Interfaces in medicine: Asthma

Report of a conference

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On 27 April 1990 the second in a series of conferences on 'interfaces in medicine' took place at the Royal College of Physicians on the subject of asthma. The purpose of these meetings is to bring together hospital specialists and general practitioners with an interest in a particular disease area to present their clinical and research interests and to discuss future directions in management. The meeting was attended by 150 delegates, two-thirds of whom were general practitioners and their practice colleagues.

The president, Dr Margaret Turner-Warwick, opened the meeting by expressing the concern shown by many that asthma is an increasing problem and that responsibility for its management is largely in the hands of general practitioners. With recent concern over the possible rising prevalence and severity of asthma, a meeting to consider how the diagnosis and treatment of this disorder might be improved was both appropriate and timely.

Problems

Dr M. Cochrane of Guy's Hospital, London, started by saying that there is no universally accepted definition of asthma and that 50% or more of cases are missed, both in adults and in children. Although the morbidity from the condition at the more severe end of the spectrum is high, patients rapidly become tolerant to their symptoms and attempts by both doctors and patients objectively to assess the current activity of disease by peak flow monitoring are usually inadequate. He emphasised the importance of considering other symptoms of asthma besides wheezing and shortness of breath, particularly the importance of nocturnal cough occurring between 11 pm and 2 am, somewhat earlier than nocturnal wheeze. He found that patients comply poorly with using prophylactic drugs.

Vigorous discussion followed in which both general practitioners and hospital physicians agreed over the difficulty of patient acceptance of a diagnosis of asthma, particularly in children. However, parents are on the whole well informed about the diagnosis, and this alleviates rather than enhances their fears. Patients find it difficult to accept prophylaxis as a treatment strategy for asthma when they are feeling well, and this appears to be a major problem in certain ethnic groups, particularly Asians. The conference participants were unanimous that more support should be given for establishing asthma clinics within general practice.

Mortality

Dr D. Stableforth, from the East Birmingham Hospital, asked if mortality from asthma was increasing. The recent report on asthma by the Chief Medical Officer of Health and recent work on standardised mortality ratios in the 5–35 group during 1974–84 show a progressive increase in mortality in both sexes. This increase has also occurred in other countries, and the number of asthma deaths between countries differs eightfold. The high mortality rate continues despite an increasing number of effective drugs and of methods for administering them. One reason for it could be an increase in asthma prevalence as shown by an increase in general practitioner consultations for asthma in all age groups, with similar trends in hospital discharges. There has also been a rise in prevalence of the disease in isolated communities in Papua New Guinea and in the Polynesian Islands of New Zealand which might be due to the adoption of a Western civilisation. Possibilities include the greater consumption of table salt, exposure to environmental allergens (including the recent deaths in Barcelona linked to soya bean allergen exposure) and changes in environmental pollutants including ozone, sulphur dioxide and nitrogen dioxide.

Can death from asthma be avoided?

In most of the deaths from asthma during 1974–84 an independent panel considered that, during a severe attack of asthma, death could be prevented by attention to certain factors, including failure to establish a diagnosis (10%), insufficient supervision (77%), absent assessment of progress in response to treatment (90%), doctors not appreciating the severity of the attack, the underuse of inhaled corticosteroids and the absence or inadequate use of oral corticosteroids. In the 90 deaths reviewed, 72 were considered as having been potentially avoidable. A review of treatment of acute/severe asthma in hospitals found that adequate
corticosteroid therapy was used in only 21–34% of patients, sedation given in 33–79%, and failure to intervene with assisted ventilation occurred in 20–100% of those at high risk. Dr Stableforth emphasised that physicians need to be more aware of the severity of asthma.

Another topic briefly touched upon was the association between asthma mortality and the excessive use of anti-asthma drugs. During the lively discussion of this presentation particular concern was expressed about the use of home nebulisers to administer β₂-agonists indiscriminately and about the delay by patients in seeking medical help. Dr Stableforth said that there was no direct evidence to incriminate the abuse of nebulisers as the cause of death in 271 such cases analysed in New Zealand. Considerable emphasis was laid on the medical profession’s failure to make an impact on asthma mortality compared with the effect of prophylactic measures in the management of hypertension or for improving maternal mortality.

