Classic diseases revisited

Asthma

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Summary

Bronchial asthma is now recognised to be a major cause of morbidity and even mortality in people of all ages. Two important ideas have changed our approach to asthma management. The first is understanding that asthma is a chronic inflammatory disorder which needs regular treatment with anti-inflammatory drugs such as inhaled corticosteroids to prevent further attacks. The second development is the availability of prescribable peak flow meters, which allows both confident diagnosis and early prediction of relapse. Asthma management guidelines provide a logical treatment framework for most patients, but a few difficult cases still consume large amounts of medical time. The commonest problem is one of compliance with treatment which may respond to patient education, although this is not universally so. Other problems include misdiagnosis, acid reflux and, rarely, true corticosteroid-resistant asthma. Several potentially important new treatments have been developed. These include longer acting anticholinergic drugs, drugs with bronchodilator and some anti-inflammatory properties which antagonise or inhibit the production of leukotrienes, sub-types of phosphodiesterase inhibitor with anti-inflammatory properties and immunosuppressive drugs such as cyclosporin. Ultimately these new treatments must be rigorously tested and integrated into a care plan that remains centred on patient education.

Keywords: asthma, inflammation, compliance, British Thoracic Society guidelines

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Bronchial asthma is still a major source of morbidity and occasionally of mortality throughout the world. Despite 20 years of remarkable therapeutic advances, it is still increasing in prevalence^{1,2} and although it is not yet a Health of the Nation target, it may soon become one. The development of specific general practitioner-based asthma clinics has meant that more patients are seeking advice from their family doctors about how best to use present treatments, and information on future developments. This article will briefly review the current approach to asthma management in the out-patient clinic and consider the potential of newer therapies to modify patient care. Like most tales of medical progress, this one contains several false starts and blind alleys, as well as roads likely to lead to patient benefit.

Key concepts in asthma

Two different, but complementary changes in our approach to asthma have improved the management of this disease. These changes are, the recognition that asthma is an inflammatory disease, and the advent of readily available, prescribable, peak flow meters.

How has our approach to asthma management changed?

The theoretical basis on which management goals were formerly built has shifted, and with it some of the goals of treatment. In so far as theory ever dictated practice, most physicians used to believe that asthma was a disease in which airway smooth muscle showed an exaggerated contratile response to exogenous or endogenous stimuli. They supposed that, in many cases, this was the result of increased mediator release in the airways; for example, histamine release caused by IgE-mediated immunological responses. Hence, it was thought that bronchodilator drugs that relax the smooth muscle would functionally antagonise these effects and, if given regularly throughout the day, would be sufficient to control the disease. Patients with frequent exacerbations, or those with a marked 'immunological' response might benefit from regular sodium cromoglycate or corticosteroids, the former acting by stabilising mast cells and the latter by blocking immunological reactions.

Inflammatory processes in asthma

Our present views on the causes of asthma are very different. Studies on airway smooth muscle from patients with asthma undergoing lung resection or dying from their disease³ have shown that the response to chemical and electrical stimuli is almost normal. At the same time, fibre-optic bronchoscopic biopsy studies, electron microscopy, and use of sophisticated molecular probes^{4–6} have substantiated what authors claimed many years earlier⁷: that asthma is a chronic inflammatory disorder of the airways. Such studies have largely been confined to mild asthma, but a consistent picture of increased mast cell numbers, epithelial disruption and eosinophilic infiltration of both the epithelium and sub-mucosa has been seen (figure 1). Two particularly important findings are that the sub-epithelial basement membrane is thickened, and that a particular subset of T lymphocytes (TH2 cells), which orchestrate the inflammatory response, are found in chronic asthmatics.^{8,9} The cellular but not the fibrotic changes can be reversed by regular treatment with inhaled corticosteroids.¹⁰ Many convincing and conflicting cascades of mediators have been proposed to explain the contraction of airway smooth muscle, but it is clear that histamine has only a small role in this event and that other mediators, particularly the leukotrienes, and possibly prostaglandins, are important. Moreover, some of these mediators recruit other inflammatory cells into the airway and may prolong the inflammatory process, perhaps by increasing leakage of plasma from the microcirculation.

