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INHIBITION OF THE PLASMALEMMAL H+ATPASE IN HUMAN ALVEOLAR MACROPHAGES (HAMS) AND PERIPHERAL BLOOD MONOCYTES (HPBMS) IS ASSOCIATED WITH IMPAIRED EFFECTOR FUNCTION

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Regulation of cytosolic pH is vital for normal cellular function. Pathological microenvironments are associated with acid loading and cell metabolic processes generate acid equivalents. Cells have therefore evolved several mechanisms for proton extrusion, including plasmalemmal H+ATPase (active, when cells are acid loaded) and the Na/H+ antiporter (which in HPBMs is activated during formylmethionyl-leucyl phenylalanine induces acidosis. We have shown that inhibition of H+ATPase is associated with a mild intracellular acidosis (approx. 00.2-0.3 pH unit below physiological pH) in HAMs and that this is associated with reduced Fc mediated phagocytosis. The aim of these experiments was to assess the role of H+ATPase in HPBM pH regulation and phagocytosis and assess its role in the generation of intracellular reactive oxygen species (a vital cytotoxic mechanism) in HAMs and HPBM. PH changes were monitored flow cytometrically using pH sensitive intracellular probes. Respiratory burst was assessed by the reduction of dihydrorhodamine. Fc mediated phagocytosis was assessed flow cytometrically following exposure to Fc opsonised FITC labelled E.Coli

HPBMs failed to recover physiological pH following acid loading in the presence of a specific H+ATPase inhibitor bafilomycin A1 (0.002 pH units/min(baf) vs 0.21 pH units/min, $p<0.05$), but recovery was insensitive to the antiporter inhibitor amiloride. Bafilomycin reduced Fc mediated phagocytosis (mean channel fluorescence (mcf) vs 465, $p<0.005$. Respiratory burst was reduced in HAMs (mcf 379 vs 480, $p<0.05$) and in HPBMs (224 vs 302, $p<0.05$). These results suggest a critical role for H+ATPases in regulation of cytosolic pH and effector function of these cells.

FC GAMMA RECEPTOR ACTIVATION IN PERIPHERAL BLOOD MONOCYTES AND NEUTROPHILS IS ASSOCIATED WITH TRANSIENT CYTOSOLIC ACIDIFICATION, RECOVERY FROM WHICH IS BOTH AMILORIDE AND BAFILOMYCIN SENSITIVE

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Monocytes and neutrophils express receptors for the various subclasses (I, II and III) of the Fc portion of the immunoglobulin molecule. Activation of these receptors, by cross linkage, mediates a wide variety of effector functions including phagocytosis (II), secretion of reactive oxygen intermediates (I, II), antibody mediated cellular cytoxicity (I), and tumour cell cytoxicity (III). Cellular activation by the chemotactic peptide FMLP, a non specific stimulus, in monocytes causes acidification whose recovery is amiloride sensitive. Human monocytes recover cytosolic pH following external loading by activating a plasmalemmal H+ATPase. Recovery of pH is vital for maintaining normal cellular metabolism. We evaluated changes in cytosolic pH following cross linkage of "mouse anti-human monoclonal antibody against FcR gamma I, II, and III" using a "goat anti-mouse (GAM)" anti-Fc monoclonal antibody. Changes in pH were monitored flow cytometrically using an intracellular pH sensitive probe, carboxy SNARF. Cross linkage of FcRI, II, II in monocytes and Fcr II, III in neutrophils was accompanied by a rapid mild intracellular acidosis (0.25 units $\pm$ 0.02 S.D. $p<0.0005$). The fall in pH was most marked after cross linkage of FcRI (0.3 units $\pm$ 0.018 S.D.) in monocytes and FcRII (0.33 units $\pm$ 0.011 S.D.) in neutrophils. Recovery commenced after several min and was impeded by both bafilomycin A1 and amiloride suggesting activation of 2 separate means of proton extrusion both plasmalemmal H+ATPase and the Na+ /H+ antiporter respectively.

MATRIX METALLOPROTEINASES IN EMPHYSEMA

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To date, the role of the matrix metalloproteinases (MMPs, a group of potent matrix-degrading enzymes) in alveolar matrix destruction in emphysema has received little attention. The aim of this study was to assess bronchoalveolar lavage (BAL) levels of 2 major MMPs, collagenase and gelatinase B (gel 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 and 12 matched controls were analysed for collagenase and gel B Neutrophil elastase (NE) levels were also assessed. Collagenase activity was detected in BAL samples from all emphysematous patients but in only 1 smoking control ($p<0.001$). By comparison, gel B was present in 7 of the 12 emphysematous patients and in 2 smoking controls ($p<0.01$) and NE was detected in 8 of the 12 emphysema patients and also in 2 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 gel B and may be a better indicator of alveolar destruction than NE

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MATRIXMETALLOPROTEASE 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

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whether or not their expression is directly up-regulated in emphysema has not been examined. The aim ot this study was to assess MMP gene expression in AMs from emphysema patients. AMs isolated from bronchoalveolar lavage (BAL) of 12 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 uslng semi-quantitative reverse transcriptase-polymerase chain reactlon (RT-PCR). Interstitial collagenase was expressed by AMs trom all 12 emphysema patients but only 3 controls ($p<0.0001$). Similarly, gelatinase B mRNA levels were elevated in AMs trom the emphysema group compared to controls ($p<0.0001$). In the case of gelatinase A and MME, however, no significant difference in expression was 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.

INFLAMMATORY MEDIATORS IN BRONCHOALVEOLAR LAVAGE FLUID FROM PATIENTS WITH CHRONIC NON-PRODUCTIVE COUGH

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In non-asthmatic patients with chronic non-productive cough (CNPC) increased mast cell and eosinophil numbers have been reported in BAL and induced sputum samples respectively. However there are no reports regarding mediator levels in BAL from patients with CNPC. BAL (180 ml right middle lobe) samples were obtained from 15 CNPC patients (50±3.0 y) with a median duration of cough of 98 months (range 4-456 months) and 7 control subjects. All subjects were non-smokers and spirometry was within normal limits. Lavage volume return differential cells counts tryptase and ECP concentrations were compared in both groups.

Volume return was significantly less in the CNPC patients (70±2 ml vs 91±7 ml. $p<0.01$). The percentage mast cell count was significantly greater. In CNPC patients ($p<0.05$), however other cell counts did not differ. Tryptase concentrations were significantly higher in CNPC patients (1.97±0.09 U/L vs 1.75±0.09 U/L, $p<0.05$). ECP was detected in BAL from 5 of 15 CNPC subjects (measured range 3.56-15.95 µg/L) but below the level of detection (2 µg/L) in all other CNPC and control subjects.

These findings demonstrate an increase in mast cell numbers and mast cell derived mediators in CNPC. Furthermore, raised ECP concentrations were found in a subgroup of CNPC patients suggesting ongoing eosinophil activation. However only 2 of these 15 subjects had mild non-specific bronchial hyperresponsiveness (PC_{20} (histamine) = 4 mg/ml) and fulfilled the current diagnostic criteria for cough variant asthma. Analysis of BAL mediators may allow a more accurate characterisation of the underlying pathophysiology of chronic non-productive cough.

ALLERGEN-INDUCED CYTOKINE PRODUCTION IN ATOPIC ASTHMA: RELATIONSHIP TO DISEASE SEVERITY

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The Th2 cytokines, interleukin (IL)-4 and -5, have an accepted role in the immunopathology of atopic asthma. However the role of atopy in asthma is poorly understood i.e. why some patients are atopic in only the skin or upper respiratory tract and not in the lower respiratory tract?

The objectives were to compare the effect of house dust mite antigen on in vitro cytokine production by lymphocytes in atopic asthmatics, atopic non-asthmatics and healthy individuals and whether cytokine release could be correlated with the clinical situation in vivo.