On average, a general practitioner will see an asthma death only once in 20 years. Some form of national system for collecting information on asthma deaths and evaluating current diagnostic and therapeutic strategies needs to be introduced. Mrs Carey Goode, Director of the National Asthma Campaign, made the important point that patients still do not accept that asthma is a severe illness and much remains to be done to educate the community and professions alike about its potentially dangerous outcome.

Basic mechanisms of asthma

Dr J. Hopkin described some of the work which his group was undertaking in Oxford on the molecular genetics of atopy and its relationship to asthma. He reviewed the clinical and epidemiological evidence that atopy is found in association with asthma particularly in the younger age group. Environmental factors are necessary to reveal the state of atopy in which the enhanced capacity to direct IgE synthesis toward common environmental allergens is inherited in a dominant basis. The autosomal dominant genetic abnormality has been localised to the long arm of chromosome 11. The Lod score (the logarithm of odds favouring a genetic marker being closely associated with the gene responsible for the increased IgE response) for a particular genetic marker indicated a million-to-one chance of the two genes being associated.

Can a similar genetic analysis be applied to non-atopic, late onset (intrinsic) asthma? Dr Hopkin replied that atopy is only one abnormality in asthma and does not in itself represent the disease. Airways hyperresponsiveness itself might be genetically determined but Dr Hopkin had not found this to be the case.

Airway inflammation

Professor S. Holgate from the University of Southampton picked up on the theme developed by Dr Hopkin and described how atopy might be translated through the immune system to airway inflammation in asthma. In many patients with asthma the airways respond in an exaggerated manner (hyperresponsive), as illustrated by the marked diurnal variation in airway calibre and other features including asthma attacks induced by exercise and those provoked by exposure to environmental non-specific factors such as cold air and chemical irritants. Death is often due to asphyxiation caused by large amounts of secretions which occlude the large and small airways. The high protein content of these secretions together with the presence of inflammatory cells, both in the airway wall and in the mucous plug, demonstrate the importance of inflammatory responses in this terminal event. Activated mast cells and eosinophils in the bronchial mucosa indicate ongoing mediator secretion which is probably the basis of the clinical and physiological abnormalities in asthma. Further, eosinophil leukocytes, which are commonly associated with active asthma, are selectively recruited from the bronchial circulation. Eosinophils adhere to the endothelial cells of postcapillary venules and in an animal model of allergen provoked asthma the receptor responsible for adherence of eosinophils to endothelial cells, the intercellular molecule 1 (ICAM-1), appears to be upregulated in the endothelium and in the epithelium. This provides a mechanism whereby eosinophils are recruited and retained within the airway wall. The recent discovery that ICAM-1 expressed on epithelial cells is also the major receptor for rhinovirus provides a possible mechanism for the common virus induced asthma particularly noted in children during the school term.

Immunological factors responsible for eosinophil and mast cell recruitment in atopic asthma include the upregulation of the class 2 restricted major histocompatibility antigen HLA-DR in the submucosa and epithelium. This indicates an enhanced capacity for allergens to be presented to the T cell receptor of the mucosal immune system for subsequent immunological amplification. The secretion of cytokines involved in the isotype switch of B cells to IgE synthesis (interleukin 4), and in mast cell and eosinophil proliferation, priming and migration (granulocyte macrophage colony stimulating factor, IL5 and IL3), provides a possible mechanism whereby individuals genetically predisposed to be atopic have an enhanced capacity for allergen driven mast cell and eosinophil involvement in this special form of inflammation. In a group of symptomatic atopic asthmatic subjects, inhalation of beclomethasone dipropionate (2,000 µg daily for 2 weeks followed by 1,000 µg daily for a further 4 weeks) dramatically ameliorated symptoms and reduced airway responsiveness in parallel with a reduction in the numbers of mast cells and eosinophils colonising the bronchial epithelium and submucosa.

The ensuing discussion touched on the possibility that similar inflammatory responses occur in other forms of asthma such as late onset intrinsic asthma and the occupational forms of asthma. Professor Holgate had found much the same changes in intrinsic
asthma as in the atopic allergic type apart from there being a greater number of activated T cells. By contrast, in most cases, ethylenediamine induced asthma eosinophils and mast cells did not dominate although all patients were hyperreactive and symptomatic. Could long-term sequelae of airway inflammation result in chronic airway obstruction? In reply Professor Holgate drew attention to the excess collagen secreted by fibroblasts proliferating just underneath the epithelium in asthma but there was no direct evidence to prove that this was the irreversible component of airway obstruction in poorly controlled asthma.