Key concepts in asthma

- asthma is an inflammatory disorder of the airways
- the characteristic variability in airflow limitation seen in asthma is best monitored by serial peak flow measurement

Box 1

Figure 1 The airway wall. (1) Damaged epithelium with a permanently thickened subepithelial basement membrane. (2) Thickened, hypertrophied airway smooth muscle, which occupies most of the airway wall, but is functionally normal. (3) Parasympathetic nerve fibres, which are mostly efferent, although some are afferent from the epithelium. They influence the airway smooth muscle and the microcirculation. Other neural inputs are less well defined. (4) The microcirculation, which is complex, poorly understood and present on both sides of the smooth muscle layer. Vascular leak may be important, as the source of inflammatory cells. (5) T-lymphocytes and eosinophils, the cells which mediate inflammatory damage and mediator release

Home peak flow recording

- needs explanation
- following deep inhalation, blow air out as hard and as fast as possible – record the best of three attempts
- recording of PEF 3–4 times daily for two weeks is better than twice daily for two months
- some patients falsely record their results – beware of totally regular recordings

Box 2

Several conclusions can be drawn from understanding the role of inflammation in asthma:

- Although regular bronchodilators may block the effects of the disease, they will not treat the underlying pathology. Only treatment which suppresses inflammation will be likely to reduce bronchial hyperresponsiveness and reduce the frequency and severity of exacerbations.
- Anti-inflammatory therapy will be needed at the point in management when regular bronchodilators were previously being introduced.
- Blocking one of the steps in the complex web of mediators leading to airway narrowing will not necessarily be effective if other pathways are still operating.

The distinction between bronchodilator and anti-inflammatory treatment is becoming increasingly blurred and new terminology is probably needed to describe new drugs which have both bronchodilator and anti-inflammatory actions. Although in practice most asthmatic inflammation is corticosteroid-responsive, in some asthmatic patients, corticosteroids do not block mediator production effectively and these individuals are essentially resistant to this therapy.¹¹

Prescribable peak flow meters

The other major change in practice – the advent of prescribable peak flow meters – has allowed characteristic patterns of variable airflow obstruction to be documented and the effects of treatment to be observed (figure 2). Previous reliance on symptoms and sporadic signs contributed to the ‘hit and miss’ nature of asthma care which made it hard to develop specific patient plans, or monitor progress. Several studies have shown that the severity of diurnal peak expiratory flow (PEF) variation is a good surrogate for more complex laboratory tests of bronchial reactivity.¹² PEF charts are helpful diagnostically, for example, in detecting precipitants or occupational factors and are also a powerful tool in improving the patients’ understanding of their illness.

These advances have changed the goals of asthma treatment and how we monitor whether they are achieved. Ideally, we would like to see the patient asymptomatic without loss of time from work or school, able to sleep, exercise and grow normally without any fluctuation in PEF, and without side-effects from treatment. Such a utopian state is not easily reached and at best will involve some form of regular treatment, adherence to which poses its own problems.

Current approaches to management

Although asthma care is sometimes reduced to a step-wise recipe of drug prescription, this is not the only approach to treatment. It is important to discover reversible causes or precipitants of attacks. This can be simple, such as reviewing the patient’s medication for use of drugs such as β -blockers (even eye drops) or non-steroidal anti-inflammatory drugs (NSAIDs), or more complicated, such as seeking an occupational sensitizer (eg, trimetallic anhydride), which may be worthwhile when symptoms worsen during the working week. Cold, damp air can easily precipitate exercise-induced wheezing or cough and this can be readily prevented by prior β_2 -agonist use or, if necessary, by wearing a special heat-exchange mask.¹³ Avoidance of smokey or dusty atmospheres can decrease cough and wheeze but allergen avoidance is much less effective, as only trivial changes in symptoms or bronchial reactivity occur after even the most stringent aero-allergen avoidance regimes.¹⁴ Isolating specific food precipitants (eg, tartrazine dyes in foods) is much more successful. Nonetheless, vacuum-cleaning bedding and use of non-allergic pillows or covers may help some younger, milder asthmatics. Another important aspect of management is patient education. All patients should have some understanding of the precipitants of their symptoms, the expected course of their illness, how it is to be monitored, what their treatment does, and how to recognise an acute attack and take appropriate action.¹⁵ Explaining this takes time and is probably better done by a practice nurse than by a harassed doctor. Asthma clinics, whether practice- or hospital-based, should have the resources to meet these basic educational aims and be able to spot the patients who are having compliance problems.

