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LESSONS FROM A SYMPOSIUM ON MOVING POINTS IN RESPIRATORY MEDICINE HELD IN THE COLLEGE ON 6 NOVEMBER 1997*

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There are exciting developments in the understanding and treatment of both common and unusual respiratory illnesses. A large audience comprised of hospital practitioners and primary health care workers assembled at the Royal College of Physicians in Edinburgh to hear lectures on these innovations in the fields of asthma, chronic obstructive pulmonary disease, respiratory infection and pulmonary imaging.

ASTHMA

Over the last 20 years the prevalence of asthma, bronchial hyper-responsiveness and other atopic diseases has increased.[1] Studies on the genetics of asthma reveal a heritability of 40–60%. Determinants for the development of asthma include atopy,[2] family history of atopy, age, gender and race. The increase in asthma has occurred over a single generation, arguing against a solely genetic explanation. Twin and migration studies provide evidence for environmental influences. The increase in asthma in industrialised countries suggests that something in the 'westernisation' process may be relevant.

Prenatal and neonatal influences on childhood asthma

Animal models and studies on human cord blood suggest that an 'allergic phenotype' (Th2 rather than Thl T helper cells) may be established by 24 weeks gestation. *In utero* influences on the development of atopy include:

- maternal atopy,
- exposure to cigarette smoke and allergens,
- fetal nutrition.

Allergen exposure in the first few months of life may lead to increased risk of atopy; children born to households with a cat are more likely to develop asthma. Surprisingly, early life infections may be protective; measles, viral upper respiratory tract infections (URTI's) (except those due to respiratory-syncytial viruses [RS-viruses]), and gastrointestinal infections promote the development of the 'nonallergic' phenotype by an unknown mechanism. Thus:

- Disease risk begins with genetic factors and early life (pre- and post-conception) influences which select the Th2 phenotype.
- Th2-derived cytokines drive chronic inflammation, and disease induction is consolidated by exposure to allergens, progressing with airway remodelling induced by cytokines and growth factors.

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Methods of primary prevention under evaluation include allergen avoidance, inhibition of B-cell isotype switching to IgE production (nedocromil, cromoglycate), inhibition of T-cell signalling (corticosteroids), and down-regulation of cell adhesion molecule expression.

Asthma guidelines

Many of the 3.4 million UK asthma sufferers are regularly symptomatic, and asthma medications account for 11% of UK prescription charges. Asthma exacerbations are characterised by inflammation, which may lead to airway remodelling and chronic disease, with development of airways obstruction. Asthma guidelines are becoming increasingly complex, aimed not only at hospital physicians but at those involved in primary care (general practitioners, specialist nurses and pharmacists).[3] Guidelines should be evidence-based, practical, systematic, up-to-date, widely disseminated, and locally modifiable; they should promote effective therapy and stimulate audit and research.

Aims of asthma therapy

These include:

- accurate diagnosis and monitoring,
- abolition of symptoms and airway inflammation,
- normalisation of lung function,
- prevention of acute exacerbations and chronic deterioration,
- minimisation of side-effects,
- improvement of strategies for primary prevention.[4]

Indices of disease activity include PEFR (peak expiratory flow rate) variability, bronchial hyperreactivity to histamine or methacholine, partial versus maximal flow-volume loops, frequency of exacerbations/courses of prednisolone, decline of FEV1, and inflammatory markers (e.g. exhaled NO, sputum eosinophilia). Clinical trials need to address steps in the asthma therapy decision-making progress. For example, the FACET study (in press) shows that long-acting β2 agonists may improve symptoms and reduce exacerbations, and that this effect may synergise with increased inhaled corticosteroid dosage.

As few as 15% of patients comply with asthma therapy. Frequent dosing, multiple medications and chronic therapy all contribute to poor compliance. Combination preparations may help, but this is as yet unproven.

New and developing treatments for asthma

Current research into anticholinergic agents is aimed at identifying selective antagonists. M1 receptors facilitate cholinergic neurotransmission, M3 receptors are effectors of smooth muscle contraction, and M2 receptors provide negative feedback. Ipratropium is a potent antagonist at all three receptors; an M1/M3 receptor antagonist would theoretically be advantageous.[5]