**Treatment and drug prophylaxis**

Dr Peter Barritt, a general practitioner from Shrewsbury, spoke on asthma diagnosis and treatment in general practice. An average practice of 2,000 would have approximately 140 asthmatic patients. In his own practice 15% of asthmatic patients had never been admitted to hospital, 30% had never attended outpatient departments, 1% currently attended outpatients. Only 50% had ever had short courses of prednisolone. The commonest causes provoking asthma attacks were upper respiratory tract virus infections and exercise. In his practice the strong emphasis on asthma prophylactic drugs had resulted in a 40% increase in costs but this was largely compensated by a reduction in the prescribing of antibiotics and antidepressants. Thirty per cent of his asthmatic patients had regular peak flow monitoring and 98% had had peak flow monitoring on at least one occasion. Dr Barritt emphasised the importance of teaching patients good inhaler technique and the value of using spacer devices whenever possible, not only to improve deposition of drugs in the lung but to minimise oral and pharyngeal drug deposition. Two-thirds of his patients were worried about side effects of long-term prophylaxis, a fifth were concerned about the need to rely on drugs for treatment, 12% were apprehensive of the use of corticosteroids even if given topically, and 2% were afraid of the possibility of becoming dependent on the drugs. However, the benefit of high implementation of prophylaxis for asthma coupled with close monitoring had greatly reduced morbidity among his patients and the overall asthma workload in his practice.

Dr P. Ind, Hammersmith Hospital, London, compared the aims of treatment of asthma in the 1990s with traditional aims. Today there is a stronger emphasis on improving the quality of life for patients with asthma, to aim therapy at healing airway inflammation to minimise bronchial hyperresponsiveness, to treat exacerbations promptly, and to prevent death. In patients with severe asthma he used high-dose (1,000–2,000 μg daily) prophylactic inhaled corticosteroids. He mentioned also the use of sodium cromoglycate and nedocromil sodium as disease modifying agents in asthma, and discussed the potential of long-acting inhaled β₂-agonist bronchodilators (salmeterol and formoterol) which will soon be introduced into the asthma therapeutic armamentarium. The potential problem with this therapy is that it may suppress symptoms without affecting inflammation.

The audience asked for guidelines as to when to implement prophylactic therapy with inhaled corticosteroids and with other drugs such as sodium cromoglycate and nedocromil sodium. The point was made that patients should not be indiscriminately treated with high doses of inhaled corticosteroids but that the ideal is to use the minimum dose that will maintain patients free of symptoms and normalise their pulmonary function. The cost of implementing prophylactic therapy for asthma in this way was more than offset by the reduced need for acute crisis management and by fewer prescriptions for antibiotics and oral corticosteroids. Dr Turner-Warwick drew attention to the importance of controlling airway inflammation in relation to the development of irreversible airflow obstruction, and Dr Cochrane added that in uncontrolled asthma this progressive decline in pulmonary function was equivalent to smoking 7 cigarettes a day. Dr Barritt indicated that in his audit the implementation of a prophylactic approach to asthma had greatly reduced the hospital admission, but no figures were presented.

**Sudden death from asthma in hospital**

Dr Anne Tattersfield from the City Hospital, Nottingham, considered the possible relationship between drugs used to treat asthma and mortality from the disease: the drugs might be too little; they might be irrelevant; they might contribute positively to asthma death. One asthma death occurred for every 500 hospital admissions, possibly because ‘too little was often done too late’. Despite education, asthma mortality figures have continued to rise but it is not clear whether any of this can be attributed to current treatment strategies. One drug that has been linked to asthma mortality directly is theophylline and, although rare, deaths from cardiac arrhythmias due to accidental or deliberate overdosing of this drug are recorded in the literature. There is also an extensive literature suggesting, but not proving, that inhaled β₂-adrenoceptor agonists, particularly those administered by inhalation in repeated large doses, might increase the risk of death in the individual with severe asthma. Possible mechanisms are: drug-induced cardiac dysrhythmia; drug tolerance; masking of symptoms in the face of worsening disease severity. Downregulation of β₂-receptor function occurs in peripheral blood leukocytes following long-term inhaled β₂-agonist treatment, although clinical evidence for downregulation of β₂-receptor function in the airways following inhalation of large doses of β₂-agonists has not been adequately documented and is probably of borderline significance. During the 1960s a close association was found between the increased prescribing of isoprenaline forte and asthma mortality, and when this product was withdrawn from widespread use mortality fell. Epidemiologists continue to debate whether this represented a cause-and-effect relationship.
high-dose treatment with inhaled terbutaline has recently been shown to reduce the functional ability of the $\beta_2$-agonist to protect against a bronchoconstrictor stimulus such as histamine; after discontinuing therapy, rebound hyperresponsiveness occurred.