Eighteen atopic asthmatics, 6 atopic non-asthmatics and 7 healthy non-atopic individuals were studied. Peripheral blood mononuclear cells (PBMCs) were stimulated with Dermatophagoides pteronyssinus antigen (Der p) and cultured for 10 days. At day 10 culture supernatants were analysed for IL-4 and interferon (IFN)-gamma and CD4+ T cells analysed for CD30 expression.

Der p induced significant amounts of IL-4 in atopic patients (>115 pg/ml) but much less in normals (<50 pg/ml). Less IFN-gamma (770 pg/ml) was produced in atopic asthmatics compared to atopic non-asthmatics (2177 pg/ml) and normals (2438 pg/ml). Within atopic asthmatics IFN-gamma correlated inversely with symptom score. These effects were allergen-specific.

Conclusions: allergen-induced cytokine production in vitro differs in different groups of atopic patients and for atopic asthmatics correlates with disease severity.

THE CYTOKINE TNFα IS PREFERENTIALLY CONCENTRATED IN THE MUCOUS PHASE OF AIRWAY LINING FLUID

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Processing of induced sputum for cell characterisation usually involves the addition of a reducing agent such as dithiothreitol (DTT), to reduce the disulphide bonds of the mucin glycoprotein, allowing cell dispersion and the formation of a cell suspension. As many cytokines contain disulphide bonds, DTT could prevent their accurate measurement. Use of the sputum sol phase without the addition of DTT could overcome this problem. We compared the concentration of TNFα and the reproducibility of this measurement in DTT-containing 'whole sputum' supernatant (WSS), with that in the sol phase in 27 patients. Concentrations were, on average. Nineteen times higher in the WSS than in the sol phase of sputum 1218.3 (266.3) and (63.4(13.9)pg/ml respectively, and the intraclass correlation of reproducibility was superior in the whole sputum compared with that for the sol phase measurement (0.69 and 0.92 in the sol phase and WSS respectively). When samples of the gel phase and sol phase from 10 patients were assayed for TNFα concentration it was found that the cytokine was concentrated in the gel phase. 1582.9(634.5) versus 43.6(11.7)pg/ml in sol

phase, with only 16 per cent of the total TNFα is recoverable in the sol phase, suggesting concentration of the cytokine within mucus either *in vivo* or as a result of ultracentrifugation. When 4 sputum samples were 'spiked' with a known concentration of the cytokine 54.2 per cent of the exogenous cytokine was recoverable in the sol phase. These data suggest that whilst some of the cytokine TNFα becomes concentrated in the gel phase of sputum during ultracentrifugation, endogenous TNFα may be preferentially concentrated within the mucous phase of airway lining fluid *in vivo* and that the supernatant of whole sputum, regardless of DTT treatment, is a preferable phase in which to quantify this cytokine.

THE EFFECT OF EXTERNAL THORACIC RESTRICTION ON RESPIRATORY SENSATION AND BREATHING PATTERN DURING EXERCISE IN HEALTHY MALE SUBJECTS

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Ten subjects relaxed seated on a cycle ergometer (rest: 5 min) before performing a 10 min steady state exercise test (Unrestricted: "U"). A second exercise test (Restricted R) followed after thoracic expansion was minimized using a tight inelastic corset. Respiratory discomfort (RD) was recorded (30s intervals-visual analogue scale). Subjective information was obtained following each test.

Following "U" 9 subjects reported little or no RD. Following "R" 7 subjects reported shortness of breath and 6 reported pain associated with breathing. Nine subjects were confident that their ventilation during "R" was substantially greater than that achieved during "U". Restriction reduced mean FEV1 by 42 per cent TLC by 38 per cent and FRC by 31 per cent. Mean (SEM) values from the final 2 min of rest and exercise are shown.

	Rest		Exercise	
	U	R	U	R
V_1 (l/min)	11.3 (0.9)	15.8 (1.8)	49.0 (3.0)	61.2* (4.1)
PETCO2 (mmHg)	35.5(1.1)	34.8 (1.3)	43.6(1.4)	39.4* (1.4)
fR (bpm)	12.5 (1.5)	21.1* (2.4)	23.2 (1.9)	42.6* (3.2)
VT (l)	1.0 (0.1)	0.81 (0.1)	22 (0.1)	1.5* (0.1)
SaO_2 (%)	95.7 (0.3)	95.3 (0.4)	94.8 (0.4)	93.1* (0.7)
RD (mm)	0 (0)	20.1* (5.6)	20.3 (7.2)	65.4* (8.4)

At rest, thoracic restriction produced a significant increase in fR and RD (US vs S, P<0.05 ANOVA). During exercise restriction significantly decreased VT and SaO_2. fR and RD increased. These results suggest that chest strapping may be a useful model of RLD and that limitation of tidal volume may be a potent stimulus for respiratory discomfort.

COMPARISON OF DIFFERENT LEVELS OF NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NCPAP) IN PATIENTS WITH SEVERE CONGESTIVE HEART FAILURE (CHF) IN SINUS RHYTHM (SR) AND ATRIAL FIBRILLATION (AF)

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We have previously shown a reduction in awake cardiac output (CO) following 5 cm H_2O NCPAP application among patients with severe CHF in AF[1]. We wished to expand these observations by comparing the awake effects of different levels of NCPAP, and also by comparing the effects in patients with AF and SR. Ten patients (6 AF and 4 SR) were enrolled, and haemodynamic measurements were made via Swan Ganz catheterisation. All patients had severe but stable CHF (mean left ventricular ejection fraction = 25 per cent), with no recent change in cardiac therapy. After baseline measurements, 0, 5 and 10 cm H_2O NCPAP were applied in random order, each for 30 min, and a recovery period with the NCPAP mask removed was given between each pressure application. Cardiac output (CO) was measured by the thermodilution technique at times 0 and 30 min of each NCPAP application, and 20 min after mask removal.

CO rose in the SR group by 48±0.23 L/min (mean±SE) on 5 cm H_2O NCPAP and by 0.45±0.33 L/min on 10 cm H, but fell in the AF group by 0.13±0.19 L/min on 5 cm H_2O NCPAP and by 0.45±0.09 L/min on 10 cm H_2O respectively (p<0.05 for both pressures). These data indicate a fundamental difference in the response of patients with CHF to NCPAP based on underlying cardiac rhythm and give important insight into the effects of NCPAP on cardiac function. The data also support previous reports that NCPAP may provide clinical benefit to patients with CHF who are in sinus rhythm.

Reference

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DEVELOPMENT OF A NITRIC OXIDE BREATH TEST TO MONITOR CHILDREN'S ASTHMA

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Atopic asthmatic children have persisting airways inflammation. Non-invasive markers reflecting this would aid diagnosis and treatment. Adult studies suggest exhaled nitric oxide (NO) is such a marker. We report our early experience of measuring exhaled NO in children.

Thirteen asthmatics and 6 controls were studied (age range 5-14 yr). Exhaled NO was measured in parts per billion (ppb) with a Dasibi chemiluminescence analyser using techniques A forced vital capacity (FVC) manoeuvre through the sampling tube was carried out and continuous sampling of mixed expired air during tidal breathing whilst inspiring NO free air through a mouthpiece. With the FVC manoeuvre peak NO concentration expired was used as a reflection of overall production. With the tidal breathing technique mean NO level was used.

The procedure was well tolerated. Mean values (SD) are expressed in the table

	NO peak in ppb (FVC manoeuvre)	NO mean in ppb (Tidal Breathing)	FEV1 (% Predicted)	FEF 25% (% Predicted)
Normals	11.5 (13.7)	8.4 (2.9)	90 (16)	104.4 (39)
Asthmatics	50.3 (30)	7.6 (5.6)	103 (13)	82 (75)

Exhaled NO using the FVC manoeuvre was significantly elevated in the asthmatics (p=0.009). Ninety-five per cent of repeated measures of exhaled NO (using the FVC manoeuvre) lay between 70-130 per cent of the first Conclusion: Exhaled NO using the FVC manoeuvre demonstrated a large difference between asthmatic and normal children and is likely to be a useful non-invasive marker of airways inflammation.

