87% of the patients replied. Before treatment most patients with OSAS complained of snoring , daytime sleepiness and morning tiredness which resulted in a marked improvement after CPAP in 60% , while surgery alone had a less marked effect on the symptoms. Most patients treated with CPAP were very satisfied whilst the rating by the surgical patients was more diversified with some even being very dissatisfied. In the non-OSAS group surgery was very effective with a moderate to marked improvement of all pre-treatment symptoms, all patients being quite to very satisfied with the received treatment.

Demand for sleep studies have increased exponentially with 120 patients on the waiting list but funding remains extremely limited. Proper evaluation of patients will prevent unnecessary surgery and ultimately save resources.

We conclude that the patients with OSAS were overweight (77%) and hypertensive (40%) and seemed to benefit more from CPAP than from surgery while the non-OSAS group had a greater benefit from surgery.

P214 A SURVEY OF SLEEP SERVICE PROVISION IN NORTH THAMES REGION, UK

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Following the Royal College of Physicians recommendations (1993) a postal questionnaire survey of the current sleep service provision in North Thames region was undertaken. 31 of 34 hospitals replied, serving >8.3 million population with average district size of 287,000. 21 provide an in-house service (mean 176 studies/hospital/year) while 14 (9 not providing in-house service) referred a total of 170 patients annually to another hospital. 8 had sleep nurses (night service in 4), 8 had sleep technicians and 10 had electronics technicians. 17 had at least 1 bedroom (soundproofed in 3) while 4 performed studies on open wards. 7 classified themselves as Specialist Respiratory Sleep Centres (SRSC) and 14 District General Hospital (DGH) level providers. Overall 30% of all studies were overnight oximetries (annual total 1569, median per hospital 70), 56% limited studies (annual total 2831, median per hospital 125) and 14% polysomnographies (annual total 695, median per hospital 60). At the SRSC level, 15% of all studies were oximetries, 66% limited studies and 19% polysomnographies. At the DGH level 72% were oximetries and 28% limited sleep studies. 13 had CPAP titration facilities (automatic in 9). There were multiple sources of funding for running costs.

The population of North Thames has access to sleep services and the number of studies exceeds recommendations for the population. However, many centres perform overnight oximetry alone and few have the recommended level of support in terms of facilities or staff. The number of SRSC is higher than recommended. However some provide a tertiary referral service outside North Thames. There is no consistent purchasing policy. A review of services with identified funding would help to ensure adequate provision for the population.

Ref. A report of a working party of the Royal College of Physicians. Sleep apnoea and related conditions: with recommendations for service provision, October 1993.

P215 QUALITY OF SLEEP DURING NIPPV: A COMPARISON BETWEEN THE MONNAL D AND THE PAPWORTH VENTILATOR

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While patients often report improved sleep quality after starting NIPPV there are few objective data and none comparing a volume preset ventilator (VPV) with a pressure preset ventilator (PPV). Subjects routinely admitted to our unit, who were stable using the Monnal D (MDV. Taema, Paris) a VPV, without additional oxygen, underwent 2 polysomnographic studies, one on their own ventilator and one on the Papworth ventilator (PWV. Si Plan, Stratford upon Avon) a new PPV for home NIPPV. The order of the studies was alternated for consecutive subjects.

Ten subjects (6 men) with a mean age of 56 (SD 16.4) years and a mean duration of NIPPV treatment of 36 (18.9) months were studied. Six had a scoliosis (secondary to poliomyelitis in 3), 3 COPD, 3 a thoracoplasty and one had a traumatic brain stem injury. The mean arterial oxygen saturation (SaO2) during sleep using the MDV was 90.1 (4.44) %. The total sleep time was 338 (100.6) minutes and sleep efficiency was reduced at 78.3 (12.90) %. None of the subjects had completely normal proportions of all sleep stages. The mean percentages of light, REM and slow wave sleep (SWS) were 50.4 (13.17) %, 12.5 (6.09) % and 15.5 (12.24) % respectively. The mean number of arousals was 66 (39.3) per night and the arousal index (per hour of sleep) was 11.8 (6.64). When using the PWV the mean SaO2 was very similar at 90.3 (3.59) %. The total sleep time, sleep efficiency, proportion of REM and slow wave sleep were all greater on the PWV and the proportion of light sleep was less but none of these differences was significant. The number of arousals and the arousal index were both significantly reduced with mean differences of 27 ($p = 0.007$) and 5.1 ($p = 0.004$) respectively. The expected proportion of SWS was about 7% but when using either ventilator 2 subjects had no SWS and in 5 subjects the proportion of SWS was in excess of 20%.