Receptor-bound glucocorticoid can activate glucocorticoid response elements at the genomic level, or block transcription via the nuclear transcription factors API and NFKB, giving rise to a transactivation/transrepression ratio. Dissociation of these activities may produce drugs which maintain anti-inflammatory actions (transrepression) but have a reduced side-effect profile (diminished transactivation). Anti-IgE antibodies,

treated to avoid sensitisation, have been shown to reduce immediate and late allergen responses in asthmatic subjects. Effects on non-specific hyper-responsiveness and symptoms are less clear.[6,7] Such antibodies are expensive but with improvements in biotechnology they may become more readily available. A leukotriene receptor antagonist has recently been launched in the UK, but our knowledge of leukotriene receptors and their diverse actions is incomplete, and careful evaluation is needed.[8] The action of theophylline may relate to inhibition of phosphodiesterase 4 (PDE_4), but so far attempts to identify selective PDE_4 inhibitors have not led to useful clinical effects, perhaps because of the existence of multiple isoforms of this enzyme.[9] Airway remodelling and the development of fixed airway obstruction is in some way connected to increased smooth muscle mass and the development of fibrosis; this proliferation is mediated by growth factors such as EGF and PDGF,[10] and anti-EGF receptor antibodies are currently being evaluated in animal models.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Pulmonary rehabilitation

This aims to optimise function rather than relieve airway obstruction or alter prognosis in chronic obstructive pulmonary disease (COPD). It is a multidisciplinary programme of activities including exercise training, disease education and psychosocial support.[11] Disability in COPD may be delayed relative to loss of lung function due to functional reserve and lifestyle adaptation, but once it occurs it progresses rapidly. Conversely, a small improvement in physiology may have an amplified symptomatic effect. A disability spiral starting with physiological impairment leads to dyspnoea, exercise avoidance, loss of fitness and confidence, social and economic isolation and disability. Skeletal muscle deconditioning is important in this process, and can be reversed.

Patients suitable for rehabilitation include those with chronic lung disease who are in a period of clinical stability, well-motivated and geographically suitable for the programme. The benefits of rehabilitation are independent of age and lung function at commencement. Associated cardiovascular or orthopaedic disease may cause problems, but requirement for supplemental oxygen does not. Exercise training is muscle group-specific (although respiratory muscle training is of no proven benefit) and is supplemented by educational and counselling sessions. Outcome measures include exercise capacity (maximal or submaximal), dyspnoea scores, activities of daily living and quality of life questionnaires (general and disease-specific). A meta-analysis of 14 studies[12] demonstrated slight improvement in maximal workload achieved, an increase of 55 metres in the six-minute walking distance and improved quality of life scores following rehabilitation. With home exercise/activity programmes and encouragement to stop smoking, improvements are maintained at 12, and possibly, 18 months. Compared to lung volume reduction surgery, pulmonary rehabilitation is universally applicable, cheap and low risk, but does not affect impairment. However, questions remain unanswered in areas including:

- the optimum format and setting of the programme,
- the duration/intensity of training and the cost-effectiveness of the process.

RESPIRATORY INFECTION

Community-acquired pneumonia is an acute respiratory illness with radiological evidence of pulmonary shadowing at least segmental in nature or involving more than one lobe; tuberculosis, infection distal to bronchial obstruction, and hospital-acquired infection are to be excluded. In a population of one million, 5,000/year will develop pneumonia with 20% requiring hospital admission. Ten per cent of the latter will require admission to an intensive therapy or high dependency unit or die. Organisms do not produce a characteristic X-ray or clinical pattern sufficient for diagnosis. In about 40% of patients, no microbiological diagnosis is made. *Streptococcus pneumoniae* is the most frequently isolated pathogen, but *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*, and *Haemophilus* are also common.

- Staphylococcal pneumonia is fatal in up to 75% of cases (approaching 100% in the context of Influenza A infection), and Gram-negative pneumonia in 50% of cases.
- Blood culture positive pneumococcal pneumonia has an 11% mortality, and Haemophilus pneumonia an 8% mortality.

Prognostic features in community acquired pneumonia

Clinical predictors of severe disease include age (>60 years), chronic illness, tachypnoea (>30 breaths/minute), diastolic hypotension (<60 mmHg), confusion and poor peripheral perfusion. Investigations predicting poor outcome include multilobe involvement, elevated blood urea (>7 mmol/l), hypoxaemia (pO_2<8 kPa), acidosis (pH<7.35), hypoalbuminaemia (<35 g/l) and a high (>20 x 10^9/1) or low (<4 x 10^9/1) white cell count.[13] The British Thoracic Society (BTS) have formulated two rules to help identify high risk patients. The presence of two out of three features (respiratory rate >30/min, diastolic BP <60 mmHg, blood urea >7.0 mmol/l - *rule one,* or respiratory rate >30/min, diastolic BP <60 mmHg and confusion - *rule two*) respectively confers a 21-fold or 10-fold increase in the risk of death. A modification to the BTS rules states that two or more of four features (tachypnoea, diastolic hypotension, elevated urea and confusion) carry a 36-fold increase mortality.[14] These rules are not applicable to exacerbations of COPD.