Despite these steps, the mainstay of treatment remains pharmaceutical. The principal classes of drugs, their doses and side-effects are briefly summarised in table 1. The most recent British Thoracic Society guidelines provide a consensus view of current ‘best practice’ and are outlined in table 2. The universal application of this approach would produce considerable improvement in asthma care and there are signs that some fund-holding practices and purchasing groups are including adherence to such standards within their hospital contracts.

Non-pharmacological therapy

- allergen avoidance, eg, pets, specific foods
- drug withdrawal, eg, β -blockers, NSAIDs
- desensitization – still controversial
- avoid non-specific trigger factors, eg, cold air, smokey rooms

Box 3

However, there are still unresolved dilemmas which this view of ‘best practice’ does not fully address. This is particularly true for the place of newer agents such as long-acting β_2 -agonists, for example, salmeterol (Serevent). There are also differences in approach between treatment in children and adults and, for example, continuing uncertainties about the best way to handle the ‘wheezy’ toddler who may not have asthma but who behaves like or even has the same pathology as that of his wheezy older siblings. Finally, specific advice in the guidelines is lacking on how to deal with the ‘non-standard’ or difficult patient. Hopefully, these issues will be addressed in the revision of the British Asthma Guidelines planned for late 1995.

Practical aspects of management

It is a sad fact that many patients only seek medical help when their asthma exacerbates and they attend the surgery or hospital emergency department for nebulised bronchodilator treatment. Good management should avoid this. Diagnosis relies on the recognition of the significance of chest tightness in the morning, cough at night and after exercise, as well as nocturnal wheeze, sleep disruption and protracted symptoms after respiratory tract infections. A low threshold in instituting home peak flow assessment is necessary. No minimum or maximum periods over which recording should take place have been agreed upon, but data generated over a two-week period will usually suffice. In addition, evidence of significant diurnal variation and/or PEF improvement in recordings before and after inhaled β_2 -agonists should be recorded. Referral for hospital assessment is necessary if in doubt and if significant symptoms still exist. PEF recording provides objective evidence of good asthma control and response to therapy, and should be routine following exacerbation to confirm clinical stability.

Applying this combination of guidelines, advice and education requires a team approach involving both doctors and asthma nurse specialists. Specific self-management plans do appear to reduce morbidity and hospitalisation, and