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SEQUENTIAL PATHOPHYSIOLOGIC EFFECTS OF INHALED FLUTICASONE PROPIONATE IN ASTHMA: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED BIOPSY STUDY

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Although corticosteroids are the first line of therapy for asthma, their precise effects on disease activity remain unclear. It is unknown what components of airway inflammation are the key targets of corticosteroid therapy.

This randomised, double-blind, placebo-controlled trial of high-dose inhaled fluticasone propionate (FP), 2mg/day, in mild/moderate asthma, examines sequential pathophysiological effects after short-term (2 weeks) and then prolonged (8 weeks) therapy. At baseline, 2 weeks and then 8 weeks, histamine bronchial challenges, bronchial reversibility studies, and fibreoptic bronchoscopy with bronchial mucosal biopsies were performed. Frozen sections of bronchial mucosa underwent immunological analysis and numbers of immunocompetent cells were compared at the 3 time points.

Twenty-five adult subjects (13 placebo, 12 FP) (age: 19-45 yr, mean: 28.5 yr) completed the protocol. FP-treated subjects reported significantly improved asthma control compared to the placebo group. Compared to placebo, inhaled FP caused significantly increased (pre-bronchodilator) FEV_1 at 2 weeks ($p<0.006$) and 8 weeks ($p<0.03$); FEF_{25-75} at 2 weeks ($p<0.008$) and 8 weeks ($p<0.006$) and FEV,/FVC percentages after 2 weeks ($p<0.03$) and then 8 weeks ($p<0.03$), in addition to significant reductions in bronchial reversibility at 2 weeks ($p<0.02$) and 8 weeks ($p<0.005$). In terms of airway inflammation, compared to the placebo group, significantly reduced numbers of memory T lymphocytes ($p=0.04$), macrophages (CD68+) ($p=0.03$), and eosinophils EGI ($p<0.05$) were seen after 2 weeks of therapy with inhaled FP. After 8 weeks, significant reductions in activated eosinophils EG2 ($p=0.0057$), and reduced HLA-DR expression ($p=0.0569$) were apparent.

Conclusions: In addition to improved asthma control and bronchial reversibility, short-term (2 weeks) therapy with high-dose inhaled FP results in significant reductions in memory T cells, macrophages and resting eosinophils. Prolonged (8 weeks) therapy causes significant reduction in eosinophil activation.

COMPARISON OF POSITIVE CULTURE PATIENTS FOR ATYPICAL MYCOBACTERIAL INFECTION (1085-1995) WITH BACKGROUND POPULATION OF PATIENTS WITH M. TUBERCULOSIS

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We compared patients with a diagnosis of MOTT with the background population[1] of patients with M. TB. Comparison was done using X^2 analysis

Forty patients with MOTT were identified (MAI 32.5 per cent: Malmoense 17.5 per cent: Xeopi 12.5 per cent.

	MOTT	M. TB
Age	1-88 yr	15-85 yr
Negative 100 TU	40%	5%
Male/Female ratio	60:40	68:32
Chest X-ray		
Unilateral disease	85%	45%
Cavities	10%	58%
Pleural disease	8%	10.1
Non TB pulmonary	14%	9.75

Patients with MOTT were more likely to be married ($p=0.02$), more likely to be female ($p=0.004$), more likely to have negative 100 TU ($p<0.00000001$), more history of non TB pulmonary fibrosis ($p=0.0005$), less peptic ulcer disease ($p=0.005$). No difference was found in terms of smoking history, alcohol consumption, previous treatment/history for TB, extrapulmonary involvement, death, presence of COAD, asthma, malignancy, diabetes mellitus, thyroid disease, major psychiatric illness, atrial fibrillation, ischaemic heart disease, history of previous confirmed diagnosis of sarcoidosis.

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CIRCULATING NEUTROPHIL ß2-INTEGRIN EXPRESSION AND INTRACELLULAR OXIDATIVE METABOLISM IN PNEUMONIA

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As neutrophil migration to the lungs in pneumonia is partly dependent on neutrophil $ß_2$-Integrin (CD11b) expression, this may be increased in pneumonia. Neutrophil activation associated with increased intracellular oxidative metabolism could be of prognostic significance. Peripheral blood neutrophils from 17 healthy controls and 24 patients with pneumonia were labelled with FITC-conjugated monoclonal antibodies to CD11b, and analysed by flow cytometry. Intracellular oxidative metabolism was measured by respiratory burst activity pre- and post-stimulation with E Coli, using flow cytometric analysis, and expressing the results as mean channel fluoresence (MCF).

There was a trend towards increased baseline respiratory burst on day 1 in the pneumonia patients: 11.3(8.1) vs. controls 6.0(2.3), $p=0.07$, but no difference in respiratory burst post E Coli stimulation: 177(157) vs. 131(47) or in CD11b expression: 405(266) vs. 280(126). Three patients died and they had significantly reduced respiratory burst response to E Coli compared to the other patients: 55.5(34) vs. 197(161), $p<0.05$, and compared to controls: 55 5(34) vs. 131(47), $p<0.05$, although CD11b was similar in both patient groups. We conclude that in a patient group with non-bacteremic pneumonia CD11b expression and oxidative metabolism were comparable to controls. However, the patients who died had low intracellular oxidative metabolism and this may be of prognostic significance.

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SHORT DURATION HYPEROXIA IN NORMAL SUBJECTS IS ASSOCIATED WITH INCREASED OXIDATION OF BRONCHOALVEOLAR LAVAGE PROTEINS AND DECREASED LUNG ANTI-PROTEASE PROTECTIVE SCREEN

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Hyperoxia (administration of <95 per cent oxygen of less than 24 h duration) is regarded as relatively benign apart from occasional symptoms such as retrosternal pain. We evaluated 5 normal volunteers before and immediately after exposure to hyperoxia (>95 per cent oxygen delivered by face mask at 60L/min) for 14±0.05 h (mean±SE) to determine whether more objective changes may occur in the lungs. The study subjects underwent bronchoalveolar lavage 2 weeks before and immediately after exposure to hyperoxia. Average arterial partial pressures of oxygen were 98±3 Torr increasing to 503±19 Torr following exposure to hyperoxia. The study subjects were asymptomatic following hyperoxia exposure, apart from 1 individual who complained of mild retrosternal pain which abated on cessation of hyperoxia. Pulmonary function tests and chest X-rays were unchanged. Bronchoalveolar lavage fluid was analysed by (1) Western blot analysis of protein carbonyl content as an index of oxidation of BAL proteins and (2) determination of anti-neutrophil elastase (NE) capacity in epithelial lining fluid (ELF). No difference was observed in ELF volume recovered in BAL pre- and post-hyperoxia (p=0.9). Western blot analysis of BAL showed increased carbonyl content in all subjects following hyperoxia. Furthermore, anti-NE capacity in the lung ELF fell from 3.3±0.3 μM pre-hyperoxia to 1.9±0.2 μM post-hyperoxia ($p<0.05$). Thus, even relatively brief exposure of normal volunteers to hyperoxia results in oxidation of lung proteins and impairment of lung antiprotease defenses. This impairment may be even more severe with prolonged exposure, particularly in the setting of lung disease.