Treatment of community acquired pneumonia[15]

Patients suffering from uncomplicated pneumonia may require hospital admission, and should be treated with a penicillin and/or a macrolide. If staphylococcal pneumonia is suspected, high dose intravenous flucloxacillin should be added. *Mycoplasma*, psittacosis and Q fever respond to macrolides and to tetracycline. Macrolides are the treatment of choice for legionella; rifampicin or ciprofloxacin may be added in severe cases. Patients with severe pneumonia should receive high dose intravenous antibiotics; either a combination of amoxycillin, flucloxacillin plus a macrolide, or cefuroxime/cefotaxime plus a macrolide. Since most deaths occur within five days of the onset of illness, antibiotics should be started without waiting for a microbiological diagnosis, particularly when poor prognostic features are present.

Management of aspergillus in the lung

Disease secondary to aspergillus may take the form of an allergic reaction (allergic bronchopulmonary aspergillosis - ABPA), formation of an aspergilloma, or invasive illness. A high index of suspicion is required for diagnosis. Fungal culture should be specifically requested and performed by a mycologist.

ABPA usually occurs in asthmatics, and is characterised by X-ray abnormalities (fleeting pulmonary infiltrates or lobar/segmental collapse with progression of the latter to proximal bronchiectasis), eosinophilia, precipitating antibodies to *Aspergillus fumigatus*, elevation of total serum IgE, a positive skin test and fungal hyphae in sputum. Pulmonary infiltrates usually respond to short courses of systemic corticosteroids. Lobar/segmental collapses are due to mechanical obstruction of the bronchus by casts containing mycelial elements, and may lead to proximal bronchiectasis. If collapse does not respond to corticosteroids, vigorous physiotherapy and bronchodilators, then bronchospcopy should be performed without delay to remove the endobronchial obstruction. This may require general anaesthesia. Long-term treatment of ABPA is controversial. Asthma therapy should be optimised, and while studies suggest that prednisolone (approximately 12.5 mg/day) will control the disease and prevent exacerbations, this therapy is not to be undertaken lightly in young patients. The value of oral itraconazole is uncertain, although there is increasing interest in the use of therapy initially for six weeks to abolish colonisation and then two to three-week pulses approximately three-monthly to discourage recolonisation.

Aspergilloma may be diagnosed on the basis of:

- a characteristic X-ray appearance,
- fungal hyphae in sputum (mutant strains on culture),
- precipitating antibodies in serum.

The patient is usually asymptomatic but may present with haemoptysis (often massive), or non-specific symptoms (which may respond to brief prednisolone therapy). There is no reliable medical treatment for aspergilloma, though anecdotal reports claim success with topical instillations into the cavity. Acute haemoptysis may be controlled by surgical embolisation, but usually recurs. Recent reports have shown a dramatic improvement in the success of surgery in controlling symptoms and prolonging life, suggesting that early surgical intervention may be appropriate in patients with adequate lung function.[16,17]

Invasive aspergillosis may develop in the immunocompromised host or in patients with aspergilloma receiving corticosteroid therapy, and can present acutely or chronically. The acute form should be treated with amphotericin and flucytosine. The chronic form is more difficult to treat: itraconazole may be used, but the timing and duration of therapy are uncertain. The combination of aspergillus and atypical mycobacteria carries a poor prognosis.

Surgical management of empyema and lung abscess

Most lung abscesses resolve with medical therapy, but percutaneous drainage may be required if the abscess ruptures into the pleural space (leading to empyema), or if it enlarges relentlessly despite antibiotics and physiotherapy (commoner with *Klebsiella* infection). Necrotising pneumonia secondary to aspiration may spread with multiple abscess formation, and surgical intervention may be required. A lung abscess can become chronic after four to six weeks, the fibrosed cavity wall failing to collapse. Such patients are usually systemically unwell, and if the remainder of the lung tissue is healthy the lesion may be removed by lobectomy. Haemoptysis from a lung abscess may be dramatic as the blood supply derives from the bronchial circulation at systemic circulatory pressure. Surgery should be considered if the initial bleed is life-threatening, fails to settle medically, or recurs. Both surgery and bronchial embolisation may be

technically difficult if the abscess receives an additional blood supply from intercostal vessels via adhesions.

Amoebic lung abscesses arise by rupture of hepatic abscesses through the diaphragm. As they rarely develop a fibrous cortex, percutaneous drainage is usually successful. Hydatid cysts require a formal surgical approach and usually present major technical difficulties.