Table 1 Drug treatment of asthma

Drug	Action	Dose/route ¹	Side-effects	Comment
Bronchodilators				
β_2 -agonists ² eg, salbutamol (Ventolin), terbutaline (Bricanyl), salmeterol (Severent)	Relax airway smooth muscle	Usually inhaled, sometimes oral; inhaled 50 μ g prn; 2.5 mg nebulized ³ ; salmeterol 50 μ g bid	Tremor, tachycardia, transient fall in serum potassium	Despite recent anxieties they appear safe. Turbuhaler/diskhaler are easy-to-use dry powder devices. Salmeterol is valuable in nocturnal asthma.
Anticholinergics eg, ipratropium (Atrovent), oxitropium (Oxivent)	Relax airway smooth muscle	Inhaled only; 40–80 μ g bid/tid (ipratropium); 200 μ g bid/tid (oxitropium); 500 μ g nebulized ipratropium	Dry mouth, bitter taste; very rarely glaucoma with the nebulized solution	Valuable in COPD and acute asthma but not usually needed in uncomplicated asthma
Xanthines eg, theophylline (Uniphyllin) aminophylline (Phyllocontin)	Relax airway smooth muscle; low doses may have an anti-inflammatory effect, of which the significance is as yet unclear	Oral or iv 200–400 mg usually bid; 250–500 mg iv slowly (adults)	Nausea, vomiting, headaches – at toxic levels cardiac arrhythmias (SVT, VT) and convulsions. Monitor serum levels for safety	Declining use, but they can reduce overnight falls in PEF
Anti-inflammatory/prophylactic				
Cromoglycate and related drugs eg, disodium cromoglycate (Intal) or nedocromil sodium (Tilade)	Unclear but unlikely to involve mast cells	Inhaled, 10–20 mg qid (disodium cromoglycate); 4 mg bid/qid (nedocromil)	Very few; there can be a bitter taste with nedocromil, which is masked by a mint flavour	Relatively mild preventative drugs – may be useful if worries about corticosteroids and especially in children
Corticosteroids eg, beclomethasone (Becotide, Becloforte), budesonide (Pulmicort), fluticasone (Flixotide), oral prednisolone	Complex actions involving steroid-responsive genes and their products especially cytokines	Inhaled: 200 μ g – 2 mg daily; oral: minimum dose possible	Inhaled: thrush, hoarseness, some potential for systemic absorption at very high dose; oral: bone, skin, adrenal, gastric and Cushingoid effects – more than 20 recorded	Inhaled therapy is now the cornerstone of asthma care Fluticasone may be more potent than the others but more data is needed to be sure

¹All inhaled therapy requires a check on the ability to use the device properly—change to spacer or dry powder may be needed.
²Other effects, eg mast cell inhibition are seen *in vivo* – significance uncertain. Salmeterol is not anti-inflammatory.
³Nebulized treatment is useful acutely but is seldom needed chronically in asthma.
COPD: chronic obstructive pulmonary disease

Table 2 Management of chronic asthma 1993

Adults	Step	Children
Inhaled β_2 -agonists as required	Step 1	Inhaled β_2 -agonists as required
Inhaled β_2 -agonists + regular inhaled anti-inflammatory agents (low-dose beclomethasone dipropionate or budesonide, alternatively disodium cromoglycate or nedocromil sodium)	Step 2	Inhaled β_2 -agonists + regular inhaled anti-inflammatory agents (disodium cromoglycate)
Inhaled β_2 -agonists prn + high-dose inhaled corticosteroid: beclomethasone dipropionate or budesonide (800–2000 μ g). Alternatives in patients with problems with high-dose steroids: salmeterol, sustained release theophylline or possibly disodium cromoglycate or nedocromil	Step 3	Inhaled β_2 -agonists + regular inhaled low-dose (50–200 μ g bid) corticosteroid (budesonide or beclomethasone). Consider a 5-day course of soluble prednisolone or temporary increase in inhaled steroids.
As step 3 + regular bronchodilators (sequential trial of inhaled, long-acting β_2 -agonists, sustained release theophylline, inhaled ipratropium or oxitropium, long-acting po β_2 -agonists, high-dose inhaled bronchodilators and cromoglycate/nedocromil sodium)	Step 4	Inhaled β_2 -agonists + high dose inhaled corticosteroids 400–800 μ g daily (consider a short prednisolone course or adding salmeterol)
As step 4 + oral prednisolone	Step 5	As step 4 + xanthines or nebulized β_2 -agonists (step 5a) or oral prednisolone and consider regular ipratropium or sc infusion of a β_2 -agonists (step 5b)

Asthma self-management

- involves education about the nature of asthma, what treatment does, how to take it and what to do if it fails
- requires patient co-operation and commitment
- use pre-set levels of PEF (usually morning levels) to step up (or down) treatment intensity or medical attention

Box 4

Figure 2 The effect of a bronchodilator on the peak expiratory flow of an asthmatic patient

should be formulated jointly with the patient. Despite this, a few asthmatic patients remain ‘difficult’ to control.

Difficult asthma

Some patients with asthma continue to be symptomatic and/or have very variable PEF recordings despite aggressive treatment which may reach steps 4 or 5 of the guidelines. Several factors are worth considering in such patients.

