LESSONS FROM A SYMPOSIUM ON EMERGING PROBLEMS IN RESPIRATORY MEDICINE HELD IN THE COLLEGE ON 6 NOVEMBER 1998

*P.T. Reid**

Diseases of the respiratory system account for a significant proportion of suffering and disability both in the UK and abroad. Tuberculosis (TB), once thought to be in decline, has re-emerged as a major threat to world health. Pneumonia continues to exert substantial morbidity and mortality, and concern grows over the emergence of antibiotic resistance to common organisms such as *Streptococcus pneumoniae*. Cigarette smoking represents the leading cause of preventable death in Europe and is the major factor implicated in the increasing incidence of lung cancer. An appreciation that the working environment contributes substantially to disease has led to improvements in health and safety at work, but occupational asthma is becoming increasingly common and is often missed with implications for the wider workforce. Despite this, research into lung disease remains chronically underfunded. These topics formed the basis for a recent symposium at the College.

THE MANAGEMENT OF CHRONIC COUGH

Cough is a common symptom which is more prevalent in men and increases with age. The majority of studies on cough rely on the subjective assessment of symptoms by the patient (or an observer) but where this has been objectively validated by ambulatory cough monitoring a poor correlation between the two is observed. Changes in symptoms appear to be reported with greater reliability.[1]

In the presence of an abnormal chest radiograph, the cause of cough is often self-apparent; but in cases of chronic cough in which the chest radiograph is normal, the cause may be elusive. European studies often contain a significant group in whom the diagnosis remains unclear, but American studies employing a more aggressive diagnostic algorithm report identification of a cause in most patients.[2] The majority of cases appear to be due to asthma or upper airway disease (sinusitis and post-nasal drip [PND]) or a combination of the two. Gastro-oesophageal reflux (GOR) appears to represent a less important but significant cause of cough. Less common causes include bronchiectasis, extrinsic allergic alveolitis, post-viral cough and drugs. In any given individual more than one cause may be identified.[3]

Diagnosis can be made from history, physical examination and a bronchial challenge test in nearly all patients: a negative bronchial challenge excludes asthma as the cause of cough. In patients in whom sinusitis and PND are suspected, an ENT opinion should be sought. CT imaging of sinuses often has little to add, although may be helpful when upper airway disease is suspected but the cause is not apparent.[4] Chronic cough may be the sole presenting symptom of GOR although the relationship to causality remains a subject of debate. When negative, 24-hour gastro-oesophageal pH monitoring excludes GOR as the cause of the patient's symptoms.[3,4] Unless one suspects a large airway abnormality which cannot be identified on chest radiograph, fibreoptic bronchoscopy is unlikely to add to the diagnostic yield. CT scan may be helpful in the identification of bronchiectasis or diffuse interstitial lung disease.

Chronic cough often requires prolonged, aggressive and appropriate therapy. Cough-variant asthma shares many of the histological inflammatory features of classical asthma. High doses of inhaled, and in some instances oral, corticosteroids are often required to produce an amelioration in symptoms. Patients in whom the bronchial challenge test is negative are unlikely to benefit from inhaled steroids and bronchodilators.[4,5] Where sinusitis contributes to cough, up to six weeks of appropriate therapy may be required before symptoms abate; and in studies which identified GOR as a contributing factor, anti-reflux strategies may take up to six months.

LEUCOTRIENE RECEPTOR ANTAGONISTS

It is now almost 60 years since Felding and Kellaway identified a potent smooth muscle spasmogen, later termed slow reacting substance of anaphylaxis (SRS-A), in experimental models of asthma. SRS-A was later identified as a mixture of the three cysteinyl-containing leukotrienes (LTC_4, LTD_4, LTE_4) which are formed by the oxidative metabolism of cell membrane arachadonic acid via the 5-lipoxygenase pathway. Once thought to occur at the plasma membrane, the steps involved in the synthesis of the leukotrienes have now been shown to take place at the nuclear membrane.[6]

Although the asthmatic airway contains a multitude of inflammatory mediators, evidence that the cysteinyl leukotrienes play an important role rests on a number of cumulative observations demonstrating that these mediators can effectively reproduce many of the functional and histological features of clinical asthma. They are potent bronchoconstrictors, increase vascular permeability and enhance mucus production. Recently, cysteinyl leukotrienes have been implicated in eosinophil recruitment and activation and may also play a role in cell proliferation with potential implications for airway remodelling. Evidence that the cysteinyl leukotrienes are of importance in clinical asthma arises from studies demonstrating that urinary LTE_4 (a marker of endogenous cysteinyl leukotriene production) is increased following bronchoconstrictor challenge by allergen, exercise and the administration of aspirin to aspirin intolerant individuals. Significant elevations of urinary LTE_4 have also been demonstrated in patients in