These results show that sleep remains abnormal on NIPPV and this is particularly striking for the proportion of SWS. Despite similar overall levels of ventilation and sleep architecture there were important differences in the frequency of arousals from sleep between the two ventilators. Further studies to determine the underlying mechanisms and the effects on daytime alertness and quality of life are indicated.

P216 CELL COUNTS IN SPONTANEOUS SPUTUM DURING EXACERBATIONS OF ASTHMA AND COPD

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Asthma (As) and COPD are distinct diseases but overlap is a common clinical problem. Previous studies of bronchial histology have distinguished patients with stable asthma (As) from those with COPD but differences are less clear during exacerbations. Histological changes are mirrored by findings in induced sputum and BAL samples. We have assessed differential cell counts in spontaneous sputum (SS) expectorated during exacerbations of As and COPD.
25 patients (14 male) attending Hammersmith Hospital with moderate/severe acute exacerbations of airway disease (26 events) produced an adequate sample of SS within 48 h of presentation. They were classified by history, peak flow (PF) records and bronchodilator response into one of 3 groups: 10 asthmatics (A), mean age (range) 43 (18-79) yr; 9 with COPD, mean age (range) 66 (45-87) yr; and 7 with mixed clinical features (AC), mean age (range) 71 (64-78) yr. All patients in groups COPD and AC were ex- or current smokers (mean pack-years 45 and 32 respectively) as were 3 in A (group mean 1 pack-year). Only 2, both in AC, had bacteriologically confirmed infections. SS was fixed in formalin, embedded in paraffin wax and stained using chromotrope 2R. One investigator, blinded to clinical diagnosis, counted 200 cells per sample to provide differential counts (mean % ±SD).

	macrophages	neutrophils	eosinophils	lymphocytes
A	16.8 (±11.1)	50.1 (±32.4)	32.8 (±37.6)	1.3 (±1.4)
AC	21.1 (±9.7)	76.3 (±11.0)	4.6 (±4.0)	1.4 (±1.4)
COPD	15.6 (±9.8)	73.8 (±24.7)	7.2 (±16.6)	0.9 (±1.3)

Severity of exacerbations was assessed (mean PF l/min [% predicted]: A 158 [42%], AC 162 [40%], COPD 177 [39%]). COPD patients had significantly more neutrophils ($p<0.05$ by Mann-Whitney U) than A but not AC, despite the infrequency of bacterial infection. Asthmatics as a group had more eosinophils ($p<0.05$) with 4 having prominent eosinophilia and 6 prominent neutrophilia. AC did not significantly differ from COPD. We conclude that sputum examination may be potentially useful in patients with exacerbations of airway disease but did not aid diagnostic classification of individuals in this initial study.

P218 INDUCED SPUTUM PROFILES IN ASTHMA OF DIFFERING SEVERITY

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Inflammatory cells and cytokines in induced sputum may differ between asthmatics of differing severity and on different anti-asthmatic treatments. To investigate this, we compared the cellular profile and TNFα concentration in induced sputum obtained by 3.5% saline inhalation from 3 different groups of asthmatic patients : well controlled (FEV_1>80%pred) with β_2-agonist alone, well controlled with inhaled steroids and poorly controlled (FEV_1<80%pred) with or without oral steroid ; with normal controls. 16 subjects were included in each group.

Eosinophils(%) in induced sputum were significantly higher in each group of asthmatic patients compared with normal (4.8 ± 1.0, 2.4 ± 0.9, 10.1 ± 2.6, 0.4 ± 0.2 % in well controlled asthmatics with β_2-agonist alone, well controlled with inhaled steroids, poorly controlled asthmatics and normal controls, respectively, $p < 0.05$). Between the different asthma groups, eosinophils(%) were higher in asthmatics who were well controlled with β_2-agonist alone and those whose asthma were poorly controlled compared with well controlled asthmatics using inhaled steroids. TNFα (pg/ml of sputum) was significantly higher in asthmatics who were well controlled with β_2-agonist alone (118 ± 28) and poorly controlled asthmatics (135 ± 26) compared with normal (39 ± 12) ($p < 0.01$). TNFα was also higher in asthmatics who were well controlled with inhaled steroids (95 ± 15) but not significantly different from normals .

We conclude that asthma severity measured by FEV_1(%pred) and glucocorticoid treatment influence the percentage of eosinophils and the amount of TNFα in induced sputum.