THE AUTOCRINE ROLE OF THE CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR IN CALCIUM SIGNALLING IN NORMAL AND CYSTIC FIBROSIS LUNG

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In cystic fibrosis (CF), ΔF508 mutation of the cystic, fibrosis transmembrane conductance regulator (CFTR) causes abnormalities of ionic transport in human airway epithelia, such as reduced cAMP-dependent Cl- secretion and hyperabsorption of Na^+. This dysfunction of NaCl transport appears to produce a dehydration of airway secretions. Intracellular calcium $[Ca^{2+}]_i$ is an important regulator of ion secretion and here we have tested for Ca^{2+} signalling (mediated by ATP release via CFTR), using fura-2 fluorescence spectrometry in normal primary culture of human lung (HPL), in a normal human bronchial cell line (HBE) and in a ΔF508 CFTR human tracheal cell line (CFTE). Externally applied nucleotides produced a release of Ca^{2+} from intracellular stores with order of potency UTP=ATP>ADP>>AMP, indicating the presence of a P_{2U}-type receptor in all 3 cell types. In support of an autocrine effect mediated by ATP release via CFTR, we found forskolin, an activator of CFTR, increased $[Ca^{2+}]_i$ in HPL and HNPE cells at temperatures between 14-37°C. However, forskolin had no effect on $[Ca^{2+}]_i$ in CFTE cells at body temperatures but produced calcium mobilization at low temperatures (14°C) . The latter stimulation of $[Ca^{2+}]_i$ may be mediated by the insertion of ΔF508-CFTR into the plasma membrane at low temperature. Pre-treatment with hexokinase (which consumes extracellular ATP by phosphorylation of D-glucose) or 2,2'-iminodibenzoic acid (a CFTR channel inhibitor), or suramin (a purinergic receptor antagonist) significantly inhibited the forskolin-induced $[Ca^{2+}]_i$ increase in HBE and CFTE cells. Taken together, these results show that CFTR can act as an autocrine regulator of $[Ca^{2+}]_i$ in human airway epithelial cells and this signalling pathway is intact in CF trachea at low temperature. Activation of purinergic receptors at body temperature by aerosol delivery of nucleotides may have therapeutic potential via effects on $[Ca^{2+}]_i$ to simultaneously stimulate chloride secretion while down-regulating sodium hyperabsorption in CF airway epithelia.

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A COMPARISON BETWEEN ALVEOLAR TYPE I CELL DAMAGE AND INCREASED LUNG PROTEIN PERMEABILITY IN DIFFERENT RAT MODELS OF ACUTE LUNG INJURY

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Alveolar epithelial damage results in a general condition referred to as acute lung injury. We have recently described a novel method for biochemically assessing the extent of injury to alveolar epithelial type I cells[1]. In this study we compared the extent of type I cell damage with changes in lung permeability, in 3 different rat models of acute lung injury.

Bacterial pneumonia was caused by instilling live *Psedumonas aeruginosa* into the right lung of anaesthetized rats for 2 h. Nitrogen dioxide-induced lung injury was established by exposing rats to 18 ppm NO_2 for 12 h while hyperoxic lung injury was established by exposing rats to 95 per cent oxygen for 60 h.

Type I cell injury was determined by measuring the amount or rT140 in samples of bronchoalveolar liquid. Increased epithelial permeability to protein was determined by measuring the amount of a distal airway tracer (^{125}I-albumin) found in the vascular space; while endothelial permeability to protein was determined by measuring the amount of vascular tracer (^{131}I-albumin) recovered in the air compartment.

	rT140 in alveolar fluid	Distal airway protein tracer in blood (^{125}I-albumin)	Vascular protein tracer in air space fluid (^{131}I-albumin)
	Relative increase over control values		
Ps	2-fold increase*	5-fold increase*	3.6-fold increase*
NO_2	2-fold increase*	8.6-fold increase*	4.7-fold increase*
O_2	1.7-fold increase*	No change	5-fold increase*

*P<0.05, n=5-7

These data demonstrate that similar degrees of alveolar epithelial type I cell injury, in different rat models of acute lung injury, are not associated with similar increases in distal airway permeability to protein tracers. These data suggest that increased

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lung protein permeability depends more on the causative agent of acute lung injury than the extent of type I cell injury.

Support: NHLBI-HL-24075, HL-41958, HL-19155, American Lung Association - California.

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CYTOKINE PRODUCTION AT SINGLE CELL LEVEL IN PULMONARY LYMPHOCYTES FROM SARCOIDOSIS PATIENTS

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T-lymphocytes from many infective and auto-immune diseases demonstrate a bias towards one of the active effector phenotypes T helper 1 (Th1), associated with interferon-gamma production, or Th2, associated with interleukin-4 production. The aim of this study was to investigate the pattern of lymphocyte differentiation in pulmonary sarcoidosis by direct assessment of cytokine production at single cell level using flow cytometry. Bronchoalveolar lavage (BAL) samples were obtained from 14 sarcoidosis patients with lymphocytic alveolitis (mean percentage lymphocytes 49.8 per cent, range 31 per cent to 85 per cent), 4 of whom had persistent BAL lymphocytosis despite established steroid therapy.

BAL cells were stimulated for 4 h with phorbol myristate acetate and ionomycin in the presence of brefeldin A, to enhance the accumulation of intracellular cytokine. Following fixation and permeabilisation, fluorochrome-conjugated antibodies to interferon-gamma (INF-γ) interleukin-4 (IL-4) and to lymphocyte surface antigens including CD4 were added. Samples were analysed using 2- and 3-colour flow cytometry.

In all patients in the untreated group, accumulation of INF-γ was observed within BAL lymphocytes, (mean percentage of lymphocytes positive 46.8 per cent, range 27.7 per cent to 66.75 per cent). In contrast, in the 4 patients on steroid therapy, very few lymphocytes expressed INF-γ (mean 2.2 per cent, range 0.2 per cent to 5.13 per cent, $p<0.001$). In both groups, fewer than 2 per cent of lymphocytes were positive for interleukin-4.

These results indicate that the lymphocyte population in untreated sarcoid alveolitis contains a large subset of Th1-like cells and very few Th2-like cells. The distinct non-INF-γ-producing CD4+ve subset may represent long-term memory cells which have reverted to a cytokine-secreting phenotype similar to that of naive T cells. The results also suggest that patients on steroid therapy with persistent alveolitis do not display a pattern of cytokine production which reflects a Th1 or Th2 bias.

MUCOSAL IMMUNE RESPONSE TO A RESPIRATORY PATHOGEN: CELLULAR INFILTRATION AND T CELL ACTIVATION IN THE LUNG

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We have previously reported that cellular responses, mediated by T cells which secrete IFN-γ and IL-2, termed Th1 cells, play an important role in protective immunity against the respiratory pathogen *Bordetella pertussis*. A study of the kinetics of cells infiltrating the lung during the course of a primary infection of mice demonstrated an early influx of macrophages, and more transiently, neutrophils. Surprisingly, the numbers of neutrophils were also high following a secondary infection. Infiltration lymphocytes were also significantly increased between 7 and 21 days after primary infection. Phenotypic analysis of purified lung T cells revealed >60 per cent $CD4^+$, 20 per cent $CD8^+$ and 10 per cent $\gamma\delta TCR^+$ T cells. Analysis of antigen-specific T cell responses revealed a defect in local T cells from *B. pertussis* infected mice. Lung T cells recovered during the acute phase of infection failed to proliferate or secrete cytokines to purified bacterial antigens, whereas splenic cells from the same animals responded to a range of *B. pertussis* components. In an attempt to establish a basis of this apparent anergy, the expression levels of B7-1/2 and CD28/CTLA-4 costimulatory molecules was examined. Although murine lung macrophages appear to preferentially express B7-1(CD80), during infection the levels of expression of B7-1/2 antigen were not significantly reduced on alveolar when compared with splenic macrophages. Conversely lung T cells exhibited a profound reduction in the surface expression of CD28 in the acute phase of infection. This downregulation of CD28 expression, which was most pronounced at the peak bacterial load in the lung, may be a mechanism for polarization of naive Th0 precursors into Th1 effector cells. In conclusion, these results suggest that Th1 cells may compartmentalize to different lymphoid organs in *B. pertussis* infected mice or that infected with *B. pertussis* may have immunomodulating properties on local T cells in the lung.