COMPLIANCE

Studies of compliance with both inhaled and oral treatment have shown just how poor this can be in up to a third of patients.^{16,17} The hidden monitoring of inhaler use, which not only records activations but also the time at which they occur, has produced alarming results. The psychology of poor compliance is under-researched but fears about the long-term side-effects of treatment, the social stigma of inhalers and differences in the aims of treatment between patient and doctor all probably play important parts.

MISDIAGNOSIS

Heavy-smoking ‘wheezy’ bronchitics may resemble patients with adult onset asthma and indeed, may have some response to bronchodilator treatment.

However, they are likely to remain symptomatic and be more subject to respiratory tract infection. Likewise, bronchiectasis or even pulmonary oedema can be associated with wheezing and breathlessness which is not helped by high doses of inhaled steroids.

ACID REFLUX

The clinical association between acid reflux in the lower oesophagus and wheezing, particularly at night, is a strong one. In at least one study, acid regurgitation has been demonstrated in patients with symptomatic reflux who show falls in peak flow during the night.¹⁸

UNSUSPECTED PRECIPITANTS

The role of occupational sensitization has already been discussed but other factors may produce a characteristic pattern of symptoms. Some women develop pre-menstrual wheezing, the mechanism for which remains obscure. In other patients, contact with a specific allergen, like animal fur, may lead to attacks only when they visit particular places.

CORTICOSTEROID-RESISTANT ASTHMA

Some patients appear genuinely resistant to the effects of even high doses of corticosteroids. Defects in monocyte function and in the cellular response to non-specific stimuli have been described.¹⁹ Recent evidence suggests that there may be a specific genetic defect associated with this failure of the normal modulation of inflammation, although this appears to be very uncommon. Such patients may prove to be the general practitioner's most troublesome asthmatic individuals.

Future prospects in asthma therapy

As more is being learned about the pathophysiology of asthma, more potential sites of drug action have suggested themselves. In general, three areas of attack have been identified. Drugs can act on the smooth muscle cell membrane to block or enhance receptor activity and hence modify contraction. This is where most existing bronchodilator drugs, for example, β_2 -agonists such as salbutamol (Ventolin) and salmeterol, and antimuscarinic drugs such as ipratropium (Atrovent) and oxitropium (Oxivent), operate. The second option is to interfere with the generation of lipid membrane products, namely leukotrienes, prostaglandins and platelet-activating factor. These compounds can cause smooth muscle contraction but also have anti-inflammatory properties, resulting in plasma leakage from small vessels and cellular infiltration. Antagonism of these mediators is a promising area of pharmaceutical research. Finally, the number and function of inflammatory cells, particularly T lymphocytes, within the airway can be modified. This is thought to be where corticosteroids have their role, although other actions have been suggested.

RECEPTOR-MEDIATED BRONCHODILATION

Several different pathways exist within the cell membrane that can initiate smooth muscle contraction (figures 3 and 4). Calcium channels, both receptor operated and voltage dependent, seem to be very important in vascular smooth muscle but attempts at blockade of airway smooth muscle have been disappointing.²⁰ Beta-receptor stimulation produces a cascade of effects as well as relaxation of the airway smooth muscle but despite the fact that the receptor system has now been well worked out, the action of salmeterol and other long acting β_2 -agonists remains contentious. Muscarinic receptors have been subclassified, those on the smooth muscle being the M_3 subtype. New, long-acting anti-muscarinic drugs like tiotropium bromide, offer some promise of blocking an alternative pathway to that conventionally affected by β_2 -agonists,²¹ however, the role of these drugs is yet to be established. Potassium channel blockade, for a time, seemed to be the most promising area of all, with the development of a drug called cromakalim²² but problems with toxicity led to a reformulation which proved ineffective.²³ Moreover, systemic effects, particularly postural hypotension and headache, make clinical potassium channel blockade a remote possibility at present.