Acute empyema is a purulent pleural effusion managed by placement of a percutaneous chest drain. Undrained, the pleural surfaces become covered by an organised fibrin matrix leaving a rigid cavity which will continue to fill with pus. If an air-fluid level (and hence a broncho-pleural fistula) is present, the pus must be removed prior to the administration of a general anaesthetic; such patients require rib resection and open drainage. Only a fit patient with a large cavity and normal underlying lung should undergo decortication of the visceral pleura. Tuberculous empyema should be treated medically not surgically.

PULMONARY IMAGING

CT scanning uses conventional X-rays with rotation in a single plane yielding axial images. Imaging in other planes requires computer reconstruction of raw data. MR relies on the proton densities within the thorax to produce a signal in a strong magnetic field, producing an image in any plane.

Roles of CT and MR imaging in diffuse lung disease, thoracic malignancy[18] *and pulmonary thromboembolism*[19,20]

CT scanning has revolutionised the investigation of diffuse lung disease, ascertaining distribution and severity. High resolution CT can help make specific diagnoses such as lymphangitis. MR cannot equal CT scanning in diffuse lung disease, as it relies on tissue and not air to generate a signal. It may be useful for delineating the extent of a known interstitial disease, and in patients requiring repeated scans it avoids radiation.

CT scanning cannot reliably determine whether a solitary pulmonary nodule is malignant, although a spiculated nodule of >3 cm is likely to be so. CT guidance allows biopsy of lesions $\geq$1.5 cm. In the investigation of mediastinal lymphadenophathy, node size is currently the only available criterion, with 1 cm at the minimum diameter being taken as the upper limit of normal. However, reactive nodes may exceed this, and tumour may be identified histologically in nodes of <1 cm. Respiratory and cardiac movement can cause MR to overestimate lymph node size, but its multiplanar capability may be advantageous. Hilar assessment is possible with MR, as there should be no tissue visible at the hilum on T1 images. CT may give spurious results in the hilar region. Mediastinal invasion may be assessed with both CT and MR, but MR is superior as the mediastinal fat plane is more clearly defined. Intravascular invasion can also be defined by both modalities. MR can demonstrate vascular flow patterns more accurately, although thin section vascular reformats (a computer enhancement technique to improve image quality) allow CT to give near-comparable results. MR excels in the imaging of superior sulcus tumours, with imaging of brachial plexus involvement. MR and CT are complementary in investigating anterior and middle mediastinal masses, MR being better at demonstrating vascular flow, while CT confers higher resolution. MR is the investigation of choice for posterior mediastinal lesions.

VQ (ventilation/perfusion) scanning cannot image pulmonary thromboembolism

reliably in the abnormal chest. Helical CT demonstrates central emboli with the same sensitivity and specificity as conventional pulmonary angiography, but when all emboli are considered, the sensitivity falls to 60-70%. With improvements in scanner design, this figure is improving. MR can visualise central emboli with similar sensitivity to CT, but only second order vessels can be defined, and a sick patient is more difficult to attend in an MR than in a CT scanner.

Interventional thoracic radiology

An increasing array of procedures can be carried out with radiological assistance, including biopsy (chest wall, pleura, lung, mediastinum and myocardium), drainage (abscess, pleural effusion/empyema and pericardium), stenting (trachea, bronchi, superior vena cava or oesophagus), embolisation, angioplasty, caval filters' placement, topical therapeutic instillation (e.g. into mycetoma cavities), thrombolysis and thrombectomy. Haemoptysis may be treated medically, surgically or by embolisation. Indications for bronchial artery embolisation include massive or recurrent haemoptysis, cavities (tuberculous or fungal), inoperable bronchiectasis, aneurysms (post-surgery or irradiation), pulmonary arterio-venous malformations (PAVMS) and abscesses.

Complications of bronchial artery embolisation include:

- embolisation of the spinal cord (causing transverse myelitis and paraplegia),
- embolisation of oesophagus, lung, myocardium, and also retrograde aortic embolisation.

It is essential to perform selective studies to identify non-bronchial systemic feeding vessels and normal anatomical variations in the bronchial arterial anatomy. Liquid embolic material (alcohol, buprolate) should never be used in the chest as it may occlude small vessels not revealed by angiography, leading to complications.

PAVMS are congenital communications between pulmonary arteries and veins which act as left-to-right shunts and are strongly associated (80-90%) with hereditary haemorrhagic telangiectasia. Complications include cerebral abscess, cerebrovascular accident, transient ischaemic attacks, polycythemia and arterial desaturation (especially in the erect position). Shunting can be quantified by peripheral injection of labelled microspheres. During embolisation, balloons or coils should be positioned as near to the shunt as possible to preserve the blood supply to the remaining lung. Many patients have multiple lesions and may require several embolisation sessions. Embolisation of PAVMS increases the patients' resting arterial saturations and reduces shunting, and has replaced surgery as the treatment of choice for this condition.

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