**Specialist Registrar,*
Western General Hospital, Crewe Road South,
Edinburgh EH4 2XU

the early stages of acute severe asthma which diminish on clinical recovery.[7]

These and other observations led several therapeutic companies to identify the cysteinyl leukotreines as a novel therapeutic target in clinical asthma. Compounds have been targeted either to inhibit 5-lipoxygenase (the enzyme responsible for the initial metabolism of arachadonic acid), or selectively block the cysteinyl leukotriene cell surface receptor. Zileuton, the most notable 5-lipoxygenase antagonist, provided some of the first evidence for the potential of these drugs but it is the selective leukotriene receptor antagonists zafirlukast and montelukast which are receiving most interest in the UK market.

The asthmatic response to allergens classically takes the form of an immediate bronchoconstriction or early-phase reaction which gradually resolves, followed approximately 24 hours later by a further period of bronchoconstriction: the late-phase reaction. Cysteinyl leukotriene antagonists have been shown to significantly inhibit both the allergen-induced early- and late-phase reactions, suggesting that the leukotrienes play an important role in mediating both events.[8] It is currently thought that mast cell synthesises cysteinyl leukotrienes in the early phase and probably a range of cells including the eosinophil contribute to the late phase.

Exercise is a common stimulus of bronchoconstriction, particularly in children. Blockade of the cysteinyl leukotriene pathway has been demonstrated to be effective in inhibiting the maximum fall in FEV_1 associated with both exercise and cold-dry air challenge in the majority of symptomatic asthmatic patients.[9-11]

Aspirin sensitive asthma represents an important subgroup of asthmatic patients, characterised by nasal polyposis and severe intolerance to non-steroidal anti-inflammatory agents. It is suggested that the disease is mediated by 'shunting' arachidonic acid metabolism through the 5-lipoxygenase pathway following blockade of the cyclo-oxygenase enzyme. These patients appear to display significant overproduction of leukotrienes both before and after aspirin provocation.[12] In a randomised double-blind crossover study of eight patients with aspirin intolerance, the use of an oral leukotriene receptor antagonist produced a significant improvement in basal lung function with a mean improvement in FEV_1 of 18% above the baseline.[13]

Leukotriene antagonism may also prove useful in facilitating a reduction in inhaled or oral corticosteroid therapy. Professor Erikson reported data from a Japanese study recruiting asthmatic patients on 1,500 mcg or more of inhaled beclomethasone. Following a reduction in steroid dose by one half, the introduction of pranlukast (a selective cysteinyl leukotriene receptor blocker) prevented the worsening of symptom scores and the increase in surrogate markers of inflammation observed in the placebo group.

Cysteinyl leukotriene antagonists appear to have an unexpected additive effect with corticosteroid therapy. *In vitro* steroids act to block the phospolipase A2 pathway, thereby inhibiting the mobilisation of arachidonic acid from the cell membrane. Thus, in appropriate doses, corticosteroids would be expected to block the production of arachidonic acid metabolites including leukotrienes. However *in vivo* leukotriene production appears to be unaffected by corticosteroids, and urinary LTE_4 production following two weeks' treatment with inhaled flucticasone is unchanged. In a study of stable asthmatics using a mean dose of 1,000 mcg inhaled corticosteroid therapy per day including oral prednisolone use in 35%, zileuton led to a significant improvement in both morning and evening peak flow.

Antagonism of the cysteinyl leukotrienes represents an encouraging novel therapeutic endeavour in the management of patients with clinical asthma. Modest but significant improvements in the control of asthma in patients with allergen, exercise-induced and aspirin-sensitive asthma have been demonstrated, as has evidence of a steroid-sparing effect. Their place in the management of the broader community of asthmatic patients remains unclear but further studies are in progress to address these and other related issues.

LUNG CANCER, CHEMOTHERAPY AND CIGARETTE SMOKING

Lung cancer is the commonest cause of cancer death in men and in many parts of the UK, including Scotland, has overtaken breast cancer as the commonest cause of cancer death among women. A number of guidelines for the management of patients with lung cancer have been produced, but it is apparent that there are large regional variations in standards and provision of care with many patients failing to receive the appropriate investigations and necessary specialist management. The challenge to improve and establish systems which deliver a more effective service to the lung cancer patient is a national priority.