Hypokalaemia may represent an additional risk factor. All $\beta_2$-agonists reduce circulating potassium, causing an increase in cardiac excitability. This is further enhanced by the hypoxaemia of deteriorating asthma. These two events therefore become potential risk factors when high doses of $\beta_2$-agonists are administered.

Members of the audience expressed concern over the widespread use of the United Kingdom of nebulised bronchodilators and the possible link that this might have with mortality. Dr Tattersfield emphasised the importance of measuring asthma severity when nebulisers were used and suggested that the peak flow meter be used for this. In severe asthma many studies have shown that patients’ perception of symptoms and severity was poor and that some form of objective assessment of severity is essential if nebulisers are to be used in the community.

Environmental prophylaxis

Dr A. Woodcock from Wythenshawe Hospital, Manchester, reviewed environmental prophylaxis as a possible therapeutic approach within the home. The major allergen from the house dust mite Dermatophagoides pteronyssinus (DerP) is responsible for sensitising the respiratory tract and inducing episodic asthma in atopic individuals, particularly children. When house dust mites are deprived of a damp warm environment exposure to this allergen is dramatically reduced, with consequent symptomatic improvement. Historically, spending time in the Swiss Alps has proven to be a highly effective treatment of severe asthma in children. There is a widely held view among general practitioners and specialists that mite control measures are ineffective in treating asthma, but most of the methods currently available to reduce the number of mites in soft furnishings and the levels of mite allergen are singularly ineffective. When considerable efforts have been made to reduce mite exposure by sealing bedding and pillows with plastic covers and by using various agents to kill mites and inactivate allergens, these have had a measurable effect in reducing bronchial hyperresponsiveness and symptomatic asthma.

Dr S. Burge from Solihull Hospital expanded the theme of environmental exposure by reviewing the importance of thinking of the workplace as a source of sensitising agents. The clinical expression of occupational asthma is often confused with a chronic bronchitis since cough and sputum are common symptoms of both. In a surveillance of occupational asthma in his health region Dr Burge pointed to the economic importance of this form of disease by showing that in Birmingham in 1985 the average family income of diagnosed patients fell from £8,000 to £6,000 (including government compensation). Physicians must be sensitive in dealing with such patients because, once the diagnosis has been established, many may not be able to return to the work for which they were trained. Although the diagnosis of asthma related to occupational chemicals is important for the individual patient, it is equally important for the others in the workplace who may be similarly exposed. He emphasised the value of peak flow monitoring of work-related changes in airway calibre and suggested that the most critical question to be asked of patients in order to diagnose the condition was whether their chest tightness wheeze or shortness of breath is better on days away from work. Following occupational exposure, symptoms of asthma may not be fully manifest until many hours after exposure (late phase response) and at least one to two days may be necessary for patients to detect any form of remission when removed from the sensitising agent. When a diagnosis of occupational asthma has been made it is important to contact the occupational physician who is responsible for investigating the workplace and ensuring that the appropriate environmental changes are made. The only sure treatment for occupational asthma is removal from the sensitising agent; this may best be achieved not necessarily by removing the patient from the workplace but by changing the industrial process.

Childhood asthma

Dr J. Warner from Brompton Hospital, London, discussed the value of measuring bronchial hyperresponsiveness as an index of asthma in children. Children with seasonal symptoms show a progressive increase in bronchial responsiveness to inhaled methacholine in relation to four symptom groups: hayfever alone, hayfever with cough, hayfever with cough and wheeze, and pollen related asthma in addition to perennial symptoms. Dr Warner emphasised the importance of repeated cough as a presenting feature of asthma in children and the need for doctors to have a low threshold for the diagnosis of asthma as an underlying cause of this. While bronchial hyperresponsiveness is one index of asthma it does not represent clinical asthma. Indeed there are many children with symptoms of asthma who are non-responsive to methacholine, and there are methacholine hyperresponsive children who have not asthma. This may be the result of repeated virus respiratory tract infections which also cause changes in airway responsiveness.