ANCA-POSITIVE VASCULITIS: A FOLLOW-UP STUDY OF 32 PATIENTS

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We studied 32 patients who presented to Beaumont Hospital over a 3 yr period with ANCA-positive vasculitis, to compare patterns of serology (including antigen specification), organ involvement and long term damage in the different diagnostic groups. Fifteen patients were C-ANCA positive, with Wegener's granulomatosis (WG). Seventeen were P-ANCA positive, 15 with microscopic polyarteritis (MPA). The WG group had higher disease activity at diagnosis, with Birmingham vasculitis activity score (BVAS, max. score 63) of 22.1±6.01, compared to the MPA group: 16±4.17, $p<0.01$, and more pulmonary involvement ($p<0.05$). At the end of a mean of 31.5 months follow-up period, the vasculitis damage index (VDI, max. 59) was similar in the 2 groups, at 4.6 (2.79), with the same degree of pulmonary involvement. Fifteen patients developed end stage renal failure, 5 died. A high BVAS score correlated with a high VDI score ($p<0.05$), however there was no correlation between the frequency of relapses and VDI score. Initial pulmonary or renal involvement was prognostic of long term damage in the same organ system ($p<0.001$). We conclude that more disease activity at first presentation was associated with a worse prognosis, even in the absence of overt relapses, and that prognosis was similar in WG and MPA

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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). Thirty-three patients (22 female, median age 53 [range 26-77 yr]) 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 3.20) 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.

DEMOGRAPHICS OF LUNG CANCER IN SOUTHERN HEALTH BOARD REGION

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Lung cancer is a common condition that affects millions world wide. Most patients afflicted have a history of smoking tobacco. It accounts for approximately 30 per cent of cancer death and although more common in males, the number of women with lung cancer is increasing. The overall prognosis is poor with 5 yr survival of 10-12 per cent.

In order to implement further measures for earlier detection and disease prevention it is essential to perform audit and population studies to define targets. Therefore we undertook such a study of lung cancer in the catchment area of Cork and Kerry.

The incidence rate was compared to other countries and we found that, although total number was similar, the proportion of women affected was higher in this region than any other e.g. 28 per cent vs 20 per cent in Florence, Italy.

Age distribution for both sexes demonstrated a biphasic peak of 70 and 80 yr males and 65 and 75 yr females. 17.2 per cent underwent surgery. Of these 11 per cent received no other treatment. 30.5 per cent received radiotherapy or chemotherapy (20.7 per cent and 9.8 per cent respectively) and half of these patients had no other treatment. Forty-one per cent died having not received any therapy.

The percentage of each histological type was 45 per cent squamous cell 15 per cent small cell carcinoma, 7 per cent adenocarcinoma, 2 per cent large cell and 13 per cent other. The histology was insufficient in 18 per cent. The incidence of lung cancer is high in females in this region. This may reflect a high proportion of smokers.

We conclude that audit and population study is an integral and essential task in identifying such aberrations.

THE INCIDENCE OR SIGNIFICANT CARDIAC RHYTHM DISTURBANCES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

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Disturbances in cardiac rhythm are commonly seen in patients with obstructive sleep apnoea with an incidence as high as 58 per cent in some studies. The most frequently occurring disturbance is the development of bradycardia during apnoeic episodes. This results from a vagally mediated reflex resulting from the hypoxic stimulation of peripheral chemoreceptors. More significant dysrythmias are considerably less common.

This paper presents the results of a study of the incidence of cardiac rhythm disturbances in 36 patients with obstructive sleep apnoea and without significant cardiac histories. Baseline ECG and nocturnal Holter monitoring was performed on the patients followed by repeat Holter monitoring with the patients receiving CPAP via nasal mask.

Nine of the 36 subjects (25 per cent) had disturbances in cardiac rhythm on baseline Holter monitoring, of these 8 were episodes of vagally mediated bradycardia. One of these developed a pause of 2.7 s which constitutes sinus arrest. Two subjects developed episodes of ventricular bigemini, 1 of these was also noted to have bradycardia during apnoeic episodes the other developed ST segment changes while apnoeic. There were no episodes of significant atrial or ventricular dysrythmias noted.

Results from the holter monitors while on CPAP revealed complete resolution of bradycardic episodes in all subjects. The ventricular bigemini also resolved, completely in 1 subject, and with only infrequent ventricular extrasystoles in the other. The ST segment changes resolved completely.

In conclusion we feel that serious dysrythmias are uncommon in obstructive sleep apnoea and while other disturbances in rhythm are common, these resolve when the patient is treated with nasal CPAP.

PRE-OPERATIVE EXERCISE TESTING IN SUBJECTS UNDERGOING PULMONARY RESECTION FOR BRONCHIAL CARCINOMA

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Sixty-eight patients with bronchial carcinoma were prospectively studied, to determine whether pre-operative pulmonary function and cardiopulmonary exercise testing were

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predictive of cardiopulmonary complications post-thoracotomy. Twenty-three (34 per cent) patients had medical cardiopulmonary complications, including pneumonia, atelectasis, pulmonary oedema and atrial fibrillation. Nineteen (28 per cent) patients had surgical complications, including air-leak, haemorrhage and sepsis. There were 6 (9 per cent) in-hospital deaths, all with both medical and surgical complications. Those with medical complications (Group 1) were compared to those without (Group 2). There was no significant difference between the groups in age: Gp 1=67.1±7.65, Gp 2=62.5±10.4 yr), body mass index (22.6±7.65 vs 25.1±6.06 kg/m^2), FEVI (73.6±194 vs 75.8±188 per cent predicted), maximum ventilation (Ve_2 Max) (84.1±19.7 vs 78 3±19.6 per cent predicted) or maximum O_2 consumption (VO_2 max) (73.95±16.3 vs 73.94±15.0 per cent predicted). Diffusion capacity (DLCO) was lower in Group 1: 55.4±14 per cent predicted, vs 71.3±17.3 in Group 2, P<0.001. The patients who died post-operatively had similar pulmonary function and exercise variables to the survivors, apart from a lower maximal heart rate on exercise (126±22.1 vs 145±20.6 beats/min, P<0.05). We conclude that DLCO is the only pre-operative pulmonary function or exercise variable that is predictive of medical post-operative complications.

SARCOIDOSIS: A PROSPECTIVE STUDY OF THE DIAGNOSTIC MODALITIES

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Sarcoidosis, although carrying in general a good prognosis, requires a tissue diagnosis to exclude mimicking conditions such as lymphoma, TB and other interstitial lung diseases. The main diagnostic modality is transbronchial lung biopsy (TBLB) through the fibreoptic bronchoscope (FOB) with a diagnostic yield of 40-70 per cent. Wang needle biopsy of mediastinal lymph nodes and bronchoalveolar lavage (BAL) have been proposed as being of use in the diagnosis.

The study objectives were to compare the diagnostic yield from TBLB, Wang needle biopsy and BAL in sarcoidosis (stage I and II).

Ten patients with clinical and radiological features consistent with stage I and II sarcoid underwent FOB with TBLB, Wang needle biopsy and BAL (cell count differential and CD4:CD8 ratio).

TBLB was positive in 50 per cent (5/10). Wang needle biopsy was positive in 40 per cent (4/10), 3 of which patients had negative TBLB. Fifty per cent (5/10) had classical 'sarcoid' BAL findings. Combining TBLB, Wang and BAL gave diagnostic sensitivity of 90 per cent. The remaining patient required mediastinoscopic biopsy which showed non-Hodgkin's lymphoma.

Conclusions: Combining diagnostic modalities gives best results in sarcoidosis. Even with this small patient group Wang needle biopsy saved 3/10 patients the need for an open diagnostic procedure under general anaesthesia and it would appear to have a role in sarcoid diagnosis especially when conventional TBLB is negative.