A detailed discussion of the many guidelines is outwith the remit of this manuscript, but in general they emphasise the need for prompt specialist referral, the establishment of multidisciplinary teams and the appropriate and timely use of diagnostic and staging modalities. In addition, they underscore the requirement for much-needed improvements in communication systems between hospital and GPs as well as between the medical profession and patients.[14-16]

Guidelines often assume a patient's path through the hospital system to be a linear one, but a significant proportion of lung cancer patients present to hospital without the diagnosis being suspected. Those that are referred to a cancer specialist often appear after considerable delay from the first chest radiograph. Lack of specialist assessment has important implications for the patient. Such patients are less likely to have histological confirmation of the diagnosis and are approximately half as likely to receive surgery, radiotherapy or chemotherapy.[17,18] The management of lung cancer, in common with other solid tumours, appears subject to profound regional variations with as much as a threefold variation in surgical intervention, twofold variation in delivery of radiotherapy and an almost twofold variation in delivery of chemotherapy for patients with small cell carcinoma.[19,20] It is important to note that the variations in care between regions appear to be independent of social class.

These alarming discrepancies are motivating specialists to reassess the delivery of services within their regions, but it is not only specialists who express disquiet regarding lung cancer management. In a recent study by the MacMillan service, a significant number of patients reported considerable dissatisfaction as regarding waiting times (more than 60% waited more than two months following diagnosis), poor interview techniques by the medical staff and insufficient help following confirmation of the diagnosis.

Important leads on how to improve standards are being seen at both local and national levels. Locally, the introduction of parallel multidisciplinary clinics comprising a respiratory physician, oncologist, surgeon and a specialist nurse provides an opportunity to change the culture of referrals within the hospital, resulting in both an increased number of patients receiving specialist assessment and a reduction in the length of delays associated with investigation and treatment. On a regional level, many areas are adopting the so-called 'hub and spoke' model of cancer care in which district clinics are centred around a unified service directed by a multidisciplinary team. In Scotland, the model of managed care networks is being adopted. Lead cancer physicians have been appointed in each health board and are co-ordinating this process.

Chemotherapy for non-small cell lung cancer

The treatment of choice for patients with non-small cell lung cancer (NSCLC) is surgery but it is precluded in the majority of patients who present with local or distant spread. Systemic therapy represents the best hope for such patients but the use of chemotherapy in NSCLC has been the subject of much prejudice and nihilism. In part this reflects the reporting of small poorly-designed studies using single agents. However, significant response rates and small survival advantages appear to be conferred by regimens which include cisplatin. Meta-analysis of studies incorporating cisplatin-based regimens have demonstrated a modest increase in two-year (4%) and five-year (2%) survival in patients with localised disease and in patients with advanced disease have demonstrated an increase in median survival of 8% at one year.[21]

Following a small phase II study of 74 patients in which chemotherapy with mitomycin C, ifosfamide and cisplatin (MIC) was well tolerated and associated with response rates of between 30-50%, a large multicentre randomised trial was designed to test whether the addition of MIC chemotherapy to standard treatment (radical radiotherapy for localised disease or palliative care for advanced disease) provided a survival and quality of life benefit to patients with unresectable disease. 805 ambulatory patients aged less than or equal to 75 years were enrolled. The combined results demonstrated a small survival advantage in the chemotherapy arm which was seen regardless of the patients age, gender, performance status, histology or disease stage. Multivariate analysis of the data demonstrated that survival depended most on the stage of disease followed by performance status of the patient and then the histology of the tumour. Age should not be considered a bar to therapy if otherwise appropriate.

Three centres performed a quality of life study on 67 patients with localised disease and 109 patients with advanced disease. The EORTC lung cancer instrument assessment was used and scores averaged to produce a mean quality of life score (MQS). Patients were interviewed at three weekly intervals (up to a maximum of five interviews) from diagnosis. The change in mean score between the first and the third visit (six-week period) was used to determine whether quality of life improved or deteriorated over time. Excepting scores for nausea and vomiting, patients with both localised and advanced disease receiving chemotherapy reported an improvement in quality of life whereas patients receiving radiotherapy or, surprisingly, palliative care reported a deterioration. These results are supported by a recent survey in which 68% of patients who had received a cisplatin-based regimen confirmed that they would be prepared to undergo such treatment again if it was found it would only improve their symptoms but not the duration of their survival.

Whilst the effects of chemotherapy are currently short-lived and associated with small survival advantages they are nevertheless encouraging. Newer and potentially more effective drugs continue to be developed offering the prospect of further progress in what has previously been a dismal field.