P217 REPRODUCIBILITY OF INDUCED SPUTUM CELL COUNTS AND FLUID PHASE ECP

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Induced sputum examination is a non-invasive method to directly study airway inflammation. The aim of this study was to determine the reproducibility of sputum cell counts and fluid phase ECP concentration and to compare the counts and ECP in asthmatics (A) with those in subjects with seasonal allergic rhinitis (AR) and normals (N). 49 stable A mean age ±SD 39±17 y, mean FEV_1 96±19 % predicted, 15 AR (outside the pollen season) mean age 34±12, FEV_1 112±14, and 20 N, mean age 37±12, FEV_1 113±14 were studied. Subjects inhaled hypertonic saline (4.5%) for increasing time periods (1-16 min) on 2 occasions separated by 1 week. Sputum analysis was performed as described by Popov T et al (Clin Exp Allergy 1994; 24: 778-783). The solution was centrifuged and supernatant was stored at -70°C for later ECP assay. The pellet was resuspended for total and differential cell counts. The reproducibility of cell counts was determined using the coefficient of reliability (R) on 2 occasions separated by 1 week (Rb), between 2 portions of the same plug (Rw) and between 2 examiners (Re). Sputum cell counts and ECP from A, AR and N were compared using Mann Whitney U testing, $p<0.05$ being considered significant.

	Rb	Rw	Re	
TCC	0.44	0.92	—	
Mac	0.64	0.87	0.97	
Neu	0.65	0.87	0.98	For all subjects
Eos	0.83	0.98	0.99	(n=84)
Lym	0.47	0.76	0.90	
Ep	0.53	0.83	0.94	
ECP	0.70	0.93	—	

A significant difference between groups was found for eosinophils (A 12.7±12.3%; AR 1.0±0.3; N 0.4±0.7) and for ECP (A 212±124 mg/l; AR 37±38; N 24±30). The results illustrate that induced sputum differential counts of macrophages, neutrophils and eosinophils and fluid phase ECP are reproducible and that asthmatics have higher % eosinophil counts and ECP levels in induced sputum compared with allergic rhinitics and normal subjects.

P219 BLOOD AND SPUTUM SOL INFLAMMATORY MARKERS

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The inflammatory response to pulmonary sepsis in cystic fibrosis (CF) is usually determined in the circulation or airways compartments. Circulating C-reactive protein (CRP) and neutrophil elastase-α_1-antiproteinase complex (NEAPC) concentrations are raised in respiratory exacerbations and fall after antibiotic treatment. Sputum may give a better index of inflammatory activity, though it contains host and bacterial products. We compared the concentration of inflammatory markers in sputum sol and blood. Sputum sol neutrophil elastase (NE) was measured by double antibody ELISA able to detect free NE and NEAPC. Plasma NEAPC was determined by ELISA. IL-6 and TNFα were measured by high sensitivity ELISA (R&D Systems Europe). Dilutions of sputum were linear in all assays, and 'spiking' with standards gave 98% recovery. Concentrations were consistently greater /g sputum than in plasma or serum; IL-6(x9), TNFα(x64), NE(x2500). Sputum TNFα correlated with circulating levels r=-0.708; p=0.0005. In 20 patients not in exacerbation sputum sol IL-6 and NE related differently to FEV1: r=+0.661;p=0.002 and r=-0.582;p=0.006 respectively. After antibiotic treatment of a respiratory exacerbation in 10 patients the change in sputum NE and sputum IL6 was inversely related (r=-0.683;p=0.05). Mean NE (/g protein) fell from 18.8 to 10.1mg, and IL-6 increased from 5.8 to 13.7pg. Circulating levels of NEAPC and IL-6 both fell in the same patients. It is unclear which compartment best reflects inflammatory activity in the lung. However, NE and NEAPC were both reduced after antibiotic treatment, indicating a similar signal from both compartments for neutrophil activity.
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P220 SPUTUM LEUKOTRIENE B4 DURING INFECTIVE EXACERBATIONS OF CHRONIC BRONCHITIS

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Neutrophil mediated damage of the airways is believed to be important in the pathogenesis of several chronic lung diseases including chronic bronchitis (CB) and emphysema. Leukotriene B4 (LTB4) is a potent chemokine which is released by neutrophils, and may thus augment neutrophil recruitment to, and activation of these cells in the airway. We have investigated the role of LTB4 in CB by measuring its concentration in sputum and comparing this with sputum myeloperoxidase (MPO) during the course of an infective exacerbation treatment with antibiotics. Samples from six patients were taken at the start of treatment, day 3, day 5, end of treatment and a further sample at clinical stability. Sol phase was obtained and LTB4 was measured by ELISA and myeloperoxidase by chromogenic assay. Results are summarised in the table.