Allergen exposure is important as a cause of childhood asthma, and removal from allergens not only reduces symptoms and hyperresponsiveness but also objective indices of airway inflammation. It is often difficult to assess the nature of recurrent airway disease in a child less than 3 years old. Almost all newborn babies appear to exhibit airway hyperresponsiveness, although this may be due to technical problems in performing the test at this age. It raises the possibility of asthma having its origin from birth or even earlier.

Do children ‘grow out of asthma’? Dr Warner was not very optimistic about this, saying that many children who apparently grew out of asthma regained
their symptoms as adults. Should skin testing be done in children to identify the allergen? Dr Warner said that a positive skin test to certain environmental allergens, particularly animal danders, may lead to useful environmental interventions in highly symptomatic patients.

An audit of childhood asthma conducted by Dr T. Usherwood, Senior Lecturer, Department of General Practice, Sheffield University, resulted in an increase in his practice’s use of inhaled bronchodilator drugs and a parallel prescription for oral preparations. He expected that there would be further change to a greater use of drugs that controlled inflammation. Absence from school because of asthma was reduced by almost 50% with the increased use of bronchodilators, although he conceded the point that the intervention itself rather than any drug treatment might be a possible explanation for this. A positive and well explained diagnosis of asthma does much to alleviate anxiety among parents who have children with recurrent respiratory symptoms, but although education alone improves knowledge it has no impact on asthma morbidity. He further encouraged the audience to have a low threshold for considering repeated lower respiratory symptoms as asthma.

Education and management

Dr Michael De Souza, a general practitioner from Kingston upon Thames, addressed the important area of education in asthma and the misconceptions in the management of asthma. The somewhat surprising statistic of sixteen consultations being required before a diagnosis of asthma is made emphasises that doctors still are reluctant to establish a diagnosis of asthma in the face of recurrent respiratory symptoms. In reviewing patient attitudes towards their asthma, 55% said they felt different from others, 8% were angry, 67% depressed, 27% blamed themselves, and a ‘staggering’ 82% claimed that they were not able to live life to the full. He drew attention to the disparity between hospital physicians and general practitioners in their management strategies for asthma and the relatively poor communication between these health care workers. One way forward was to have special asthma clinics in general practice where attention to detail could be given, although there are other opportunities for conducting careful asthma surveillance. Dr De Souza emphasised the need for increased awareness of asthma not only by medical practitioners but also in schools and the workplace. The major objective should be to try and normalise airway function to enable children and adults to lead as normal lives as possible. Prophylactic asthma therapy plays a major role in achieving this even though there might be concern on the revenue consequences to the health service. However, when viewed from the amount of work lost by those suffering from asthma \(5.7 \times 10^6\) man-days per year, well directed prophylactic health care in this common disease could have enormous cost benefits. At present approximately one hundred million pounds per year is spent on asthma, and half of this represents drug sales. More emphasis should be placed on self management plans and on ensuring that patients and health care workers can give appropriate support in the absence of crisis management.

Continuing with this theme, Dr I. Charlton from the Department of Primary Care, Southampton University, described a self management plan for asthma. Peak flow meters can be used by patients as indicators for changes in therapeutic strategy to be made by patients rather than relying on the medical profession to implement them. It is important to provide patients with written plans and how to use prophylactic therapy in the form of inhaled corticosteroids and other disease modifying drugs to achieve good asthma control. He found that self management is a highly effective way of implementing asthma care, although peak flow meters did not prove any more informative than when patients used their symptoms alone. After 6 months use of self management, patient contacts with the general practitioner were reduced from an average of 7 to 2–3 per patient, oral corticosteroids fell from 240 prescriptions to 70, acute administration of nebulised salbutamol was down from 64 to 18 and the number of days lost from work reduced from 129 to 51. Overall, by adopting such a plan, each general practitioner saved 7 days work each year. Self management also had a major impact on patients’ work and physical activities, reinforcing the effectiveness of this approach.

Overall the conference was considered to be a success and to be an important step forward in bringing hospital physicians and general practitioners closer together for a better understanding of this common group of disorders. There was a widely held view that a conference of this type should be repeated in the future.