Cigarette smoking

These disappointing aspects in the management of lung cancer appear more tragic when one considers that the majority of cases ought to be considered preventable by removing the major aetiological factor of cigarette smoking. Smoking has been an integral part of society for centuries, but it is only recently that we have recognised its health implications and more recently still that governments have begun to introduce legislation to curtail tobacco advertising and enforce responsibility on the tobacco companies for the loss of health in smokers. Smoking is more common in those from less affluent socio-economic groups and, in Western society, particular prevalent in young women and school-age children. Once started, the powerful physiological and psychological aspects of addiction which accompany the habit make it notoriously difficult to stop; making these individuals a particular target of tobacco companies.

Smoking cessation is possible in highly-motivated populations but few resources are devoted to assisting smokers in discontinuing the habit. Much of the emphasis has been targeted at the level of the individual, and specifically directed towards educating the individual smoker on the dangers of the habit to their health. The largely unsuccessful outcomes from these campaigns probably arise from a failure to recognise the multiplicity of factors which contribute to continued smoking. These include a variety of personal (micro-) factors including the influence of parents, friends and other role models; and macrofactors such as the regulation of availability, pricing and advertising. Pressure is now being directed towards governments to take seriously these macrofactors by increasing tobacco taxation, banning smoking in public areas and banning tobacco advertising.[23] If such measures are widely adopted the expected benefits, in terms of health, to society will be huge although an interesting debate continues as to whether the expected reductions in health care expenditure will be offset by an increased need to support an increasing healthy but ageing population.[24]

OCCUPATIONAL ASTHMA AND INDUSTRIAL BENEFITS

Occupational asthma refers to asthma which arises from exposure to dusts and chemicals encountered in the work place. Its incidence increases with age and is more common in smokers. The diagnosis carries not only important implications for the patient but in many instances unrecognised sufferers may be detected in the rest of the workforce. It is important to recognise occupational factors early as removal of the patient from the exposure can result in cure. Two useful screening questions to identify individuals in whom the diagnosis may be suspected clinically are: do your symptoms improve on days away

from work and do your symptoms improve on holiday? Subsequent validation of the diagnosis may be obtained by employing either two-hourly peak flow recordings, non-specific bronchial hyper-reactivity testing or before-and-after shift peak flow readings, although it should be noted that the natural diurnal variation in peak flow will often obscure work related changes. Two-hourly peak flow monitoring may be both cumbersome and confusing but may be clarified by the use of a computer-based programme (OASYS) available from *vitalograph* which reformats the data in a user-friendly manner and allows the diagnosis of occupational asthma to be made with a sensitivity of just under 70% and a specificity of 94%.[25]

Although a patient may be recognised to suffer from occupational asthma, identification of the causative agent may prove difficult. Depending on the circumstances, the measurement of specific IgE, the performance of specific challenge tests, epidemiological studies of similar workforces or, more rarely, assays of biological markers or air-sampling may prove useful. Assistance is often required from the appropriate occupational physician.

Occupational asthma and other diseases which may be attributed to a person's occupation may be eligible for compensation. This is currently decided by the Industrial Injuries Advisory Council (IIAC), an independent organisation consisting of experts in social security welfare, occupational medicine and industry. To be eligible for compensation an individual must suffer from a prescribed disease in which it must be shown that the disease represents a hazard of a particular occupation and is not a risk to the general population. Furthermore, the attribution of individual cases to occupation must be proved or presumed with reasonable certainty.

There are a number of prescribed respiratory diseases and a range of benefits are available. Industrial Injuries Disablement Benefit (IIDB) may be payable, the level of which is set according to the degree of disability associated with the disease. This may be difficult to assess in an objective manner although with experience it is possible to achieve a degree of uniformity. For persons at the upper levels of the scale, an additional constant attendance allowance may be available and indeed for patients with malignant disease and a particularly poor prognosis an attendance allowance under special rules may be sought which facilitates a fast-track claim preceding approval by the relevant medical board.

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THE SPEAKERS WERE:

Dr I. Campbell	Mycobacteria other than tuberculosis.*
Prof. R.J. Shaw	Rapid diagnosis of drug resistant tuberculosis.†
Dr M. Woodhead	Severe community-acquired pneumonia.
Dr J. Rees	Diagnosing and dealing with cough.
Prof. S-E Dahlen	Anti leukotrienes in asthma.
Dr M.F. Muers	Organising a lung cancer service for optimal care.
Dr M.H. Cullen	Progress in the treatment of patients with inoperable disease.
Dr P.S. Burge	Occupational asthma.
Dr F. Ward	Compensation for occupational lung disease - what you need to know.
Dr A. Charlton	A smoking free society - just a pipe dream?

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