	Day 1	Day 3	Day 5	Day 14	Stable
LTB4 (nM) mean (SE)	63.8 (19.7)	24.6 (16.8)	9.8 (4.1)	4.5 (1.9)	14.5 (6.8
MPO (units) mean (SE)	2.97 (1.66)	2.19 (1.72)	0.69 (0.35)	0.31 (0.14)	0.25 (0.05)

LTB4 was present at physiologically active concentrations throughout the study. LTB4 was greatest at the start of therapy compared with day 5, day 14 and the subsequent stable state ($p < 0.05$) but did not differ significantly from day 3. There was a positive correlation with MPO ($n = 30$, $r_s = 0.352$, $p < 0.05$). These data indicate a potential role for LTB4 in neutrophil recruitment to the airway in chronic bronchitis, particularly during infective exacerbations.

P221 INFLAMMATORY ACTIVITY IN SPUTUM CHRONIC BRONCHITIS AND BRONCHIECTASIS DURING CLINICAL STABLITY

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Neutrophil elastase has been implicated in the pathogenesis of both chronic bronchitis (CB) and bronchiectasis (BE). However these diseases differ in the intensity of neutrophil infiltration found in bronchial secretions and this may influence the pathophysiology of the two conditions. For example in the stable clinical state elastase activity is usually only found in BE. In order to characterise these differences further we have compared inflammatory activity in the two diseases in the stable clinical state by collecting sputum from 7 patients with CB and 14 patients with BE. Sol-phase was obtained and neutrophil content was assessed by the measurement of myeloperoxidase (MPO) by chromogenic assay. The chemokines interleukin-8 (IL-8) and leukotriene B4 (LTB4), and the proteinase inhibitors alpha 1 proteinase inhibitor (α-1-PI) and secretory leukoprotease inhibitor (SLPI) were measured by ELISA. Finally neutrophil elastase (NE) and cathepsin B (Cat B), (which is activated in the lung by NE), were measured by chromogenic assay. Mean results are summarised in the table.

	MPO units	Elastase μM	Cat B U/ml	IL-8 nM	LTB4 nM	α1PI μM	SLPI μM
BE mean (SE)	31.48 (6.98)	1.7 (0.65)	1.49 (0.27)	23.4 (4.4)	25.2 (5.93)	2.02 (0.83)	1.13 (0.36)
CB mean (SE)	0.28 (0.03)	0	0	6.05 (1.17)	11.34 (3.51)	0.69 (0.24)	2.92 (0.52)

Values for patients with BE were significantly higher for all factors measured (range $p < 0.001$ to $p < 0.05$). The results indicate that BE is associated with a greater degree of inflammation than CB. During clinical stability elastase and cathepsin B activity are only a feature of patients with BE and may be related to greater bronchial damage in these subjects. The lower concentration of SLPI in BE may reflect the presence of elastase activity.

P222 ENDOTHELIN-1 LEVELS IN INDUCED SPUTUM FROM ASTHMATICS, NORMAL SUBJECTS AND SMOKERS - Comparison with plasma and saliva levels.

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Endothelin-1 (ET-1) is a potent bronchoconstrictor which has a suggested role in the pathogenesis of asthma. The technique of sputum induction has been used in the analysis of cell counts and mediators in sputum, as an alternative to flexible bronchoscopy with broncho-alveolar lavage. We used sputum induction to obtain fluid for analysis of ET-1 and were able to compare levels in saliva, sputum and plasma in 34 adult subjects. Sputum induction using 3% saline was performed on 9 normal volunteers, 10 smokers without lung disease and 15 asthmatics, subdivided into 8 taking inhaled ß2 agonists alone and 7 taking additional inhaled steroids. ET-1 was assayed by radio-immuno assay (RIA), following ultracentrifugation of separated sputum plugs to obtain a fluid phase.