RESPONSES TO EXERCISE IN PRIMARY PULMONARY HYPERTENSION

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Patients with primary pulmonary hypertension (PPH) have impaired exercise tolerance. We studied the responses to symptom-limited continuous incremental (ramp) cycle ergometry exercise in a group of 9 PPH patients (6 female). All patients were being treated with calcium antagonists (n=4) and/or prostacyclin infusion (n=7). They were compared with a group of age- and sex-matched controls. Values (mean±SD) are for peak exercise unless otherwise stated:

	Normals	PPH
Work rate (W)	212±39	61±22***
$\dot{V}O_{2max}$ (l min^{-1})	2.58±0.64	1.00±0.22***
Heart rate (beats min^{-1})	178±11	136±15***
Lactic acidosis threshold (LAT; l min^{-1})	1.44±0.18	0.73±0.17***
End-tidal CO_2 (mmHg)	42.4±5.8	29.7±6.8**
End-tidal O_2 (mmHg)	106.9±8.3	116.4±7.1*
$\dot{V}E/\dot{V}O_2$	35.7±7.5	49.3±11,4*
$\dot{V}E/\dot{V}CO_2$	30.1±5.4	44.2±10.7*
$\Delta\dot{V}O_2/\Delta WR$ below LAT (ml min^{-1} W^{-1})	8.1±1.0	6.7±2.1
$\Delta\dot{V}O_2/\Delta WR$ above LAT (ml min^{-1} W^{-1})	9.4±1.4	5.9±2.1**

***p<0.0001, **p<0.001, *p<0.01 t-test

Peak exercise capacity in this group of PPH patients is severely reduced. The sub normal VO_2 - work-rate slopes above the LAT indicate impairment of the circulatory response in patients. The low end tidal CO_2 and O_2 values and the elevated ventilatory equivalents for CO_2 and O_2 suggest that severe pulmonary ventilation-perfusion abnormalities exist in PPH. In addition, the presence of an intracardiac right-to-left shunt may lead to further hyperventilation of the lungs.

EFFECTS OF ENDOTHELIUM REMOVAL ON RESPONSES OF ISOLATED RAT PULMONARY ARTERIAL RINGS TO HYPERCAPNIA AND ACIDOSIS

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Extracellular acidosis at constant PCO_2, normocapnic acidosis (NA), causes relaxation of isolated rat pulmonary arterial rings. Furthermore, hypercapnia at constant extracellular pH (HN) does not affect tension development[1]. The present experiments were undertaken to determine if these responses were modulated by the endothelium.

Isolated pulmonary arterial rings were mounted in physiological saline solution, for recording of isometric tension. Presence of a functional endothelium was demonstrated by relaxation of precontracted rings (phenylephrine) in response to acetylcholine (10^{-5}M). Absence of endothelium (following deliberate removal) was confirmed by failure of acetylcholine-stimulated relaxation. For each ring, all tensions were expressed as a percentage of the maximum tension developed by that ring (per cent Tmax). Rings were submaximally contracted under control conditions. In rings with endothelium (n=8), switch to HN caused mean (±SEM) tension to increase by 2.2 (±2.7 per cent Tmax. In rings without endothelium (n=8) similar tension (+6.6±4.0 per cent Tmax) was attained (P=0.33, ANOVA). In

rings with endothelium (n=9), switch to NA caused a significant (P<0.01) reduction in tension (-17.6±2.6 per cent Tmax), which was similar (P = 0.13) in rings (n = 12) without endothelium (-21.4±1.3 per cent Tmax).

These results suggest that the inhibition of tension development in NA is not endothelium-dependent. HN does not affect isometric tension in the presence of an intact endothelium, nor in its absence.

We wish to acknowledge the financial support of Forbairt and The Irish Lung Foundation

Reference

1. Sweeney, M., O'Regan, R. G., McLouglin, P. Effects of hypercapnia on steady state, phenylephrine induced, tension in isolated rings of rat pulmonary artery. Adv. Exp. Med. Biol. 1996; (in press).

EFFECTS OF NORMOCAPNIC ACIDOSIS ON TENSION DEVELOPMENT IN ISOLATED RINGS OF RAT PULMONARY ARTERY

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We have previously reported that extracellular acidosis at constant PCO_2, normocapnic acidosis (NA) causes relaxation of isolated rat pulmonary arterial rings[1]. These experiments were undertaken to determine if this relaxation was due to increased endothelial nitric oxide (NO) production. Isolated pulmonary arterial rings, were mounted in physiological saline for recording of isometric tension

A cumulative concentration-response curve (CCRC) to phe (10^{-9} to 10^{-5}M) was elicited under control or NA conditions. Control rings (n=12) and rings in NA (n=17) developed a similar mean (±SEM) maximum tension (P=0.76, ANOVA). Mean pD_2 (negative logarithm of concentration required to elicit half maximal response) phe was significantly less (P<0.01) in NA (7.22±0.06) than in control conditions (7.54±0.06).

In the presence of phe ($3.3*10^{-9}$M), CCRC (10^{-7} to 10^{-3}M) for N-ω-Nitro-L-Arginine Methyl Ester (L-NAME) was not significantly different (P=0.96) from control (n=11), in NA (n=17) conditions. Endothelium-mediated relaxation was examined by determining a concentration-response curve for acetylcholine (10^{-9} to 10^{-5}M). In control (n=9) and NA (n=8) conditions, similar response curves were obtained (P=0.52)

These results confirm our previous findings that NA inhibits tension development at submaximal phe concentrations, and that this effect is not mediated by increased NO production.

We wish to acknowledge the financial support of Forbairt, the Irish Lung Foundation and the Health Research Board.

Reference

1. Sweeney, M., O'Regan, R.G., McLoughlin, P. Effects or hypercapnia on steady state, phenylephrine induced, tension in isolated rings of rat pulmonary artery. Adv. Esp. Med. Biol. 1996; (in press).

THE EFFECT OF GROWTH HORMONE AND NUTRITIONAL SUPPORT IN COPD MALNUTRITION

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Malnutrition is a common feature of chronic obstructive pulmonary disease (COPD) and is associated with an increased mortality. Recombinant growth hormone (rhGH) has been shown to be effective in inducing weight gain and an increase in lean body mass and respiratory muscle function in COPD in an inpatient setting. We are assessing the feasibility of an outpatient weight-gain programme in malnourished COPD patients using rhGH (Genotropin, Kabi Pharmacia) and a nutritionally complete supplemented drink (Ensure Plus, Abbott Laboratories). Malnourished COPD patients are recruited and assigned to receive rhGH alone, in combination with Ensure Plus or to receive Ensure Plus alone. rhGH is administered as a subcutaneous injection of 81U daily for 21 days. The nutritional supplement is taken daily between meals for 3 months. Anthropometry is carried out before and after the treatments, as is bioelectrical impedance to assess fat free mass, pulmonary function testing and serum levels of albumin. Five patients have completed each of the groups (Age 66±9 yr, FEVI 36.8±11.4 per cent predicted). Both groups receiving rhGH showed an increase in weight at the end of 21 days treatment: +0.7kg (rhGH alone) and +1.8kg (rGH + Ensure Plus, p<0.05). The group receiving Ensure Plus alone showed a decrease in weight after 3 months, -0.3kg. All 3 groups however increased their fat free mass: +0.3 per cent (rGH alone), +3.7 per cent (rGH + Ensure Plus) and +0.8 per cent (Ensure Plus alone). No enhancing effect of any treatment on FEVI was demonstrated. A nonsignificant improvement in inspiratory muscle strength (PiMax) was noted in the 3 groups. Anthropometric measurements or albumin levels did not differ significantly from baseline. In conclusion, rhGH alone or in combination with nutritional supplements, through its effects on weight, lean body mass and respiratory muscle strength may have a role in COPD malnutrition.

FARMERS LUNG IN IRELAND (1983-1994) REMAINS AT A CONSTANT LEVEL

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A current and prospective study was undertaken by the Department of Respiratory Medicine and the Medical Microbiology Department at the Cork University Hospital to investigate 1. the epidemiology of farmers lung (FL) in Ireland (pop. 3.5 million), with special reference to the South Western Region of this country (pop. 536,000) and 2. to assess any relationship between the prevalence/incidence of farmers lung with climatic factors (obtained from the National Meteorological Office) in South West Ireland between 1983 and 1994 Hospital discharges with a primary diagnosis of farmers lung, or a secondary diagnosis were used to assess incidence and prevalence respectively. Percent positive serological results per annum for farmers lung antibodies (ie Thermoactinamycetes Vulgaris and Micropolyspora Faeni) in the South West were also used as markers of prevalence. This was called the FL index Farmers lung incidence remained constant (0.74 cases per 100,000 pop in 1983 0.55 cases in 1994, with a peak number of cases 3.73 in 1986) throughout the 11 yr studied, in the South West region. There was a significantly similar relationship between the incidence (p<0.0002) and prevalence (p<0.005) of farmers lung in the South West region when compared with the whole of Ireland The other epidemiological marker used (FL index) also remained constaht at 21 per cent positive in 1983 to 22 per cent positive in 1994. A significant relationship was found between total rainfall (in millimetres) each summer (June-August inclusive) and farmers lung incidence and prevalence

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over the following year ($p<0.005$). No significant relationship, however, was found between hours of sunshine during that same period and these indices. The persistence of farmers lung in Ireland at a constant level therefore suggests that the working environment and dairy farm practices have remained unchanged.