A related approach, not involving the membrane receptors, is to inhibit the enzyme phosphodiesterase which is involved in the metabolism of cyclic AMP. Although theophylline-like drugs are no longer believed to act on this enzyme at clinically acceptable concentrations, new, more specific drugs act on enzyme sub-types. Thus, 6 mg of the phosphodiesterase 3/4 inhibitor zardaverine was shown to produce a 12% increase in FEV₁ in 12 asthmatic patients, but this was

Figure 3 The smooth muscle cell membrane. The muscarinic receptors are M_3 receptors responding to local acetylcholine release

Figure 4 The inflammatory cell wall. PAF: platelet-activating factor; ADP: adenosine diphosphate; FLAP: 5-lipoxygenase activating protein; ECP: eosinophil cationic protein; LT: leukotriene

still less than the 23% rise in the same patients after 200 μ g salbutamol.²⁴ Other drugs with greater efficacy are being studied.

MEMBRANE-GENERATED LIPID PRODUCTS

Leukotrienes

It is more than 10 years since the characterisation of the slow-reacting substance of anaphylaxis as a mixture of leukotrienes made the *Nine O'Clock News* on BBC1. Only now are the first pharmacological products of this revolution being tested in patients. Leukotriene receptor antagonists appear to produce both short term bronchodilatation and some longer term 'anti-inflammatory' effects, possibly because of reduced small vessel leakiness. Three compounds are worth specific mention: MK-571 (now withdrawn from development) is a selective leukotriene D₄ antagonist which produced a 22% increase in FEV₁ after intravenous administration to 12 stable asthmatics.²⁵ Its effects were additive to those of salbutamol and greatest in the most bronchoconstricted subjects. Similar results have been seen with 40 mg of the oral leukotriene inhibitor zafirlukast (AccolateTM),²⁶ which is to be marketed in the near future. Finally, inhibition of 5-lipoxygenase, a crucial enzyme in leukotriene generation, has been shown to reduce leukotriene E₄ excretion and produce a dose-dependent increase in FEV₁ in a large (139 patient) parallel-group double-blind study.²⁷

Prostaglandins

In contrast, drugs modifying prostaglandin production have been disappointing and, in fact, some non-steroidal agents appear to promote bronchospasm by stimulating local prostaglandin activity. Until recently platelet-activating factor antagonism was thought to offer the best hope of blocking asthmatic inflammation and reducing bronchial reactivity²⁸ but studies with two different clinically potent platelet activating factor antagonists have been very disappointing, with one drug unable to block allergen challenge in human volunteers, and the other completely ineffective in improving asthma control or reducing the requirement for inhaled steroids in a significant number of asthmatic out-patients.²⁹

CELLULAR MANIPULATION

Most drugs which work in this way have been borrowed from other areas of medicine, particularly chemotherapy and rheumatology. Anecdotal reports that methotrexate and gold injections improved asthma control led to open studies which appeared to support this view. One double-blind steroid-sparing study using methotrexate (Maxtrex) raised high hopes³⁰ but these data have not been confirmed by others³¹ and our own experience is that any benefit can usually be obtained at less risk to the patient by modifying other drug treatment. Although oral gold is a little more effective, it is nonetheless quite toxic and even the best clinical studies of gold can be criticized for underuse of inhaled corticosteroids.³² The most promising drug in this field is cyclosporin (Sandimmun) which is

normally used as an anti-rejection agent in transplant recipients. It is the only drug in this category to improve asthma control in otherwise corticosteroid-resistant patients³³, possibly because of an effect on T lymphocyte function. However, it is expensive, requires regular monitoring of renal function and causes hirsutism in many patients. Its use is still strictly experimental but it does offer some promise for the future and has given useful confirmation of the importance of T lymphocytes in the inflammatory processes of chronic asthma.

Conclusion

Improved understanding of the pathological basis of asthma is changing attitudes towards care and modifying treatment goals. Sadly, there is still no comparable improvement in our understanding of why the disease arises and why it is increasing in incidence, although tantalizing hypotheses are sometimes suggested.³⁴ Many exciting new therapies are in development and some will undoubtedly be available on prescription to add to the choice available. Steps to improve patients' understanding of their illness, deal with their anxieties about it and overcome difficulties with compliance, should always go hand in hand with selection of the appropriate medication from the widening range available.

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