Mean (SEM) ET-1 (pg/ml)

	Plasma ET-1	Sputum ET-1	Saliva ET-1
Normals	3.27 (0.6)	18.5 (4.36)	32.5 (5.13)
Asthma - ß2 agonists alone	4.15 (0.6)	10.5 (1.82)	20.0 (2.91)
Asthma - inhaled steroids	3.17 (0.52)	13.3 (1.96)	24.0 (3.38)
Smokers	4.35 (0.77)	22.5 (5.18)	38.2 (9.64)

For each group we found significant differences in the levels of ET-1 between the different fluids, with saliva, sputum and plasma in decreasing order of ET-1 concentration ($p<0.05$ in all comparisons), but comparing the groups revealed no significant inter-group differences in the levels of ET-1 in each fluid. We conclude that ET-1 can be measured in saliva and sputum obtained by sputum induction in asthmatics and non-asthmatics. Although no difference was found in basal levels of ET-1 in sputum, saliva and plasma between normals and stable asthmatics without prior bronchoconstriction, it is apparent that ET-1 is produced or released locally within the respiratory tract in concentrations higher than those in plasma.

P223 INTERRELATIONSHIPS OF INFLAMMATORY MARKERS IN BRONCHIAL DISEASE

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Elastase released by neutrophils following their recruitment to the airways is believed to play a key role in the pathogenesis of bronchial disease despite the presence of physiological inhibitors (R. A. Stockley et al, *Q.J. Med*, 1995; 88: 141-146). For example interleukin-8 (IL-8) may lead to neutrophil infiltration and subsequent degranulation. Degranulation products, such as elastase, cause epithelial cells to produce IL-8, thereby amplifying the inflammatory process. In addition elastase may potentiate its own activity by the reduction of secretory leukoprotease inhibitor (SLPI) production (J. M. Sallenave et al, *Am. J. Respir. Cell Mol. Biol*, 1994; 11: 733-741).

In order to investigate these interactions we measured elastase activity and related it to other potentially interdependent factors. Samples from fourteen patients with bronchiectasis (BE) and seven patients with chronic bronchitis (CB) were collected at monthly intervals on four occasions. All patients were clinically stable during the study period. All samples were graded and assigned numbers according to an in-house scale. Sol-phase was obtained and elastase, Cathepsin B (Cat B) and leukotriene B4, SLPI, α-1-protease inhibitor (α1PI) were measured by ELISA. Elastase activity in the BE samples showed a positive Spearsman rank correlation with purulence number ($n = 53$, $r_s = 0.786$, $p < 0.001$), MPO ($n = 40$, $r_s = 0.804$, $p < 0.001$), IL-8 ($n = 53$, $r_s = 0.367$, $p < 0.01$) and α1PI ($n = 52$, $r_s = 0.733$, $p < 0.001$) and a negative correlation with SLPI ($n = 53$, $r_s = 0.492$, $p < 0.001$).

These results confirm that; (i) elastase activity is dependent upon neutrophil infiltration as determined by sputum colour and MPO, (ii) it also relates to IL-8 which may be a combination of cause and effect and (iii) elastase activity is associated with Cat B which it activated *in vitro* and negatively associated with SLPI.

P224 THE USE OF A SPUTUM COLOUR CHART IN THE ASSESSMENT OF BRONCHIAL INFLAMMATION

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Bronchial inflammation in patients with chronic bronchitis is related to protein exudation and neutrophil influx. This latter effect is associated with the presence of myeloperoxidase (MPO) that gives the yellow/green coloration. Previous studies using a subjective classification of sputum (mucoid, mucopurulent and purulent) have confirmed the relationship to inflammation (R. A. Stockley et al, Thorax, 1984; 39, 408).

We have assessed the use of a matching colour chart (numbered 1-8) for sputum assessment by comparison with a series of inflammation related markers (neutrophil elastase - NE, Cathepsin B, IL-8, LTB4, alpha-1-antitrypsin - α_1AT and the locally produced NE inhibitor SLPI) in 79 sputum samples obtained from patients with chronic expectoration. MPO, IL-8, NE, Cat B and α_1AT all showed stepwise increases from mucoid to mucopurulent and purulent sputum (assessed subjectively). LTB4 concentrations were less in purulent samples than mucopurulent samples though still greater than in mucoid samples. SLPI showed a stepwise fall in concentration from mucoid to purulent.

Sputum number (using the colour chart) showed a significant correlation with MPO ($r = 0.867$, $p < 0.001$), IL-8 ($r = 0.728$, $p < 0.001$), NE ($r = 0.826$, $p < 0.001$), Cat B ($r = 0.808$, $p < 0.001$), α_1AT ($r = 0.648$, $p < 0.001$) and LTB4 ($r = 0.342$, $p < 0.01$) and a significant negative correlation with SLPI ($r = -0.584$, $p < 0.001$).

The data confirms our previous findings and indicates the usefulness of the sputum colour chart as a simple assessment of bronchial inflammation associated with neutrophil influx.