IS FUSARIUM SPECIES A CAUSE OF FUNGAL ATOPY IN ADULT CYSTIC FIBROSIS?

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Fusarium (a common soil and plant organism), was identified in the past as a cause of allergic fungal sinusitis. However, only recently has it been associated with allergic bronchopulmonary mycosis[1]. In an earlier study, at this centre, atopy to a variety of fungal antigens was reported in an adult cystic fibrosis (CF) population[2]. 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, 18 asthmatic and 18 control volunteers (matched for age and sex) were investigated. Immediate hypersensitivity skin testing to Aspergillus fumigatus, Penicillium notatum, Fusarium moniliforme and Fusarium vasinfectum was performed on each subject. Total serum IgE and fungus-specific RAST testing was also performed. A positive Fusarium skin test was found in 33 per cent of CF and 16.5 per cent 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.

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

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Neutrophil migration involves the sequential rolling of neutrophils (using L-selectin) and firm adhesion to the endothelium (mediated by Mac-1). Neutrophil stimulation triggers shedding of L-selectin and upregulation of the Mac-1 complex (CD18/CD11b). Recent studies suggest circulating neutrophils in patients with acute lung disease may be hyperresponsive to stimuli. 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, SM), 16 stable CF patients (8F, 8M) and 15 matched 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 was observed, upon stimulation with interleukin-8 (Il-8) and n-formylmethionylleucylphenylalanine (fMLP), acute CF patients shed significantly less L-selectin than both stable CF patients ($p<0.05$) and controls ($p<0.01$). Significantly less L-selectin was also shed by neutrophils from stable CF patients compared to 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, especially during acute infection

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CHARACTERIZATION OF A NOVEL MONOCLONAL ANTIBODY AGAINST RAT ALVEOLAR EPITHELIAL TYPE II CELLS

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The alveolar epithelium of the lung is composed of type I and II cells. Alveolar type II cells are important for lung repair since they divide and differentiate to new type I and II cells in response to injury. Although the factors which regulate the differentiation of type II to type I cells are poorly understood, the expression/amount of cell-specific marker antigens can be used as a tool to investigate this transition. The purpose of this study was to develop a monoclonal antibody (MoAb) against type II cells. Mice were immunized with isolated rat type II cells and the hybridoma supernatants screened by immunofluorescence on thin frozen rat lung sections. Two MoAbs reactive against type II cells were identified. Here we report the preliminary characterization of one MoAb, MMC4. Immunofluorescence studies using frozen lung sections showed expression of the antigen on the apical surfaces of Type II and Clara cells, but not on type I cells, macrophages, or blood vessels. Dot blot analysis also revealed the presence of the antigen in the kidney, small intestine and thymus, but not in liver, brain, heart, diaphragm, spleen, stomach, or testes. The antigen, identified by MMC4, could be used to study factors which regulate the type II to type I cell transition.

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THE RESPONSE OF BRONCHOALVEOLAR LAVAGE MAST CELLS TO SUBSTANCE P IN PATIENTS WITH CHRONIC NON-PRODUCTIVE COUGH

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Neurogenic inflammation is thought to play an important role in the pathogenesis of inflammatory diseases such as asthma. In non-asthmatic patients with chronic non-productive cough

(CNPC) there is preliminary evidence to show increased mast cell and eosinophil numbers in bronchoalveolar lavage (BAL) and induced sputum samples respectively. We have previously demonstrated that BAL mast cells from atopic asthmatic patients release more histamine on challenge with substance P than do those from non-atopic control subjects. The aim of this study was therefore to examine the action of this neuropeptide on cells obtained from patients with CNPC.

BAL (180 ml, right middle lobe) samples were obtained from 6 non-asthmatic CNPC patients and 4 non-atopic control subjects. All subjects were non-smokers and spirometry was within normal limits, (PC_{20} (histamine) >8 mg/ml). The cells were washed, resuspended in Tyrode's buffer and stimulated with substance P (20 min). Histamine release was measured in supernatants and cell pellets using an automated fluorometric assay. Data are presented as percentage histamine release, given as means±SEM.

BAL cells from patients with CNPC released significantly more histamine on challenge with substance P than did those from non-atopic control subjects (SP 25 μM, 18.4±4.1 per cent vs 5.2±1.6 per cent, $p<0.05$.

These data are similar to those found using cells from asthmatic subjects, indicating that in chronic non-productive cough mast cell reactivity is increased. Investigation of the role of airway mast cells, including their response to other neuropeptides, and their mediators in the pathophysiology of chronic non-productive cough may therefore aid the further understanding of this common and troublesome condition.

INTERLEUKIN 1-ß 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). The aim of this study was to determine whether PMNs adhere to IL-1ß stimulated HPAECs, as has been observed with HUVECs. Confluent HPAECs were pre-incubated with IL-1ß, 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 percentage of total MPO. Significant adhesion (**$p<0.01$) of PMNs to HPAECs occurred even at the lowest concentration of IL-1ß used (Table).

Table	Control	IL-1ß 2.5 U/ml	IL-1ß 5 U/ml	IL-1ß 10 U/ml	IL-1ß 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 than on PMN may be of more significance in PMN adhesion to endothelial cells of pulmonary origin than to those of umbilical vein origin.

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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 2 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 min). 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.

AUDIT OF ASTHMA ADMISSIONS TO ST. JAMES'S HOSPITAL VIA THE ACCIDENT & EMERGENCY DEPARTMENT IN 1994

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We reviewed 177 asthma admissions (96 females; 81 males) Through the A&E department of St. James's Hospital for 1994. The median age was 38 yr. Admissions varied throughout the year with an increase in winter. The mean stay in A&E was 4.8 h and the mean hospital stay was 6.4 days. Most (91) patients had single admissions only, 19 had 2, 4 had 3, 1 had 5, and 1 had 10 admissions. Forty-eight patients were current smokers. On admission to A&E, tachycardia (>100 bpm) was noted in 129 of 168 patients (mean 110.1 bpm), with tachypnoea (>24 bpm) in 141 patients (mean 29.4 bpm). Fifteen patients were cyanosed, 2 were confused and 3 were unconscious. Pulsus paradoxus was not recorded in any case. Peak flow (PEF) was noted in only 128 patients (mean 125 L/min) and unrecordable in 21 patients. A CXR was performed in 144 patients (42 were abnormal). On blood gas analysis hypoxia (pO_2 < 8 kP) was noted in 44 of 159 cases with pCO_2 > 6 kP in 36 cases.

Leucocytosis (WCC>11,000) was present in 72 of 146, while sputum cultures were positive for pathogens in 3 of 168 cases. In A&E, all patients received supplemental oxygen, 50 of 168 received nebulised bronchodilators alone, 112 bronchodilators and systemic steroids of which 24 also received intravenous aminophylline. Ten were admitted to ICU. PEF was recorded after initial treatment in only 79 cases (mean 197 L/min). On the ward, the PEF was noted in 126 patients (mean 184 L/min). Prior to discharge home, the mean PEF in 137 cases was 337

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L/min. Following discharge, 136 attended out-patients, 15 failed to attend for review and 17 were followed by their family doctor alone. In conclusion, almost half the patients were repeatedly admitted to hospital. The reasons for this are unclear. While respiratory tract infections are important, continuing smoking is a possible aggravating factor. Adherence to the asthma treatment BTS guidelines in A&E appeared to be sub optimal in some cases. Currently each SHO rotating in A&E is now provided with the asthma guidelines.

BENEFITS OF SELF MANAGEMENT PLANS IN THE CONTROL OF ASTHMA

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Uncontrolled asthma is a major cause of avoidable mortality and morbidity. Recent international guidelines have suggested that improved patient education is required to reduce this. We investigated the value of written advice in the form of 'self management plans' (SMP) in improving control of asthma. Patients attending respiratory out-patient clinics in 1 hospital with asthma, were admitted to an open prospective study. A questionnaire assessing objective and subjective indices of asthma control was administered at study entrance and 6 months later. Following instruction, they were then requested to chart twice daily peak expiratory flow rate (PEFR) readings for a period of 4 weeks. Following this, a potential normal range of PEFR was determined and a SMP was administered i.e. guidelines were given on action to be taken on deterioration of symptoms and PEFR. These were determined by discussion with a doctor, asthma nurse specialist and the patient. The SMP was tailored for each individual. Spirometry, steroid usage, courses of antibiotics, visits to GP, compliance with medication and quality of life were assessed at entry into the study and at review 6 months later. Significant improvement was noted in spirometry, quality of life, confidence in managing an attack and inhaler technique. We conclude that SMPs have an important role in the control of asthma.

WHEEZY BABIES IN HOSPITALS

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The study aim was to define the risk factors for hospitalisation in infancy with wheeze.

This was a case controlled study. All infants admitted from the beginning of November '95 and the end of April '96 were enrolled. A proforma was completed for each case detailing personal data, home environment, family structures and feeding methods. Two controls were selected from the maternity records matched for the day of birth and questionnaires were sent to these families to ascertain a similar dataset.

Eighty-four cases were enrolled. One hundred and sixty-three controls were selected of whom 110 returned questionnaires - a 67 per cent response. Infants admitted with wheezing were more likely to be male, medical card holders, with parents who smoked. No differences were noted with respect to parental atopy, immunisation status, feeding methods or daycare attendance.

Our study confirms the strong association of severe infant wheeze and passive smoking. The absence of any relationship to atopy supports other data indicating that infant wheeze is a distinct entity. "Wheezy bronchitis" is alive and well!

EPIDEMIOLOGY OF INFANT WHEEZING IN GALWAY CITY

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The study aim was to assess the prevalence of, and risk factors for infant wheeze in Galway City children.

Questionnaires were sent to the parents of the 690 infants delivered at U.C.H.G. in 1994 with Galway City addresses. The questionnaires assessed the prevalence of wheeze under 1 yr and personal and environmental factors relevant to respiratory illness. Further information was abstracted from the maternity records. Comparisons were made between "wheezers" and "non-wheezers" using chi squared tests.

Three hundred and ninety completed questionnaires were returned - a 56 per cent response rate. The prevalence of wheeze was 26 per cent. Wheezers were more likely to be male, have parents who smoked, attend day care, and have parents with a history of atopy. No differences were noted with respect to feeding method, medical card status, or immunisations.

Interpretation of the data is confounded by the disappointing response rate.

Wheeze in infancy is common and is influenced by parental smoking habits. The association with atopy may reflect a link between infant wheeze and atopic asthma in later childhood, or a self-selection bias.

AUDIT ON THE MANAGEMENT OF ACUTE BRONCHIAL ASTHMA IN THE A & E DEPARTMENT

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The study aim was to audit the management, based on the 1993 B.T.S. guidelines*, of adult patients presenting with acute bronchial asthma to the A & E Department.

This was a retrospective study, patients' age ≥13 yr, over a 3 month period. It was noted if the following parameters were recorded - peak flow (L/min), pulse, respiratory rate/min and B.P. on arrival. Based on peak flow (if recorded), expressed as percentage predicted, patients were divided into 4 risk categories.

1) ≤33 per cent life-threatening. 2) 33-50 per cent severe. 3) 50-70 per cent moderate. 4) ≥75 per cent mild.

There were 89 patients (median age 32) - 54 female, 35 male, peak flow was recorded in 74 patients (83 per cent), pulse 75 (84 per cent), BP 73 (82 per cent) and resp. rate 41 (46 per cent). Thirty-seven (42 per cent) had a repeat peak flow. Two (2 per cent) had blood gas analysis.

Of the 37 patients with life threatening or severe asthma, none received high-dose oxygen, not all received nebulized bronchodilators and 46 per cent received systemic corticosteroid. Twenty-two (59 per cent) were discharged with less than one-third on oral corticosteroids.

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Of the 20 patients with moderate asthma, 12 (60 per cent) were discharged unsafely.

The management of acute bronchial asthma at our hospital is inadequate and needs urgent revision.

*Guidelines on Management of Asthma: Thorax March 1993; 48: S1-S24.

TREATMENT OF SMALL CELL LUNG CANCER IN A SMALL REGIONAL CENTRE

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Small cell lung cancer (SCLC) is the most aggressive of the 4 common cell types of lung carcinoma. Less than 10 per cent of patients with SCLC are alive 2 yr after diagnosis.

Staging procedures, treatment regimens and survival results were reviewed in a small Regional centre to make a comparison with larger treatments centres.

Thirty-one cases of SCLC seen by 1 physician from 1985-1993 were reviewed, Staging was clinical. Treatment was undertaken in conjunction with the local oncology and radiotherapy services. Forty-two per cent of patients had limited disease, whereas 58 per cent had extensive disease at diagnosis. In patients with limited disease, 20 per cent were alive at 18 months and there was a 10 per cent long term survival rate i.e, greater than 3 yr. Average length of survival in limited disease was 456 days. Survival results were comparable amongst those treated with chemotherapy alone and those treated with combination chemotherapy and radiotherapy. In patients with extensive disease the best results were amongst those treated with a combination of chemotherapy and radiotherapy with an average survival of 353 days. These figures compare favourably with those from larger multi-disciplinary centres. The factors contributing to our relative success may relate to continuity of care achieved in a smaller centre.

SPONTANEOUS RESOLUTION OF OBSTRUCTIVE SLEEP APNOEA WITH MATURATION IN THE ROBIN SEQUENCE

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A 12 yr old girl with Robin sequence and a 1 yr history of snoring, witnessed apnoeas and daytime hypersomnolence was referred for assessment of suspected obstructive sleep apnoea (OSA). Previous surgery in childhood consisted of cleft palate repair, tonsillectomy, adenoidectomy and palatoplasty more than 5 yr before the symptoms of OSA were noticed. Micrognathia was confirmed on a lateral cephalometrograph and an ECG revealed features of right heart strain. Full overnight polysomnography using standard techniques confirmed severe OSA with an apnoea-hypopnoea index (AHI) of 49 per h with repetitive oxygen desaturations to levels below 50 per cent. OSA was fully controlled with nasal continuous positive airway pressure (ncpap) at 14 cm H_2O pressure. Following a period of 3 yr of ncpap therapy the patient requested discontinuation of this therapy and was fully re-assessed. A repeat cephalometrogram demonstrated increased mandibular length (Gonion to Menton) from 71.5 to 76 mm and enlargement of the posterior superior and inferior airway spaces from 2.5 to 4 mm and 13 to 16 mm respectively. No evidence of abnormality persisted on repeat ECG. Repeat sleep studies following 1 week off ncpap showed an AHI of 7 per h with no desaturations below 90 per cent and normal sleep quality. The patient remains well 3 months after discontinuation of ncpap therapy. This case indicates that reassessment of the need for ncpap therapy for OSA in older children with micrognathia is relevant, as it seems likely that mandibular growth and the subsequent increase in mandibular length is at least partly responsible for the enlargement of the posterior airway spaces. The size of these spaces have been shown to correlate with the degree of OSA severity, and enlargement of these spaces will lead to a significant fall in AHI, as demonstrated in this case.